NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Xarelto® (rivaroxaban) for the treatment of pulmonary embolism and prevention of recurrent VTE

Bayer plc

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Executive summary

Xarelto® (rivaroxaban) has been licensed in the UK since 2008 for the prevention of VTE in adults undergoing hip and knee surgery[1], and since December 2011 for `the treatment of DVT and prevention of recurrent DVT and pulmonary embolism following acute DVT in adults' (DVT treatment) and prevention of stroke and systemic embolism in non-valvular atrial fibrillation[2,3]. It has been evaluated in eleven phase III studies with exposure to over 32,000 patients.[4]

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi (Figure 1). Rivaroxaban does not directly inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.[1-3,5]

In October 2012, the European Committee for Medical Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation, which would extend the DVT treatment indication to include the treatment of PE.[6] The new indication would be:

> *`Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 [of the SmPC] for haemodynamically unstable PE patients.)'*[4]

Bayer announced on 20 November 2012 that Xarelto® (rivaroxaban) has been approved by the European Commission (EC) for the new indication.[7]

The draft SmPC referred to in this submission is that which followed the CHMP opinion. The draft SmPC indicates that certain groups of PE patients would not be suitable for treatment with rivaroxaban, including those who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy (see section 2.2 of this submission).[4]

In groups of PE patients who would be potentially suitable for rivaroxaban according to its licence, the NICE clinical guideline on management of venous thromboembolic diseases (NICE CG144) indicates that current treatment requires initial Low Molecular Weight Heparin (LMWH) therapy (or fondaparinux) started as soon as possible, alongside a Vitamin K Antagonist

(VKA) initiated within 24 hours of diagnosis, with the LMWH continued for 5 days or until the international Normalised Ratio (INR) is 2 or above for at least 24 hours, whichever is longer.[8] INR stabilisation normally takes 6 to 10 days, and the pathway generally involves some initial inpatient care.[9]

The main comparator for rivaroxaban in PE treatment is the current UK standard of care in patients for whom rivaroxaban would be an appropriate treatment option according to its licence: dual therapy of LMWH such as enoxaparin (until anticoagulation is established) overlapping with a VKA, typically warfarin.[4] Anticoagulation treatment for PE is recommended to continue for at least 3 months, with assessment at 3 months in discussion with the patient as to the continued risk-benefit of treatment, to prevent recurrent VTE.[8]

Dosing of LMWH can be dependent on weight and renal function, and this has previously led to safety issues.[10] Self-administration is troublesome in patients with poor dexterity, which is not uncommon in the age-group affected. Warfarin has a number of limitations, not least its narrow therapeutic index, requirement for dose adjustment and frequent INR monitoring, and a response which is easily influenced by diet, concomitant medication or intercurrent illness.[11,12]

By contrast, rivaroxaban provides a single drug approach for the acute and continued treatment of PE, which avoids the need for bridging therapy with injectables, does not require dose adjustment and does not require routine ongoing monitoring of coagulation parameters.[4]

The indication for rivaroxaban recommends a dosage of 15 mg bid for 21 days followed by 20 mg od thereafter unless a patient has moderate or severe renal impairment (creatinine clearance < 50 ml/min) and if the patient's assessed risk for bleeding outweighs the risk for recurrent PE and DVT. If this is the case, the reduced dose would be 15 mg bid for 21 days, then 15 mg od. The reduced dose may also be considered for patients receiving other medicinal products which increase rivaroxaban plasma concentrations. The NHS list price is £2.10 per tablet; this may be further enhanced by local rebate agreements between Bayer and appropriate NHS budgetholders.

Evidence as to the safety and effectiveness of rivaroxaban arises primarily from EINSTEIN-PE, which was a head-to-head RCT of rivaroxaban vs

enoxaparin/VKA for 3-12 months of treatment following a PE.[13] This study demonstrated the non-inferiority of rivaroxaban to the standard of care:

- The primary efficacy outcome, recurrence of VTE, was experienced in 2.1% rivaroxaban vs 1.8% dual LMWH/VKA therapy patients (HR: 1.12, 95% CI 0.75 to 1.68, $P_{non\text{-}inf}$=0.003, P_{sup}=0.57).
- The primary safety outcome, clinically relevant bleeding, was experienced in 10.3% rivaroxaban vs 11.4% dual LMWH/VKA therapy patients (HR: 0.90, 95% CI 0.76 to 1.07, P=0.23).
- Major bleeding was experienced in 1.1% rivaroxaban vs 2.2% dual LMWH/VKA therapy patients (HR: 0.49, 95% CI 0.31 to 0.79, P=0.003), see Table 16).

In addition, there was evidence from EINSTEIN-PE of reduced length of hospital stay in patients randomised to rivaroxaban vs enoxaparin/VKA (P<0.0001)[14] and increased treatment satisfaction[15], measured using a validated scale[16]. Similar benefits were observed in EINSTEIN-DVT in the use of rivaroxaban for the treatment of DVT and prevention of recurrent VTE.[14,17]

The EINSTEIN-Ext study provides evidence as to the relative effectiveness and safety of rivaroxaban vs placebo for 6-12 months further treatment, after an initial 6-12 months of anticoagulation in a study population who had clinical equipoise as to risk:benefit of 6-12 months of further treatment. This study found a treatment effect in favour of rivaroxaban in time to recurrence of VTE (HR: 0.18, 95% CI 0.09 to 0.39), no significant difference in rates of major bleeding (0.7% with rivaroxaban vs. 0% with placebo, P=0.11) and significantly favourable net clinical benefit (HR: 0.28, 95% CI 0.15 to 0.53, P<0.001).[18]

The scope lists three subgroups for consideration where the evidence allows: patients with underlying risk of bleeding, with provoked/unprovoked VTE, and with active cancer. Adopting intended treatment duration as a proxy for underlying risk of bleeding, the relevant treatment by subgroup interaction effects for these subgroups were not statistically significant for these groupings for the primary efficacy outcome or, where reported, for the primary safety outcome (P>0.1). The dataset of studies of VTE patients with cancer presented for the appraisal of rivaroxaban in DVT treatment is extended by data from EINSTEIN-PE, but no network meta-analysis is conducted owing to the issues of heterogeneity identified in that appraisal. There therefore

appears to be little evidence to suggest that rivaroxaban is any more or less clinically effective in these patient subgroups.

A cost-utility model was developed for this submission using model states relevant to patients incident with PE in a similar structure to what was developed previously for evaluating rivaroxaban in DVT treatment (TA261).[19] Such patients are exposed, depending on treatment, to risks of recurrence of further VTE, incidence of bleeding, mortality, and complications such as post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). Model inputs were informed by the EINSTEIN-PE trial[18], the development of an economic model to evaluate rivaroxaban in DVT treatment[19] and updated systematic literature reviews. Discounting was applied as per the NICE Reference Case and the horizon was a patient's remaining lifetime. The model's structure and outputs were variously validated. The cost-effectiveness of rivaroxaban is evaluated in patients according to their intended duration of treatment, thereby accounting in a proxy manner for variation in underlying risk of bleeding and VTE.

Regardless of whether patients were appropriate for 3, 6 or 12 months of anticoagulation, rivaroxaban was associated with lower costs and greater QALYs (dominated) the current standard of care in the base case analysis (Table 1). In probabilistic analysis, rivaroxaban dominated the standard of care with probabilities of 99.1%, 84.9% and 63.9% in patients requiring 3, 6 or 12 months of treatment respectively. For patients requiring lifelong anticoagulation, rivaroxaban provided a cost-effective option relative to the standard of care, with an incremental cost-effectiveness ratio (ICER) in the base case of £13,252 per QALY and probability of cost-effectiveness of 59.1% at a willingness to pay threshold of £20,000 per QALY. These conclusions were robust to sensitivity analyses. A cost-minimisation analysis demonstrated that treatment with rivaroxaban would be associated with cost savings of £903 per patient in relation to the standard of care, dalteparin, a LMWH.

The oral single drug approach of rivaroxaban without the need for injections or routine blood monitoring can improve patients' satisfaction[15,16] and experience of treatment, including reduced hospital stay[14]. With consistent safety data from phase III studies in acute VTE involving over 8,200 patients[13,18], rivaroxaban has a proven safety profile, and represents a clinically effective and highly cost-effective option in the treatment of PE with simplicity of dosing

and administration, providing anticipated budgetary savings (of £4.8m over five years) and the opportunity for service redesign to the NHS.

Table 1: Base case cost-effectiveness results

	Rivaroxaban	Dual LMWH / VKA therapy
Patients appropriate for 3 months of anticoagulation		
Technology acquisition cost	216.74	0
Other costs	4294.59	4907.14
Total costs	4511.33	4907.14
Difference in total costs	-395.80	
LYG	14.571	14.546
LYG difference	+0.025	
QALYs	11.940	11.912
QALY difference	+0.027	
ICER	Dominant	Dominated
Patients appropriate for 6 months of anticoagulation		
Technology acquisition cost	392.52	0
Other costs	4153.16	4758.89
Total costs	4545.68	4758.89
Difference in total costs	-213.21	
LYG	14.630	14.622
LYG difference	+0.008	
QALYs	11.992	11.979
QALY difference	+0.013	
ICER	Dominant	Dominated
Patients appropriate for 12 months of anticoagulation		
Technology acquisition cost	727.71	0
Other costs	4153.77	5014.60
Total costs	4881.48	5014.60
Difference in total costs	-133.13	
LYG	14.679	14.668
LYG difference	+0.011	
QALYs	12.032	12.012
QALY difference	+0.019	
ICER	Dominant	Dominated
Patients appropriate for lifelong anticoagulation		
Technology acquisition cost	5969.36	0
Other costs	4898.46	9493.09
Total costs	10867.82	9493.09
Difference in total costs	+1374.73	
LYG	15.333	15.303
LYG difference	+0.03	
QALYs	12.479	12.375
QALY difference	+0.104	
ICER	13252	

Abbreviations

AAFP	American Academy of Family Physicians
ACCP	American College of Chest Physicians
ACP	American College of Physicians
ACS	Acute Coronary Syndrome
ACTS	Anti Clot Treatment Scale
AE	Adverse Event
BCSH	British Committee for Standards in Haematology
CHMP	European Committee for Medical Products for Human Use
CG	Clinical Guideline
CI	Confidence Interval
CIAC	Central Independent Adjudication Committee
CONSORT	CONsolidated Standards Of Reporting Trials
CrI	Credible Interval
CRNM	Clinically Relevant Non Major
CSR	Clinical Study Report
CT	Computed Tomography
CTEPH	Chronic ThromboEmbolic Pulmonary Hypertension
DSU	Decision Support Unit
DVT	Deep Vein Thrombosis
EC	ExtraCranial
EED	Economic Evaluation Database
EOSM	End Of Study Medication
EU	European Union
GP	General Practitioner
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQL	Health Related Quality of Life
HTA	Health Technology Assessment
IC	IntraCranial
ICER	Incremental Cost Effectiveness Ratio
INR	International Normalised Ratio
IQR	InterQuartile Range
ISTH	International Society of Thrombosis and Haematosis

ITT	Intention To Treat
LMWH	Low Molecular Weight Heparin
LYG	Life Years Gained
NCGC	National Clinical Guideline Centre
NHS	(British) National Health Service
NICE	National Institute for Health and Clinical Excellence
NMB	Net Monetary Benefit
NPSA	National Patient Safety Agency
OAC	Oral AntiCoagulant
OR	Odds Ratio
PE	Pulmonary Embolism
PEA	Pulmonary Endodardectomy
PP	Per Protocol
PSA	Probabilistic Sensitivity Analysis
PSSRU	Personal Social Services Research Unit
PTS	Post Thrombotic Syndrome
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
TIA	Transient Ischaemic Attack
TSQM	Treatment Satisfaction Questionnaire
TTR	Time in Target Range
UH	Unfractionated Heparin
UK	United Kingdom
USA	Univariate Sensitivity Analysis
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolic Event

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Xarelto®

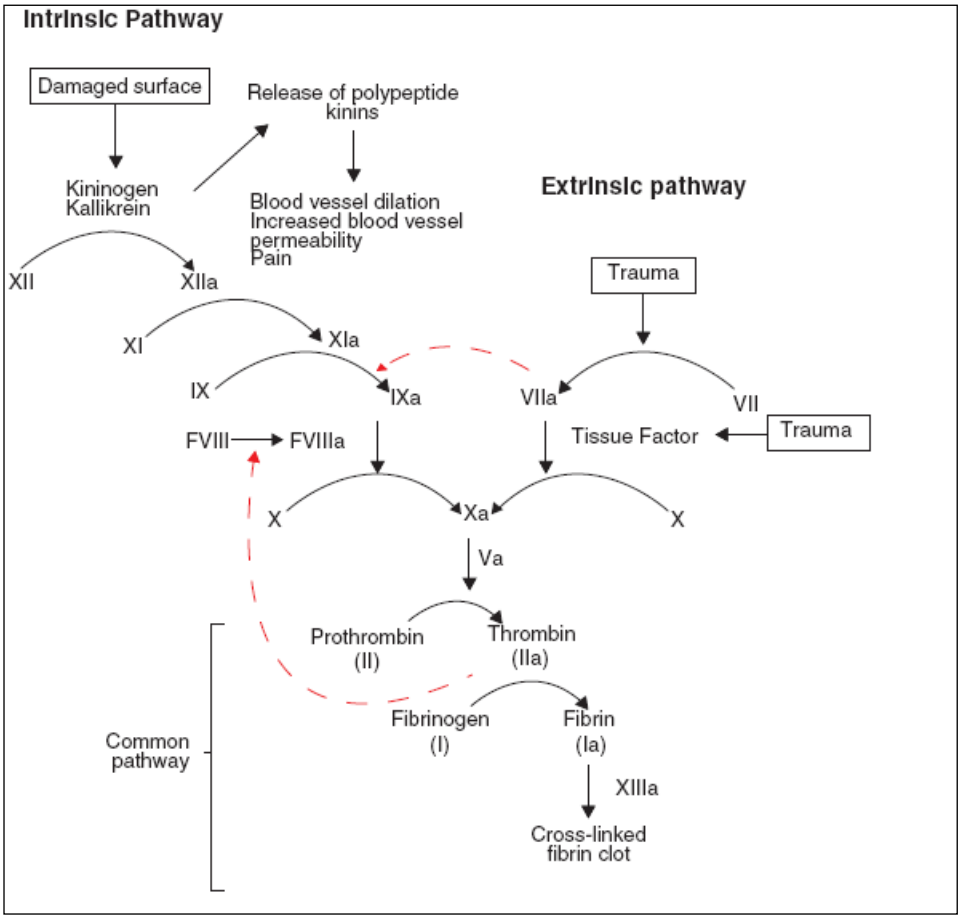
Approved name: Rivaroxaban

Therapeutic class: Oral anticoagulant

1.2 What is the principal mechanism of action of the technology?

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi (see Figure 1 below). Rivaroxaban does not directly inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.[1-3,5]

Figure 1: Schematic representation of the clotting cascade



1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Xarelto® (rivaroxaban) has been licensed in the UK since September 2008 for `prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery'.[1]

Xarelto® (rivaroxaban) was licensed in the UK in December 2011 for 'the treatment of DVT and prevention of recurrent DVT and pulmonary embolism following acute DVT in adults' and for the `prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors'.[2,3]

Bayer submitted a Marketing Authorisation Application for Xarelto® (rivaroxaban) to the EMA in April 2012 via the Centralised Procedure for the indication considered in this STA.[20]

On 18 October 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a variation to the terms of the marketing authorisation for Xarelto (rivaroxaban) 15 and 20 mg strengths.[6]

Bayer announced on 20 November 2012 that Xarelto® (rivaroxaban) has been approved by the European Commission (EC) for the new indication.[7]

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

This information is not currently available.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The current licence for rivaroxaban at 15 mg and 20 mg strengths includes the following therapeutic indication:[2,3]

> *`Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults'.*

The CHMP has adopted a positive opinion in relation to a variation of this indication to the following:[6]

> *`Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)'*

Bayer announced on 20 November 2012 that Xarelto® (rivaroxaban) has been approved by the European Commission (EC) for the new indication.[7]

Draft SmPCs are provided.[4] (The reference to section 4.4 relates to the SmPC not this submission.)

Following the previous NICE STA for rivaroxaban in the treatment of DVT[19], this submission therefore relates to the use of rivaroxaban for the treatment of PE and prevention of recurrent DVT and PE in adults.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

No completed or ongoing studies are likely to be available in the next 12 months providing additional evidence for the technology and indication being appraised.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

It is anticipated that rivaroxaban will be available in the UK for this indication in November/December 2012.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Rivaroxaban obtained regulatory approval in the United States in November 2012 for the treatment of DVT and PE and prevention of recurrent DVT and PE.[21]

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Yes.

- NICE: NICE has scheduled two other technology appraisals (ID 463, ID 532) in addition to this one (ID 569).
- Scottish Medicines Consortium (SMC): Bayer plc made a full submission to the SMC for rivaroxaban in this indication in October 2012. The SMC indicates that its advice will be due in March 2013.[22] Bayer has not made any other submissions to the SMC for rivaroxaban which are currently under consideration.

- All Wales Medicines Strategy Group (AWMSG): There have not been any appraisals of rivaroxaban by the AWMSG and we are not aware of any having been scheduled.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 2 has been completed as required.

Table 2: Unit costs of technology being appraised

Pharmaceutical formulation	15 mg and 20 mg film-coated tablets are relevant to this appraisal
Acquisition cost (excluding VAT)	The NHS list price is £2.10 per 15 mg or 20 mg tablet. The acquisition cost may be further enhanced by local rebate agreements between the manufacturer and appropriate NHS budgetholders (as per PPRS 2009, paragraph 6.45).
Method of administration	Oral
Doses	15 mg and 20 mg
Dosing frequency	15 mg twice daily for 21 days, then 20 mg once daily.
Average length of a course of treatment	3-12 months according to assessment of individual risk-benefits
Average cost of a course of treatment	The cost would be £235.86, £427.61 or £811.13 for 3, 6 or 12 months of treatment respectively
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	The SmPC advises considering a reduced dose in patients with moderate or severe renal impairment (ie creatinine clearance < 50 ml/min) and if the patient's assessed risk for bleeding outweighs the risk for recurrent PE and DVT. The reduced dose would be 15 mg bid for 21 days, then 15 mg od.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

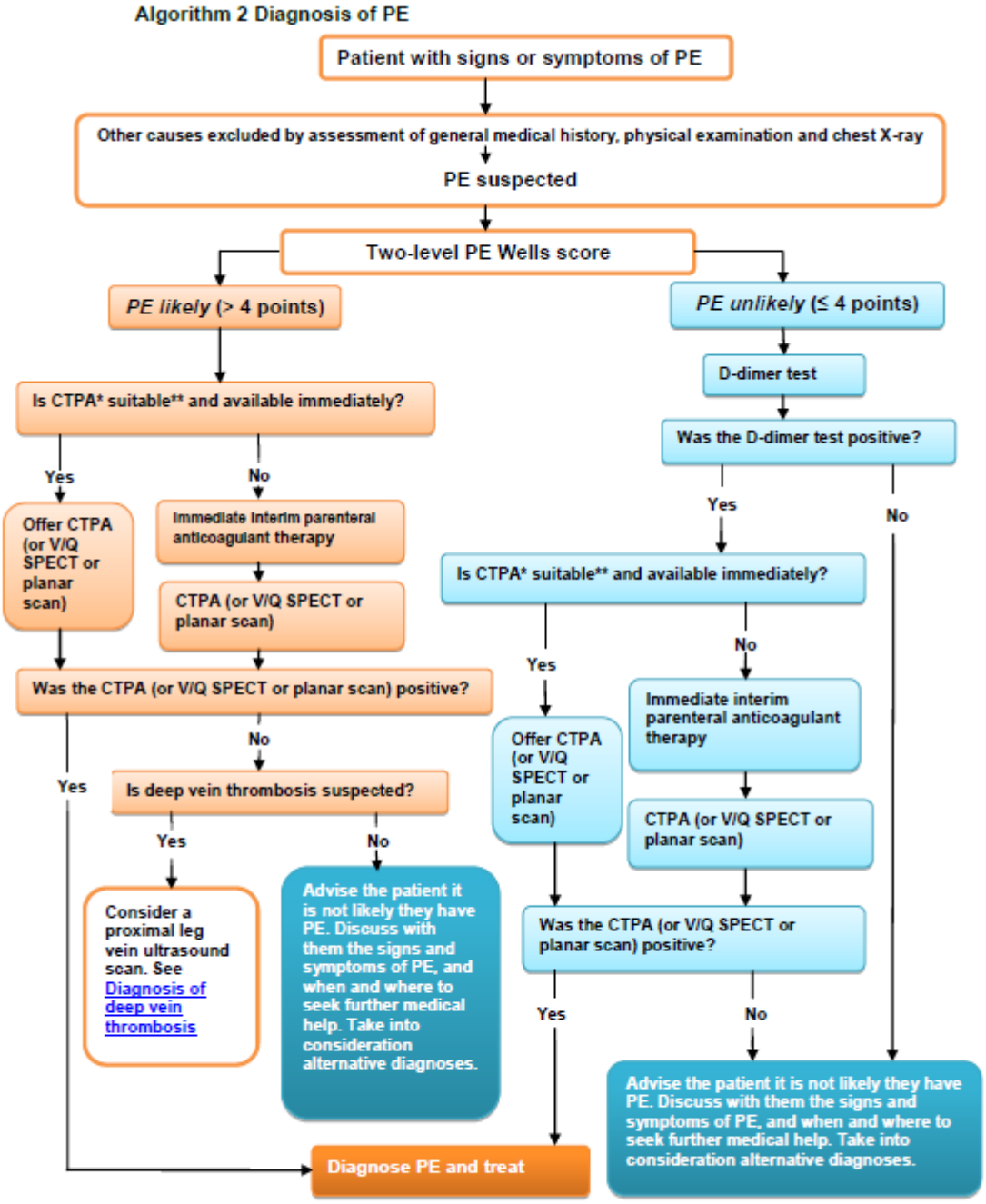
1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No. NICE CG144 provides an algorithm for the diagnosis of PE, which is reproduced below as Figure 2.[8]

In section 2.2, we list groups of patients who would not be suited for rivaroxaban based on recommendations in the draft SmPC. No additional tests or investigations are required for selection of patients appropriate for rivaroxaban.[4]

Section 4.4 of the draft SmPC provides special warnings and precautions for the use of rivaroxaban. There are no particular administration requirements for routine use.[4]

Figure 2: Algorithm for diagnosis of PE, from NICE CG144



1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No, in fact the absence of a need for routine INR monitoring is one of rivaroxaban's advantages.

Rivaroxaban is administered at a fixed dose once daily (after initial bid dosing for 21 days) and there is no requirement for routine monitoring of coagulation parameters during treatment.

By contrast, warfarin, the oral anticoagulant used most frequently in current clinical practice, has a narrow therapeutic index with a need to balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage. As a result, warfarin requires dose adjustment using frequent, inconvenient and costly monitoring of International Normalised Ratio (INR) levels.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

None. Rivaroxaban would be used alone in accordance with its licensed indication

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Venous thromboembolism (VTE) is a common disorder, with about 1 per 500 people per year in the general adult population presenting with clinical symptoms. The incidence of VTE varies substantially with age - for people under 40 years the annual incidence of venous thromboembolism is 1 in 10,000, whereas for people over 80 years the incidence rises to 1 in 100.[23,24]

Approximately two-thirds of cases of VTE present as deep vein thrombosis (DVT), the formation of a thrombus in a deep vein, usually of the lower limbs.[25] Around one third of VTE cases present as pulmonary embolism (PE), which occur when dislodged thrombi (from a DVT) travel to the lungs. PE can cause sudden death and those who survive an episode occasionally require intensive care, with recovery taking several weeks or months. The clinical course of PE may also be complicated by recurrent episodes of DVT or PE as well as chronic thromboembolic pulmonary hypertension (CTEPH). Patients with DVT may progress to developing post-thrombotic syndrome (PTS).[8]

NICE Clinical Guideline 92 (Reducing the risk of venous thromboembolism in patients admitted to hospital) identifies various risk factors for venous thromboembolism. These include active cancer or cancer treatment, age over 60 years, critical care admission, dehydration, known thrombophilias, obesity, the presence of comorbidities such as heart disease and metabolic pathologies, family history of thromboembolic disease, use of hormone replacement therapy or oestrogen containing contraceptive therapy and varicose veins with phlebitis. Other risk factors include pregnancy, recent surgery, trauma and immobilisation.[26]

NICE Clinical Guideline 144 (Management of venous thromboembolic diseases) provides recommendations for diagnosing and treating DVT and PE. Confirmatory diagnosis should involve Wells score test and a computed tomography pulmonary angiogram (CTPA) procedure.[8]

Depending on the nature of the PE, unless there is renal impairment or significant additional bleeding risk, UK clinical practice is generally either (i) thrombolysis followed by unfractionated heparin (UH) for stabilisation, with a

longer-term vitamin K antagonist anticoagulation (eg: warfarin); or (ii) where thrombolysis is not required, dual therapy of low molecular weight heparin (LMWH) for stabilisation, with a longer-term anticoagulant, typically warfarin.[8,9,11,27-29]

Despite anticoagulation treatment, patients with a PE (or DVT) remain at risk of recurrence. This risk can continue for months into years, depending on each patient's underlying risk factors. Prandoni et al reported a cumulative incidence of recurrent VTE of 11% after one year and 50% after ten years[30]; a cumulative incidence of 24.6% at two years and 31.8% after ten years has been reported in a large cohort from Vienna[31].

VTE therefore has a substantial burden for patients and healthcare systems and is associated with mortality and considerable morbidity in terms of the long-term sequelae: recurrent VTE, post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).

Effective treatment for VTE and prevention of recurrent VTEs is important to reduce this burden, as is the introduction of new effective treatments which can offer reduced burden and improved health outcomes for healthcare providers and patients.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Patients in this indication (pulmonary embolism and prevention of recurrent VTE)

We estimate that there would be in the region of 38,600 incident cases of adults with acute PE in 2013 in England and Wales, of which around 34,600 (90%) would be first PEs. This would rise to a projected 41,300 incident cases in 2017 due to growth and ageing in the population. These projections are based on PE incidence rates derived from a combined analysis of UK hospital and primary care databases (General Practice Research Database, Hospital Episode Statistics database and Office for National Statistics linkage data) for incidence and recurrence of DVT and PE, which have been applied to population projections for England and Wales made by the Office of National

Statistics.[23,32,33] See also section 8.1. Prevalent cases (ie patients being treated on a longer-term basis after a PE for prevention of a recurrent VTE) are not known.

The following groups of PE patients listed in the SmPC would not be suitable for treatment with rivaroxaban[4]:

- Patients with clinically significant active bleeding, who are specifically contraindicated.
- Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C, who are specifically contraindicated.
- Patients who are pregnant or breastfeeding, who are specifically contraindicated.
- Patients with an increased bleeding risk, like other antithrombotic agents, such as: congenital or acquired bleeding disorders; uncontrolled severe arterial hypertension; active ulcerative gastrointestinal disease; recent gastrointestinal ulcerations; vascular retinopathy; recent intracranial or intracerebral haemorrhage; intraspinal or intracerebral vascular abnormalities; recent brain, spinal or ophthalmological surgery; or bronchiectasis or history of pulmonary bleeding.
- Patients who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.
- Patients with very severe renal impairment (creatinine clearance < 15 mL/min).

The proportion of patients who present with haemodynamically unstable PE was estimated to be 5-10% in NICE CG144.[8] We have previously used (in the 2011 submission for rivaroxaban in DVT treatment) an estimate of 1.6% of patients being contraindicated for rivaroxaban in DVT treatment due to hepatic impairment. This was taken from a US study of VTE prophylaxis among over 30,000 patients with total hip or knee replacements.[34] We have also previously approximated that 0.2% of patients would have very severe renal impairment (creatinine clearance < 15 mL/min), from data reported in a recent chart review of 524 patients in Canada with objectively diagnosed acute VTE,

which found a mean creatinine clearance of 94.3 mL/min and levels of <30 mL/min in 5%, 40-59 mL/min in 20% and 60-88 mL/min in 27% of patients.[35]

It is difficult to estimate the proportion of all patients who would be unsuited to rivaroxaban due to active or an increased risk of clinically significant bleeding, as this may involve an element of clinician judgement in relation to individual patients' risk-benefit.

On the assumption that in total 15% of PE patients would not be suitable for rivaroxaban, there would be a total of 32,800 cases of PE in 2013 which could be treated with rivaroxaban.

Rivaroxaban is to be used with caution where creatinine clearance is 15-29 mL/min. A reduction of the dose from 20 mg od to 15 mg od should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE.[4]

Patients in all licensed indications

We consider each of the other three licensed indications in turn.

We have estimated numbers of patients covered by the indications relating to the prevention of VTE following elective hip or knee surgery from procedures reported in the HES database. In England and Wales in 2010/11, there were 84,167 hip operations (procedure codes W37-W39 and W93-W95) and 81,090 knee operations (procedure codes W40-W42).[36] From this, we assume that all require pharmacological prophylaxis, and that one-third of these patients use rivaroxaban, given that two other oral anticoagulants have also been recommended in these settings.[37]

We have estimated the numbers of patients treatable with rivaroxaban in 2013 for stroke prevention in atrial fibrillation (AF) based on a prevalence of 782,386 in England and Wales[38,39], of whom 93% have non-valvular AF[40]. This yielded 727,600 patients who may be considered `covered'. Of these, 87% are estimated to have a $CHADS_2$ score of at least 1 and therefore be suitable for treatment[41] and, as two other oral anticoagulants are also recommended as an option in this setting[42,43], that at most 35% may receive rivaroxaban.

We have estimated the numbers of patients treatable with rivaroxaban in 2013 for DVT treatment using the same approach, and source for incidence rates,

as for the PE treatment indication.[23,32,33] Based on the draft SmPC for 15 mg and 20 mg rivaroxaban following the variation[4], we assume that 7.5% of DVT patients would not be suitable for treatment with rivaroxaban. There are no alternatives in routine use in the NHS beyond those considered in the Single Technology Appraisal (STA) of rivaroxaban for DVT treatment.[19] In estimating patient numbers, we have used ONS's forward projections of the national population for 2013 from a 2010 rather than 2008 calendar year starting point as in the STA submission.[33]

The results are summarised in Table 3. In total, although 833,900 patients may be `covered' by licensed indications for rivaroxaban in 2013 (38,600 with PE), the number of patients potentially treatable with rivaroxaban would be around 353,000 (32,800 with PE).

Table 3: Estimate of number of patients treatable with rivaroxaban in 2013

Indication / patient group	Patients `covered by the indication' in 2013	Patients treatable with rivaroxaban in 2013	Source
Prevention of VTE in patients undergoing elective hip replacement surgery	84,200	28,100	HES database[36], NICE CG92[26], NICE pathways[37]
Prevention of VTE in patients undergoing elective knee replacement surgery	81,100	27,000	HES database[36], NICE CG92[26], NICE pathways[37]
Stroke prevention in atrial fibrillation	633,000	221,600	NHS Information Centre[38], Stewart 2001[40], Gallagher 2008[41], NICE pathways[37]
DVT treatment and prevention of recurrent VTE	47,000	43,500	Database linkage study[23,32], ONS population projections[33], less 7.5% unsuited for treatment
PE treatment and prevention of recurrent VTE	38,600	32,800	Database linkage study[23,32], ONS population projections[33], less 15% unsuited for treatment
Total	833,900	353,000	

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Our estimate here is taken from the economic model evaluating duration of treatment developed to evaluate duration of anticoagulation treatment for the NICE VTE management clinical guideline (NICE CG144, appendix I[8]). The base case evaluation for a patient cohort with an initial unprovoked PE, aged 58 years, resulted in a period of expected life years (undiscounted) of 22.561 years with long-term treatment and 22.178 years with treatment for three months only.[8]

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Treatment of PE is covered within the NICE VTE management clinical guideline (CG 144). Section 1.2 of this guideline is particularly relevant.[8] The guideline was finalised before the completion of the STA for rivaroxaban in the treatment of DVT (July 2012) and therefore does not include rivaroxaban.[19]

The variations in recommendations by patient subgroups may be summarised as follows. These are contrasted with recommendations for the use of rivaroxaban in the draft SmPC.[4]

- Recommendations for pharmacological thrombolytic therapy depend on whether the patient is haemodynamically stable. Most patients (90-95%) are haemodynamically stable and therefore are not recommended pharmacological thrombolytic therapy. In its draft SmPC, rivaroxaban is not recommended in patients who are haemodynamically unstable.

- Recommendations for the type of anticoagulant (UH, LMWH or fondaparinux) used to stablise a patient's INR depend on whether the patient has severe renal impairment, established renal failure or an increased risk of bleeding. Rivaroxaban is generally not recommended in these circumstances (see section 2.2 and the draft SmPC[4]) and LMWH is generally recommended for INR stablisation unless there are these concerns.

- Recommendations for the type of long-term anticoagulant use depend on whether the patient has active cancer. A VKA is generally recommended unless the patient has active cancer, in which case a LMWH is recommended. Rivaroxaban may be used in patients with cancer.
- Recommendations for the duration of long-term anticoagulation depend on the patient's risk-benefit for continued treatment. Treatment should be for at least 3 months, with assessment of risk-benefit for continued treatment in discussion with the patient at 3 months. Patients with cancer are recommended a duration of 6 months.

The NICE website reports five technology appraisals in development in relation to venous thromboembolism events, though it is not clear how many of these are active.[44]

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The proportion of patients with PE who would be potentially appropriate for rivaroxaban was estimated at 85% of all PE cases in section 2.2, mindful of the recommendations on use of rivaroxaban given in the SmPC.[4]

Current pathway of care

The current pathway of care is described in NICE CG 144.[8] Following a confirmed diagnosis of PE, the current pathway of care for patients who might now be appropriate for treatment with rivaroxaban typically involves treatment with LMWH and VKA, initiated in secondary care, and typically involving some inpatient admission.

NHS Reference Cost data indicates that the average duration of hospital stay for PE patients is 2.8 days. This is based on a comparison of 161,184 bed-days to activity of 56,803 for HRGs relating to PE (DZ09A, DZ09B and DZ09C).[45]

In patients without cancer who might now be appropriate for treatment with rivaroxaban, NICE CG 144 indicates that treatment should consist of LMWH to be started as soon as possible, alongside a VKA initiated within 24 hours of diagnosis, with the LMWH continued for 5 days or until the INR is 2 or above for at least 24 hours, whichever is longer.[8] SIGN have estimated that INR stablisation normally takes a period of 6 to 10 days.[9] Treatment is recommended to continue for at least 3 months, with assessment of risk-benefit for continued treatment in discussion with the patient at 3 months.[8]

A patient requires monitoring of INR while receiving anticoagulation treatment, more frequently at first.[8,46]

Patients with cancer are recommended to be treated with 6 months of parenteral LMWH.[8,47,48]

Clinical pathway for rivaroxaban

We describe in Table 4 the current clinical pathway of care and the proposed pathway involving rivaroxaban, in the population of patients with PE suitable for treatment with rivaroxaban.

Table 4: Comparison of current and proposed pathway of care in PE patients indicated for rivaroxaban

	Current pathway	Proposed pathway
Patients without cancer	Inpatient admission is typically required.	Any requirement for inpatient admission would be unchanged.
	LMWH to be started as soon as possible, alongside a VKA initiated within 24 hours of diagnosis, with the LMWH continued for 5 days or until the INR is 2 or above for at least 24 hours, whichever is longer.	Rivaroxaban (oral)
	Treatment should be for at least 3 months, with assessment of risk-benefit for continued treatment in discussion with the patient at 3 months.	Duration and risk-benefit assessment as current practice.
Patients with cancer	6 months treatment with parenteral LMWH	Rivaroxaban (oral)

Rivaroxaban offers a single drug approach which will increase flexibility of treatment according to the patient and simplify management of PE and

subsequent risk of VTE recurrence, as has already been recognised in the management of DVT.

There are no additional monitoring costs associated with rivaroxaban. There is no need for parenteral injections of heparin or routine monitoring of coagulation parameters with rivaroxaban, easing treatment administration for patient and healthcare practitioners. Introduction of rivaroxaban is therefore likely to result in a reduced demand on costly anticoagulant services. It is anticipated that in the majority of cases, rivaroxaban will be initiated in secondary care with follow-up in primary care.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

We describe issues relating to the use of LMWHs, use of warfarin and the requirement and practice of INR monitoring. These issues would not apply to a clinical pathway based around rivaroxaban, as neither LMWH, warfarin or INR monitoring would be required. We also cover the initial setting of care.

Setting of care

The British Thoracic Society recommended in 2003 that the current arrangements for the outpatient management of DVT should be extended to include stable patients with PE.[27] However, there are no widely accepted criteria for defining PE patients who can be deemed eligible for outpatient treatment. A recent systematic literature review has suggested that certain subgroups of haemodynamically and respiratorily stable patients may be safely treated completely or partially (early discharge) at home using a well-defined management programme. However, the safety of home therapy was not based on high-quality evidence and PE is still mainly treated in hospital.[49] NICE CG 144 `did not consider PE risk stratification or the outpatient management of PE as these were beyond [its] scope.'[8]

LMWHs

LMWHs are administered by subcutaneous injection, which can be self-administered. Injections may cause problems in patients with a needle phobia, elderly patients or patients with poor dexterity. For patients who require assistance with the LMWH administration, this may require a daily visit to or from, a healthcare professional e.g. district nurse and/or time to train the

patient or carer to self-inject. For cancer patients who require longer term treatment with LMWH, this can be particularly resource intensive.[50]

Prescribed doses of LMWH for the treatment of VTE are dependent on the weight of the patient and renal function. This can lead to safety issues associated with inappropriate dosing which was the subject of a recent National Patient Safety Agency (NPSA) Rapid Response Report.[10]

Warfarin

Warfarin, the VKA used most frequently in clinical practice has a number of well reported limitations[11], including:

- A narrow therapeutic index with a fine balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage
- Response that is significantly influenced by genetic polymorphisms, diet, concomitant medications (which may be of particular concern in a co-morbid population), herbal supplements and intercurrent illness
- The requirement for dose adjustment using frequent, inconvenient and costly INR monitoring. The frequency of monitoring varies depending on individual patient characteristics.

The NPSA issued a patient safety alert to healthcare organisations in 2007 regarding best practice actions to make anticoagulation therapy safer.[12]

INR monitoring

Anticoagulant services are managed in a number of settings in the UK depending on the locally commissioned arrangements[51], including:

- Secondary care
- Secondary care satellite clinics
- Primary care – GP led, nurse led, community pharmacy led
- “Hybrid” – where there is a mixture of the different settings involved at different stages of the care pathway or for different patient types

As mentioned previously, a patient requires monitoring of INR while receiving anticoagulation treatment, more frequently at first.[8,46]

2.7 Please identify the main comparator(s) and justify their selection.

As described in section 1.5, this submission is intended to relate to the use of rivaroxaban for the treatment of PE and prevention of recurrent DVT and PE in adults.

The proportion of patients with PE who would be potentially appropriate for rivaroxaban was estimated at 85% of all PE cases in section 2.2, mindful of the recommendations on use of rivaroxaban given in the SmPC.[4]

The current clinical pathway for such patients and limitations of this practice were described in sections 2.5-6, following the relevant NICE clinical guideline.[8] The pathway involves initial inpatient secondary care, with follow-up treatment involving LMWH, warfarin (a VKA) and INR monitoring. In the group of patients potentially treatable with rivaroxaban, the clinical pathway generally does not involve UH. This is reflected in the comparators given in the final scope.

Accordingly, the appropriate comparator to rivaroxaban would be initial treatment with a LMWH with continued therapy of VKA, where VKA is considered an appropriate therapy. However, where continued therapy of VKA is not considered an appropriate therapy (eg: patients with cancer), then the comparator to rivaroxaban would be LMWH.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

For clinically significant bleeding, usual treatment measures should be considered, including fluid replacement and haemodynamic support, blood transfusion, and fresh frozen plasma. In addition, specific measures may be required depending on the site of bleeding, eg: upper GI endoscopy for GI bleeding. See also the current[1-3] and draft SmPCs[4].

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

It is anticipated that rivaroxaban would be initiated whilst the patient is admitted in hospital once a PE has been diagnosed. There is no additional

resource use associated with the use of rivaroxaban and there is no requirement for routine monitoring of coagulation parameters.

This is in contrast to LMWHs and warfarin, the comparators, which are managed within an established infrastructure in the NHS, for:

- provision of anticoagulation (eg anticoagulation clinics)
- providing administration (injections) and / or training for self-administration
- blood sampling, testing and dose adjustment.

As mentioned in section 2.4, anticoagulant services are managed in a number of settings in the UK depending on the locally commissioned arrangements.[51] Resource use associated with warfarin management is significant, since INR monitoring and dose adjustment is required, more frequently at first.[8,46]

2.10 Does the technology require additional infrastructure to be put in place?

No, rivaroxaban does not require additional infrastructure to be put in place.

Indeed, over time, the availability of rivaroxaban will allow for reconfiguration of existing anticoagulation services. It will also assist with managing demand for such services in the future, which will inevitably rise with the ageing population.

3 Equality

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

We are not aware of any equity or equality issues.

3.1.2 How has the analysis addressed these issues?

None identified.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Yes, rivaroxaban is highly innovative in this regard. There are many challenges with current therapy provided to patients and, as outlined in section 2.6, several health-related benefits from rivaroxaban that offer the NHS a step-change in the management of patients with PE and in the prevention of further recurrence of DVT and PE.

The advantages that rivaroxaban could bring to the NHS include[4]:

- Treatment of VTE could be made with a single oral agent, administered at a fixed dose.
- No requirement for routine monitoring of coagulation parameters during treatment.
- No need for "bridging" therapy with LMWH injections.
- Continued therapy with a secondary prevention dose after an initial intensified regimen.
- Ease of treatment administration for patients and healthcare practitioners, due to the simplicity of dosing, minimal drug and food interactions, and no routine coagulation monitoring requirements. (Rivaroxaban must be taken with food.)
- Reduced NHS resource consumption and costs for those patients who would otherwise have required assistance with injections, and the potential for earlier hospital discharge.

Being a fixed dose oral anticoagulant without any requirement for routine monitoring or coagulation parameters and with no need for bridging therapy, rivaroxaban potentially offers a novel single drug approach with significant opportunities for service redesign.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The various limitations of the QALY are well-known. The benefits of treatment relevant to this assessment that may not be captured by the QALY are anticipated to include:

- Ease of treatment administration for patients and healthcare practitioners, due to the simplicity of dosing, lack of drug and food interactions and lack of coagulation monitoring, and resultant patient satisfaction.
- Reduced fear and anxiety among patients of the risk and consequences of being out of INR range.
- Reduced safety risks to patients and reduced litigation risks to the NHS from a fixed-dose regime.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

The three factors listed in section 4.1.2 are discussed in turn.

Greater patient satisfaction with rivaroxaban than standard therapy

Patient-reported satisfaction was measured by Anti Clot Treatment Scale (ACTS) and Treatment Satisfaction Questionnaire (TSQM) instruments in EINSTEIN-PE and EINSTEIN-DVT. Results from EINSTEIN-DVT have been presented[15]; results from EINSTEIN-PE have been accepted for poster presentation[17]. The ACTS instrument has been validated.[16]

Results from the EINSTEIN-PE trial are most relevant to this submission, and are provided below on an academic in confidence basis. ACTS consists of two scales, ACTS Burdens (12 items) and ACTS Benefits (3 items), and was evaluated at day 15 and months 1, 2, 3, 6 and 12 in a subgroup of 2283 patients from seven countries (Canada, France, Germany, Italy, Netherlands, UK and USA). For each scale, higher total scores indicate higher satisfaction.

A pre-specified repeated measures regression analysis was used to compare ACTS scores in the ITT population. Patients reported higher satisfaction in the rivaroxaban group compared with the enoxaparin/VKA group with higher mean ACTS scores across visits.

Mean ACTS Burdens scores were 55.4 vs. 51.9 ($p<0.0001$) in favour of rivaroxaban with a consistent treatment effect over time. Mean ACTS Benefits scores were 11.9 vs. 11.4 ($P<0.0001$); showing an improvement in satisfaction for the rivaroxaban group. The difference in ACTS Benefits scores between the groups in months 2-12 than at earlier timepoints.

TSQM (version 2) is an 11 item instrument representing four subscales: effectiveness (2 items), side-effects (4 items), convenience (3 items) and global satisfaction (2 items). Higher scores indicate higher satisfaction with a treatment. This instrument was evaluated in the same subgroup of 2283 patients at months 1, 3, 6 and 12. Scores were consistently higher in patients treated with rivaroxaban than LMWH/VKA in all subscales and at all time points evaluated.

As in patients with DVT, patients with PE taking rivaroxaban had improved treatment satisfaction compared with patients receiving dual enoxaparin/VKA, in particular, a reduced patient-reported anticoagulation burden.

Reduced fear and anxiety of the risk and consequences of being out of INR range

This issue is discussed further in section 7.4.1. The risk of recurrence can continue, depending on each patient's underlying risk factors. If the blood clot occurred as a result of surgery or trauma, and the risk factor was considered temporary, then the risk of having another DVT or PE may be low.

Websites run by patient organisations (including charities)[52-54] and the NHS[55,56] recount the experiences of numerous patients affected by PE. These patient experiences reflect at an individual level the broad conclusions of the HRQoL research described above. Themes from these patient experiences are the pain and discomfort of the original PE, difficulties with current treatment modalities, and the underlying fear of a recurrent VTE.

It has been noted that the detrimental HRQoL measured in patients with DVT may be attributable in part to the risk and fear of recurrent VTE. Given the

shared risks of DVT and PE this is likely to be the case in patients with a PE.[57-59]

Reduced safety litigation risks to the NHS from a fixed-dose regime

Prescribed doses of LMWH for the treatment of VTE are dependent on the weight of the patient and renal function.[60] This can lead to safety issues associated with inappropriate dosing which was the subject of a National Patient Safety Agency Rapid Response Report.[10]

Warfarin is an oral anticoagulant that has a number of limitations[11], including:

- A narrow therapeutic index with a fine balance between decreasing the risk of thrombosis and increasing the risk of haemorrhage.
- The requirement for dose adjustment using frequent, inconvenient and costly INR monitoring. The frequency of monitoring varies depending on individual patient characteristics.
- Response that is influenced by diet, concomitant medications, herbal supplements and intercurrent illness.
- The need for individualised patient dosing and adjustment, often requires warfarin to be supplied in a number of different strengths. This may increase the risk of accidental overdose and requires additional patient education, especially in confused, older people.

The NPSA issued a patient safety alert to healthcare organisations in 2007 regarding best practice actions to make anticoagulation therapy safer.[12]

The dosing regime for rivaroxaban (15 mg bid for 21 days, 20 mg od for the remainder of treatment) is by contrast a simpler regime for patients to adhere to.

5 Statement of the decision problem

The decision problem statement is summarised in Table 5, with further discussion of the inclusion of fondaparinux below that.

Table 5: Decision problem statement

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with pulmonary embolism	No difference	No difference. However, rivaroxaban is not recommended in all categories of patients with PE, according to its SmPC
Intervention	Rivaroxaban	No difference	No difference
Comparator(s)	Initial treatment with a low molecular weight heparin (such as enoxaparin, tinzaparin and dalteparin) or fondaparinux with continued therapy as follows: ▪ vitamin K antagonist (such as warfarin, acenocoumarol and phenindione) ▪ low molecular weight heparin for people for whom a vitamin K antagonist is not considered an appropriate treatment	As stated, but without fondparinux	There is a lack of evidence specific to fondaparinux, and fondaparinux appears to be very seldomly used. Bayer considers that fondaparinux is not an appropriate comparator. See also discussion below within section 5 (page 43).
Outcomes	▪ Mortality ▪ Venous thromboembolism	▪ Mortality ▪ Venous thromboembolism	Clinically relevant bleeding (major / non-major / all) has standard definitions

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	recurrence ▪ Complications of pulmonary embolism such as pulmonary hypertension and heart failure ▪ Complications following deep vein thrombosis, including post thrombotic syndrome ▪ Adverse events of treatment (including clinically relevant bleeding) ▪ Health-related quality of life	recurrence ▪ Pulmonary hypertension ▪ Cardiac failure ▪ Post thrombotic syndrome ▪ Clinically relevant bleeding (major / non-major /all) ▪ Adverse events of treatment ▪ Treatment satisfaction	accepted by regulatory authorities.[61,62] Cardiac failure is a MedDRA term, whereas heart failure is not. Health-related quality of life was not measured in the EINSTEIN programme of trials, other than treatment satisfaction[13,63,64] (using a validated instrument[16]).
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a NHS and Personal Social Services perspective.	No difference	No difference
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: ▪ Underlying risk of bleeding	Consideration will be given to the three subgroups. Further consideration of comparisons of	There is data in EINSTEIN-PE relevant to the subgroups of interest, and this will be discussed in terms of clinical

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	▪ Provoked or unprovoked venous thromboembolism ▪ Presence of active cancer If the evidence allows, consideration will be given to a comparison of rivaroxaban with unfractionated heparin for: ▪ Patients with severe renal failure or established renal failure (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.72m2) ▪ For patients with an increased risk of bleeding ▪ For patients with PE and haemodynamic instability	rivaroxaban to UH cannot be given.	effectiveness and cost-effectiveness of rivaroxaban. However, we believe little further consideration can be given to a comparisons of rivaroxaban with UH: ▪ Rivaroxaban is recommended in its draft SmPC only in patients for whom UH would not be an appropriate therapy. ▪ In particular, as noted in section 2.2, the draft SmPC recommends against use of rivaroxaban in patients with very severe renal failure (creatinine clearance < 15 mL/min), or with an increased bleeding risk or who are haemodynamically unstable.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation.	No difference	No difference

Fondaparinux as a comparator

We discuss further the inclusion of fondaparinux as a comparator in the initial treatment of PE within the final scope of this technology appraisal. The draft scope was prepared in August 2010 and the final scope in 12 November 2012. The inclusion of fondaparinux as a comparator in the final scope is one difference between the draft and final documents.

A comparator is relevant if it represents `routine and best practice in the NHS,' according to the NICE Methods Guide.[65] In developing the recent NICE clinical guidelines on VTE management (CG144, which includes PE treatment), very little comparative evidence was found to support the use of fondaparinux for VTE – section 7.2.1 of CG144 lists just two RCTs[8]). One RCT was a study of fondaparinux vs UH in haemodynamically stable patients with PE – this is not particularly relevant for the UK due to the comparator treatment, because such patients would receive LMWH, if not fondaparinux.[66]. The other RCT was a study of fondaparinux vs enoxaparin in patients with DVT, so not relevant to the decision problem due to the patient population. Although the guideline recommendation includes the use of fondaparinux as an option for the initial treatment of VTE (including PEs), we suggest that this absence of evidence in relation to PE treatment means that fondaparinux may not necessarily be considered `best practice'.

To judge how routine the use of fondaparinux is in clinical practice, we undertook an analysis of hospital sales data of fondaparinux and enoxaparin. Higher dose formulations were selected as these should be more representative of treatment required for acute events (100 mg syringes and above for enoxaparin, 5 mg and above for fondaparinux). [redacted] Although high dose enoxaparin may be used outside PE or VTE treatment, the knowledge that use of fondaparinux represents [redacted].

As described in sections 2.5-7, the clinical pathway for PE treatment for which rivaroxaban is suited does not involve UH. The pivotal phase III trial for rivaroxaban in this indication, EINSTEIN-PE, did not include fondaparinux or

UH in any comparator arm, so no robust assessment of comparative effectiveness may be performed. In terms of cost-effectiveness, it should be noted that one-way sensitivity analyses included varying the daily cost of LMWH by 30% in either direction, a range that would include the daily cost of fondaparinux.

We conclude that fondaparinux is not an appropriate comparator for the initial treatment of PE, under the definition provided in the NICE Methods Guide[65].

Section B – Clinical and cost effectiveness

6 Clinical evidence

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic search of the literature was undertaken to identify randomised, comparative studies investigating rivaroxaban in the treatment of PE. There was no restriction by nature of the comparator intervention or by outcome.

The searches were undertaken in July 2012 using Medline, Medline in process, EMBASE, and The Cochrane Central Register of Controlled Trials (CENTRAL). We used the relevant filter for RCTs developed by SIGN.[68] The disease filter covered VTE rather than PE specifically. Studies of patients with VTE were included if results were published specific to the subgroup of patients whose index event was a PE.

The Bayer trialfinder database contains information on clinical trials sponsored by Bayer.[69] This database was searched in October 2012.

Additionally, reference lists of included articles, key review papers and relevant guidelines were also checked for other relevant studies. Relevant references identified from each database as well as of any additional references identified by manual reference review and supplementary searches were pooled, and duplicates were excluded.

Full details of the literature search strategy including search terms employed are provided in Section 10.2, Appendix 2, as required.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The eligibility (inclusion/exclusion) criteria used in the clinical systematic review are summarised in Table 6.

Table 6: Eligibility criteria used in clinical systematic review

	Inclusion	Exclusion
Population	Patients with symptomatic PE	Populations for which PE data cannot be separated VTE prophylaxis Non-VTE indications
Interventions	Rivaroxaban vs any comparator	Studies not involving a treatment arm of rivaroxaban
Outcomes	Efficacy and safety outcomes	Publications centred around outcomes other than efficacy or safety
Study design	Randomised controlled trials	Non-randomised trials Non-comparative trials
Language	English language	Languages other than English

The procedure for reviewing the search results was as follows.

Search results were combined in a single EndNote library and were deduplicated according to the Author, Title and Year fields. The library was then manually searched to exclude any further duplicates that were not previously identified, according to Journal details.

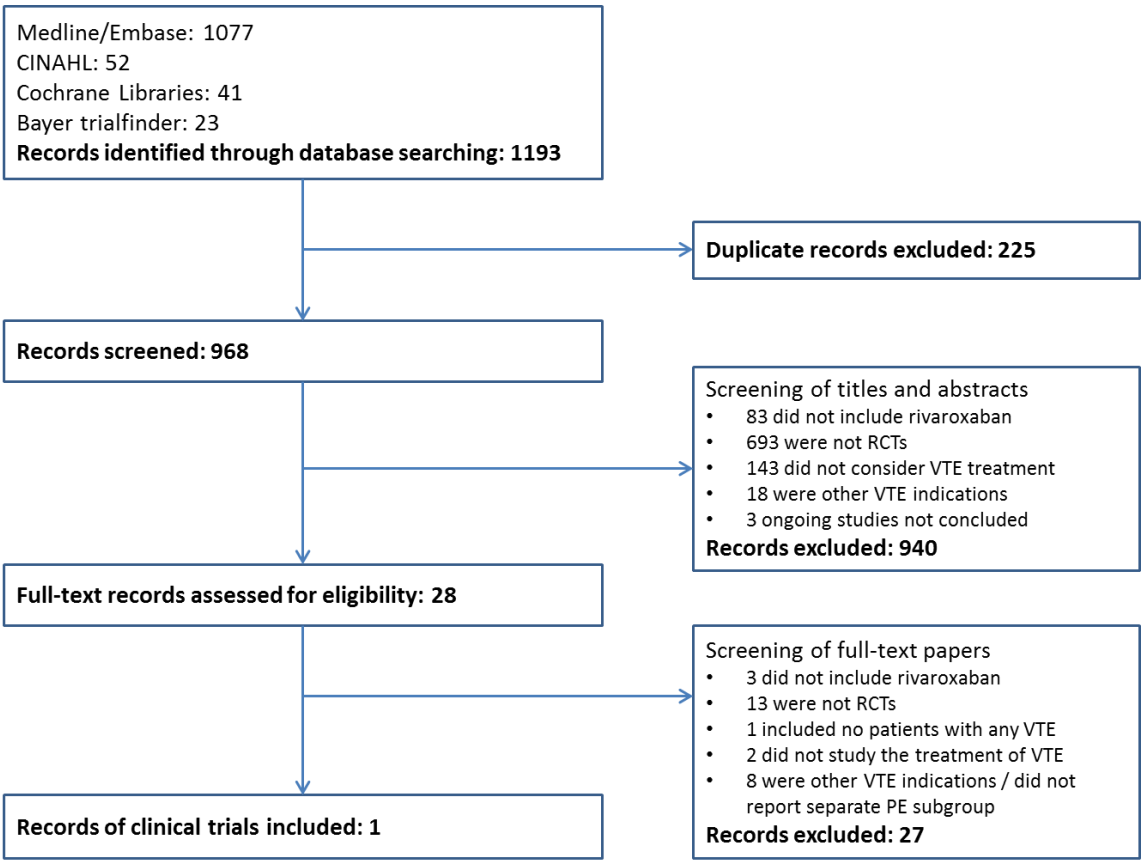
The titles and abstracts of all search results were assessed independently by two reviewers for inclusion using a pre-defined study eligibility flowchart. The full texts of all potentially eligible studies (ie those that remained after the title/abstract review) were then assessed for inclusion using a pre-defined study eligibility form. The title/abstract and full-text reviews were performed independently by two reviewers; any disagreements were resolved by consensus or arbitration. The reviewers were not blinded to the names of the studies, authors, institutions or sources of the articles.

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

The flow of studies in the systematic review is summarised in a PRISMA diagram in Figure 3. A total of 28 individual citations were included after the abstract and title review; one study remained after full-text review (EINSTEIN-PE[13]). As evident from the PRISMA diagram, most exclusions were made due to the study:

- not considering the treatment of PE
- not reporting data specific to patients whose VTE was a PE
- not being a RCT or
- not including rivaroxaban as a treatment arm.

Figure 3: PRISMA diagram for systematic review for clinical literature



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Following the systematic review, we have prepared an overview of the phase II and III trials of rivaroxaban in the treatment of VTE in Table 7.

Table 7: Overview of rivaroxaban trials

Trial name	Bayer study ID	Phase	Interventions	Population	Publications
ODIXa-DVT	11223	2	4 x rivaroxaban regimes or enoxaparin/VKA for 12 weeks	DVT without PE	Agnelli 2007[70]
EINSTEIN dose ranging	11528	2	3 x rivaroxaban regimes or heparin/VKA for 3 months	DVT without PE	Buller 2008[71]
CYP cohort	13238	2	Rivaroxaban single arm	DVT and/or PE	NA
EINSTEIN-DVT	11702a	3	Rivaroxaban vs. LMWH/VKA for 3/6/12 months	DVT without PE	Bauersachs 2010[18]
EINSTEIN-PE	11702b	3	Rivaroxaban vs. LMWH/VKA for 3/6/12 months	PE with or without DVT	Buller 2012[13]
EINSTEIN-Extension	11899	3	Extended treatment of rivaroxaban or placebo for 6/12 months	DVT and/or PE	Buller 2009 and Bauersachs 2010[18]

Source: Bayer Trialfinder database[69]

Non-inclusion of EINSTEIN-Ext

The EINSTEIN-Ext study was not included in the systematic review because it was not a study of patients with symptomatic PE.[18] The study includes patients who had previously received 6 or 12 months of anticoagulation following an index VTE (either a DVT or PE), and were in clinical equipoise as to the need for further treatment for 6-12 months. [redacted] Some but not all of the patients in EINSTEIN-Ext had participated in EINSTEIN-DVT or EINSTEIN-PE. Bayer presented some information on the EINSTEIN-Ext trial in the NICE STA submission for rivaroxaban in DVT treatment, though this was of less relevance to the decision problem than EINSTEIN-DVT.[19] Key results from EINSTEIN-Ext were[18]:

- Recurrence of VTE (the primary efficacy outcome) occurred in 8 patients (1.3%) in the rivaroxaban group as compared with 42 patients (7.1%) in the placebo group (HR: 0.18, 95% CI 0.09 to 0.39, P<0.001).
- Major bleeding (the principal safety outcome) occurred in 4 patients (0.7%) in the rivaroxaban group and in none of the patients in the placebo group (P = 0.11).
- The outcome of a net clinical benefit occurred in 12 patients (2.0%) receiving rivaroxaban and in 42 patients (7.1%) receiving placebo (HR: 0.28, 95% CI 0.15 to 0.53, P<0.001).
- The relative efficacy and safety were consistent across the prespecified subgroups.
- Vascular events occurred in 3 patients in the rivaroxaban group and 4 patients in the placebo group.
- No patient in either group had the combination of an alanine aminotransferase level exceeding three times the upper limit of the normal range and a bilirubin level exceeding twice the upper limit of the normal range.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

There is therefore just one relevant RCT, EINSTEIN-PE. The decision to treat for 3, 6 or 12 months was based on the risk profile of the patient, local preferences and was made by the investigator prior to randomisation. The intervention was rivaroxaban (15 mg bid for 21 days, 20 mg od for the remainder of the treatment duration). The comparator was dual enoxaparin / VKA therapy.[13]

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with

reference to the decision problem. If there are none, please state this.

The relevant RCT, EINSTEIN-PE, compares rivaroxaban with dual LMWH / VKA therapy, a stated comparator.[13] No RCT was identified in the systematic review that directly compares rivaroxaban with long-term LMWH therapy.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

There has been no such exclusion.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

No studies of this nature were considered relevant to the decision problem.

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The design of EINSTEIN-PE is summarised in Figure 4 and Table 8.

Figure 4: Overview of the design of EINSTEIN-PE

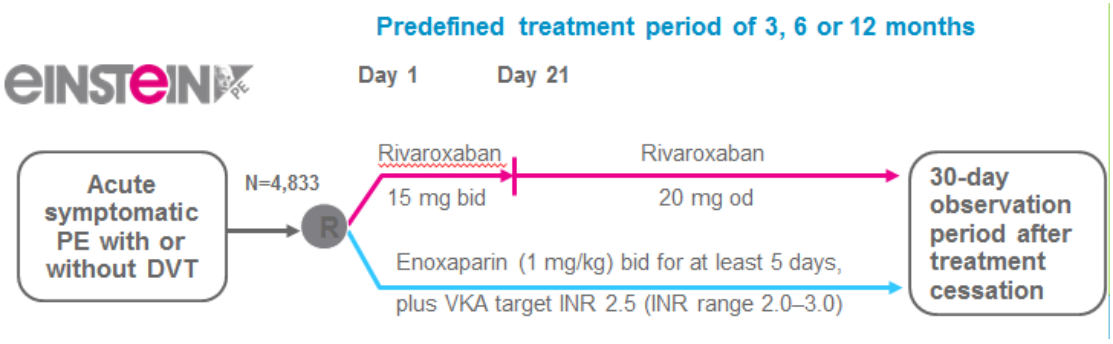


Table 8: Summary of the methodology of EINSTEIN-PE

Trial no. / acronym	EINSTEIN-PE (NCT00439777)[72], Bayer study 11702b
Location	International, multi-centre trial (including many European countries)
Design	International, randomised, event-driven, open-label, assessor-blind, phase III non-inferiority study. Patients were randomised 1:1 into two groups.
Duration of study	Study enrolment start: March 2007. Study enrolment stop: September 2009. Study duration = intended treatment duration followed by a 30-day observational period. The intended treatment duration was determined by the clinician pre-randomisation as either 3, 6 or 12 months.
Method of randomisation	Patients were randomly assigned to a study group via a central 24-hour computerised (interactive) voice-response system (IVRS), with stratification by intended treatment duration and country. A fax was sent by the IVRS to confirm treatment allocation. The fax also provided a calendar with dates of pre-scheduled contacts.
Method of blinding (care provider, patient and outcome assessor)	This was an open-label study. However, all suspected outcome events were classified by a central independent adjudication committee (CIAC) whose members were unaware of the treatment assignments. In addition, there were regular questionnaires and similar number

	of study visits for all treatment groups.
Intervention(s) (n =) and comparator(s) (n =)	Rivaroxaban orally (ITT n=2419): 15mg bid for 21 days then 20mg od for the remainder of the intended duration of treatment. Enoxaparin (ITT n=2413): 1.0 mg/kg bid subcutaneously until anticoagulation is established plus VKA (warfarin or acenocoumarol), dose-adjusted to maintain the INR within therapeutic range (target 2.5, range 2.0-3.0). The LMWH was administered for at least 5 days and was discontinued when the INR was >2.0 on two consecutive measurements at least 24 hours apart, with an advised overlap with VKA for 4 to 5 days.
Primary outcomes (including scoring methods and timings of assessments)	Efficacy: symptomatic recurrent VTE, ie the composite of recurrent DVT or fatal or non-fatal PE occurring during the intended treatment duration. Safety: Clinically relevant bleeding, ie major bleeding and clinically relevant non-major (CRNM) bleeding.
Secondary outcomes (including scoring methods and timings of assessments)	Net clinical benefit Secondary net clinical benefit measures (secondary outcomes 1, 2 and 3) Vascular events All cause mortality Other adverse events (AEs) Anti Clot Treatment Scale (ACTS) Treatment Satisfaction Questionnaire (TSQM) Discontinuation Time in target range (TTR) with enoxaparin/VKA Various healthcare resource utilisation: duration of hospital stay, visits to healthcare providers, diagnostic procedures
Duration of follow-up	Study duration = intended treatment duration (3, 6 or 12 months, determined by the clinician pre-randomisation) followed by a 30-day observational period.

Definitions of the outcomes referred to in Table 8 are provided below in Table 11, in addressing section 6.3.5.

In both studies, patients were followed for the intended treatment duration and seen at fixed intervals, at least monthly, that were identical for the rivaroxaban and comparison groups. On each occasion a checklist was used to elicit information on symptoms and signs of recurrent venous thromboembolism, bleeding, and adverse events. Patients were instructed to report to the study centre immediately if any of these events were suspected to have occurred. In cases of suspected venous thromboembolism, the protocol required objective testing. Compliance with treatment and any concomitant medication was checked at each follow-up contact. Liver function tests were performed at screening and each visit. INR tests were performed in patients in the

enoxaparin/VKA arm initially at least every 2-3 days then later at least monthly.[63]

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

The study protocol for EINSTEIN-PE is provided with this submission.[13,63]

The inclusion criteria of EINSTEIN-PE were a confirmed acute symptomatic PE with or without symptomatic DVT and written informed consent.

Patients were potentially eligible if the diagnosis of PE was based on either of the following:

- An intraluminal filling defect in segmental or more proximal branches on sCT scan.
- An intraluminal filling defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram.
- A perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy.
- Inconclusive sCT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasound or venography.

The index event was adjudicated. The adjudication packaged contained films or images of one of the above tests which was used to confirm diagnosis only. No systematic search for other sites of thrombosis was required.

The exclusion criteria of EINSTEIN-PE were:

- Additional indications for a vitamin K antagonist
- Creatinine clearance <30 mL/min

- Clinically significant liver disease (e.g. acute hepatitis, chronic active hepatitis or cirrhosis) or alanine aminotransferase >3x upper limit of normal (ULN)
- Contraindication to anticoagulation
- Bacterial endocarditis
- Active bleeding or a high risk of bleeding
- Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg
- Childbearing potential without proper contraceptive measures
- Pregnancy or breastfeeding
- Concomitant use of strong cytochrome P-450 3A4 inhibitors (e.g. human immunodeficiency virus, protease inhibitors or systemic ketoconazole) or inducers (e.g.rifampicin, carbamazepine or phenytoin)
- Participation in another clinical trial within 30 days prior to screening
- Life expectancy of less than 3 months
- Pre-randomisation therapeutic doses of LMWH, fondaparinux or UH for more than 36 hours (or up to 48 hours after protocol amendment 4)
- >1 single dose of vitamin K antagonist pre-randomisation
- Thrombectomy, insertion of a vena cava filter or fibrinolytic agent for current episode of thrombosis
- Contraindication to enoxaparin, warfarin or acenocoumarol

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

A summary of the patient characteristics at baseline in EINSTEIN-PE is provided in Table 9.

Table 9: Summary of patient characteristics at baseline in EINSTEIN-PE

	Rivaroxaban		LMWH/VKA	
ITT population	2419		2413	
Mean (SD) age (years)	57.9	(7.3)	57.5	(7.2)
Number (%) male	1309	(54.1)	1247	(51.7)
Weight – number (%)				
<50 kg	38	(1.6)	43	(1.8)
≥50 to 100 kg	2034	(84.1)	2010	(83.3)
≥100 kg	345	(14.3)	359	(14.9)
Missing data	2	(<0.1)	1	(<0.1)
Creatinine clearance (%)				
<30 mL/min	4	(0.2)	2	(<0.1)
30-49 mL/min	207	(8.6)	191	(7.9)
50-79 mL/min	637	(26.3)	593	(24.6)
≥80 mL/min	1555	(64.3)	1617	(67.0)
Missing data	16	(0.7)	10	(0.4)
Diagnostic method (n, %)				
Spiral computed tomography	2114	(87.4)	2076	(86.0)
Ventilation-perfusion lung scanning	284	(11.7)	326	(13.5)
Pulmonary angiography	20	(0.8)	10	(0.4)
Missing data	1	(<0.1)	1	(<0.1)
Anatomical extent of PE (n, %)				
Limited:≤25% of vasculature of a single lobe	309	(12.8)	299	(12.4)
Intermediate	1392	(57.5)	1424	(59.0)
Extensive: multiple lobes and >25% of entire pulmonary vasculature	597	(24.7)	576	(23.9)
Not assessable	121	(5.0)	114	(4.7)
Concurrent DVT (n,%)	606	(25.1)	590	(24.5)
Confirmed initial diagnosis of:				
PE	2396	(99.0)	2390	(99.0)
DVT	606	(25.1)	590	(24.4)
Hospitalized – number (%)	2156	(89.1)	2160	(89.5)
Admitted to ICU – number (%)	311	(12.9)	289	(12.0)
Time from onset of symptoms to randomisation				
Median (days)	4.0		4.0	
IQR (days)	2.0-8.0		2.0-9.0	

	Rivaroxaban		LMWH/VKA	
Cause of PE or DVT (%)				
Unprovoked	1566	(64.7)	1551	(64.3)
Recent surgery or trauma	415	(17.2)	398	(16.5)
Immobilisation	384	(15.9)	380	(15.7)
Oestrogen therapy	207	(8.6)	223	(9.2)
Active cancer	114	(4.7)	109	(4.5)
Thrombophilic condition (%)	138	(5.7)	121	(5.0)
Previous VTE (%)	455	(18.8)	489	(20.3)

Table 10 provides a summary of baseline characteristics by intended treatment duration group. There were similarities between the patients in each group, with a greater prevalence of risk factors tending to exist in the longer duration groups.

Table 10: Overview of EINSTEIN-PE patient characteristics by intended treatment duration group

Patients and characteristics	Intended treatment group			
	3 months	6 months	12 months	Whole study
Number of patients	249	2774	1809	4832
% Total population	5.2%	57.4%	37.4%	100.0%
Mean (SD) age	[redacted]	[redacted]	[redacted]	57.7 (17.3)
Proportion male	[redacted]	[redacted]	[redacted]	52.9%
Risk factors				
Idiopathic DVT/PE	[redacted]	[redacted]	[redacted]	49.3%
Recent surgery or trauma	[redacted]	[redacted]	[redacted]	16.8%
Immobilisation	[redacted]	[redacted]	[redacted]	15.8%
Use of oestrogen containing drugs	[redacted]	[redacted]	[redacted]	8.9%
Previous episode(s) of DVT/PE	[redacted]	[redacted]	[redacted]	19.5%
Active cancer	[redacted]	[redacted]	[redacted]	4.6%

Source: NEJM publication[13], EINSTEIN-PE CSR[73]

The proportions of patients in the 3/6/12 month intended treatment duration groups in EINSTEIN-DVT was 11.9% / 62.8% / 25.3% respectively, which can

be compared with proportions of 5.2% / 57.4% / 37.4% in the EINSTEIN-PE trial.[13,18]

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The primary and secondary outcomes investigated in EINSTEIN-PE were provided previously in section 6.3.2, Table 8. Definitions of these outcomes are provided below in Table 11.

Table 11: Definition or criteria used for each outcome

Outcome	Definition or criteria
DVT	Diagnosed confirmed through a new non-compressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography.
Non-fatal PE	Diagnosis confirmed through a new intraluminal filling defect on spiral computed tomography (CT) or pulmonary angiography, a cutoff of a vessel of more than 2.5mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non-high-probability perfusion defect associated with deep-vein thrombosis, as documented by ultrasonography or venography.
Fatal PE	Subset of PE, above. Requires objective diagnostic testing, autopsy, or death which could not be attributed to a documented cause and for which PE could not be ruled out.

Outcome	Definition or criteria
PE	Fatal or non-fatal PE
Symptomatic recurrent VTE	Composite of DVT or PE, each defined above
Major bleeding	Clinically overt and associated with a fall in the haemoglobin level of >20g per litre or if it led to transfusion of two or more units of red cells, or if it was retroperitoneal, intracranial, occurred in a critical site, or contributed to death.
Clinically relevant non-major (CRNM) bleeding	Overt bleeding not meeting the 'major bleeding' criteria but associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of study treatment, or associated with any other discomfort such as pain or impairment of activities of daily life. For example, epistaxis if repetitive or lasts longer than 5 minutes or leads to an intervention such as packing, gingival bleeding (spontaneous or lasts for >5 minutes), macroscopic haematuria or gastro-intestinal haemorrhage, rectal blood loss or haemoptysis - if more than a few spots, intramuscular haematoma.
Clinically relevant bleeding	Major bleeding and other clinically relevant non-major bleeding.
Net clinical benefit	Composite of symptomatic recurrent VTE and major bleeding, each defined above.
Vascular events	Acute coronary syndrome (ACS), ischaemic stroke, transient ischaemic attack (TIA) or systemic embolism.
Secondary Outcome 1	Composite of DVT, non-fatal PE and all-cause mortality, defined above
Secondary Outcome 2	Composite of DVT, non-fatal PE, fatal PE, all-cause mortality and vascular events, defined above
Secondary Outcome 3	Identical to Net clinical benefit, defined above
Treatment emergent AEs	AEs occurring or worsening after randomisation but not more than 7 days after stop of study medication

We discuss further the reliability and validity of these outcomes, their relevance to the Decision Problem and current use/status of each measure. We also discuss arrangments to measure compliance.

Validity of specific outcomes

Outcomes used in EINSTEIN-PE were indeed clinically important, hard, objective outcomes (VTE event, clinically relevant bleeding and death) verified by standard diagnostic methods and adjudicated by the blinded centralised committee. These outcomes are included in the decision problem (Table 5) and will be reported later in this submission. Several of the outcomes proposed in a draft NICE Quality Standard on VTE management require

regular local counts of the numbers of patients with VTE, with death from PE the underlying outcome.[74]

Other safeguards in place to protect against biases typically controlled by blinding included: standardised VTE event and bleeding questionnaires used at every visit, central automated randomisation to treatment, and the use of the ITT population to perform the primary analysis.

The treatment satisfaction measures, ACTS and TSQM, were described previously in section 4.1.3. ACTS consists of two scales, ACTS Burdens (12 items) and ACTS Benefits (3 items) and is a validated instrument.[75] For each scale, higher total scores indicate higher satisfaction. TSQM (version 2) is an 11 item instrument representing four subscales: effectiveness (2 items), side-effects (4 items), convenience (3 items) and global satisfaction (2 items). Higher scores indicate higher satisfaction with a treatment. These are the closest outcomes recorded in EINSTEIN-PE to health-related quality of life.[63] In sections 7.4.5-7, we consider health-related quality of life relevant to the long-term economic evaluation of rivaroxaban, based on systematic review.

We also intend to address other outcomes from the decision problem in this submission, namely: incidence of pulmonary hypertension, cardiac failure, post thrombotic syndrome and adverse events of treatment.

EINSTEIN-PE has strong external validity with limited risk of bias through its design – a conclusion backed-up by evidence arising from the study's results. This is discussed further in section 6.10.

Arrangements to measure compliance

The Statistical Analysis Plan defines the procedures used to measure patient compliance.[76] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

The analysis of the primary efficacy outcome in EINSTEIN-PE was performed on an Intention To Treat (ITT) basis to test the null hypothesis (as a non-inferiority trial) that rivaroxaban was inferior to the comparator treatment.

Following a hierarchical procedure, a test for superiority was to be conducted if rivaroxaban was found to be statistically noninferior. Additionally, a supportive analysis of the primary efficacy outcome was carried out based on the per protocol (PP) population, which consisted of all randomised patients without any major deviation from the protocol.

A Cox proportional hazard model was used, which was pre-specified to be stratified for intended duration of treatment and adjusted for the presence of malignancy at baseline. Rivaroxaban would be considered statistically significantly non-inferior to comparator therapy if the upper limit of the two sided 95% CI for the hazard ratio was below the pre defined non-inferiority margin of 2.0. This margin corresponds to maintenance of at least 50% of the proven efficacy of standard therapy and was derived based on a comprehensive meta-analysis of historical trials in this indication.

The following hierarchy for statistical testing was applied. If non-inferiority for the primary efficacy endpoint was satisfied, then superiority for the primary efficacy endpoint will be tested utilizing the two-sided 95% confidence interval for the hazard ratio. In addition, if non-inferiority for the primary efficacy endpoint is satisfied, then a closed testing procedure will be conducted as follows:

a) superiority for the principal safety endpoint (clinically relevant bleedings) on the safety analysis population while on treatment,

b) superiority for major bleedings (safety analysis population while on treatment).

Assuming incidence rates of 3% and equal efficacy for both treatment arms, a total of 88 events was determined to be sufficient to demonstrate non-inferiority of rivaroxaban to comparator under this statistical model, using a margin of 2.0 for the upper limit of the 95% confidence interval for the observed hazard ratio, with a two-sided alpha level of 0.05. A sample size of approximately 3000 patients was calculated to be required to reach the number of events needed. It was specified a priori however, that the steering committee could stop enrolment when it was estimated that 88 events had been reached. When enrolment was discontinued, patients completed their assigned treatment except for those in the 12 month duration who completed at least 6 months.

So as not to over-estimate the confidence with which any treatment effect was known in this non-inferiority trial, events which occurred during the intended treatment duration were taken into account, others were not. A summary of time to event and time to censoring definitions used in EINSTEIN-PE according to study population and outcome type is given in Table 12.

Table 12: Analysis populations, time to event and time to censoring in EINSTEIN-PE

Outcome type	Efficacy	Efficacy	Safety
Analysis population *	ITT	PP	Safety
Primary analysis?	Y	N	Y
Composite event	Events occurring until the end of predefined treatment period: 98, 185 and 359 days for intended durations of 3, 6 and 12 months respectively.	Minimum of [interval for ITT] and [days up to last documented study medication intake + 2 days]	Events occurring not later than last documented study medication intake + 2 days
Censoring date for subjects completing the study	Minimum of [end of treatment visit (days after randomisation)] and [preplanned treatment duration (days)]	Minimum of [interval for ITT] and [days up to last documented study medication intake + 2 days]	Last documented study medication intake + 2 days
Censoring date for subjects prematurely discontinuing the study	Minimum of [the last visit with an appropriate contact report (days after randomization)] and [preplanned treatment duration (days)]	Minimum of [interval for ITT] and [days up to last documented study medication intake + 2 days]	Last documented study medication intake + 2 days

* See Figure 5. Source: EINSTEIN-PE CSR.[73]

No interim analysis was planned, although ongoing safety and efficacy monitoring was performed by the Data Safety and Monitoring Board (DSMB).

The proportional hazards assumption was to be checked for each stratum for the treatment effect and also for the baseline presence of malignancy using graphical methods. Also, the homogeneity of hazard ratios across strata and between patients with and without baseline presence of cancer was to be tested.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

In addition to baseline presence of cancer, the impact of other baseline covariates (location of VTE, renal clearance, age, sex, mobility at randomization, pulmonary disease, cardiac disease) on the primary efficacy outcome were pre-specified in the protocol to be described by calculating adjusted hazard ratios and corresponding 95% confidence intervals of the treatment effect.[63]

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

A flow diagram of patient numbers is provided in Figure 5. Each subheading in this section is answered, and the study protocol is provided with this submission.[63]

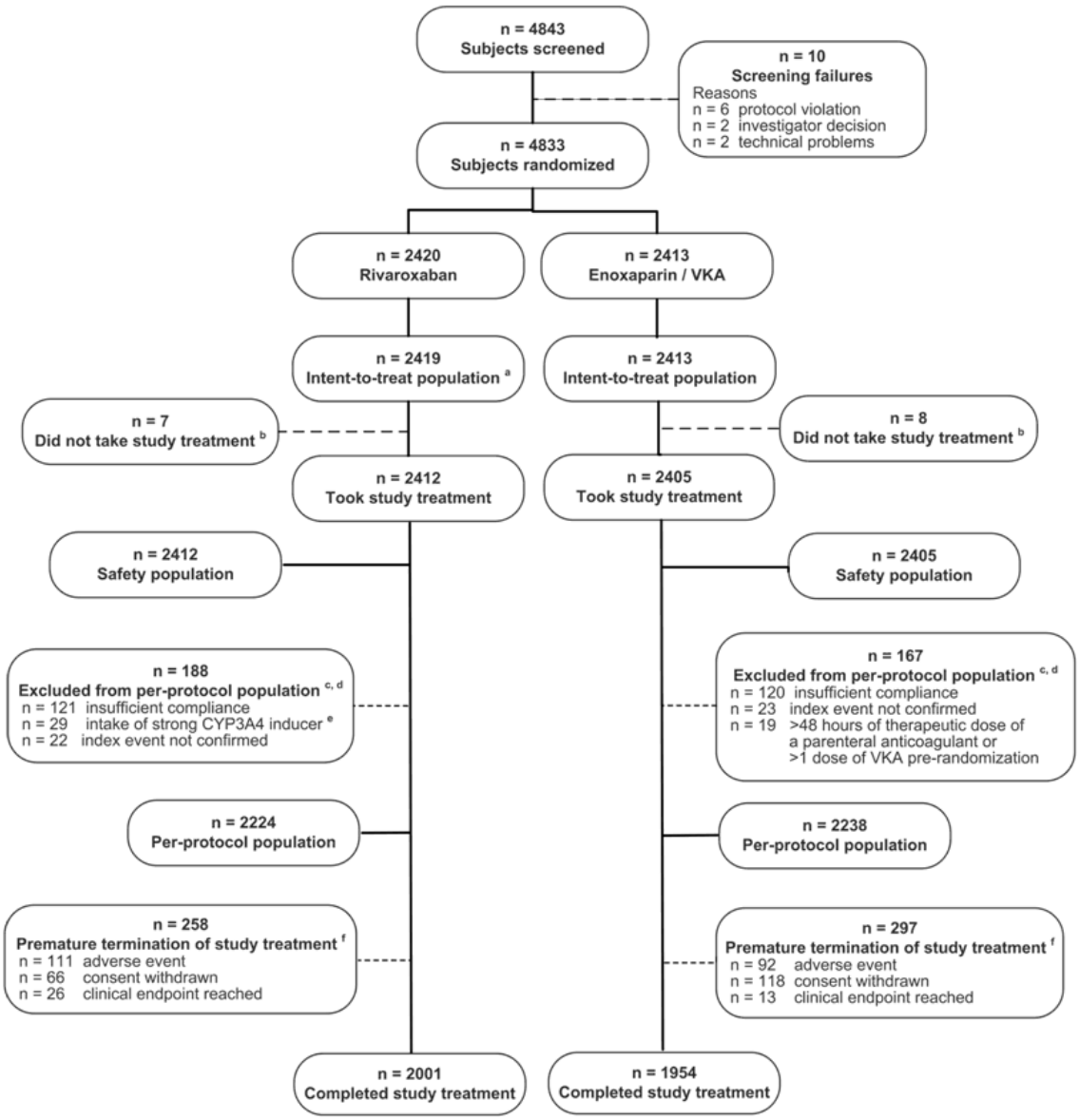
A total of 555 (11.5%) patients discontinued treatment. There were no material differences between study arms (P=0.07). Reasons for premature discontinuation of treatment are shown in Table 13.

Table 13: Reasons for premature discontinuation of treatment

	Rivaroxaban		Enoxaparin/VKA		P-value
ITT population	2419		2413		
Any reason (%)	258	(10.7)	297	(12.3)	0.07
Adverse event (%)	111	(4.6)	92	(3.8)	
Consent withdrawn (%)	66	(2.7)	118	(4.9)	
Loss to follow-up (%)	8	(0.3)	10	(0.4)	

Source: NEJM publication[13]

Figure 5: Study disposition in EINSTEIN-PE



Notes: This figure is academic in confidence. (a) Subject [redacted] was a randomized subject not valid for intent-to-treat analysis because of lack of signed informed consent. (b) No further reasons given. (c) Given are the most frequently documented reasons. (d) Since more than 1 reason applied to certain subjects, numbers do not add up. (e) Intake of strong CYP3A4 inducers for >2 days during the treatment period led to exclusion from the per-protocol population in the rivaroxaban group only. (f) Given are the most frequently documented reasons. Please note that termination of study treatment due to "death", "study terminated by sponsor", or "site closed by investigator" were not considered as "premature termination of study treatment". VKA = vitamin K antagonist (acenocoumarol or warfarin)

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to

the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

See section 10.3, appendix 3.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

The critical appraisal for the single RCT relevant to this submission, EINSTEIN-PE, is provided in Table 14.

Table 14: Quality assessment results for EINSTEIN-PE

Assessment question	Response
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	NA
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Investigators and patients were not blinded to treatment. Outcome assessors were blinded to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.

- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

We provide a response here in relation to each outcome in the Decision Problem (Table 5), namely:

- Mortality
- Venous thromboembolism recurrence – primary efficacy outcome
- Pulmonary hypertension
- Cardiac failure
- Post thrombotic syndrome
- Clinically relevant bleeding (major / non-major /all) – primary safety outcome

- Adverse events of treatment
- Treatment satisfaction

Additionally, compliance results are presented in section 6.10.4. We start with the primary efficacy and safety outcomes of EINSTEIN-PE. For these outcomes, we consider subgroups highlighted in the Decision Problem, namely, as per Table 5, patients with:

- Underlying risk of bleeding
- Provoked or unprovoked VTE
- Presence of active cancer.

Venous thromboembolism recurrence

As described previously, the primary efficacy outcome was symptomatic recurrent VTE. This was defined as the composite of recurrent DVT, non-fatal or fatal PE including unexplained death for which PE could not be ruled out. As shown in Table 15, the outcome was confirmed in 50 (2.1%) patients in the rivaroxaban group and 44 (1.8%) patients in the dual enoxaparin/VKA arm. Under the Cox regression model, this produced a hazard ratio of 1.12 with a 95% CI of 0.75 to 1.68. There was a P=0.003 for non-inferiority (one-sided test) and P=0.57 for superiority (two-sided test).

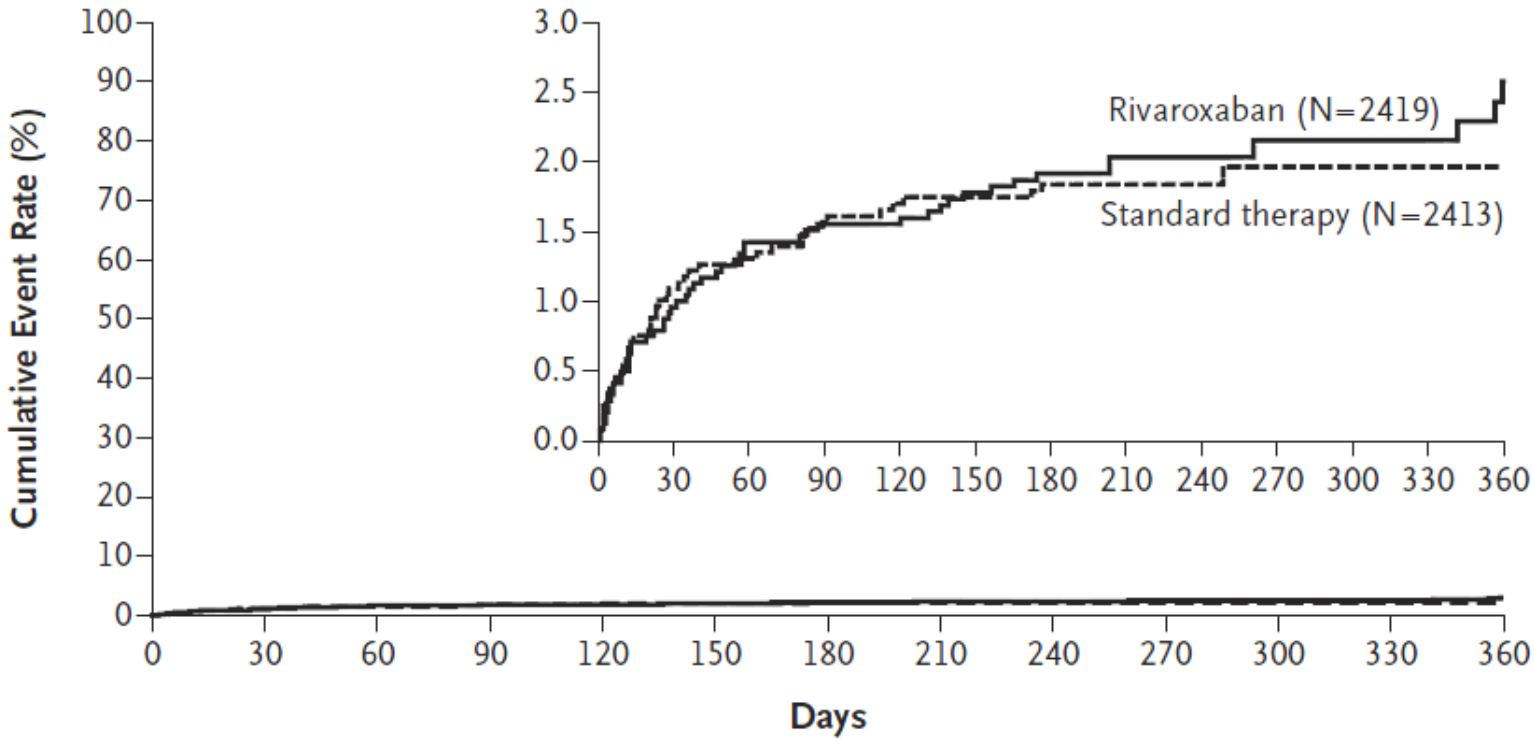
Table 15: Results of primary efficacy analysis of EINSTEIN-PE, stratified by intended treatment duration

	ITT no. of patients	Primary efficacy outcome	Death (PE)	Death (PE cannot be excluded)	Symptomatic PE and DVT	Symptomatic recurrent PE only	Symptomatic recurrent DVT only
3 months							
Riv	127	6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH/VKA	122	2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months							
Riv	1387	27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH/VKA	1387	24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months							
Riv	905	17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH/VKA	904	18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All strata							
Riv	2419	50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH/VKA	2413	44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: rec=recurrent, riv=rivaroxaban, symp=symptomatic. Note: Incidence = # of events / # at risk, where: # of events = # of subjects reporting the event after randomization up to end of intended treatment time. # at risk = # of subjects in reference population. Some patients may have experienced more than one event.

These results confirm that VTE treatment with rivaroxaban is non-inferior and has comparable efficacy with dual enoxaparin/VKA. A Kaplan-Meier plot is shown in Figure 3.

Figure 6: Kaplan-Meier cumulative event rate of primary efficacy outcome in EINSTEIN-PE



No. at Risk

Rivaroxaban	2419	2350	2321	2303	2180	2167	2063	837	794	785	757	725	672
Standard therapy	2413	2316	2295	2273	2155	2146	2050	835	787	772	746	722	675

Source: NEJM publication[13]

The analyses in different trial populations showed consistency with the ITT analysis for the primary efficacy outcome:

- HR of 1.12 (95% CI 0.75 to 1.68, $P_{non\text{-}inf}$=0.003, P_{sup}=0.57[*]) in the ITT population, as described

[redacted]

In addition, as shown in Figure 7, the effect size in the primary efficacy outcome was consistent in the wide range of pre-specified subgroups.

The degree to which patients had an underlying risk of bleeding was not something that could be easily measured or quantified in EINSTEIN-PE, though intended duration of treatment (either 3, 6 or 12 months, assigned before randomisation) may be considered a proxy measure, as this intent would have been influenced by initial assessment of the risk-benefit of anticoagulation for each patient. The characteristics of patients in these groups was previously summarised in Table 10. [redacted]

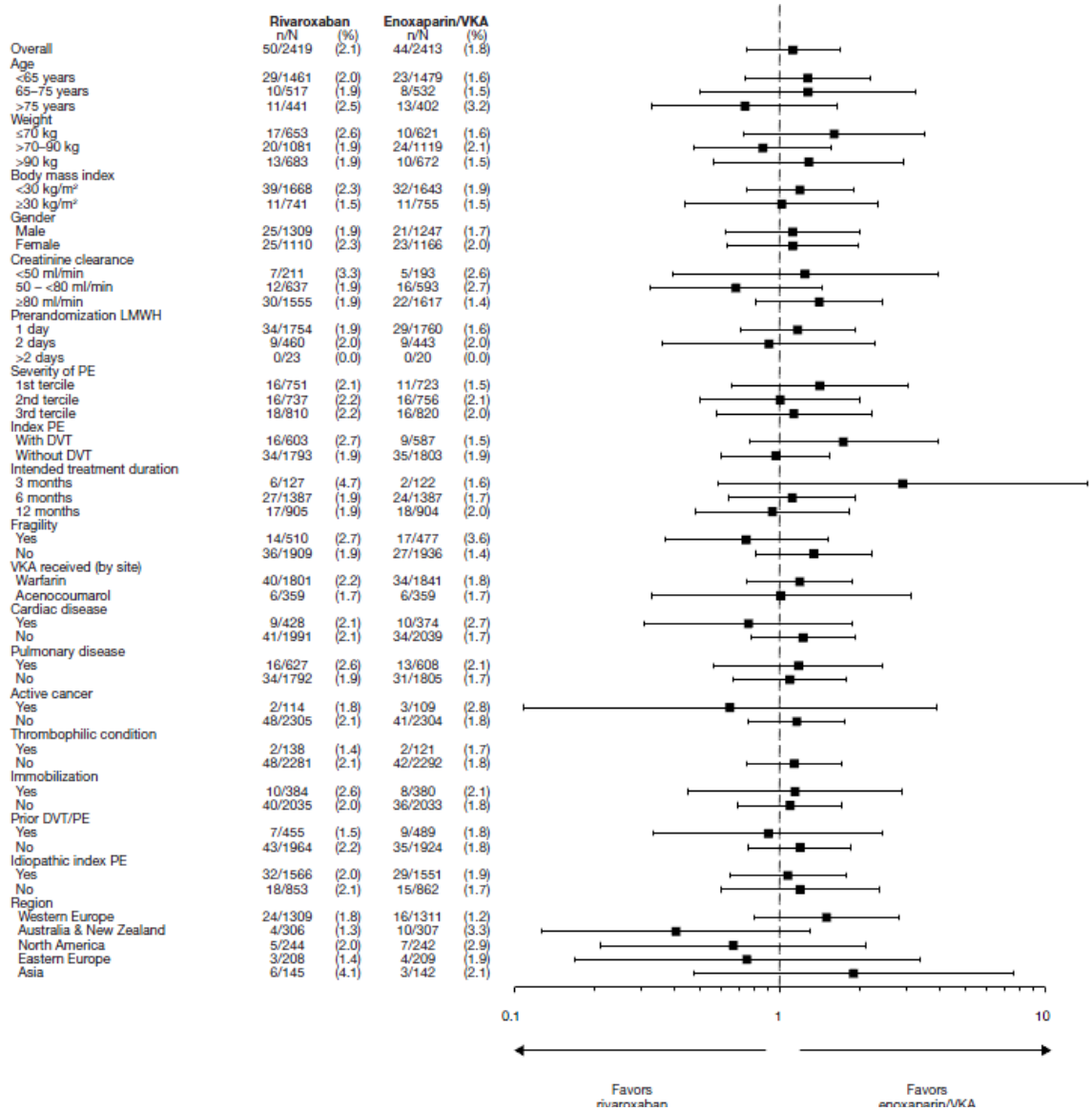
The study distinguished between patients whose index event was considered idiopathic (spontaneous or unprovoked, 15.8% of ITT patients) from those which were not (secondary or provoked, 84.2% of ITT patients). [redacted]

The study distinguished between patients who had active cancer present at baseline (4.6% of ITT patients) from those who did not (95.4% of ITT

[*] Throughout this submission, P or P_{sup} refer to tests of superiority (ie null hypothesis of no difference); $P_{non\text{-}inf}$ refers to a test for non-inferiority (null hypothesis of inferiority).

patients). [redacted]

Figure 7: Relative efficacy across subgroups in EINSTEIN-PE



Source: NEJM publication[13]

Clinically relevant bleeding (major / non-major / all)

The safety analyses included all patients who received at least one dose of study treatment. This population was composed of 4817 patients (n=2412 rivaroxaban; n=2405 enoxaparin/VKA). Table 16 presents results of the primary safety outcome (clinically relevant bleeding) as well as the major bleeding and non-major bleeding consituents of this composite outcome.

Table 16: Bleeding outcome results from EINSTEIN-PE

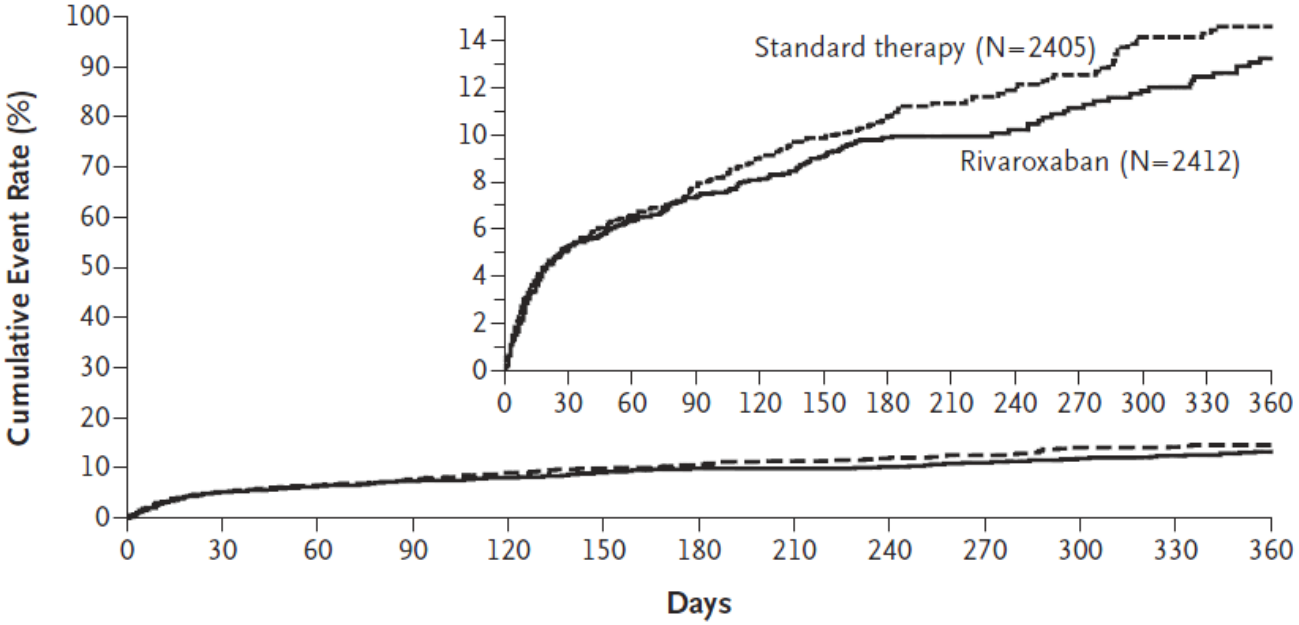
	Rivaroxaban		**Enoxaparin / VKA**		**Hazard ratio**	
	n	(%)	n	(%)	(95% CI, p-value)	
Study population	2412		2405			
Primary safety outcome	249	(10.3)	274	(11.4)	0.90	(0.76-1.07, P=0.23)
Major bleeding	26	(1.1)	52	(2.2)	0.49	(0.31-0.79, P=0.003)
Fatal	2	(<0.1)	3	(0.1)		
Non-fatal into a critical site	7	(0.3)	26	(1.1)		
Associated with a fall in haemoglobin of ≥2 g/dl or transfusion of ≥2 units of blood	17	(0.7)	26	(1.1)		
Clinically relevant non-major bleeding	228	(9.5)	235	(9.8)		

Source: NEJM publication[13]

Note: Some patients may have experienced more than one event.

The primary safety outcome was observed in 249 (10.3%) patients in the rivaroxaban arm and 274 (11.4%) patients in the enoxaparin/VKA arm. These results indicated a comparable safety profile of rivaroxaban to enoxaparin / VKA (HR: 0.90, 95% CI 0.76 to 1.07, P=0.23). A Kaplan-Meier plot is shown in Figure 8.

Figure 8: Kaplan-Meier plot of cumulative rate of treatment-emergent major and non-major clinically relevant bleeding in EINSTEIN-PE

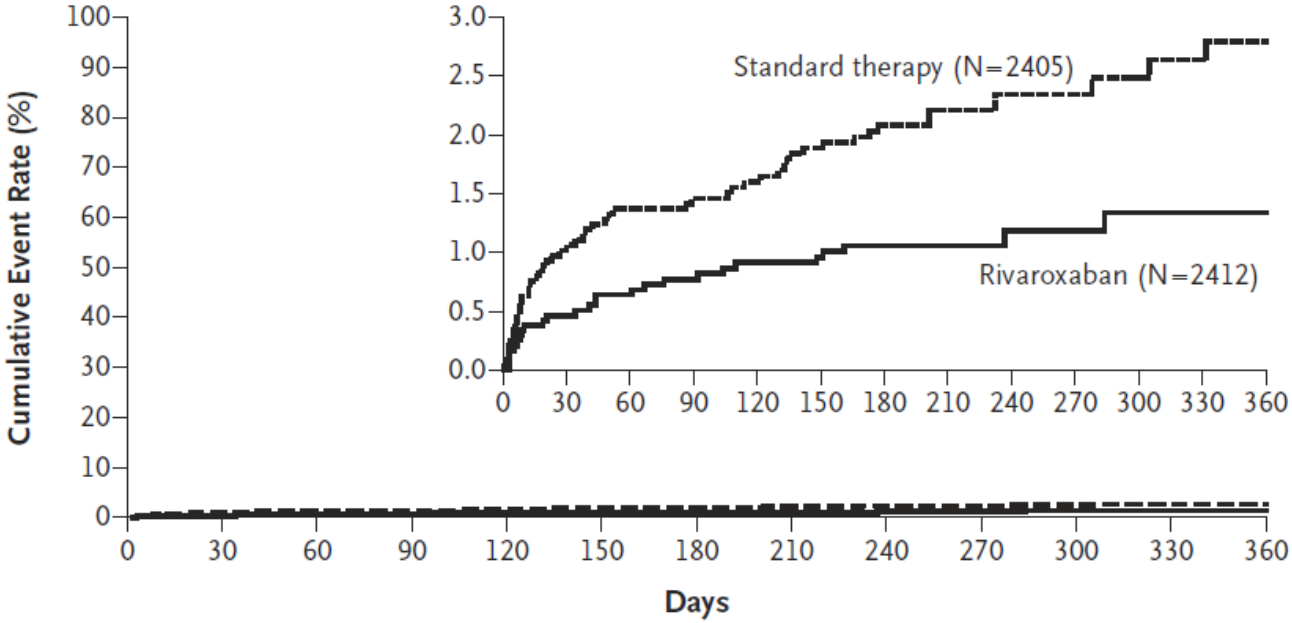


No. at Risk													
Rivaroxaban	2412	2183	2133	2024	1953	1913	1211	696	671	632	600	588	313
Standard therapy	2405	2184	2115	1990	1923	1887	1092	687	660	620	589	574	251

Source: NEJM publication[13]

Major bleeding was observed in 26 (1.1%) patients in the rivaroxaban arm and 52 (2.2%) patients in the enoxaparin/VKA arm. These results indicated a significantly lower incidence of major bleeding with rivaroxaban compared to dual enoxaparin/VKA therapy (HR: 0.49, 95% CI 0.31 to 0.79, P=0.003). A Kaplan-Meier plot is shown in Figure 9. As illustrated in Table 16, much of this reduction is due to differences in incidence of major bleeding which was non-fatal into a critical site.

Figure 9: Kaplan-Meier plot of cumulative rate of major bleeding in EINSTEIN-PE



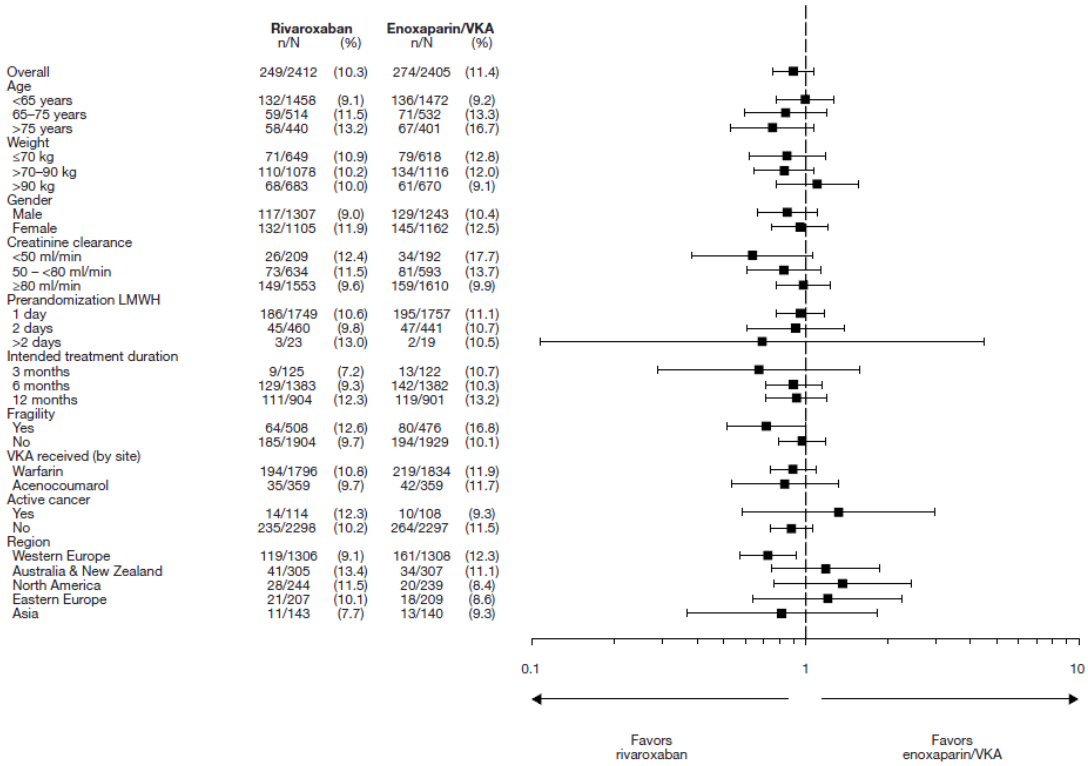
No. at Risk													
Rivaroxaban	2412	2281	2248	2156	2091	2063	1317	761	735	700	669	659	350
Standard therapy	2405	2270	2224	2116	2063	2036	1176	746	719	680	658	642	278

Source: NEJM publication[13]

Several subgroup analyses were performed on the primary safety outcome using the safety population, as shown in Figure 10, with consistent results.

[redacted]

Figure 10: Relative safety in the pre-specified subgroups in EINSTEIN-PE



Source: NEJM publication[13]

Mortality, pulmonary hypertension, cardiac failure and post thrombotic syndrome

The incidence of these events during EINSTEIN-PE, summarised in Table 17, may be compared with a safety population of 2412 patients in the rivaroxaban arm and 2405 in the enoxaparin/VKA arm.

During the intended treatment period, there were 58 deaths among patients in the rivaroxaban arm in comparison with 50 deaths among patients in the enoxaparin/VKA arm. The hazard ratio was 1.13 (95% CI 0.77 to 1.65, P = 0.53).

Table 17: Mortality and incidence of pulmonary hypertension, cardiac failure and post thrombotic syndrome in EINSTEIN-PE

	Rivaroxaban		Enoxaparin/VKA	
Safety population	2412		2405	
Deaths	58	(2.4%)	50	(2.1%)
Caused by PE or where PE not ruled-out	11	(0.5%)	8	(0.3%)
Caused by bleeding	5	(0.2%)	4	(0.2%)
Pulmonary hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]	[redacted]
Post thrombotic syndrome	[redacted]	[redacted]	[redacted]	[redacted]

Adverse events of treatment

The incidence of treatment-emergent adverse events (excluding bleeding and recurrent VTE) was comparable between treatment groups, as shown in Table 18. [redacted]

This table also includes other AE results of interest, including cardiovascular results and an AE relating to liver function.

Table 18: Summary of adverse events in EINSTEIN-PE

	Rivaroxaban		Enoxaparin/VKA		P-value
Treatment-emergent adverse events					
Any	1941	(80.5)	1903	(79.1)	0.29
Serious event	476	(19.7)	470	(19.5)	0.86
Resulting in permanent discontinuation of study drug	123	(5.1)	99	(4.1)	0.10
Leading to prolonged hospitalisation	475	(19.7)	430	(17.9)	0.82
Adverse events experienced in at least 4% of patients in either arm					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Other AEs of interest					
Acute coronary event	15	(0.6)	21	(0.9)	
Cerebrovascular event	12	(0.5)	13	(0.5)	
Systemic embolism	5	(0.2)	3	(0.1)	
Alanine aminotransferase level of more than three times the upper limit of the normal range and a bilirubin level of more than twice the upper limit of the normal range	5	(0.2)	4	(0.2)	

Source: NEJM publication[13], EINSTEIN-PE CSR[73].

Treatment satisfaction

Patient-reported satisfaction was measured by Anti Clot Treatment Scale (ACTS) and Treatment Satisfaction Questionnaire (TSQM) instruments in EINSTEIN-PE and EINSTEIN-DVT. Results from EINSTEIN-DVT have been presented[15]; results from EINSTEIN-PE have been accepted for poster presentation[17]. The ACTS instrument has been validated.[16]

Results were presented previously in section 4.1.3.

6.6 Meta-analysis

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

No meta-analysis is presented as there is only one study.

6.7 Indirect and mixed treatment comparisons

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

Evidence as to the clinical effectiveness and cost-effectiveness of rivaroxaban vs long-term LMWH in the cancer subgroup specified in the Decision Problem might only arise from an indirect comparison, since the clinical development programme for rivaroxaban (Table 7) does not include a relevant head-to-head trial in this patient group. No indirect or mixed treatment comparison was required in this submission for any other reason.

A scoping search of the Cochrane library for existing systematic reviews was first undertaken using the search terms ‘anticoagulation and cancer’. This yielded 7 publications, including a systematic review of long-term treatment of VTE in patients with cancer by Akl et al of the Cochrane Collaboration published in June 2011, based on literature searches to February 2010.[77]

This is the same Cochrane review as cited in Bayer’s STA submission for rivaroxaban in DVT treatment for the evaluation of the relative effectiveness of treatments for VTE patients with cancer.[19] In evaluating Bayer’s submission in January 2012, the ERG (ScHARR) stated in their report that the review was limited by update searches not having been performed to see if any additional relevant literature had been published. However, the ERG stated that they then conducted update searches following the Cochrane review’s search strategy, and no further eligible RCT studies were identified.

The indirect comparison was variously criticised in the ERG report. One set of criticisms related to the numerous sources of heterogeneity across the included studies. Ultimately, the Appraisal Committee acknowledged that the ERG did not find the cancer subgroup analyses to be robust.

As the evidence for this subgroup is likely to be substantially similar at time of writing as it was in January 2012 at the time of the ERG report, and because this evidence was disparate and considered limited, it has not been considered worthwhile to conduct a network meta-analysis to estimate the relative effectiveness of rivaroxaban vs long-term LMWH in this patient group. Neither has it been considered worthwhile to formally update the underlying Cochrane/ERG systematic review. However, a summary of key data is provided and details of the underlying literature database searches and quality assessment of included studies are included in the relevant appendices (4 and 5, sections 10.4-5).

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Further information as to the searches and objectives of this systematic review can be found in the publication itself[77] and in Appendices 4 and 5 of this submission, including an overview of the reviewers' study selection criteria in Table 102 and the reviewers' assessment of the quality of included studies, all of them RCTs, in Table 103.

Of 8187 identified citations resulting from the systematic searches within the Akl et al. review, nine RCTs were eligible and reported data for 1908 patients with cancer. From these nine RCTs, five contributed data to meta-analyses of VTE recurrence and bleeding outcomes:

1. Deitcher et al 2006[78] was an RCT of 102 active cancer patients with DVT and/or PE. Patients were randomised to one of three groups: (i) 1 mg/kg enoxaparin bid for five days followed by 1-1.5 mg/kg daily for 175 days; (ii) 1.5 mg/kg enoxaparin daily for 175 days; or (iii) 1 mg/kg enoxaparin for five days followed by warfarin targeting an INR of 2-3 for 175 days.

2. Hull et al 2006[79] was an RCT of 200 patients with cancer (solid or haematological) and proximal DVT with or without PE. Patients were treated for 12 weeks with either (i) tinzaparin (175 antiXa/kg daily) or (ii) UH for five days (5000 units or 80 units/kg) followed by VKA targeting an INR of 2-3.

3. Lee et al 2003[80] was an RCT of 979 patients with cancer and either DVT or PE or both. Patients were treated for 6 months with either (i) long-term dalteparin (200 IU/kg daily in month 1 and 150 IU/kg in months 2-6) or (ii) dalteparin for 5-7 days (200 IU/kg daily) followed by VKA targeting INR 2-3.

4. Meyer et al 2002[81] was an RCT of 146 patients with cancer (solid or haematological) with DVT and/or PE. Patients were treated with either (i) 3 months of enoxaparin (1.5 mg/kg daily) or (ii) 4 days of enoxaparin (1.5 mg/kg daily) followed by 3 months of warfarin targeting an INR of 2-3.

5. Romera-Villegas et al 2010[82] was an RCT of patients with symptomatic proximal DVT in which a subgroup of 69 patients additionally had cancer. Patients were treated with either (i) tinzaparin for 6 months (175 IU anti-xa / kg od) or (ii) 3 mg acenocoumarol od targeting an INR of 2-3.

To these five studies, we add the EINSTEIN-DVT and EINSTEIN-PE studies.

6. EINSTEIN-DVT[18] was an RCT of patients with acute, symptomatic objectively confirmed DVT (without PE) in which a subgroup of 207 (6.0%) additionally had cancer. Patients were treated for either 3, 6 or 12 months with either (i) enoxaparin overlapping with VKA therapy or (ii) rivaroxaban (15 mg bid for 21 days, then 20 mg od for the remainder of the treatment period).

7. EINSTEIN-PE[13] was an RCT of patients with acute, symptomatic, objectively confirmed PE, with or without DVT, in which a subgroup of 223 (4.6%) additionally had cancer. Patients were treated for either 3, 6 or 12 months with either (i) enoxaparin overlapping with VKA therapy or (ii) rivaroxaban (15 mg bid for 21 days, then 20 mg od for the remainder of the treatment period).

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

An overview of the treatment comparisons made in RCTs involving rivaroxaban, heparin/VKA and long-term LMWH in VTE patients with cancer is provided in Table 19.

Table 19: Overview of RCTs involving rivaroxaban, heparin/VKA and long-term LMWH in VTE patients with cancer

Study	Rivaroxaban	Dual heparin / VKA	Long-term LMWH	Other
EINSTEIN-DVT[18]	✓	✓		
EINSTEIN-PE[13]	✓	✓		
Deitcher et al 2006[78]		✓	✓	
Hull et al 2006[79]		✓	✓	✓
Lee et al 2003[80]		✓	✓	
Meyer et al 2002[81]		✓	✓	
Romera-Villegas et al 2010[82]		✓	✓	

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

We have updated the dataset using data from the relevant trials previously presented for the DVT treatment evaluation, plus relevant data from EINSTEIN-PE as per Table 19.

No network meta-analysis is presented due to the limitations highlighted previously in the evaluation of rivaroxaban in DVT treatment among patients with cancer.[19]

Table 20: Data on VTE recurrence, time to event, from trials of VTE patients with cancer

Study	Comparison	Point estimate (Log Hazard Ratio)	Standard error of point estimate
EINSTEIN-PE – whole population[13]	Rivaroxaban vs dual heparin / VKA	0.1160	0.2067
EINSTEIN-PE – cancer subgroup[13]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
EINSTEIN-DVT – whole population[18]	Rivaroxaban vs dual heparin / VKA	-0.3857	0.2194
EINSTEIN-DVT – cancer subgroup[18]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
Deitcher et al 2006[78]	Long-term LMWH vs dual heparin / VKA	NA	NA
Hull et al 2006[79]	Long-term LMWH vs dual heparin VKA	-0.8819	0.455
Lee et al 2003[80]	Long-term LMWH vs dual heparin VKA	-0.734	0.24
Meyer et al 2002[81]	Long-term LMWH vs dual heparin VKA	-0.3567	0.9
Romera-Villegas et al 2010[82]	Long-term LMWH vs dual heparin VKA	NA	NA

Source: Analysis 1.5 of Akl et al[77], EINSTEIN-DVT and EINSTEIN-PE CSRs[73,83].

Table 21: Data on VTE recurrence, dichotomous methods, from trials of VTE patients with cancer

Study	Comparison	n/N - intervention 1	n/N - intervention 2
EINSTEIN-PE – whole population[13]	Rivaroxaban vs dual heparin / VKA	50/2419	44/2413
EINSTEIN-PE – cancer subgroup[13]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
EINSTEIN-DVT – whole population[18]	Rivaroxaban vs dual heparin / VKA	36/1731	51/1718
EINSTEIN-DVT – cancer subgroup[18]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
Deitcher et al 2006[78]	Long-term LMWH vs dual heparin VKA	4/61	3/30
Hull et al 2006[79]	Long-term LMWH vs dual heparin VKA	7/100	16/100
Lee et al 2003[80]	Long-term LMWH vs dual heparin VKA	27/336	53/336
Meyer et al 2002[81]	Long-term LMWH vs dual heparin VKA	2/71	3/75
Romera-Villegas et al 2010[82]	Long-term LMWH vs dual heparin VKA	2/36	7/33

Source: Analysis 1.5 of Akl et al[77], EINSTEIN-DVT and EINSTEIN-PE CSRs[73,83].
Abbreviations: n = patients with outcome, N = number of patients in study population.

Table 22: Data on incidence of major bleeding from trials of VTE patients with cancer

Study	Comparison	n/N - intervention 1	n/N - intervention 2
EINSTEIN-PE – whole population[13]	Rivaroxaban vs dual heparin / VKA	26/2412	52/2405
EINSTEIN-PE – cancer subgroup[13]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
EINSTEIN-DVT – whole population[18]	Rivaroxaban vs dual heparin / VKA	14/1718	20/1711
EINSTEIN-DVT – cancer subgroup[18]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
Deitcher et al 2006[78]	Long-term LMWH vs dual heparin VKA	6/67	1/34
Hull et al 2006[79]	Long-term LMWH vs dual heparin VKA	7/100	7/100
Lee et al 2003[80]	Long-term LMWH vs dual heparin VKA	19/338	12/335
Meyer et al 2002[81]	Long-term LMWH vs dual heparin VKA	5/71	12/75
Romera-Villegas et al 2010[82]	Long-term LMWH vs dual heparin VKA	NA	NA

Source: Analysis 1.5 of Akl et al[77], EINSTEIN-DVT and EINSTEIN-PE CSRs[73,83].
Abbreviations: n = patients with outcome, N = number of patients in study population.

Table 23: Data on incidence of minor bleeding from trials of VTE patients with cancer

Study	Comparison	n/N - intervention 1	n/N - intervention 2
EINSTEIN-PE – whole population[13]	Rivaroxaban vs dual heparin / VKA	228/2412	227/2405
EINSTEIN-PE – cancer subgroup[13]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
EINSTEIN-DVT – whole population[18]	Rivaroxaban vs dual heparin / VKA	126/1718	119/1711
EINSTEIN-DVT – cancer subgroup[18]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
Deitcher et al 2006[78]	Long-term LMWH vs dual heparin VKA	39/67	17/34
Hull et al 2006[79]	Long-term LMWH vs dual heparin VKA	20/100	17/100
Lee et al 2003[80]	Long-term LMWH vs dual heparin VKA	28/338	51/335
Meyer et al 2002[81]	Long-term LMWH vs dual heparin VKA	5/71	9/75
Romera-Villegas et al 2010[82]	Long-term LMWH vs dual heparin VKA	NA	NA

Source: Analysis 1.5 of Akl et al[77], EINSTEIN-DVT and EINSTEIN-PE CSRs[73,83].
Abbreviations: n = patients with outcome, N = number of patients in study population.

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

6.7.6 Please present the results of the analysis.

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

No network meta-analysis is presented for the cancer subgroup due to the limitations highlighted previously in the evaluation of rivaroxaban in DVT treatment among patients with cancer.[19]

6.8 Non-RCT evidence

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

There are no relevant non-RCTs included in this submission.

6.9 Adverse events

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality

assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

The systematic review for relevant RCTs was described in sections 6.1-6.2 (and further in section 10.2, appendix 2). This review did not exclude studies designed primarily for safety. EINSTEIN-PE was not designed primarily for safety.[13] All outcomes relevant to the Decision Problem, including adverse events and mortality, were reported in section 6.5.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Incidence of adverse events in EINSTEIN-PE have previously been summarised in section 6.5 and Table 18 in absolute and proportionate terms. The relative risks and absolute risk differences (ARDs), with 95% CI, are presented as requested in Table 22.

In light of the liver function abnormalities produced by ximelagatran, an oral thrombin inhibitor now withdrawn from research[84], liver function was also closely monitored in the EINSTEIN RCTs.[63] Monthly liver function tests did not reveal any signs of impaired liver safety in patients receiving rivaroxaban.[13,18]

Table 22: Relative and absolute risk differences (ARD, %) for the adverse events in EINSTEIN-PE listed previously (95% CI)

	Risk ratio (95% CI)	ARD (%, 95% CI)
Treatment-emergent adverse events		
Any	[redacted]	[redacted]
Serious event	[redacted]	[redacted]
Resulting in permanent discontinuation of study drug	[redacted]	[redacted]
Leading to prolonged hospitalisation	[redacted]	[redacted]
Adverse events experienced in at least 4% of patients in either arm		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	Risk ratio (95% CI)	ARD (%, 95% CI)
[redacted]	[redacted]	[redacted]
Other AEs of interest		
Acute coronary event	[redacted]	[redacted]
Cerebrovascular event	[redacted]	[redacted]
Systemic embolism	[redacted]	[redacted]
Alanine aminotransferase level of more than three times the upper limit of the normal range and a bilirubin level of more than twice the upper limit of the normal range	[redacted]	[redacted]

Note: See Table 18 for underlying data

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The STA / decision problem requires an evaluation of rivaroxaban within its licensed indication. The variation made to the indication is to include treatment of adult patients with PE, not all of whom may be appropriately treated with rivaroxaban: in section 2.2, we suggested that 85% of adult patients with PE might be eligible for rivaroxaban according to the indication, recommendations and contraindications specified in the draft SmPC.[4]

As the draft SmPC notes, the safety of rivaroxaban has been evaluated in eleven phase III studies including 32,625 patients exposed to rivaroxaban. In patients treated with either 15 mg bid or 20 mg od rivaroxaban for the treatment of DVT or PE, bleeding events occurred in approximately 27.8% of patients and anemia occurred in 2.2% of patients.[4]

EINSTEIN-PE demonstrated the non-inferiority of rivaroxaban to the standard of care, dual enoxaparin/VKA therapy.[13] The EINSTEIN-Ext study provides evidence as to the relative effectiveness and safety of rivaroxaban vs placebo for 6-12 months further treatment, after an initial 6-12 months of anticoagulation in a study population who had clinical equipoise as to the risk:benefit of 6-12 months of further treatment.[18] Principle safety findings for both studies are included in response to section 6.10.1.

The incidence of other treatment-emergent AEs was comparable between rivaroxaban and dual LMWH/VKA therapy, [redacted]. Vascular events and AEs related to the liver function were low and similar between treatment groups.[13]

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Rivaroxaban was shown to be comparable with the standard of care in the treatment of PE in EINSTEIN-PE[13]:

- The primary efficacy outcome, recurrence of VTE, was experienced in 2.1% rivaroxaban vs 1.8% dual LMWH/VKA therapy patients (HR: 1.12, 95% CI 0.75 to 1.68, $P_{non\text{-}inf}$=0.003, P_{sup}=0.57).

- The primary safety outcome, clinically relevant bleeding, was experienced in 10.3% rivaroxaban vs 11.4% dual LMWH/VKA therapy patients (HR: 0.90, 95% CI 0.76 to 1.07, P=0.23).
- Major bleeding was experienced in 1.1% rivaroxaban vs 2.2% dual LMWH/VKA therapy patients (HR: 0.49, 95% CI 0.31 to 0.79, P=0.003).
- The outcome of a net clinical benefit was experienced in 83 patients (3.4%) in the rivaroxaban group and 96 patients (4.0%) in the dual LMWH/VKA therapy group (HR: 0.85, 95% CI, 0.63 to 1.14, P=0.28).

Greater satisfaction with treatment was reported with rivaroxaban in EINSTEIN-PE using the ACTS and TSQM instruments.[15] This may be a reflection of the additional benefits to patients of a rivaroxaban single-drug approach. These include removing the need for:

- frequent laboratory monitoring of INR
- consequent dose-adjustment
- dietary changes necessitated through interactions with warfarin

Treatment with rivaroxaban was also associated with a shorter length of hospital stay (LOS) in EINSTEIN-PE compared with patients treated with dual enoxaparin/VKA, as shown in Table 23. The difference between treatment arms was statistically significant (P<0.0001) as judged by two separate statistical tests: (i) non-parametric Van-Elteren test (stratified Wilcoxon rank-sum test) and (ii) a parametric test assuming Normality on a log-transformed scale.[14,73]

Table 23: Length of hospital stay among patients in EINSTEIN-PE (days)

	Rivaroxaban	**Enoxaparin/VKA**
ITT patients	2419	2413
Patients with hospitalisation data	2412	2409
Patients hospitalised (%)	2163 (89.7)	2165 (89.9)
Median stay (days)	6	7
Range (days)	4-9	5-10
Arithmetic mean (days)	8.6	9.1
Geometric mean (days)	6.7	7.6

The EINSTEIN-Ext study provides evidence as to the relative effectiveness and safety of rivaroxaban vs placebo for 6-12 months further treatment, after an initial 6-

12 months of anticoagulation in a study population who had clinical equipoise as to risk:benefit of 6-12 months of further treatment. This study found a treatment effect in favour of rivaroxaban in time to recurrence of VTE (HR of 0.18, 95% CI 0.09 to 0.39), no significant difference in rates of major bleeding (0.7% with rivaroxaban vs. 0% with placebo, P=0.11) and significantly favourable net clinical benefit (HR of 0.28, 95% CI 0.15 to 0.53, P<0.001).[18]

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The aim of PE treatment is to prevent mortality in patients presenting with shock or hypotension, and prevent further, or recurrent VTE events. A recurrent PE can lead to re-hospitalisation, or can lead to patient mortality. After a PE, a patient is at increased risk of chronic thromboembolic pulmonary hypertension (CTEPH)[85]; and after a DVT, a patient is at increased risk of post thrombotic syndrome (PTS)[86,87]. These are all clearly negative health outcomes for patients and can place considerable burden on healthcare systems.

The pivotal study in this submission was EINSTEIN-PE, a randomised controlled trial with an active comparator regimen (dual enoxaparin/VKA) of wide international acceptance and use.

In line with the aim of therapy, the primary and secondary efficacy outcomes in EINSTEIN-PE (in common with other studies in the EINSTEIN programme) therefore included a wide range of outcomes based on the incidence/recurrence of DVTs, PE, bleeding and mortality. All outcomes were hard endpoints, internationally accepted and widely used to assess efficacy in patients with VTE and, in line with European guidance, all events were objectively verified using validated procedures and adjudicated by a blinded clinical events committee.[61,62] Care was taken to make sure all possible outcomes were reported and evaluated. This included regular follow-up between investigators and study participants and written instructions on key symptoms that were to trigger formal evaluation of possible outcome events.

Below, we discuss the open-label design and general validity, use of non-inferiority statistical testing, diagnosis of PE event and treatment before randomisation.[13,63]

Open-label design and general validity

The trial had a Prospective Randomised Open Blinded Endpoint (PROBE) design. This was selected so that rivaroxaban and the standard of care regimen of LMWH/VKA could be evaluated as they are, or would be, used in clinical practice.

Administration of LMWH/VKA differs markedly to rivaroxaban. Administration of a placebo in the rivaroxaban group would have required subcutaneous injection of placebo LMWH twice a day for some of the time which may have unnecessarily increased the potential for bleeding events at the puncture site, including abdominal wall bleeds. The European Agency for the Evaluation of Medicinal Products (EMA) Committee for Proprietary Medical Products (CPMP) has recognised that blinded studies are difficult to perform in this area.[61]

Open-label studies may be validly criticised in certain circumstances for their potential for bias arising in patients and/or investigators knowing what treatment has been allocated.

However, a recent meta-epidemiological study found little evidence of bias in circumstances where study outcomes are clearly objective rather than subjective, have predefined internationally accepted criteria and are verified centrally by an independent and blinded adjudication panels.[88] EINSTEIN-PE has these characteristics: outcomes used in EINSTEIN-PE were indeed clinically important, hard, objective outcomes (VTE event, major bleeding and death) verified by standard diagnostic methods and adjudicated by the blinded centralised committee. Other safeguards in place to protect against biases typically controlled by blinding included: standardised VTE event and bleeding questionnaires used at every visit, central automated randomisation to treatment, and the use of the ITT population to perform the primary analysis.

Results from the trial further demonstrate its internal validity. Although there were more patients with a suspected VTE recurrence in the rivaroxaban arm than in the LMWH/VKA, following adjudication (which was blinded to treatment allocation), the proportion of patients with confirmed events was similar (10.2% in the rivaroxaban group vs 9.7% in the dual enoxaparin/VKA arm). This finding suggests that the open design may have caused a slight bias against rivaroxaban. However, the rate of recurrence seen in the active control group (of around 2%) was also consistent with rates observed in other recent studies.[89-91]

Further evidence for the study's validity comes from consideration of time in therapeutic range (TTR) and low loss to follow-up. Overall TTR in the LMWH/VKA arm (62.7%[13]) is comparable with results from other recent thrombosis studies.[89-91] In terms of reasons for discontinuation in EINSTEIN-PE that may be generalised to real-world experience, there was low loss to follow-up equivalent to a three month discontinuation probability of [redacted] – see also section 7.3.1 and Table 13.

Together this provides evidence of a well-managed trial where therapy was administered to a high standard, consistent with standard UK practice. The enoxaparin regime is discussed in later sections.

The intended duration of treatment selected before randomisation was 3 months in 5.2% of patients (249/4832), 6 months in 57.4% of patients (2774/4832) and 12 months in 37.4% of patients (1809/4832) across both arms. In selecting treatment durations for/with patients, clinicians involved in the trial will have been aware of clinical guidelines, which generally recommend treatment for `at least 3 months'.

EINSTEIN-PE has strong external validity with limited risk of bias through its design – a conclusion backed-up by evidence arising from the study's results.

Use of non-inferiority statistical testing

The EINSTEIN-PE trial was designed to involve sequential testing of the primary efficacy endpoint for non-inferiority and then, if statistically significant, superiority. As described previously:

- the primary efficacy outcome (recurrence of VTE) was hazard ratio of 1.12 with a 95% CI of 0.75 to 1.68. This was statistically significantly non-inferior to LMWH/VKA (P=0.003) but not statistically significantly different (P=0.57)
- the primary safety outcome was a hazard ratio of 0.90 numerically favouring rivaroxaban, with a 95% CI 0.76 to 1.07, P=0.23 for superiority.

The use of non-inferiority testing may be perceived by some audiences as a limitation. We also highlight the consistent effects shown across trial subgroups demonstrated in Figure 7 (VTE recurrence) and Figure 10 (clinically relevant bleeding). Analyses including the margin for the non-inferiority test were pre-specified as recommended in EMA guidance.[61]

Diagnostic confirmation of PE event

Whilst doctors use clinical signs and symptoms to determine the probability and likelihood of a PE event they must rely on laboratory testing and imaging techniques to confirm diagnosis of the condition.

In the UK, computed tomography pulmonary angiography (CTPA) has become the gold standard diagnostic imaging technique, as recommended by NICE and SIGN guidelines.[8,9] CTPA has been shown to have a high sensitivity (83-100%) and specificity (89-97%) in confirming clinically suspected PE.[9]

The confirmatory tests required of the index PE in EINSTEIN-PE were described previously in section 6.3.3. Most cases in the trial were also confirmed on the basis of (spiral) computed tomography results (Table 9).

Treatment before randomisation

The EINSTEIN-PE study was designed to allow a limited amount of treatment before randomisation: up to 36 hours of treatment with LMWH, heparin or fondaparinux were permitted (or up to 48 hours after protocol amendment 4, see section 6.3.3).[63] The median time from onset of symptoms to randomisation was 4 days (Table 9). The reasons for this included the following:

- Patients presenting with suspected VTE at the local practitioner sometimes receive parenteral anticoagulation before they are admitted to hospital; and
- Some hospitals administer parenteral anticoagulation in the emergency ward or outpatient clinic as a standard procedure prior to the diagnosis/confirmation of VTE.
- Enrolment onto a clinical study, which must precede randomisation, can be time consuming due to obtaining consent and conducting screening. It can be helpful or even necessary to bridge this gap with treatment with parenteral anticoagulation.

The risk with allowing pre-treatment is that if it was not consistently applied across the study as a whole, or was more common or more intensive in one arm than another, that the relative treatment effect may be affected.

On consideration of the results of the study, it appears that any such risks have not confounded the study results, which remain internally and externally valid.

- A similar proportion of patients in both arms received pre-randomisation anticoagulation: 92.5% in the rivaroxaban arm vs. 92.1% in the LMWH/VKA arm (P=0.62, post hoc binomial test).
- The intensity of pre-randomisation anticoagulation was small. Among those receiving any pre-randomisation anticoagulation, the treatment was received for just one day in 62.5% of cases.
- The effect of treatment on the incidence of the primary efficacy outcome was similar regardless of degree of pre-randomisation anticoagulation, with no apparent trend (Figure 7).

[redacted]

6.10.4 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The outcomes used in EINSTEIN-PE were described further in previous sections. Efficacy outcomes centred around rates of recurrent VTE; safety outcomes centred around rates of bleeding, but also considered mortality and vascular events (stroke, myocardial infarction, cardiovascular death). Events were routinely assessed by a central independent adjudication committee.

AEs relating to the liver were monitored because of a suspected increase in such events seen with some other novel anticoagulants, in particular ximelagatran[84]. Vascular events were monitored because of a suspected increase in cardiovascular events seen with other novel anticoagulants, especially after cessation of treatment.

In addition net clinical benefit outcomes were defined to explicitly evaluate the risk-benefit profile of rivaroxaban in acute and extended treatment settings (Table 11). The evidence base is therefore highly relevant to the decision problem.

6.10.5 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology

was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

We consider the results of EINSTEIN-PE (Table 7) to be applicable to patients routinely treated in England and Wales for PE or prevention of recurrent VTE, according to the draft SmPC.[4] We discuss here the choice of eligible patients, trial and licensed dosing, demographics of the trial population, time to achieve therapeutic INR, time in INR range, trial design (in particular, pre-randomisation selection of intended treatment duration), enoxaparin regime and compliance.

Choice of eligible patients

EINSTEIN-PE was open to all adult patients newly experiencing a PE, with or without a DVT, subject to the inclusion/exclusion criteria stated previously in section 6.3.3. In particular, the diagnosis of PE was to be made on the basis of confirmatory adjudicated testing, and in 87% of cases this was by spiral computed tomography (Table 9). Patients with active bleeding or high risk of bleeding, renal impairment (creatinine clearance < 30 mL/min) or who had received thrombectomy, insertion of vena cava filter or fibronolytic agent for the current episode of thrombosis were excluded.[13,63]

NICE CG144 provides recommendations an algorithm for diagnosing PE, based around clinical suspicion, Wells score and computed tomography pulmonary angiogram (Figure 2).[8] The SmPC for rivaroxaban notes that various PE patients would be unsuited to rivaroxaban. These groups were listed in section 2.2. In particular, patients with active bleeding or high risk of bleeding, severe renal impairment (creatinine clearance < 15 mL/min), or who are haemodynamically unstable or may receive thrombolysis are not recommended for rivaroxaban.[4]

The procedures and patient population of EINSTEIN-PE therefore closely matches UK recommended diagnostic algorithms and the group of PE patients potentially eligible for rivaroxaban under its draft SmPC.

Demographics of trial population

We have described previously the baseline characteristics of EINSTEIN-PE (Table 9 and Table 10). [redacted]

[redacted]

However, there are a number of other factors relating to baseline demographics that support the study's generalisability to the NHS in England and Wales.

The mean age at baseline in EINSTEIN-PE was 57.7 years and not out of line with clinical expectations. The interquartile range of ages at baseline was 45 to 72 years with a full range of 18 to 97 years, supporting broad generalisability.

The proportion of patients in EINSTEIN-PE describing themselves as `white' was 65.6%, as compared with 83.3% of the population in England and Wales in the ethnic group `white British', according to latest estimates from the Office for National Statistics.[92]

Time to achieve therapeutic INR

Time to therapeutic INR in EINSTEIN-PE from randomisation was [redacted] not out of line with what would be expected in routine UK clinical practice with dual LMWH/VKA therapy.[73]

Time in INR range

The proportion of time that patients' INR was in the target range (TTR, ie an INR of 2-3) was 62.7% across all centres. The TTR in EINSTEIN-PE is in line with various external observations:

- In a review for the ACCP guidelines, the mean TTR in RCTs ranged between 42% and 83%, mostly around 60%.[93]
- A recent observational study in UK secondary care anticoagulation services observed TTR of 53% during the first 12 weeks of treatment and 59% thereafter.[46]
- Guideline recommendations from the Scottish Executive Health Department and National Patient Safety Agency are for TTR of at least 60%.[94,95]

It is important to highlight an observation made in the SmPCs that, after extensive analysis involving ranking centres by TTRs achieved, there was no clear relation observed in EINSTEIN-PE between TTR and treatment effect[4], just as there was no interaction observed in EINSTEIN-DVT[2,3].

Trial design

One aspect of the design of EINSTEIN-PE (and other studies in the EINSTEIN sudy programme) that makes their results particularly applicable to routine clinical practice is the pre-randomisation determination by clinicians of patients' appropriate duration of treatment reflecting individual risk-benefit. The entry criteria in both studies allowed inclusion of a broad range of patients with various risk factors for VTE and bleeding and extensive co-morbidities.

Providing this flexibility in trial design, reflective of clinical decision-making and respecting clinical guidelines, and consequently including in the trial cohorts of mixed risk characteristics enhance the applicability of trial results to real-life patients.

Rivaroxaban regime

The regime for rivaroxaban in EINSTEIN-PE matches the standard dose of rivaroxaban stipulated in the draft SmPC: 15 mg bid for 21 days followed by 20 mg od.[4,13]

However, the draft SmPC recommends that in PE (or DVT) patients with moderate or severe renal impairment (creatinine clearance 15-49 ml/min), the dose after the first three weeks is recommended to be 15 mg od rather than 20 mg od if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. This recommendation is based on PK modelling and has not been studied in this clinical setting.[4]

Enoxaparin regime

EINSTEIN-PE was designed to require, after entry to the comparator arm of the trials, treatment with enoxaparin at 1.0 mg / kg bid until `the INR is ≥ 2.0 on two consecutive measurements at least 24 hours apart' and for a minimum period of 5 days (as per section 5.1.3 of the trial protocol). In this way, the study enabled patients to be treated, in the comparator arm, according to US Prescribing Information for enoxaparin, which requires enoxaparin to be administered at 1.0 mg / kg bid (without recommendation on timing) or 1.5 mg / kg od (at the same time each day). Treatment is to be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (INR 2.0 to 3.0).[96] The UK and European licence for enoxaparin is slightly different in that 1.5 mg / kg od is required for at least 5 days and `until adequate oral anticoagulation is established.[97] Current US clinical guidelines now recommend once daily over twice daily LMWH.[98]

It has been suggested that this difference in enoxaparin dosing may potentially limit the generalisability of EINSTEIN-PE to practice in England and Wales in the treatment of PE. We consider this fairly implausible, for various reasons.

1.The two dosing regimens are consistent in their principle provisions, in requiring enoxaparin to be taken for the same minimum period and until adequate anticoagulation has been achieved, which in both UK and US clinical practice would be assessed through INR monitoring.

2. Regardless of how it was achieved, time to therapeutic INR in EINSTEIN-PE was in line with what would be expected in routine UK clinical practice with enoxaparin, as discussed previously.

3. Literature suggests that such minor differences in the dosing of LMWH does not affect outcomes and that efficacy is equivalent.

- Firstly, Merli et al found that patients with symptomatic lower extremity DVT randomly assigned to treatment with enoxaparin of doses 1.0 mg/kg bid or 1.5 mg/kg od delivered subcutaneously had `equivalent efficacy'. The primary endpoint used in this study was the recurrence of a DVT or PE within 3 months of randomisation.[99]

- Secondly, Hacobian et al found similar rates of recurrent VTEs within 30 days of a DVT among cases followed prospectively and treated in an outpatient setting with LMWH at a dose of 1.5 mg/kg od compared with age- and gender-matched retrospective controls treated with LMWH at a dose of 1.0 mg/kg od.[100]

4. The size of any effect of enoxaparin doses on study outcomes could not be readily evaluated in the trial (since enoxparin was only administered in one trial arm and at one dose). However, it is worth highlighting that there was no significant effect on primary efficacy or safety outcomes attributable to the interaction between treatment and prerandomisation medication (Figure 7 and Figure 10).

5. The period in which enoxaparin was delivered in EINSTEIN-PE was very short in comparison to the length of the trial as a whole, over which outcomes are measured and compared between arms. As noted previously in this section, [redacted] This level of pre-treatment is not inconsistent with NICE or SIGN guidelines.[8,9]

Trial vs licensed dosing regime

The trial dosing regime was 15 mg bid for 21 days followed by 20 mg od for the remainder of treatment.[13] This matches the licensed dosing regime given in the draft SmPC[4], with the exception of one group.

The group in question is of patients with renal impairment which is moderate (creatine clearance 30-49 mL/min) or severe (creatinine clearance 15-29 mL/min) and where the patient's assessed risk for bleeding outweighs the risk for recurrent VTE. For this group, the draft SmPC recommends that a dose reduction be considered from 20 mg od after the first 21 days to 15 mg od. This recommendation is based on PK modelling rather than having been studied in the clinical setting.

Compliance

The arrangements for measuring compliance were discussed previously in section 6.3.5. EINSTEIN-PE demonstrated high levels of compliance for rivaroxaban, confirming its simplicity and convenience for patients, another important factor in routine clinical practice. In the ITT population, 94.2% of all patients had a compliance outcome of at least 80%.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

The NICE CG144 guidance on management of VTE diseases and the role of thombophylia testing included a systematic review of the health economics and quality of life associated with VTE disease.[8] This review was conducted in August 2011 by the National Clinical Guideline Centre (NCGC), and this was refined and updated to 25 October 2012 for this submission.

The objective of the NCGC review was to identify health economic and quality of life articles of relevance to `all questions' considered in the guideline (see appendix D1 to the guideline). The objective of a systematic review to address this section of the TA submission was more specific, as summarised in Table 24, which meant that the NCGC review could be used as a basis for an update.

Table 24: Inclusion/exclusion criteria for the systematic review of cost-effectiveness evaluations

Inclusion criteria		
Category	**Criteria**	**Rationale**
Study type	A relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis)	The aim of the review was to identify relevant economic evaluations.
Outcomes	Incremental costs and QALYs; any other measure of effectiveness reported together with costs	The aim of the review was to identify relevant economic evaluations, which must report both costs and effects.

Population	Patients with suspected or confirmed PE or DVT	Patients with PE are the population of interest for this appraisal. Patients with DVT were also included in case the data on PE was insufficient.
Interventions	Any pharmaceutical for the treatment and secondary prevention of VTE	Devices or other non-pharmaceutical interventions are not of relevance to the decision problem.
Comparators	Any	Study of at least one pharmaceutical is required, but the comparator does not need to be specified.
Exclusion criteria		
Category	**Criteria**	**Rationale**
Publication type	Unpublished reports; letters; editorials; reviews of economic evaluations (although reference lists of these would be hand-searched)	Primary study articles were required. Unpublished data held by the manufacturer were sourced separately.
Language	Non-English language articles	

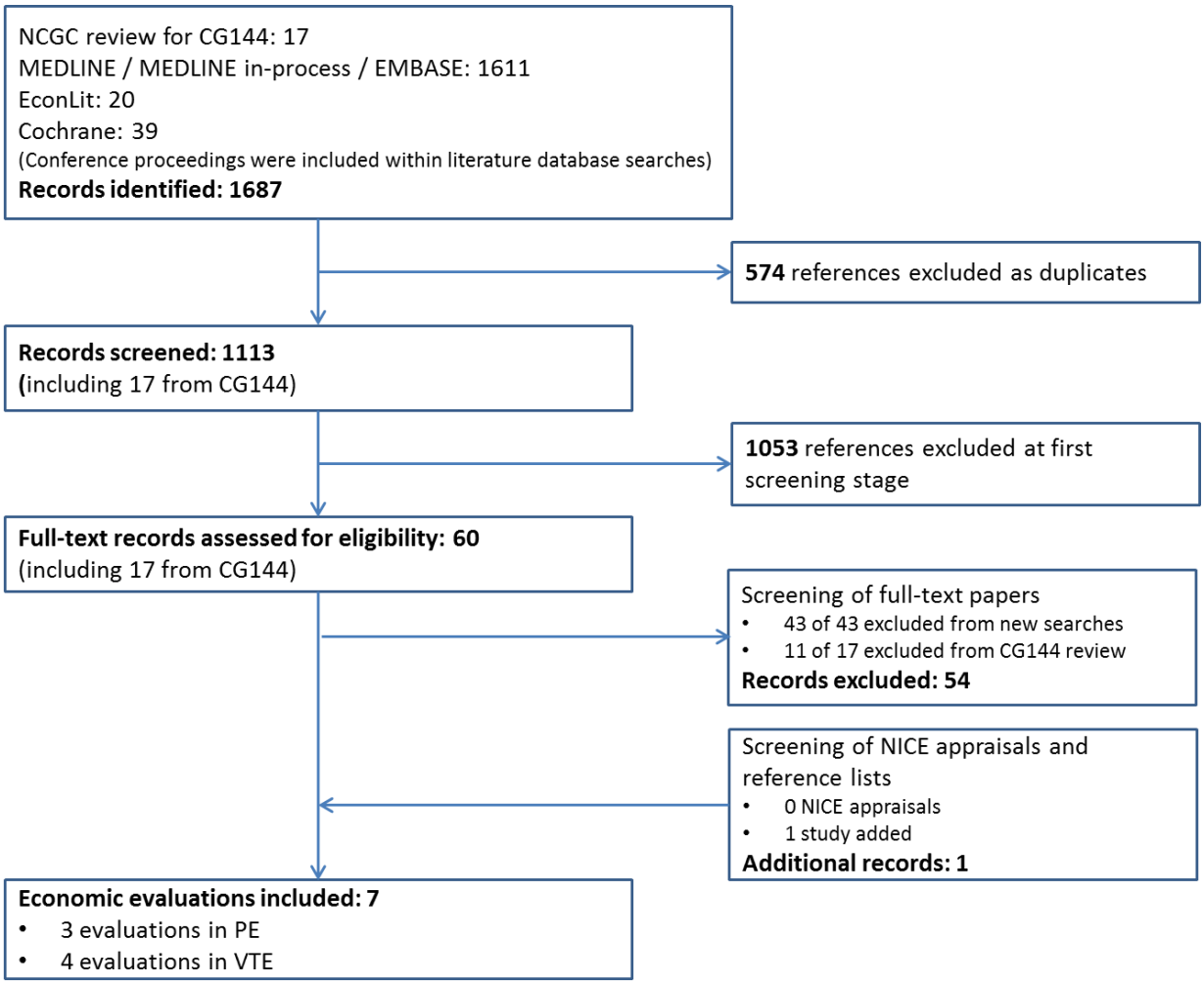
Comprehensive searches, using the same search terms as employed by the NCGC review were run across EMBASE, MEDLINE, MEDLINE In-Process, NHS Economic Evaluations Database (via Cochrane Library), the Health Technology Assessment Database (via the Cochrane Library), from 2011). In order to only include studies published since the previous review was conducted, abstracts with a publication date before July 2011 were manually deleted, such that results were studies published from 01/07/11 to 25/10/12. EconLit was additionally searched from database inception to 25/10/12, as this database was not previously searched by the NCGC. In addition to the online database searches, horizon scanning using key words and a search of the NICE website were conducted. Proceedings from two congresses of interest were included within the literature database searches so were not searched separately (International Society for Pharmacoeconomics and Outcomes Research, Congress of the International Society on Thrombosis and Haemostasis). See also section 10.10, appendix 10.

Abstracts of citations found through the searches were initially assessed by two independent reviewers for inclusion based on the abstract alone. Full-text copies of studies that potentially met the inclusion criteria were obtained and reviewed against the inclusion criteria by two independent reviewers. Studies that met the eligibility criteria after the second screening stage were extracted by a reviewer and checked

by a second party. Where more than one publication was identified describing a single study, the data were compiled into a single entry in the data extraction table.

The flow diagram of the studies included in this systematic review is shown in Figure 11. The diagram includes the 17 studies identified in the NCGC review.

Figure 11: Study flow diagram for systematic review of economic evaluations



Of the 17 studies included in the NCGC review, six were included in this review after applying the inclusion/exclusion criteria of Table 24.[101-106] The literature database searches identified a further 1670 studies, but none of these satisfied the inclusion/exclusion criteria. The previous technology appraisal of rivaroxaban for DVT treatment was identified in searches but not included according to the inclusion/exclusion criteria.[19] A review of reference lists, including the systematic review conducted to the corresponding section of the submission for rivaroxaban in DVT treatment identified one further study.[107] Seven studies were therefore included.[101-107]

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

The seven included summaries are summarised in Table 25. Further data extraction for those six studies[101-106] also included in the NICE CG144 review is reported in appendix F to that guideline[8]. None were directly relevant to the decision problem.

Table 25: Summary of cost-effectiveness evaluations included in the systematic review

Study	Year	Country(ies) where study was performed	Summary of model	Patient population	QALYs	Costs (2009 UK pounds unless stated)	ICER (per QALY gained, 2009 UK pounds)
Aujesky 2005a[102]	2002	USA (societal perspective)	Decision tree. Cost-utility analysis. Six months of either: (i) dalteparin or (ii) dual LMWH / warfarin	65 year old patients with cancer-related VTE	(i) 1.097 (ii) 1.046	(i) £9620 (ii) £4845	£93,635
Aujesky 2005b[101]	2002	USA (societal perspective)	Markov model. Cost-utility analysis. Three months of either: (i) dual enoxaparin / warfarin (ii) dual UH / warfarin	60 year old with acute submassive PE	(i) 7.677 (ii) 7.493	(i) £8159 (ii) £8021	£754
Aujesky 2005c[107]	2005	USA	Markov model of 6 treatment strategies to	Patients with first idiopathic VTE.	Various. 4.419-	Various. $10,579-	Various depending on

Study	Year	Country(ies) where study was performed	Summary of model	Patient population	QALYs	Costs (2009 UK pounds unless stated)	ICER (per QALY gained, 2009 UK pounds)
			determine optimal duration and intensity of warfarin therapy	Male/female. Ages 40, 60 and 80 years considered.	17.551.	$34,252	strategies compared and population considered.
Dranitsaris 2006[103]	2005	Canada (health care system perspective)	Decision model based on CLOT RCT. Six months of either: (i) dalteparin (ii) dual dalteparin / warfarin	Cancer patients with newly diagnosed VTE, mean age 64 years.	(i) 0.33 (ii) 0.17	(i) £2182 (ii) £1050	£7073
Marchetti 2001[104]	2001	Italy (societal)	Cost-utility analysis, decision analytic model. Three months of either (i) enoxaparin (ii) dual LMWH / warfarin	Patients with DVT (20% with signs of PE), mean age 60, 15% with cancer, 20% had had a previous VTE.	(i) 13.039 (ii) 13.003	(i) £745 (ii) £550	£5427
Perlroth 2007[106]	2006	USA (societal)	Cost-utility analysis. Markov model incorporating an initial decision node where treatment could be escalated. Either: (i) heparin (ii) heparin + alteplase	Haemodynamically stable patients (systolic blood pressure >90nnHg) with submassive PE and right ventricular dysfunction, mean age not reported (mixed sources).	(i) 8.04 (ii) 7.99	(i) £27,137 (ii) £27,547	Intervention (i) was dominant, had 67% probability of cost-effectiveness at $50,000 / QALY threshold
Perez-de-Llano 2010[105]	2008	Spain (Spanish healthcare system)	Cost-consequence analysis based on open-label RCT. Six months of either: (i)	Symptomatic patients with confirmed acute PE, mean age 72 years.	Not reported	(i) £5,744 (ii) £5,368	NA

Study	Year	Country(ies) where study was performed	Summary of model	Patient population	QALYs	Costs (2009 UK pounds unless stated)	ICER (per QALY gained, 2009 UK pounds)
			tinzaparin or (ii) acenocoumarol + tinzaparin				

Note: Converted to 2009 UK pounds in NICE CG 144 using Purchasing Power Parities[8]

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)* or Philips et al. (2004)†. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

The quality assessment table suggested is completed in respect of the included studies in appendix 11, which is in section 10.11.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient group included is adults with an acute PE, to match the licensed indication[4], EINSTEIN-PE trial population (Table 9) and stated Decision Problem (chapter 5). Results are presented by patient group, defined by the duration of anticoagulation therapy appropriate (Table 10). The duration of therapy in EINSTEIN-PE was selected by clinicians for each patient to reflect the underlying risks arising from the nature of the index PE, characteristics of the patient and ongoing risk of recurrent VTE or bleeding. This approach is consistent with current clinical guidelines[9,11,27,29,50], including NICE CG144[8]. The characteristics of patients in EINSTEIN-PE and their index events were summarised in Table 9 and Table 10, in section 6.3.4.

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* Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

† Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

A lifelong treatment duration cohort has been included in this economic evaluation. This reflects recommendations in CG144 to `offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding'.[8] It is also consistent with recommendations made regarding the use of rivaroxaban in patients following DVT.[19] Estimates of the proportion of patients requiring continued treatment beyod one year are limited. However, consistent with TA261 it is anticipated that it represents a minority of patients.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

For patients initially treated for 3, 6 or 12 months the model was a Markov design comprising thirteen health and treatment states describing the management and complications of VTE, including:

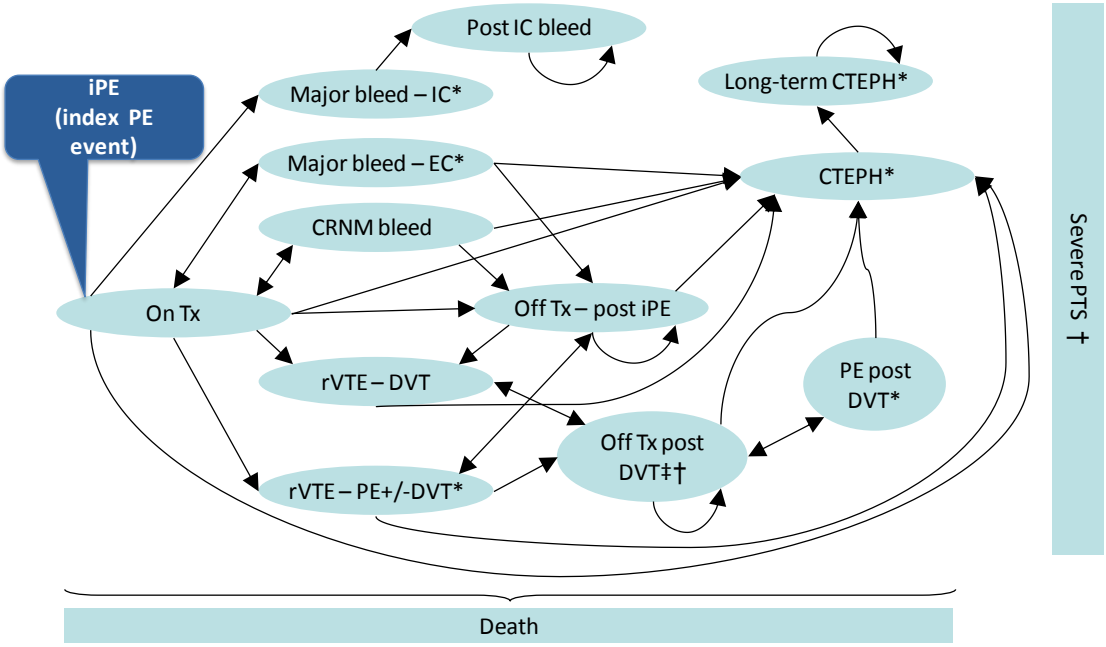
- On-treatment for index event;
- Two off-treatment states: off-treatment post index PE and off-treatment post DVT;
- Recurrent event: DVT, PE and PE post DVT;
- Acute bleeding states: extra-cranial (EC) major bleeds, intra-cranial (IC) major bleeds and clinical relevant non-major bleeds (CRNM)
- Long-term complications: CTEPH (initial diagnosis and longterm). Note PTS payoffs are calculated separately and not included as standalone states;
- Post-IC bleed (an absorbing state for all patients who experience an IC bleed);
- Death.

Patients enter the model following diagnosis of an acute PE event and receive treatment. Patients progress between states according to transition probabilities. Each health state is associated with a particular resource and utility weighting. Expected costs and outcomes are calculated across the cohorts according to the chosen treatment regimen.

All patients who experience a DVT within the timeframe of the model (ie after an index PE event) were considered at risk of PTS. The incidence of PTS was calculated outside of the Markov model with the consequences applied as costs and health related quality of life payoffs to patients in the off treatment post-DVT state.

The detailed model structure is shown in Figure 12.

Figure 12: Structure of the economic model



Notes: *Additional mortality; ‡ A proportion of patients with rPE also experience a symptomatic DVT (PTS risk); † At risk of PTS: cost applied to % patients in this state

Abbreviations: **On Tx**: On treatment; **Off Tx**: Off treatment; **rVTE**: recurrent VTE event; **DVT**: Deep vein thrombosis; **PE**: Pulmonary embolism; **PTS**: Post Thrombotic syndrome; **CTEPH**: Chronic thromboembolic pulmonary hypertension; **IC**: intracranial; **EC**: extracranial; **CRNM**: clinically relevant nonmajor

To evaluate lifelong treatment with rivaroxaban vs dual LMWH/VKA a number of modifications to the Markov model were necessary. In order to track patients at risk of PTS complications following an incident DVT the lifelong model included an additional state for “On treatment post-DVT”. From here patients may transit to recurrent VTE states, off treatment post-DVT, IC bleed and death.

Due to the memoryless nature of Markov models patients in this state do not transit through the EC bleed and minor bleed states. Instead, they are assigned pay-offs (disutilities and costs) associated with the likelihood of EC and CRNM bleeds for that cycle. The excess mortality associated with EC bleeds is accounted for within the “On treatment post-DVT “ state.Transitions out of “On treatment post-DVT” to the IC bleed state were included on the

basis that this is a complication associated with higher costs and worse outcomes than PTS (Table 43 and Table 51).

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Based on the review described in section 7.1 and following previous work[8,19], a Markov model was selected so as to allow flexibility in consideration of multiple treatment durations. The structure was designed to focus on costs and events that occurred during the treatment period, since it is the choice of anticoagulation treatment which is being evaluated. However, long term complications were included so that a life time horizon could be modelled, consistent with the NICE Reference Case.

The clinical pathway of care, discussed in section 2.5, involves initial anticoagulation treatment of the PE according to the clinical aspects of the case. During treatment, a patient may be subject to the risk of bleeding. Also, during treatment and subsequent to it, patients are at risk of a VTE recurring, which may be a DVT or a PE. Bleeds may be of varying severity. Bleeding and PE may be associated with excess mortality risk. CTEPH may emerge from PE, and this also attracts excess mortality. There is an underlying risk of PTS for those patients that experience a DVT.

This approach therefore captures clinically important stages of a patient's experience of PE in distinct states. With the assignment of costs and health related quality-of-life (HRQL) to these states, the structure ensures that financially and humanistically important consequences of PE are captured.

7.2.4 Please define what the health states in the model are meant to capture.

The model states referred to in Figure 12 are described in Table 26.

Table 26: Descriptions of modelled health states

Number	State name	Description
1	On tx	Patients who have just experienced an acute PE, and are receiving one of the acute treatments being evaluated (either 3, 6, 12 months or lifetime treatment with rivaroxaban or dual LMWH/VKA therapy)
2	rVTE – DVT	Patients who have just experienced a recurrent DVT. Assigned therapy was discontinued and all patients assumed to receive

Number	State name	Description
		6 months of dual LMWH/VKA. The duration of utility impact was assumed to be one month in the base case. DVT events were not associated with excess mortality.
3	rVTE – PE+/- DVT	Patients who have just experienced a recurrent PE. Patients with coincident DVT transit to a post-DVT state to capture PTS risk. Assigned therapy was discontinued and all patients assumed to receive 6 months of dual LMWH/VKA. The duration of utility impact was assumed to be one month in the base case. Pulmonary embolism events were associated with excess mortality.
4	Major bleed – IC	Patients on assigned therapy who have just experienced an intracranial bleeding event. Therapy was withheld during the cycle in which the intracranial bleeding event took place. Intracranial bleeding events were associated with excess mortality.
5	Major bleed – EC	Patients on assigned therapy who have just experienced a major extra-cranial bleeding event (e.g. gastrointestinal bleeds). Therapy was withheld during the cycle in which the bleeding event took place. The duration of utility impact was assumed to be one month in the base case.
6	CRNM bleed	Patients on assigned therapy who have just experienced a CRNM bleeding event. Defined as overt bleeding that did not meet the criteria for major bleeding but was associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of a study drug, or discomfort or impairment of activities of daily life. Therapy was temporarily withheld for 1 month during the cycle in which the bleeding event took place. An example of this would be spontaneous bleeding from gums which requires acute medical intervention. CRNM bleeding was assumed not to impact on utility.
7	Post IC bleed	Patients who previously experienced an IC bleeding event within the model. Any assigned therapy is assumed to stop. IC bleeds are associated with major risks of residual disability stemming from their impact on the central nervous system. The health related quality of life and costs associated with this are included.
8	Off Tx-post iPE	Patients currently off treatment after index PE. These patients are not at ongoing risk of PTS.
9	Off Tx Post DVT	Patients who have experienced an incident DVT within the time frame of the model and who are currently off treatment. These patients are at risk of PTS.
10	On treatment post-DVT	This state is only applicable to analyses of lifelong treatment duration. Patients who have experienced an incident DVT within the time frame of the model and who are currently on treatment. These patients are at risk of PTS.
11	PE post DVT	Patients with recurrent PE and a history of DVT within the

Number	State name	Description
		model. Survivors return to relevant post-DVT states so as to continue exposure to a risk of PTS conferred by their DVT history.
12	CTEPH	Patients diagnosed with CTEPH who are exposed to management costs, health related quality of life loss and excess mortality.
13	Long-term CTEPH	State to which patients with CTEPH transition longterm.
14	Death	Terminal state. Patients could die either due to events captured in the model such as PE or IC bleed, and could also die due to all-cause mortality.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Anticoagulation in the treatment of PE is associated with both a reduction in recurrent VTEs alongside the potential for increased risk of bleeding compared with no anticoagulation treatment. Disease progression was not modelled as DVT and PE are, for the majority of patients, an acute condition that is not categorized by severity. Bleeding does vary in severity, and this is captured in the model. Consequently, the model captures, in a sufficiently graduated manner, health states relevant to the potential risks and benefits of treatment.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

The required information is presented in Table 27.

Table 27: Key features of analysis.

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (assumed to be 40 years)	NICE Reference Case	NICE Methods Guide[65]
Cycle length	3 months	Appropriateness with reference to treatment duration and model horizon	NA
Half-cycle correction	Not applied	NA, with sufficiently short cycle length	NA
Were health effects measured in QALYs; if not, what was used?	Yes, QALYs	NICE Reference Case	NICE Methods Guide[65]
Discount of 3.5% for utilities and costs	Yes, 3.5% pa discounting	NICE Reference Case	NICE Methods Guide[65]
Perspective (NHS/PSS)	Yes, NHS/PSS	NICE Reference Case	NICE Methods Guide[65]
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The analysis compares the following treatment strategies delivered over 3, 6 or 12 months or lifetime:

- Rivaroxaban (Xarelto®) according to its licence for PE treatment: 15 mg bid for 21 days followed by 20 mg od for the remaining duration of anticoagulation treatment[4]
- Dual therapy LMWH and VKA. LMWH therapy is continued at UK licensed dose until the INR is at least 2.0 or until therapeutic anticoagulation has been established. VKA overlaps with LMWH and is continued for the full duration of anticoagulation treatment.[8]

There are three LMWH treatments licensed for treatment of DVT or PE: Fragmin® (dalteparin sodium), Clexane® (enoxaparin sodium), and Innohep® (tinzaparin sodium). The Patient Information Leaflets refer to the possibility of patient self-administration.[108-110] [redacted][67] On the basis that enoxaparin has dominant market share in England and Wales among LMWHs used for VTE treatment, may be used for nurse or self-administration, and was also the LMWH used in the trial, we use the daily cost of Clexane® (enoxaparin) as the LMWH in the cost-effectiveness evaluation, for which a dose of 1.5 mg/kg od is indicated in the UK, eg 120 mg od for an individual of 80 kg.[97]

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

As noted in CG144 `there are no valid and reliable tools to accurately predict risk of bleeding or VTE recurrence', therefore no clinical continuation rule is assumed. The periods of anticoagulation considered are the intended treatment durations from EINSTEIN-PE (reflecting physician judgement) or lifelong treatment.

7.3 Clinical parameters and variables

7.3.1 Please demonstrate how the clinical data were implemented into the model.

We consider here model inputs relating to:

- Probability of recurrent VTE whilst on treatment
- Probability of major bleeding whilst on treatment
- Probability of CRNM bleeding whilst on treatment
- Discontinuation
- Probability of VTE after treatment cessation
- Probability of CTEPH
- Probability of PTS
- Risk of mortality for the patient population, associated with age
- Risk of mortality on treatment associated with particular model events

Probability of recurrent VTE whilst on treatment

Probabilities for treatment up to 12 months

The assumed probabilities of recurrent VTEs occurring in the LMWH/VKA arm are given in Table 28 and were taken directly from trial data. Probabilities are presented for each of the intended treatment duration subgroups included in EINSTEIN-PE. Data for the 12-month population was also used to model events over the first 12 months of therapy for patients receiving lifelong treatment.

Table 28: Probability of a VTE in patients on LMWH/VKA

Patient group (treatment duration) and period	Base case	Upper	Lower	alpha	beta
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifelong Ongoing rate	0.7%	1.1%	0.3%	N/A	N/A

Source: EINSTEIN-PE CSR[73] . Parameters alpha and beta are to inform a Beta distribution in all cases apart from lifelong treatment where a LogNormal distribution was used.

The probability of a recurrent VTE in the rivaroxaban arm is calculated by applying the appropriate treatment effect to the probability of recurrent VTE in the LMWH/VKA arm. The following formula was used, which accounts for the fact that the model inputs are probabilities/risks rather than rates of VTE occurrence:

$$Risk_{RIV} = 1 - (1 - Risk_{LMWH/VKA})^{HR}$$

where:

- $Risk_{LMWH/VKA}$ is the risk of recurrent VTE in the LMWH/VKA arm for a particular patient group and time period (Table 28);
- HR is the hazard ratio, specifically 1.123 (95% CI 0.749 to 1.684) – see also section 6.5.3[13,73];
- $Risk_{RIV}$ is the risk of recurrent VTE in the rivaroxaban arm for that patient group and time period.

The treatment effect used is from the whole study following the approach judged appropriate for the evaluation of rivaroxaban for DVT treatment, which was based on an economic model and clinical trial of similar design to those considered in the DVT treatment appraisal.[19] The probability that a recurrent

VTE is a DVT (conditional on one occurring) was assumed to be 37.2%, on the basis of 35 of 94 VTEs being DVTs without PEs in EINSTEIN-PE.[73]

To inform transitions to states associated with a risk of PTS the model includes the probability of a recurrent PE occuring with a symptomatic DVT. On the basis that 2 of the 59 recurrent PE events in EINSTEIN-PE were coincident with DVTs, 3.4% of recurrent PEs were assumed to be coincident with a recurrent DVT (Table 15).[73]

Probabilities for lifelong treatment (beyond first 12 months)

The evidence available regarding the risk of recurrent VTE whilst receiving VKA treatment for periods of greater than one year is limited. A systematic review was conducted with the broad objective to identify trial-based and observational literature providing evidence on rates of recurrent VTE in patient populations with index DVTs, PEs, or VTEs generally who experienced treatment durations greater than one year. Literature searches were first conducted in March 2010 on the MEDLINE, EMBASE, and Cochrane Library literature databases followed by updates in July 2011 and May 2012. In total, before de-duplication, 18,029 potentially relevant studies were identified. Following title, abstract and full-text review, 3 studies were included reporting recurrent VTE event rates in patients on long-term treatment (see Table 29).[111-113] These three studies were meta-analysed by Streiff et al.[114]

Table 29: PRISMA-type study flow for systematic review of recurrent VTE with treated durations greater than one year

	Original	Update July 2011	Update May 2012
Database search hits	15,318	1,477	1,234
Less: duplicates	5,145	370	196
Available for title/abstract review	10,173	1,107	1,038
Less: excluded	9,962	1,049	1,006
Available for full-text review (studies of any duration)	211	58	32
Less: excluded	114	45	23
Plus: articles identified from reference lists	10	9	3
Final included studies (> 1 year treatment duration)	3	0	0
Combined included studies	3		

Source: Table 2 from systematic review report[115]

The objective of the Streiff review was to evaluate the evidence on the optimal duration of VKA therapy for VTE by identifying randomized controlled trials and summarizing event rates.

Although there was heterogeneity across the three studies, limitations with the available evidence base indicate this to be the most robust evidence source available. This paper was therefore used to support assumptions for long-term outcomes amongst a group of patients receiving lifelong VKA treatment.

The review found that the ongoing risk of recurrent VTE after 4-12 months of anticoagulation was 7.9 (95% CI: 5.2 to 10) events per 100 patient-year and that this reduced to 0.7 (95% CI: 0.3 to 1.1) events with ongoing warfarin treatment (target INR 2-3).

Using this data produces rates of VTE recurrence similar to those which may be derived from assumptions adopted for an economic model in the NICE guideline on management of venous thromboembolic diseases.[8] This model assumes an ongoing rate of 6.0 VTEs per 100 patient-years without anticoagulation and a relative risk of anticoagulation vs no treatment of 0.09. This equates to a rate on treatment of 0.5 events per 100 patient-years, similar to the rate of 0.7 (95% CI 0.3 to 1.1) events per 100 patient-years identified in the Streiff review.[114]

Probability of major bleeding whilst on treatment

Probabilities for treatment up to 12 months

The assumed probabilities of major bleeding of any type occurring in the LMWH/VKA arm are given in Table 30 and were taken directly from trial data. Probabilities are presented for each of the intended treatment durations included in EINSTEIN-PE. Data for the 12-month population was also used to model events over the first 12 months of therapy for patients receiving lifelong treatment.

Table 30: Probability of major bleeds in LMWH/VKA arm of the EINSTEIN-PE trial

Patient group (treatment duration) and period	Base case	Upper	Lower	alpha	beta
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifelong					
Ongoing rate	1.6	2.7	0.5		

Source: EINSTEIN-PE CSR.[73] Parameters alpha and beta are to inform a Beta distribution in all cases apart from lifelong treatment where a LogNormal distribution was used.

The probability of a major bleed in the Xarelto® (rivaroxaban) arm is calculated by applying the appropriate whole trial population treatment effect to the probability of major bleed in the LMWH/VKA arm. The following formula was used, which accounts for the fact that the model inputs required are probabilities/risks rather than rates of occurrence:

$$Risk_{RIV} = 1 - (1 - Risk_{LMWH/VKA})^{HR}$$

where:

- $Risk_{LMWH/VKA}$ is the risk of major bleeding in the LMWH/VKA arm for a particular patient group and time period (Table 16);

- HR is the hazard ratio, specifically 0.493 (95% CI 0.308 to 0.789)[13,73] – see also section 6.5.3, Figure 9); and
- $Risk_{RIV}$ is the risk of major bleeding in the Xarelto® (rivaroxaban) arm for that patient group and time period.

The probability that a major bleeding event is an IC bleed (conditional on one occurring) was assumed to be [redacted] on the basis of [redacted] of the 68 major bleeding events which occurred during EINSTEIN-PE being IC bleeding events. The remainder of bleeds were taken to be EC.

Probabilities for lifelong treatment (beyond first 12 months)

The evidence available regarding the risk of major bleeding whilst receiving VKA treatment for periods of greater than one year is limited. The aformentioned systematic literature review identified three studies reporting the risk of major bleeding. These were meta-analysed by Streiff et al, which found that, without further anticoagulation the risk of major bleeding was estimated at 0.3 (95% CI: 0-0.5) per 100 patient years, but 1.6 (95% CI: 0.5-2.7) per 100 patient years with continuous warfarin.[114]

Probability of CRNM bleeding whilst on treatment

Probabilities for treatment up to 12 months

The assumed probabilities of CRNM bleeding of any type occurring in the LMWH/VKA arm are given in Table 31 and were taken directly from trial data. Probabilities are presented for each population and treatment group.

Table 31: Probability of CRNM bleeds in LMWH/VKA arm of the EINSTEIN-PE trial

Patient group (treatment duration) and period	Base case	Upper	Lower	alpha	beta
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: EINSTEIN-PE CSR.[73] Parameters alpha and beta are to inform a Beta distribution in all cases.

The probability of a CRNM bleed in the Xarelto® (rivaroxaban) arm is calculated by applying the appropriate whole trial population treatment effect to the probability of CRNM bleed in the LMWH/VKA arm. In this instance, a risk ratio was used rather than a hazard ratio, as hazard ratios were not available or specified in the trial statistical analysis plan. The following formula was used:

$$Risk_{RIV} = RR \times Risk_{LMWH/VKA}$$

where:

- $Risk_{LMWH/VKA}$ is the risk of a CRNM bleed in the LMWH/VKA arm for a particular patient group and time period (Table 31);
- RR is the risk ratio, specifically 1.001 (95% CI 0.842 to 1.191)[13,73] – see also section 6.5.3
- RiskRIV is the risk of a CRNM bleed in the Xarelto® (rivaroxaban) arm for that patient group and time period.

Probabilities for lifelong treatment (beyond first 12 months)

Limited information regarding CRNM bleeding in patients requiring lifelong VKA treatment was available from the Streiff meta-analysis.[114] Therefore, the long-term rate of CRNM bleeding on treatment was assumed to be that experienced in the final six months of all patients in the EINSTEIN-PE trial [redacted].

Discontinuation

Probabilities for treatment up to 12 months

Discontinuation in EINSTEIN-PE, which was described in detail in sections 6.3.8 and 6.5.3 and was similar between treatment arms. Consequently, we assume no difference in risk of discontinuation between rivaroxaban and LMWH/VKA.

This is a conservative assumption, because, as described in section 4.1.1 there are significant challenges with use of LMWH and warfarin and substantial potential advantage with rivaroxaban. Consequently real-world use of LMWH/warfarin may be associated with greater discontinuation than assumed here based on data from a selected trial population treated according to protocol. Treatment satisfaction amongst patients with DVT treated with rivaroxaban has been shown to be higher than with LMWH/VKA, as has treatment satisfaction in patients with PE treated with rivaroxaban.[15,17,75]

In terms of determining a model input, we judged the following reasons for discontinuation to be relevant: non compliant with study medication, protocol violation, patient convenience, switch to commercial drug, insufficient therapeutic effect, and adverse events (non-bleeding).

[redacted]

This compares with a trial by Monkman et al which found voluntary discontinuation occurred in 0.9% of VTE patients in the first three months of VKA treatment.[116]

Patients who experience bleeding whilst on anticoagulation treatment are all assumed to discontinue treatment at least temporarily. The temporary

discontinuation is assumed to be for one month in the case of non-major bleeds and three months in the case of major bleeds. (This temporary discontinuation is handled in the model without a transition from the relevant bleeding state, and is reflected in cost calculations.) Permanent discontinuation may then occur, depending on the severity of the bleeding event according to assumptions stated in Table 32, which were informed by data reported in the CSR and advice from Bayer clinicians. Permanent discontinuation is applied in the subsequent cycle.

Table 32: Probability of permanent discontinuation (per 3 month cycle)

Patient / bleeding type	Point estimate	Sensitivity range	
		Lower	Upper
Patients with IC bleeds*	[redacted]	[redacted]	[redacted]
Patients with major EC bleeds	[redacted]	[redacted]	[redacted]
Patients with CRNM bleeds	[redacted]	[redacted]	[redacted]
For any other reason (general)	[redacted]	[redacted]	[redacted]

Source: EINSTEIN-PE CSR[73], * advice from Bayer clinicians

Probabilities for lifelong treatment (beyond first 12 months)

The value of any treatment intended for lifelong usage depends critically on the persistence and adherence of patients to such a regime. To model the benefits and costs associated with rivaroxaban lifelong treatment, an assumption is required in relation to patients' longer-term persistence with rivaroxaban.

It was considered that such an assumption would be better informed by real-life, longer term observational data rather than trial data, as trial data may be biased towards reflecting the short-term experience of patients motivated to participate in a trial. As there was known to be limited data in relation to rivaroxaban, an analogue approach was taken to capture evidence from long-term observational studies of discontinuation and persistence in other preventive cardiovascular medication. A brief review of the recent literature was carried out which focused on persistence for periods longer than 1 year. A limited number of relevant papers were identified and are summarised in Table 33.[117-130]

Table 33: Patient adherence to preventative cardiovascular medication

Study	Country	Description	Persistence data	Comment on applicability
Boggon et al. 2011[117]	UK	UK database linkage study of the Myocardial Ischaemia National Audit Project (MINIP) registry, General Practice Research Database (GPRD), Hospital Episode Statistics (HES) and death certificates. 7,543 patients were included in the study.	Proportion of patients at 12 months on: Clopidogrel; 53% in nSTEMI patients and 54% in STEMI patients. Statins: 84% in nSTEMI and 89% in STEMI patients.	UK study, Time horizon greater than EINSTEIN-PE. Secondary prevention study. Relatively low (conservative) statin discontinuation rate.
Carey et al. 2012[118]	UK	Analysis of initiation and continuation of the use of statins in 9,367 patients having a first MI from the UK primary care database DIN-LINK	Point prevalance of statin use: 85% at 3 months 80% at one year 76% by year five onwards	UK study, Time horizon greater than EINSTEIN-PE. Acute event study. Less conservative discontinuation rate.
Donnelly et al. 2008[121]	UK	Retrospective study of 6462 patients with diabetes who were resident in Tayside, Scotland from 1989 – 2003 to determine the patterns and predictors of long-term adherence to statin therapy	Adherence to statins after 13 years was less than 65%	Includes primary prevention
Gislason et al. 2006[122]	Denmark	Database study of 55,315 patients with first AMI between 1995 and 2002 surviving longer than 30 days after discharge from linked nationwide administrative registers	Statin persistence at: 1 year: 85% years: 80% 5 years: 82%	Non-UK study. Secondary prevention, conservative discontinuation rates.
Glader et al. 2010[123]	Sweden	Database study of a 1 year cohort (21,077 survivors) from the Swedish Stroke Register linked to the Prescribed drug Register	Persistence at 2 years on: Statins: 56.1% Warfarin: 45%	Non-UK. Secondary prevention, high discontinuation rate so non-conservative

Study	Country	Description	Persistence data	Comment on applicability
Gomes et al. 2012[124]	Canada	Population based cohort study of Ontario residents with atrial fibrillation 66 years or older newly treated with warafrin.	Discontinuation of warfarin at: 1 year: 31.8% years 43.2% 5 years 61.3%	Non-acute event study, non-UK. High discontinuation rate, so non-conservative
Kneeland et al. 2010[126]	N/A	Review of the determinants of adherence and persistence on long-term anticoagulant therapy for atrial fibrillation and venous thromboembolism.	Persistence data presented from the ATRIA study which is an RCT: Discontinuation at 2.7 years: 33%	Review concentrating on risk factors for warfarin discontinuation.
Latry et al. 2011[127]	France	Corhort study using data from the main French national health insurance reimbursement database. 16,397 patients newly treated with statins were followed for 15 months.	Adherence to statins at 15 months varied between 44%to 59% depending on cardiovascular risk factors	Non-acute event study, non-UK. High discontinuation rate, so non-conservative
Simons et al. 2011[130]	Australia	Australia-wide Pharmaceutical Benefits Scheme claims analysis of statins in a 10% random population sample from April2005 to March 2010	Median persistence times to statins: Total population: 11 months 65-74 year olds: 19 months <55 year olds: 3-6 months	Non-acute event study, non-UK. High discontinuation rate, so non-conservative
Chang et al. 2011[119]	US	Prospective cohort study of 2,103 patients over the age of 65 years enrolled in a pharmacy benefits program in 1999 and 2000 after hospital discharge for myocardial infarction	The mean percentage of days covered for adherence to ACEIs/ARBs, β-blockers, and statins at 36 months was 50% to 60% for all three medication classes.	Non-UK. High discontinuation rate, so non-conservative

Study	Country	Description	Persistence data	Comment on applicability
Shah et al. 2009[129]	US	Prospective cohort study following 292 subjects with incident MI for an average of 52+/- 31 months.	3-year medication continuation rates: Stains: 44% Beta-blockers: 48% Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers: 43%	Non-UK. High discontinuation rate, so non-conservative.
Chodick, et al. 2008[120]	Israel	Retrospective cohort study using data from 229,918 adult enrollees of a not-for-profit health maintenance organization and from death certificates in Israel. Eligible patients initiated statin treatment between 1998 and 2006	Persistence at 2 years in patients with: Cardiovascular disease :45% Coronary artery disease: 59%	Includes primary prevention, non-UK. High discontinuation rate, so non-conservative.
Helin-Salmivaara et al. 2008[125]	Finland	Nationwide drug reimbursement registry study of persistence among new users of statins between 1995 December 31, 2005, in Finland .	10 year statin persistence: 44%	Includes primary prevention, non-UK. High discontinuation rate so non-conservative
Mantel-Teeuwisse et al. 2004[128]	Netherlands	8,335 new ly initiated statin users between 1998 and 2002 from the PHARMO medical record linkage system were assessed for persistence for at least two years	Patients persistent for primary prevention at 2 years: 48%	Includes primary prevention, non-UK. High discontinuation rate so non-conservative

Most of the studies identified were non-UK and focused on or included primary prevention (dissimilar to secondary prevention in VTE management). In all but the four studies discussed below[117,118,121,122] the persistence rates were very low. Only three studies were identified which originated in the UK; two database linkage studies and one retrospective database study.[117,118,121]

Donnelly was a retrospective study of patients with diabetes who were resident in Tayside Scotland from 1 January 1989 to 31 May 2003 and initiated statin treatment during that time. The main outcome measure was percentage of days covered (PDC) by a statin, calculated at regular intervals. In the first year, the mean PDCs were 87% and 61% in the first and second quarters, respectively, and 65% after 13 years. Less than 50% of patients maintained a PDC of > 80% after 13 years.[121]

Boggon et al was a UK database linkage study of the Myocardial Ischaemia National Audit Project (MINIP) registry, General Practice Research Database (GPRD), Hospital Episode Statistics (HES) and death certificates. Its focus was to examine the levels of clopidogrel prescribing in patients discharged from hospital after acute myocardial infarction (MI). It also compared discontinuation in clopidogrel and statin use over time between ST elevation MI (STEMI) and non-ST elevation MI (nSTEMI) patients. There were 7,543 linked patients included in the study. It found that, despite guideline recommendations for continued use for at least 12 months, the proportion of patients still prescribed clopidogrel at 12 months was 53% in nSTEMI patients and 54% in STEMI patients. Statin prescribing was 84% in nSTEMI and 89% in STEMI patients.[117]

Carey et al was an analysis of predictors of initiation and continuation of the use of statins in 9,367 patients having a first MI from the UK primary care database DIN-LINK.[118] Among patients who were prescribed a statin within 6 months of the MI, the point prevalence (patient has a valid prescription on the day) was 85% at 3 months, 80% at one year and 76% by year five onwards. Good coverage (indicating that >=80% of the previous 365 days were covered by a statin prescription) was generally about five percentage points lower. At one year, 70% had good coverage.

There are various limitations in using these data to model the discontinuation of lifelong PE treatment, including the different disease areas and treatments considered, and various outcome measures employed. The data are valuable

in that they reflect real-life persistence. The follow-up periods are not as long as would be ideal, but it was considered that there are sufficient similarities to the setting of this technology appraisal for these studies to provide reasonable analogues.

Whilst Donnelly[121] provided long-term data it was a non-acute event study so was deemed less respresentative than Boggon or Carey[117,118] and its higher rates non-conservative. The statin persistence levels in Boggon et al were approximately equivalent to a 3-month discontinuation probability of 3.6%.[117] The one year prevalence and good coverage statistics in Carey et al were equivalent to a 3-month discontinuation probability of approximately 6.9%.[118] The large (>55,000 patients) study by Gislason[122] provided comparable statin persistence rates one year after an acute event to Boggon[117] (85% vs 84% respectively) but originated in Denmark.

Consequently, beyond the initial 12 month treatment period, the UK conservative assumption of 3.6% discontinuation per 3 month timestep from Boggon et al was adopted. Sensitivity analyses on this parameter were conducted on the basis that the 95% CI was 1.9% to 6.9%. Although persistence with rivaroxaban may be higher than with warfarin due to its convenience as reflected in greater treatment satisfaction, no differential effect was assumed between treatment arms in the model in order to provide a conservative estimate of incremental QALYs.

Probability of VTE after treatment cessation

A systematic review was conducted with the broad objective to identify trial-based and observational literature providing evidence on rates of recurrent VTE in patient populations with index DVTs, PEs, or VTEs generally. Literature searches were first conducted in March 2010 on the MEDLINE, EMBASE, and Cochrane Library literature databases followed by updates in July 2011 and May 2012. In total, before de-duplication, 18,029 potentially relevant studies were identified. Following title, abstract and full-text review in comparison with pre-defined but fairly permissive inclusion/exclusion criteria, 141 studies were included (Table 34).

Table 34: PRISMA-type study flow for systematic review of VTE recurrence

	Original	Update July 2011	Update May 2012
Database search hits	15,318	1,477	1,234
Less: duplicates	5,145	370	196
Available for title/abstract review	10,173	1,107	1,038
Less: excluded	9,962	1,049	1,006
Available for full-text review	211	58	32
Less: excluded	114	45	23
Plus: articles identified from reference lists	10	9	3
Final included studies	107	22	12
Combined included studies	141		

Source: Table 2 from systematic review report[115]

Of the 141 included publications, 93 publications considered follow-up of one year or less and a further 31 considered follow-up of no more than five years. This left 17 publications which considered studies of longer follow-up:

- Three publications involving the investigator Prandoni and a cohort of 1626 patients with clinically symptomatic proximal DVT and/or PE from centres based at the University of Padua, Italy, who were initially treated with anticoagulation (Prandoni cohort). The most recent and comprehensive publication dated from 2007.[30]
- Ten publications involving the investigator Eichinger and a cohort of 929 patients with a first VTE from four thrombosis centres in Vienna, Austria, who had completed at least 3 months of anticoagulation treatment (Vienna cohort). The most recent and comprehensive publication dated from 2010 and included a risk prediction model.[31]
- Two studies which did not report outcomes in the format required.[131,132]
- One study of PE patients only, but of short duration (3.2 years mean follow-up).[133]
- One study from Andresen which considered recurrence for VTE patients up to 10 years however the sample size (n=323) was smaller than either Prandoni or Eichinger [134]

The Prandoni and Vienna cohorts produced similar long-term rates of recurrent VTE, shown in Table 35. However, the Prandoni cohort contained more patients (1626 vs 929) with longer median follow-up (50 vs 43.3 months) than the Vienna, so was used to provide inputs for the model.

The three month probability of VTE after initial anticoagulation treatment, r, was calculated as

$$r = 1 – (1 – p_{10}) \wedge [3/(10x12)]$$

where p_{10} was the 10 year risk. This gives a value of 1.26% (95% CI 1.09% to 1.46%).

Table 35: Risk of recurrent VTE (%, 95% CI) from two long-term cohort studies

Cohort	No. of patients	Timepoint	Risk (%)	95% CI (%)
Prandoni[30]	1626	1 year	11.0	(9.5, 12.5)
		10 years	39.9	(35.4, 44.4)
Vienna[31]	929	2 years	24.6	(21.6, 28.9)
		10 years	31.8	(27.6, 37.4)

Probability of CTEPH

A systematic review was conducted with the broad objective to identify trial-based and observational literature providing evidence on rates of incidence of complications of VTEs, including CTEPH and PTS, in patient populations with index DVTs, PEs, or VTEs generally. Literature searches were first conducted in March 2010 on the MEDLINE, EMBASE, and Cochrane Library literature databases followed by updates in July 2011 and May 2012. In total, before de-duplication, 4655 potentially relevant studies were identified. Following title, abstract and full-text review in comparison with pre-defined inclusion/exclusion criteria, 55 studies were included, among which, four considered incidence of CTEPH (Table 37).[135-138]

Table 36: PRISMA-type study flow for systematic review of complications of VTEs

	Original	Update July 2011	Update May 2012
Database search hits	3429	424	802
Less: duplicates	3288	97	44
Available for title/abstract review	141	327	758
Less: excluded	25	319	749
Available for full-text review	116	8	9
Less: excluded	93	7	0
Plus: articles identified from reference lists	12	6	4
Final included studies	35	7	13
Combined included studies	55		

Source: Table 36 from systematic review report[115]

Due to competing risks, differences in follow-up periods and absence of results in sufficient detail, it was not considered appropriate to attempt to meta-analyse incidence rates from these studies. Miniati et al reported that among 320 patients with confirmed PE, four subsequently developed CTEPH over a median follow-up of 2.1 years.[135] This is the largest study identified and provided an intermediate estimate of CTEPH incidence (Table 37) so this was the source chosen for use in the model.

Table 37: Incidence of CTEPH from four long-term cohort studies

Cohort	No. of patients	Median follow-up period (years)	CTEPH incidence	
			Point estimate	95% CI
Miniati 2006[135]	320	2.1	1.25%	(0.03%, 2.46%)
Poli 2010[137]	239	3	0.4%	(0.0%, 2.7%)
Surie 2010[138]	110	3	2.7%	(0.6%, 7.8%)
Pengo 2004[136]	223	2	3.8 %	(1.1%, 6.5%)

Within the model patients are exposed to a risk of CTEPH following the index PE (all patients) and also following recurrent PE (recurrent patients only). The cumulative risk of CTEPH from Miniati et al was converted into a constant risk applied in each cycle within the first two years following the index PE event such that 1.25% (95% CI 0.03% to 2.46%) of PEs would progress to CTEPH in this period.[135] For those patients who experience a recurrent PE, it was

assumed that 1.25% (95% CI 0.03% to 2.46%) of PEs would progress to CTEPH.

Probability of PTS

The systematic review described above in the determining incidence of CTEPH was also designed to identify studies for the incidence of PTS. Of the 55 studies included in that review, 41 provided data on incidence of PTS. Among these studies, the longest and most robust prospective cohort studies were described in two papers authored by Prandoni et al.[139,140]

As PTS occurs in patients with a history of DVT, it is important to track in the model those patients within the cohort who experience – or have experienced – a DVT. Whilst the number of patients in EINSTEIN-PE whose index PE was coincident with a DVT is known (24.8%, Table 9) and the number of patients who had previously experienced a VTE is also known (19.5%, Table 9), the number of patients who had ever experienced a DVT (either coincident or prior to the index event) is not. As a consequence, and without introducing any bias, it was decided to only model the impact of PTS associated with newly incident DVTs within the model. This was achieved through inclusion of a post-DVT state (Table 26). PTS patients were considered to represent 8.1% of patients within the state based upon the 5-year risk of severe PTS from Prandoni.[140] This is a simplified approach to capturing the risk of PTS. With a number of minor limitations, such as not reflecting the changing risk of PTS over time and exclusion of PTS costs when patients exit the post-DVT state. Patients are unable to transit from the post-DVT state to minor or EC bleeds but can move to the IC bleed state.

Accounting for differences in the risk of PTS over time for events downstream of the index event would require additional computational burden (numerous additional Markov states or a microsimulation approach). Such complexity was considered unwarranted in light of the objective of this evaluation and minimal difference in DVT events (and therefore PTS risk) between treatment arms. Furthermore, most PTS occurs within 1 year of event.[140] This approach assumes that PTS occurs 3 months following the event. These assumptions lead to a small over estimation of the risk of PTS, however, given that rivaroxaban is associated with a marginally greater risk of recurrent VTE (non-significant), this is a conservative assumption.

Risk of mortality for the patient population, associated with age

The general underlying risk of mortality was modelled using a cohort life table generated from the mortality assumptions underlying the 2008-2010 Interim life tables for England and Wales combined.[141] The mortality for each year of the pharmacoeconomic evaluation was calculated according to baseline patient characteristics in EINSTEIN-PE, specifically:

- the age of the cohort at the start of that year was 58 years, the mean age at baseline in EINSTEIN-PE;
- the proportion of patients of each gender was 52.9% male and 47.1% female, again reflecting the EINSTEIN-PE trial population.

Risk of mortality associated with particular model events

In addition to the general risk of mortality associated with this patient population and age, the pharmacoeconomic model accounts for additional risks of mortality in respect of specific events. The inputs and their rationale are discussed below and summarised with other model inputs in Table 40.

A systematic review was conducted with the broad objective to identify trial-based and observational literature providing evidence on rates of mortality associated with DVTs, PEs, bleeding, PTS, CTEPH, and other complications of VTE in patient populations with index DVTs, PEs, or VTEs generally. Literature searches were first conducted in April 2010 on the MEDLINE, EMBASE, Econ Lit, and Cochrane Library literature databases followed by updates in July 2011 and May 2012. In total, before de-duplication, 2974 potentially relevant studies were identified. Following title, abstract and full-text review in comparison with pre-defined inclusion/exclusion criteria, 27 studies were included (Table 38).

Table 38: PRISMA-type study flow for systematic review of case fatality

	Original	Update July 2011	Update May 2012
Database search hits	2436	319	219
Less: duplicates	1081	123	25
Available for title/abstract review	1355	196	194
Less: excluded	1286	181	187
Available for full-text review	69	15	7
Less: excluded	64	9	2
Plus: articles identified from reference lists	4	2	5
Final included studies	9	8	10
Combined included studies	27		

Source: Table 23 from systematic review report[115]

Within the included studies was a 2010 systematic review of mortality from VTE trials by Carrier et al[142], several individual VTE trials reporting mortality associated with bleeding and recurrent VTEs, a study of survival with CTEPH[143], and two relevant analyses of the RIETE database[144,145]. In addition to these included studies (and not previously found due to indexing issues), a more recent systematic review by Linkins et al[146] provided evidence on mortality associated with bleeding. Due to the availability of published reviews and meta-analyses, notably Linkins et al[146], the individual trials identified were not considered further.

Mortality associated with VTE

In assessing mortality during the acute phase of treatment, trial-based data on VTE case-fatality was considered most suitable with a preference given to EINSTEIN trials (DVT and PE) as most reflective of the modelled patient population. Epidemiological studies identified variously suffered limitations which included:

- lack of stratification of patients by nature of index VTE (ie DVT or PE);
- lack of validity in the attribution of cause of death – by contrast, trials typically require autopsies and provide standardised recording;

- entry criteria of patients to the RIETE database studies requiring prior objective testing of patients[144,145], and through this, the potential for missing sudden, relevant deaths.

There were relatively few PEs in either EINSTEIN-DVT or EINSTEIN-PE and even fewer deaths potentially attributable to PE (Table 17). The base case assumption was that 25.0% of PEs occurring in the treatment phase would lead to death (95% CI 17% to 33%), based on 28 deaths occurring across treatment arms in both EINSTEIN-DVT and EINSTEIN-PE, either attributed to PE or for which PE could not be ruled-out as an underlying cause, in comparison with 112 fatal or non-fatal PEs.

The study used to provide the model inputs in relation to the rate of VTE recurrence also presented information on the incidence of mortality among patients with recurrent PEs.[30] This study reported 43 deaths among 130 patients with an index VTE who had then experienced a recurrent PE. The pharmacoeconomic evaluation therefore assumes a case-fatality of PEs outside the acute treatment phase of 33.1% (95% CI 25.0% to 41.2%).

Mortality associated with bleeding

The most reliable data reflective of the modelled population in relation to deaths associated with bleeding was judged to arise from a review by Linkins et al.[146] This review, published in 2010, included 23 518 patients and 39 randomised controlled trials involving VKA treatment for at least 6 months, including 11 trials of VTE patients specifically. The authors found that the proportion of bleed that were fatal did not differ significantly by indication. Of 188 IC bleeds, 82 (43.6%) were fatal; and of 689 major EC bleeds, 27 (3.9%) were fatal. This equates to 95% CI of 36.5% to 50.7% and 2.5% to 5.4% respectively

This review and meta-analysis were consistent with results from a separate review on the incidence of intracranial bleeding and case fatality. Van Asch et al found a median case fatality at 1 month of 40·4% (range 13·1% to 61·0%) for 26 study populations in 35 time periods and 54.7% (range 46.0% to 63.6%) after one year in the subset of ten studies which reported that outcome and timepoint. Changes over time and age were not statistically significant.[147]

Mortality associated with CTEPH

The study which considered survival of patients with CTEPH, a category of pulmonary hypertension (PH), was an analysis of registry data from a UK specialist centre for the PH treatment.[143,148] The study prospectively included all patients diagnosed with CTEPH at that centre between 1 January 2001 and 30 June 2006.The preferred treatment for CTEPH is surgical disobliteration of the pulmonary arteries by pulmonary endarterectomy (PEA). Condliffe et al report a perioperative mortality of 5 to 10% in experienced centres, but there are significant improvements in pulmonary haemodynamics and self-reported functional class.[143] Three year survival of 70% was reported in the 148 non-surgical patients, 76% in the 321 surgical patients, and 74% in the 469 patients overall (i.e. 26% mortality in three years). This overall three year survival figure is equivalent to a 3 month mortality risk of 2.48% (95% CI 2.05% to 2.93%), which was used in the pharmacoeconomic evaluation.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The probabilities quoted in section 7.3.1 relate to the three month cycle length or one-off events as appropriate. No further transformations are required.

In order to reflect the change in risk patients face over time the model operates with four transition matrices, which cover the time periods described in Table 39. Each transition matrix used is visible within the economic model.

Table 39: Relationship between transition matrices and model cycles

Cycle(s)	Time period (months)	Transition matrix
1	0 – 3	1
2	3 – 6	2
3 & 4	6 – 12	3
5 onwards	Subsequent	4, 5, 6 and Subsequent

- When evaluating 3 months of treatment to patients requiring this duration of treatment, transition matrix 1 is specific to each treatment arm, and other transition matrices are common to both treatment arms.
- When evaluating 6 months of treatment to patients requiring this duration of treatment, transition matrices 1 and 2 are specific to each treatment arm, and other transition matrices are common to both treatment arms.

- When evaluating 12 months of treatment to patients requiring this duration of treatment, transition matrices 1-3 are specific to each treatment arm, and other transition matrices are common to both treatment arms.
- When evaluating lifelong treatment to patients requiring this duration of treatment, all transition matrices (1 – 6 and 'Subsequent') are specific to each treatment arm.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The transition probabilities vary over time to the extent described in section 7.3.2. This approach is designed to reflect a reasonable description of the natural history of the disease and the effect of rivaroxaban during 3, 6, or 12 months of treatment to patients requiring these durations.[30] Insufficient evidence is available to inform the extent to which transition probabilities for lifelong treatment patients should vary after the first 12 months of treatment.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

There was no linking of one set of outcomes to another, save for the assignment of utility values to model states for the calculation of QALYs.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[*]:

- the criteria for selecting the experts
- the number of experts approached

[*] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical parameters were taken from the trial data or a systematic literature review and therefore expert opinion was not sought for these values.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below

The assumed incidence of principle clinical events (VTE, major bleeding and CRNM bleeding) were previously presented in Table 28, Table 30 and Table 31 in section 7.3.1, so are not repeated here.

All other clinical parameters are listed in Table 40. The sensitivity ranges are the ranges used in the univariate sensitivity analyses and the 95% CIs used for probabilistic sensitivity analysis. The statistical distribution used in the PSA of all the parameters in Table 40, with the exception of treatment effect parameters, was the Beta distribution. Treatment effects (either hazard ratios or risk ratios) were assumed to arise from Lognormal distributions. All clinical parameters were simulated in the PSA independently from one another.

Table 40: Overview of pharmacoeconomic modelling assumption relating to disease epidemiology

Event/outcome	Point estimate	Sensitivity range		Source
		Lower	Upper	
Treatment effect for rivaroxaban vs dual LMWH/VKA therapy				
Recurrent VTE (hazard ratio)	1.123	0.749	1.684	EINSTEIN-PE CSR[73] REF
Major bleeds (hazard ratio)	0.493	0.308	0.789	
CRNM bleeds (RR)	1.001	0.842	1.191	
Disambiguation of composite endpoints				
Probability that a recurrent VTE is a DVT	37.2%	27.5%	47%	Buller 2012[13], EINSTEIN-PE CSR[73] REF
Probability that a major bleed is a (major) IC bleed	[redacted]	[redacted]	[redacted]	
PE patients with coincident DVT	3.4%	0%	8%	
Discontinuation from treatment (per 3 month cycle)				
Patients with IC bleeds	100%	70%	100%	EINSTEIN-PE CSR[73], Bayer clinicians
Patients with major EC bleeds	[redacted]	[redacted]	[redacted]	
Patients with CRNM bleeds	[redacted]	[redacted]	[redacted]	
For any other reason (additional)	[redacted]	[redacted]	[redacted]	
Risks of subsequent morbidities				
Recurrent VTE (per 3 month cycle)	1.26%	1.09%	1.46%	Prandoni 2007[30]
Progression to CTEPH after a recurrent PE	1.25%	0.03%	2.46%	Miniati 2006[135]
Incidence of severe PTS post-DVT	8.10%	5.8%	10.4%	Prandoni 1997[140]
Mortality associated with model events (per three month cycle)				
PE, during acute treatment phase	[redacted]	[redacted]	[redacted]	EINSTEIN-PE & -DVT CSRs[73,83]
PE, after acute treatment phase	33.1%	25.0%	41.2%	Prandoni 2007[30]
Major IC bleed	43.6%	36.5%	50.7%	Linkins 2010[146]
Major EC bleed	3.9%	2.5%	5.4%	Linkins 2010[146]
CTEPH	2.48%	2.05%	2.93%	Condliffe 2008[143]

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what

assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

The follow-up period of EINSTEIN-PE was one year and data on VTE recurrence is available to ten years.[30] However, some patients may require longer treatment durations, up to lifelong. Furthermore, the time horizon for the economic model is a patient's lifetime, as per the Decision Problem, so extrapolation has been necessary.

For the evaluation of treatment durations up to 12 months, once acute treatment with rivaroxaban or comparator ceases, patients are no longer assumed to be subject to the risk of bleeding, but are assumed to remain subject to risks of recurrent DVT, recurrent PE, PTS and mortality. Following any recurrent PE, a patient is subject to an excess mortality risk applying in that cycle and a risk of developing CTEPH. There are assumed to be no differences in the level of these risks by acute treatment (previously) received. The risk levels were informed by systematic reviews of epidemiological literature for relevant data, as described in section 7.3.1, and the values used in the model were included in Table 14.

Whilst acute treatment with rivaroxaban or comparator was provided, patients were subject to treatment-specific risks of DVT, PE and bleeding as informed by EINSTEIN-PE trial data (and previously described in section 7.3.1) rather than epidemiological literature identified in systematic reviews.

For the evaluation of lifelong treatment duration, patients on treatment continue to be exposed to a risk of recurrent VTE, bleeding and complications. In order to reflect a potentially lower risk of events long-term, the baseline risk of VTE and major bleeding on VKA therapy was informed by the meta-analysis of long-term VKA studies by Streif et al.[114] In the absence of further data the relative treatment effect observed in EINSTEIN-PE was maintained over this period.

Patients who discontinued treatment were exposed to the same risks as for patients who received shorter treatment durations, as described above.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The principle assumptions are described below. See elsewhere in this submission for various additional specific structural and parametric assumptions relating to natural history, treatment, resourcing and costs:

- baseline event rates are summarised in Table 28, Table 30, Table 31;
- other disease epidemiology assumptions, including treatment effects in Table 40;
- utility values assumed are given in Table 43 and resource usage assumptions made are given in Table 47
- unit costs adopted are summarised in Table 50.

1. Characterisation of PE and recurrence of VTE. The model structure reflects the aims and potential risks and benefits of treatment – the beneficial reduction in risk of recurrent DVT and PE, and potential for additional hazard due to bleeding during treatment for the index PE. The model also captures longer-term complications.
2. Incidence of primary events with dual LMWH/VKA therapy. The model uses the incidence of such events from the dual LMWH/VKA therapy arm of EINSTEIN-PE as the baseline level of risk, which may be adjusted while alternative therapy is offered. Once therapy ceases, patients are assumed to move to a long-term rate of VTE recurrence informed by epidemiological literature. This approach therefore captures the variation in risk among patients appropriate for differing durations of treatment.
3. Effect of rivaroxaban on incidence of primary events. The model assumes conservatively that the effect of rivaroxaban is limited to certain primary events measured in EINSTEIN-PE and applies only during treatment. The model uses only three measures of treatment effect, two of them informed by primary time-to-event analyses (hazard ratios published in the New England Journal of Medicine).[13]

4. Representativeness of EINSTEIN-PE to UK practice and patients. The features of EINSTEIN-PE have been discussed previously (including in section 6.3).

5. Cessation of treatment effect on cessation of acute treatment. PE is modelled as an acute disease. There is not assumed to be any persistence of treatment benefit once treatment ceases, other than the events already avoided and consequent avoidance of progression to complications such as PTS, CTEPH and post IC bleed.

6. Index PE patients are not exposed to a risk of PTS on model entry. This is consistent with findings from Bova et al.[86], that indicated patients post-PE (without DVT) were not at elevated PTS risk. However, some patients with a prior history would in theory be at risk of PTS. Treatment of the index event with either rivaroxaban or LMWHH/VKA is not anticipated to influence this risk and therefore it was excluded from the model.

7. Patients in the lifelong treatment cohort who have discontinued from long term treatment re-initiate on their original therapy (either rivaroxaban or dual LMWH/VKA) if they experience a recurrent VTE. This is consistent with the modelling approach adopted for an economic model in the NICE guideline on management of venous thromboembolic diseases.[8]

7.4 Measurement and valuation of health effects

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

A PE is an unpleasant and life-threatening experience, its current treatment detracts from HRQL, patients live with the risk and fear of a recurrent VTE, and the risk and fear of complications of these and the original PE.

The impact of the PE itself

Limited data is available to describe the HRQL of patients specifically with or post-PE; however, researchers are developing a disease specific HRQL outcome measure – the Pemb-QoL – and have discussed some elements of HRQL. PE patients reported fatigue, chest pains and anxiety – these

contribute to a diminished HRQL.[149] In a validation study of Pemb-QoL the SF-36 measure was used, and showed significantly impaired quality of life in patients after an initial PE across six of the seven SF-36 domains compared with an age-adjusted population sample. This is consistent with findings from a more recent study that identified a history of PE as a potential determinant of reduced HRQL over the longer term.[150]

The impact of current therapy for PE

As well as the impact of the disease per se, we know from publications in patients with DVT that the mode of therapy can also have negative effects on patients' perceptions of their HRQL.[57,58,151] There are a number of characteristics of current oral anticoagulation therapies that may potentially induce dissatisfaction and reduce HRQL. Among these are the necessity for frequent doctor visits for regular blood testing, drug-drug interactions, lifestyle limitations (including restrictions on diet and activities), and possible worry about bleedings. In the development and validation of a quality of life questionnaire for patients with DVT, the 'hassle with monitoring' domain significantly correlated with the SF-36 general health and mental health, indicating that mandatory visits to the clinic for blood monitoring interact with the perception of general health and emotional distress.[58]

The impact of the risk and fear of recurrent VTE

This risk of recurrence can continue, depending on each patient's underlying risk factors. If the blood clot occurred as a result of surgery or trauma, and the risk factor was considered temporary, then the risk of having another DVT or PE may be low.

Websites run by patient organisations (including charities) and the NHS recount the experiences of numerous patients affected by PE. These patient experiences reflect at an individual level the broad conclusions of the HRQL research described above. Themes from these patient experiences are the pain and discomfort of the original PE, difficulties with current treatment modalities, and the underlying fear of a recurrent VTE.[58]

It has been noted that the detrimental HRQL measured in patients with DVT may be attributable in part to the risk and fear of recurrent VTE. Given the shared risks of DVT and PE this is likely to be the case in patients with a PE.[57-59]

The impact of the risk and fear of complications of VTE

Venous thrombosis also poses risks of intermediate- and long-term complications. These include not only recurrent PE and DVT, but the development of CTEPH (PE related) and PTS (DVT related).[135,140]

CTEPH, chronically elevated blood pressure in the pulmonary circulation and a type of pulmonary hypertension, occurs as a late complication in between 3% and 4% of patients who survive PE.[135] Symptoms include progressive shortness of breath and exercise intolerance. Later in the course of the disorder, chest pain with exertion and syncope may occur. A UK cohort study reported three year survival of 70% in patients with nonsurgical CTEPH and 76% for those patients with CTEPH treated surgically.[143]

PTS is a chronic disorder with symptoms that range from minor signs (eg stasis pigmentation, venous ectasia, slight pain and swelling) to severe manifestations such as chronic pain, intractable oedema, leg ulcers and in very severe cases amputation. Severe PTS is not uncommon after a DVT.[140]

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Venous thrombosis poses risks of intermediate- and long-term complications, which include recurrent DVT and PE, and the development of PTS and CTEPH.[135,140]

A patient with PE is likely to experience poor HRQL if a recurrent VTE occurs, particularly if the rVTE is another PE. A PE also represents an excess risk of mortality and risk of progression to CTEPH, where HRQL is particularly poor and life expectancy short. Minor bleeding that occurs during treatment may have a far less serious and shortlived impact on HRQL than major bleeding, particularly if this is IC.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

No health preference outcomes were measured in EINSTEIN-PE suitable for the valuation of health states. The treatment satisfaction measures, ACTS and TSQM, were measured in a subset of patients in EINSTEIN-PE as described previously. These demonstrated greater satisfaction with rivaroxaban than with dual LMWH/VKA therapy.[15,16] This is consistent with published findings from EINSTEIN-DVT.[17]

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was conducted.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic literature review was conducted for relevant HRQL data.[115] The systematic review conducted for this purpose had the broad objective of finding evidence on utility associated with VTEs, including events such as PE, DVT, bleeding, CTEPH and PTS, in patient populations with index PEs,

DVTs,or VTEs generally. The review also set out to identify evidence that might suggest moderation of utilities according to the nature of treatment received.

The search strategy used is provided in section 10.12, appendix 12, as required, with a rationale for the search terms used. Literature searches were first conducted in April 2010 on the MEDLINE, EMBASE and Cochrane Library and Econ Lit literature databases (original review) and then updated twice, in July 2011 and May 2012. In total, before deduplication, 3108 potentially relevant studies were identified. Following title, abstract and full-text review in comparison with pre-defined inclusion/exclusion criteria, 6 studies were included, which provided utility values relevant to states in the model.[104,152-156] See Table 41. Note, the May 2012 update did not provide any additional studies from which data could be extracted to populate the model.

Table 41: PRISMA-type study flow for systematic review of HRQL studies.

	Original	Update July 2011	Update May 2012
Database search hits	2,447	434	227
Less: duplicates	992	109	34
Available for title/abstract review	1,455	325	193
Less: excluded	1,408	318	191
Available for full-text review	47	7	2
Less: excluded	47	4	2
Plus: articles identified from reference lists	2	1	0
Final included studies	2	4	0
Combined included studies	6		

Source: Table 45 from systematic review report[115]

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.

- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

The systematic review described in section 7.4.5 yielded six studies.[104,152-156] Additionally section 7.4.8 will describe how two further studies were used for the population baseline[157] and for the post IC bleed state[158]. One of these eight studies (Goodacre et al, 2006[152]) was a HTA report on diagnostic strategies for testing for DVT, but did not appear to measure or quote utility values, so is not considered further. This publication also featured in the review of costs and resources literature discussed in section 7.5. Seven studies were left to be extracted into Table 42.[104,153-158]

Table 42: Summary of utility studies

Study	Population	Recruitment	Sample size and response	Description of health states, & appropriateness	Adverse events	Methods of elicitation, valuation and mapping	Results with CIs	Appropriateness for cost-effectiveness analysis	Appropriateness to this submission
Kind 1998[157]	Random sample representative of the UK general adult population	76 addresses from 80 postcodes. Stratified random sampling.	3395 respondents	Own health	NA	EQ-5D visual analogue scale	Mean (SD) of 0.825 (0.17).	Highly appropriate.	Highly appropriate – for baseline HRQL assessment
Lenert 1997[153]	Healthy volunteers: 30 women aged 20-40 years – 15 second-year residents and 15 faculty members.	NA	Sample of 30	Mild PTS, Severe PTS, Stroke	NA	Standard gamble. Assessed how much patients would risk death to avoid life with the condition. Utility assigned to each health state according to balance between life with the condition and probability of	Median (95% CI) reported. Mild PTS = 1 (0.91-1.00), severe PTS = 0.95 (0.79-1.00), central nervous system bleeding = 0.60 (0.02-1.00).	Limited by small, select sample.	Appropriate – for severe PTS

Study	Population	Recruitment	Sample size and response	Description of health states, & appropriateness	Adverse events	Methods of elicitation, valuation and mapping	Results with CIs	Appropriateness for cost-effectiveness analysis	Appropriateness to this submission
						death.			
Locadia 2004[154]	Three distinct groups of patients: VTE, bleeding and PTS.	Invitation by researchers.	129 (81%) of 159 eligible gave consent	8 health states pre-defined by clinical experts	NA	Ranking, direct rating and time trade-off.	Median (IQR) valuations were reported. See Table 46.	Limited by small, select sample.	Appropriate – for various model states
O'Meara 1994[156]	General medicine patients	Random selection of 36 patients attending general medicine appointments	20 patients had experience of DVT, 16 did not. No further information.	Pre-defined states: good health, mild postphlebitic syndrome, severe postphlebitic syndrome, central nervous system bleeding, and death.	Bleeding was a state considered.	Standard gamble.	Mean (95% CI) values were: 1 (NA), 0.995 (0.990-1), 0.982 (0.962-1), 0.290 (0.127-0.453) and 0 (NA) respectively.	Not appropriate	Not appropriate
Marchetti 2001[104]	Patients attending a	NA	Sample of 48	QoL related to taking warfarin,	NA	Time trade off.	Mean (SD) reported.	Appropriate. These	Appropriate – for treatment related

Study	Population	Recruitment	Sample size and response	Description of health states, & appropriateness	Adverse events	Methods of elicitation, valuation and mapping	Results with CIs	Appropriateness for cost-effectiveness analysis	Appropriateness to this submission
	local anticoagulation clinic			or taking LMWH according to description of hypothetical patients taking either			Warfarin = 0.988 (0.016). LMWH = 0.992 (0.024).	results were used in a cost-effectiveness analysis.	disutility.
Meads 2008[155]	UK pulmonary hypertension patients	NA	Sample of 869, including 308 with CTEPH	Own health	NA	CAMPHOR scores and utility index	Mean (SD) reported by diagnosis and NYHA class. CTEPH diagnosis = 0.56 (0.29) utility.	Validated utility instrument, more discriminatory than EQ-5D. Study limited by selection of sample.	Appropriate – for states related to CTEPH.
Rivero-Arias 2010[158]	OXVASC cohort of UK patients following stroke and trans	NA	Sample of 1283 patients, two year follow-up	Own health via Modified Ranking Scale (mRS) – level of handicap	NA	EQ-5D tariff of Dolan et al, 1996	Mean (SD) EQ-5D utility by mRS (and time).	Study limited by selection of sample.	Appropriate – for states similar in severity to stroke or transient ischaemic attack.

Study	Population	Recruitment	Sample size and response	Description of health states, & appropriateness	Adverse events	Methods of elicitation, valuation and mapping	Results with CIs	Appropriateness for cost-effectiveness analysis	Appropriateness to this submission
	ischaemic attack								

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable. There were no such data reported or mapped from the principle clinical trial, EINSTEIN-PE.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Three types of bleeding related adverse events were included in the model; CRNM (EC) bleeds, major EC bleeds and major IC bleeds. The HRQL impact of bleeds depends on their location and duration of impact. See also Table 26.[153-155,157,158]

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

The starting point in the modelling of utility in the pharmacoeconomic evaluation was the population norm value of 0.825 (SD 0.17, n=3395) established in the landmark national EQ-5D survey by Kind et al[157], which was used as an anchor point in this evaluation. (This study is not specific to VTE and was not within the scope of the systematic review.)

Evidence on the disutility relative to this anchor point for DVT, PE, major EC bleed (assumed to match the disutility reported for GI bleed), and major IC bleed (assumed to match the disutility report for haemorrhagic stroke) were taken from an evaluation of patient preferences in VTE by Locadia et al.[154] Although there were limitations in this study due, for example, to its elicitation of preferences from patients rather than the general public, we considered this study preferable to others previously cited by NICE for which design and methodology were unclear.[26,159,160] We accounted for the difference between the population norm utility in this source (0.95)[154] as compared with that used for this evaluation (0.825).[157]

The systematic review described here did not yield a source for utility following an IC bleed, but literature searching for the development of

assumptions for an economic model in a separate indication identified a large health preference study.[158] In this study, the EQ-5D utility of 1283 people who had experienced stroke or transient ischemic attacks was measured over two years, producing an average value of 0.713.

The utility value applied to the post IC bleed state was taken from an analysis of EQ-5D data from the UK OXVASC study recorded two years after the IC event.[158] Some 74% of patients included in this study were considered to be independent (modified Rankin score of 0-2) 2 years post event, and 26% were dependent.

Functional outcomes after stroke have not been found to be significantly different to those following IC bleed. In an early publication from the UK OXVASC study cited in the meta-analysis by van Asch et al[147], Bamford et al reported that one year post-ischaemic stroke 65% of survivors were functionally independent (mRS 0-2).[161] Comparatively, amongst IC bleeds, 68% of intra-cerebral bleed and 76% of subarachnoid bleed survivors were functionally independent. It was noted that there was no significant difference in functional status between ischaemic stroke and all intracranial haemorrhage (odds ratio 0.74, 95% CI 0.37 to 1.48).

The reported rates of independence for bleeds from Bamford et al are marginally lower than those observed in the sample used for utility estimates.[161] However, this can in part potentially be explained by the extended follow-up (2 years), by which time more patients may have achieved independence. Furthermore, it is possible that inclusion of patients following transient ischaemic attack within the utility analysis may have led to a greater proportion of patients classed as independent than might have otherwise been expected following stroke alone.

Adopting the acute event utility value (0.33) reported by Locadia et al, the source of other utility values in the model, was considered but rejected on the grounds that patient function typically improves.[154] The UK OXVASC study was selected given the issues with functionality raised above and an intention to adopt a conservative approach (a more severe utility favouring rivaroxaban).[158]

Disutility due to PTS was available from a study of the general public and physicians, by Lenert et al.[153] This methodology was preferable to three other studies which also provided estimates since they did not measure severe PTS

specifically, the state in the economic model to be valued.[154-156] The general public sample in Lenert et al (n=30) produced a value of 0.93 (IQR 0.76 to 1.00) for serious PTS and 1.00 (IQR 0.91 to 1.00) for mild PTS.[153] By comparison, the valuation in the Locadia et al study for PTS was 0.82 (IQR 0.66 to 0.97).[154] The 95% CI have been assumed to equal the IQR due to the absence of further information and the size of the sample.

A study by Meads et al using the Cambridge PH Outcome Review (CAMPHOR) instrument, a validated instrument used in pulmonary hypertension, reported a utility for CTEPH as 0.56 (SD=0.29, n=308). The authors noted that utility values from this instrument were comparable to those from EQ-5D, so this utility was used without adjustment by the population norm.[155] No other studies provided EQ-5D utility specific to CTEPH.

Only one study shown in Table 42 considered disutility relating to treatment. Marchetti et al conducted a modified time trade-off study in a sample of patients attending an anticoagulation clinic (n=48) and found a mean utility of 0.988 (SD=0.016) for warfarin (disutility of 0.012) and 0.993 (SD=0.024) for LMWH.[104] Such an impact of warfarin on quality of life was discussed and recognised in several recent NICE Technology Appraisals.[19,42,43] Therefore a disutility of 0.012 associated with treatment with dual LMWH/VKA is applied in the model.

There is also the question of whether a disutility should apply during rivaroxaban treatment. In the case of the NICE appraisal of dabigatran in atrial fibrillation, it appears from published documentation that a disutility may have been applied to account in some way for dyspepsia and observations from a quality of life substudy of the RE-LY trial.[42]

No such disutility for rivaroxaban would be appropriate, for three reasons:

- The economic model accounts for incidence of relevant clinical events, VTE and bleeding as separate model states
- No other clinically important adverse events are significantly raised with rivaroxaban in comparison with warfarin, such as dyspepsia with dabigatran[2-4,162]
- Treatment with rivaroxaban has been associated with greater treatment satisfaction in comparison with dual enoxaparin/VKA therapy[15-17]

Therefore we have assumed no disutility to be associated with rivaroxaban treatment in the base case analyses. This is consistent with the appraisal of rivaroxaban for DVT treatment (TA261[19]).

The values adopted for the cost-effectiveness analysis are summarised in Table 43.

Table 43: Utility values assumed in the pharmacoeconomic evaluation

Model state	Point estimate	Sensitivity analyses		Notes	Source
		Lower	Upper		
Population norm	0.825	0.819	0.831		Kind 1998[157]
Disutility due to warfarin therapy	0.012	0.016	0.006		Marchetti, 2001[104]
Post IC bleed	0.71	0.70	0.72		Rivero-Arias 2010[158]
CTEPH	0.56	0.53	0.59		Meads 2008[155]
Adjustments to utility norm due to modelled events					
DVT	0.84	0.64	0.98		Locadia 2004[154]
PE	0.63	0.36	0.86		Locadia 2004[154]
EC bleed	0.65	0.49	0.86	GI bleed was the disease state valued	Locadia 2004[154]
IC bleed	0.33	0.14	0.53	Haemorrhagic stroke was the disease state valued	Locadia 2004[154]
PTS	0.93	0.76	1.00	Serious PTS was the disease state valued	Lenert 1997[153]

Notes to table:
- Locadia quoted a population norm (own health) as 0.95 (95% CI 0.81-1.00) to which the values quoted above from that source should be compared.[154]
- Lower and Upper values are estimates of 95% CIs from data presented (eg sample population size, n, and SD) in the source literature.
- For the PSA, the parameters above were modelled as arising from independent Beta distributions with alpha and beta parameters set such that the mean is the point estimate and the lower and upper values represent the 95% CI.

In developing the utility assumptions for the evaluation, we also considered a comprehensive set of EQ-5D disutilities recently developed by Sullivan et al.[163] Although interesting in its breadth, the publication was not appropriate for use in this evaluation for various reasons:

- Disutilities are only provided down to a level 3 ICD-10 code. Many of the health states considered in this model relate to level 4 of ICD-10.

- Disutilities for certain ICD-10 codes relating to PE, intracranial bleed and major/GI bleeding are not presented.
- The code that includes pulmonary hypertension actually suggests a utility increase, which is somewhat counter-intuitive. (The confidence limits for this are wide.)

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details*:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical experts were engaged to estimate HRQL values for this STA.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The duration of utility impact was assumed to be one month for DVT, PE and major EC bleeds (and varied between half and two months in univariate sensitivity analyses). This was consistent with the approach adopted in the

* Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

development of the cost-effectiveness model for NICE CG92.[26] IC bleeds were assumed to be of three months' duration (and varied between two and three months in univariate sensitivity analyses). Other events were assumed to be chronic. The three-month cycle length was assumed sufficient to capture the short-term impact of other events on health related quality of life.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

As mentioned previously, the literature review of utility studies found evidence to suggest that mild PTS was of little detrimental effect on quality of life,[153] so the cost-effectiveness evaluation focussed on severe PTS.

Similarly consideration was given to differentiating risks (eg for PTS incidence) for patients with recurrent ipsilateral or contralateral DVT, but there was limited evidence of any distinction nor of any relationship with choice of anticoagulation treatment for PE

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life assumed in the analysis was a utility of 0.825 from the landmark national EQ-5D survey by Kind et al.[157] Quality of life was modelled relative to this baseline for DVT, PE, IC bleed, EC bleed and PTS.[154] Quality of life was modelled in absolute terms for patients with CTEPH or following an IC bleed due to the methods, instruments and samples used in the valuation studies for those states.[155,158] See section 7.4.9.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The utility assumptions are constant in time (Table 43). Due to recurrence of VTE and incidence of post-VTE complications over time, the model projects a gradual deterioration in average HRQL over the lifetime of the patient cohort.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

No further amendments were undertaken.

7.5 Resource identification, measurement and valuation

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Costs of long-term anticoagulation, PE treatment and VTE prevention are incurred in the primary and secondary care NHS settings. Unit costs used in the model reflect the UK NHS perspective and are taken wherever possible from the NHS National Schedule of Reference Costs[164], the Personal Social Services Research Unit (PSSRU)[165] and the British National Formulary (BNF) 64[166]. There is one HRG for DVT (QZ20Z) and three HRGs relating to PE (DZ09A, DZ90B and DZ09C).[164]

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

This model used NHS reference costs as they provide relevant costs and volume that enable the estimation of a weighted average that reflects the pattern of care delivered in the NHS. Furthermore, Reference Costs represent the cost burden to the NHS rather than a reflection of internal reimbursement between NHS organisations. Also, when compared to Tariff values, the Reference costs allow for a greater level of granularity to be assessed and are typically more conservative.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

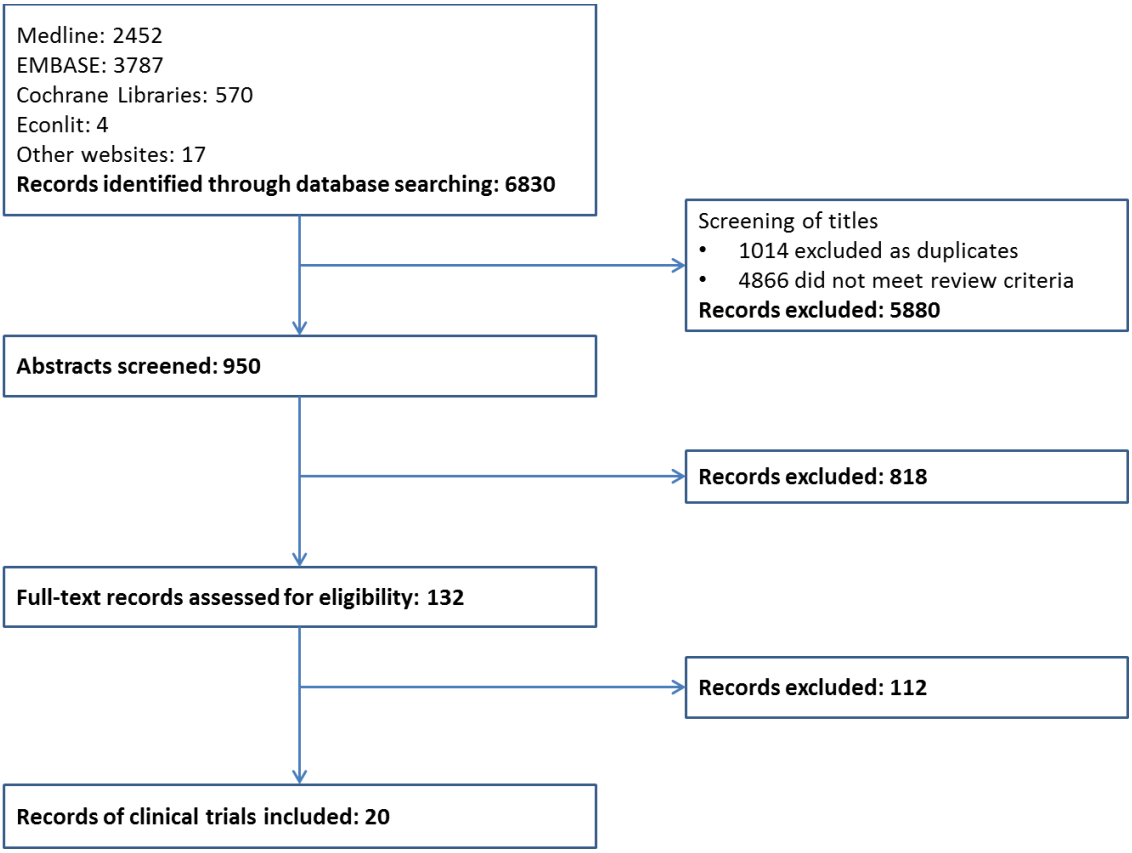
- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic review of the literature was performed by updating the review conducted for the STA of rivaroxaban in DVT treatment.[19] The updated search was designed to identify resource and cost data associated with the treatment of venous thromboembolism (VTE) and any associated published UK costings or cost analyses available from each database inception to the 3 October 2012.

Searches were kept exactly the same as previously – intentionally broad and not specific to the UK, though UK practice and costs were the aim and focus of the review. The searches were conducted across MEDLINE (including MEDLINE in-process), EMBASE, EconLIT, and Cochrane Library (including NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (HTA) database and Cochrane Groups). Additionally, searches were performed in the websites of NICE, NHS Improvement, the Department of Health, and The National Institute for Health Research Health Technology Assessment programme. The searches are described in detail in section 10.13, appendix 10 as required.

The searches identified 6830 hits of potential relevance, from which 1014 were excluded as duplicates, 4866 were excluded at title review, 818 were excluded at abstract review, and 112 excluded after reviewing full publications. This left 20 articles included. A PRISMA diagram is shown in Figure 13.

Figure 13: PRISMA diagram for systematic review for cost and resource literature



The 20 included publications comprised the 15 included in the original review[26,152,167-179] presented for the DVT treatment STA[19] plus 5 more recent publications[8,19,42,43,180]. The characteristics of these studies are summarised in Table 44.

Table 44: Summary of characteristics of resourcing studies

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Patient type & number	Follow-up
Anderson et al 2002[167]	UK	2000-1	Yes. Covers costs incurred in three relevant settings of acute VTE care. Includes enoxaparin (most widely prescribed LMWH in UK).	Cost minimisation analysis. Direct medical costs. NHS perspective. BNF September 2001; PSSRU 2000.	N/A Hypothetical patient base. Patients receiving treatment for VTE.	Acute treatment phase only
Barber & Hoffmeyer 1993[168]	UK	1991-2	UK study within hospitals, although nowadays treatment can be as outpatient or within primary care.	Cost-effectiveness analysis of administering heparin subcutaneously vs. intravenously. NHS Costs 1991/1992.	NR	Acute treatment of VTE only
Connock et al 2007[169]	UK	2005	Yes, UK-specific data reported separately	Systematic Review (NICE). Clinical and cost effectiveness of self-monitoring vs. anticoagulation clinics including economic model. NHS perspective. NHS ref costs 2005.	n/a Any patient requiring anticoagulation	Subsequent treatment (non-acute) phase only

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Patient type & number	Follow-up
Davies et al 2000[170]	UK	1997-8	Cost-effectiveness study based on UK costs and practice. NB. This study modeled cost-effectiveness of thromboprophylaxis in hip surgery patients but included resource and cost data on DVT / PE diagnosis and management	Cost-effectiveness study. NHS costs 1997-1998; BNF 1998; PSSRU 1997.	n/a Hypothetical 1000 patient cohort of patients receiving thromboprophylaxis for hip surgery	Acute and subsequent treatment of VTE
Goodacre et al 2006[152]	UK	2004	Review evaluated DVT diagnostic algorithms (both published and those used in UK, identified by hospital postal survey). Optimal diagnostic work-up assessed on basis of UK practice and costs	Cost-effectiveness study. NHS Ref costs 2003-2004. PSSRU 2003.	n/a Hypothetical patient cohort with suspected DVT	Acute phase. Suspected DVT. Non-invasive aspects of diagnosis of DVT.
Hoffmeyer et al 1998[171]	UK	1997	Yes, model built based on trial data (non-UK) and interviews with UK clinicians. UK costs.	Costing study. 1997 NHS prices.	612 Pulmonary embolism patients	Acute plus 90 days

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Patient type & number	Follow-up
Migliaccio-Walle et al 2012[180]	UK	Not specified (2009-2010)	Yes resource and unit costs based upon UK practice. Costs based on NHS.	Cost per QALY; Cost per LYG; Efficiency frontier method NHS Ref costs 2008/2009; BNF 2010	Total hip or knee arthroplasty. Hypothetical cohort of 1000 patients	90 days plus 5 years
National Audit Office 2010[172]	UK	2008	Yes resource and unit costs based upon UK practice	Economic model measuring improvements of stroke care in terms of costs and outcomes. PSSRU 2008, NHS Ref costs 2007-2008.	Stroke management	Stroke care pathway modelled over 10 year perspective
NICE CG36, 2006 (incl costing template)[175]	UK, non-UK studies considered in literature search	2005	Yes, UK-specific date reported separately where available. Costs based on NHS.	Clinical and cost effectiveness. NHS perspective. NHS ref costs 2004/2005.	Anticoagulation costs – any patient requiring anticoagulation	-
NICE CG68, 2008 (incl costing report)[174]	UK, non-UK studies considered in literature search	2007	Yes, UK-specific date reported separately where available. Costs based on NHS.	Clinical and cost effectiveness. NHS perspective. NHS ref costs 2006/2007	All stroke patients	-

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Patient type & number	Follow-up
NICE CG92, 2010[26]	UK, non-UK studies considered in literature search	2008	Yes, UK-specific date reported separately where available. Costs based on NHS.	Clinical and cost effectiveness. NHS perspective. NHS ref costs 2006/2007	Patients admitted to hospital requiring thrombo-prophylaxis	-
NICE CG144, 2012 (incl appendices and costing report)[8]	UK, non-UK studies considered in literature search	Lit searches to 1st August 2011	Yes, UK-specific date reported separately where available. Costs based on NHS.	NHS Ref costs 2009-2012; PSSRU 2010	Venous thromboembolic dsieaseas	-
NICE Anticoagulation Service Commissioning and Benchmarking tool[173]	UK	2009 / 2010	Yes, NICE commissioning guide therefore costs used in NHS service provision planning and implementation	NHS costs 2009 / 2010	All patients requiring anticoagulation	-
NICE TA 249, 2012 (incl costing template)[42]	UK	2010/2011	Yes, UK resource data & costs used.	NHS costs 2009 / 2010	Atrial Fibrillation	-
NICE TA 256, 2012 (incl costing template)[43]	UK	2010/2011	Yes, UK resource data & costs used.	NHS costs 2009 / 2010	Atrial Fibrillation	-

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Patient type & number	Follow-up
NICE TA 261, 2012 (incl costing template)[19]	UK	2010/2011	Yes, UK resource data & costs used.	NHS costs 2009 / 2010	DVT & prevention of recurrent VTE	-
Reeves et al 2004[176]	UK	2001-2002	Yes, UK hospital resource data & costs used.	Resource and cost analysis. BNF 2002, NHS ref costs 2001/2002, PSSRU 2001.	Estimated from data gathered from UK hospital across Orthopaedic, Surgical and medical prophylaxis, VTE treatment, and UA/NSTEMI. Separate models were developed for each indication.	12 month
Saka et al 2009[177]	UK	2006-7	Yes, UK registry and costings used. Resource based on actual UK practice	Cost of illness study. Direct costs – PSSRU 2006, BNF 2004, Payment by results tariff, 2005-2006	Stroke patients	12 months

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Patient type & number	Follow-up
Simpson et al 2009[178]	UK	2006	Based on UK costs and UK practice	Cost effectiveness analysis primarily looking at cost-effectiveness of thrombophilia testing vs. no testing. Costs of VTE treatment and adverse outcomes included in model / analysis. 2005-2006 NHS Ref costs. PSSRU 2006. BNF 2006.	Hypothetical cohort. Patients requiring treatment for VTE.	Lifetime
Valette et al 1995[179]	UK costing study and US clinical study	1997	Yes, model built based on trial data (non-UK) using comparable regimens to recommended UK practice. Interviews with UK clinicians used to ascertain UK resource and costs.	Cost-minimisation study. Costs expressed in 1994-1995 NHS prices.	432 deep-vein thrombosis patients	Acute plus subsequent treatment (length of treatment after acute event not stated)

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details*:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two clinical experts (one external to Bayer and based in the UK) were approached to provide validation on the initial model structure and parameter values tested in the model. The parameter values were subsequently refined following the literature review and results from EINSTEIN-PE. No declaration of interest was sought from either participant. In addition, during the development of a model for the use of rivaroxaban in stroke prevention in atrial fibrillation, advice was sought from a further expert on the duration of rehabilitation associated with an IC bleed. The suggested input value was presented and the experts were asked to agree or disagree and provide rationales. No iterations were performed in the collation of opinion.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example,

* Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

We discuss resource usage and unit costs separately. Resource usage assumptions are summarised in Table 47 and unit cost assumptions in Table 49. The NHS list price of Xarelto® (rivaroxaban), £2.10 per tablet, was previously presented in Table 2 in section 1.10 as required. When resource usage assumptions and unit costs assumptions are combined, these produce the costs for each model state presented in the following section, 7.5.6.

To avoid duplication in later sections, we also include here information in relation to sensitivity analyses. In deterministic sensitivity analyses, resource usage parameter values were varied between the lower and upper values stated for each parameter. Probabilistic sensitivity analyses involved sampling each resource item from a stipulated statistical distribution with 95% CI coincident with given lower and upper values.

Resource usage

Overview

The model includes resource consumption related to the index event in respect of drug acquisition components and associated monitoring costs. Three types of follow-up and monitoring were considered:

1. Hospital admission costs and outpatient costs for the index event. A shorter length of hospital stay has been demonstrated amongst PE patients treated with rivaroxaban. This is modelled and accounted for explicitly.

2. Standard disease monitoring. This refers to existing monitoring of patients' disease, and treatment management other than INR monitoring. Such costs are assumed to be equal across all treatment arms and not explicitly evaluated in the pharmacoeconomic model.

3. INR monitoring. VKA treatment requires frequent INR testing to ensure treatment is both safe and effective. This is modelled and accounted for explicitly.

The model also reflects other resource usage, described further below, relating to recurrent PE and incident bleeds, DVT, PTS and CTEPH. A summary of all resource usage assumptions is provided in Table 47.

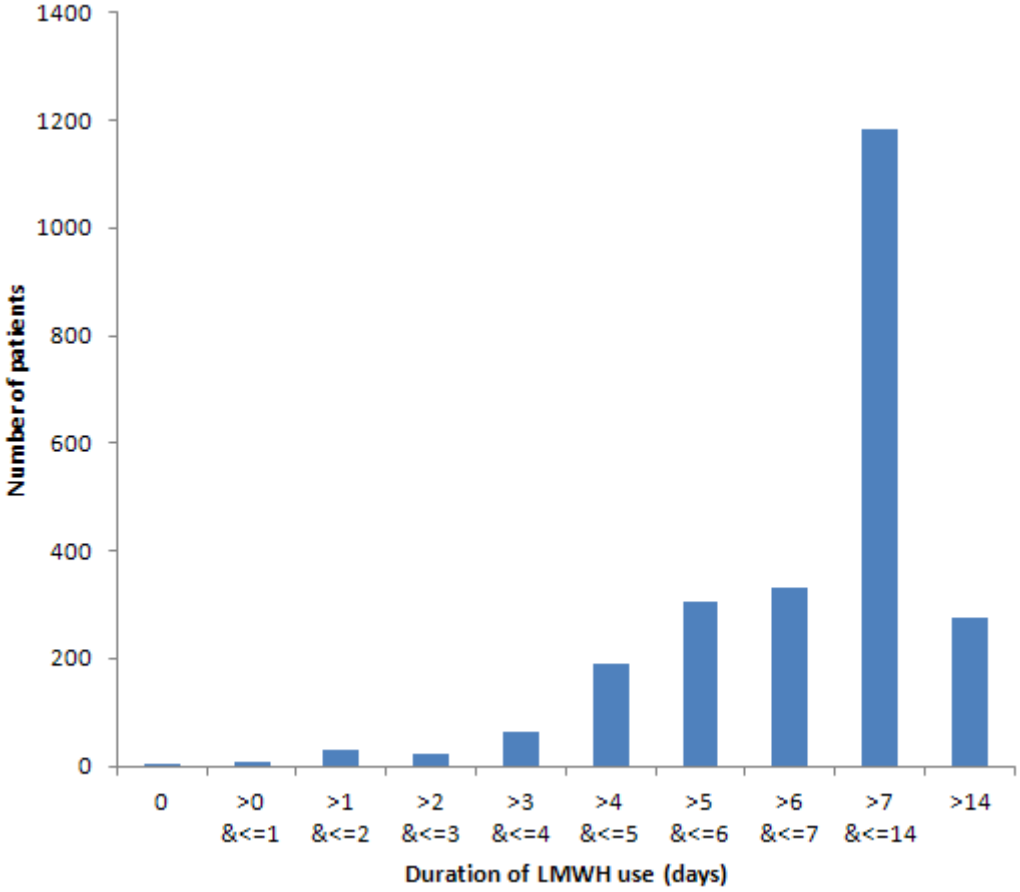
Acute treatment of the index event with LMWH

Patients in the LMWH/VKA arm of the model initially require acute treatment with LMWH. LMWH may be (i) self-administered by the patient at home, given successful education from a nurse, (ii) administered by a district nurse at the patient's home or (iii) administered by a nurse in hospital.

As discussed in section 7.2.7, three LMWH treatments are licensed for the treatment of PE or DVT, with enoxaparin the product in dominant usage. On this basis, and due to the fact that enoxaparin may be used for nurse or self-administration, and was also the LMWH used in the trial, we use the daily cost of Clexane® (enoxaparin) as the daily cost of LMWH in the pharmacoeconomic evaluation.

The enoxaparin regime delivered in EINSTEIN-PE was discussed in chapter 6. The dose delivered in the trial was 1 mg/kg bid. The cost of enoxaparin in the model was based on the UK licensed dose, namely 1.5 mg/kg od, rather than the trial regime. Differences between the trial dosage and UK licensed dosage and impact on trial validity, which is expected to be minimal, are discussed in chapter 6 (in particular section 6.10.4, enoxaparin regime). The UK regime has lower drug acquisition and treatment administration cost, so leads to a conservative evaluation of the cost-effectiveness of rivaroxaban. [redacted] Some skewness is apparent.

Figure 14: Histogram of duration of LMWH use in the LMWH/VKA arm of EINSTEIN-PE



Source: EINSTEIN-PE CSR[73]

We assume that patient education would be successfully delivered to 92% of patients managed on an outpatient basis, an assumption guided by evidence presented in the development of NICE CG92.[26] These patients would take Clexane® (enoxaparin) pre-filled syringes in their own homes at the UK licensed dose of 1.5 mg/kg od [redacted]. This input was assumed to vary in the PSA according to a Dirichlet distribution with parameters informed by data illustrated in Figure 14. In the univariate analyses, we also vary this parameter between 6.8 and 12.6 days, which is consistent with the duration in SIGN guidelines of 6 to 10 days over which patients are expected to discontinue LMWH.[9]

We assume that patient education would not be delivered or be unsuccessful in the other 8% of cases, of whom 80% of patients would be treated by a district nurse in their own home, an assumption informed by a national survey of models of care.[51] These patients would also receive enoxaparin pre-filled syringes at the same dose, frequency and treatment period as self-

administering patients. However, the treatment would be delivered by a district nurse.

Patients for whom patient education was not delivered or was unsuccessful and who are being treated at a clinic rather than at home comprise just 1.6% of the total outpatient population, given the assumptions outlined. These patients would receive Clexane® (enoxaparin) pre-filled syringes at the same dose, frequency and treatment period as self-administering and home-treated patients. In addition, we estimate that 8.55% of patients would require NHS-funded transportation to the monitoring clinic, evidenced by the national survey.[51]

Longer term care with VKA

Subsequent to LMWH treatment patients in the LMWH/VKA arm of the model require longer term treatment with VKA. Warfarin is the VKA in predominant use in the UK (as discussed previously) and was used by the large majority of patients in the LMWH/VKA arm of the EINSTEIN-PE trial. Among the 2413 patients in the ITT population of the LMWH/VKA arm of EINSTEIN-PE, [redacted] Consequently it is warfarin use whose resource consumption we evaluate in the longer term.

VKA treatment requires frequent INR testing to ensure treatment is both safe and effective. This is most intensive at initiation of treatment. On the basis of BCSH guidelines[11,50], SIGN guidelines[9], an observational research study of UK anticoagulation services[46] and information in the BNF[166], it is estimated that the frequency of monitoring visits on VKA treatment is 9 monitoring visits in the first 3 months of treatment and 5 visits per quarter thereafter. 95% CI assumptions are shown in Table 47. Note, INR monitoring during the trial was protocol driven and is therefore not necessarily generalisable to clinical practice in England and Wales

Traditionally, patients treated with warfarin, whether in the short or long term, were managed exclusively in secondary care. We conducted a national survey of models of care to better understand contemporary provision of anticoagulation care.[51] One-to-one semi-structured interviews of either healthcare professionals leading anticoagulation care, or a PCT/health board recommended knowledgeable person, were used to gather data on current

anticoagulation management. Data were collected from a total of 78 PCTs in England, 3 local health boards in Wales and 1 PCT from a health board in Scotland. The data was found to cluster into 6 groups each representing a different approach to anticoagulation care in the UK. Results suggested that instead of the traditional secondary care consultant led services, primary care is now the most common setting for the provision of these services. Additionally, many PCTs and acute Trusts operate a hybrid approach, incorporating a number of different care delivery structures within their service. The survey suggested that the proportion of patients receiving care in different settings for anticoagulation services is as follows:

- 25.6% in secondary care
- 58.5% in primary care
- 15.90% in a hybrid setting

Furthermore, of the 15.90% of patients managed in hybrid clinics, 50% of patients would be treated in Primary Care anticoagulation clinics and the remaining 50% would be treated in Secondary Care. Self monitoring was not included as it only represented a small percentage of the population and has been found to be not cost-effective.[169] Consequently, the primary care setting cost applied in 66.45% of cases and the secondary care setting cost in the remaining 33.55% of cases.

Resource usage: treatment of the index event with rivaroxaban

The individual resource usage components included in the intial outpatient treatment of PE are listed in Table 45**.**

Table 45: Components of outpatient VTE treatment

DVT	PE
Doppler ultrasound	CT angiography
D-dimer	Chest X ray
Emergency admission	ECG
	D-dimer
	Emergency admission

In addition, the model accounts for a reduction in the length of hospital stay for the index PE in patients on treatment with rivaroxaban in comparison with

dual LMWH/VKA treatment. The proportion of patients in EINSTEIN-PE who were hospitalised for their index event and the duration of stays are tabulated below. (Table 46).

Table 46: Hospitalisation observed in EINSTEIN-PE

	Rivaroxaban	LMWH/VKA	Difference
ITT population	2419	2413	-
Number (%) of patients hospitalised	2163 (89.7%)	2165 (89.9%)	-
Mean duration (SD/SE) among patients hospitalised	8.6 (23.1)	9.1 (15.5)	-0.5 (0.6)
Statistical test for difference (ANOVA)	-	-	P=0.36
Median duration (IQR) among patients hospitalised	6 (4-9)	7 (5-10)	-1 (NA)
Statistical test for difference (Van-Elteren)	-	-	P<0.0001

Source: Van Bellen et al 2012[14]

This analysis demonstrates that 90% of patients required hospitalisation regardless of their treatment and that treatment with rivaroxaban rather than dual LMWH/VKA therapy was associated with a statistically significantly shorter duration of length of hospital stay (van-Elteren test, a non-parametric Wilcoxon rank-sum test stratified on intended treatment duration, P<0.0001).[14] (The ANOVA test, although pre-specified, is not an informative or meaningful analysis of data of such skewness, as shown in Figure 14.) We have incorporated this potential saving associated with rivaroxaban use into the economic model. The measure most closely corresponding to this statistical test would be the difference in medians (1 day). Nonetheless, among patients requiring hospitalisation we have assumed that treatment with rivaroxaban is associated with a mean reduction of hospitalisation of 0.5 days (95% CI -0.7 to 1.7 days). This represents a more conservative approach and is consistent with conventions in health economics to base inputs around mean rather than median values.

Other resource usage

In addition to treatment of the original index event, the economic model also accounts for resource usage associated with incident and recurrent PEs, incident DVTs, bleeding (of various types/severities), PTS and CTEPH.

The assumed incidence of bleeding and PTS of various severities was described previously, and each severity has an associated unit cost. The incidence of CTEPH was also described previously – there are separate unit costs associated with CTEPH treated with pulmonary endodartectomy (PEA) and CTEPH treated otherwise. It was assumed that 68.4% of CTEPH patients would require a PEA.[143]

PEs and DVTs were assumed to be treated either on an inpatient basis, at a composite unit cost, or on an outpatient basis, as the sum of the costs associated with multiple outpatient treatment components (Table 45) as assumed based on expert opinion in NICE CG92.[26] Additional costs associated with six months further drug treatment were also included.

There is some consensus that outpatient management of patients with DVT can be appropriate. BCSH guidelines recommend that `outpatient therapy of DVT may be considered for selected patients with appropriate support services in place'[50] and market research has suggested that 69% of patients with a DVT would be treated as outpatients with no admission related to the index event.[181]. This is also supported by SIGN guidelines.[9]

However there is less consensus that it is possible or even appropriate to manage acute PE in the community setting. As noted in section 2.6, NICE CG144 `did not consider PE risk stratification or the outpatient management of PE as these were beyond its scope.' – so the feasibility of outpatient management was not considered further.[8] The British Thoracic Society has recommended that the current arrangements for outpatient management of DVT should be extended to include stable patients with PE but, there are no widely accepted criteria for identifying eligible PE patients.[27,49] This is recognised in the SIGN guidelines which recommend that current treatment algorithms should be updated to incorporate prognostic models in order to identify PE patients at low risk of adverse outcomes who would be suitable for outpatient management or early discharge.[9]

Given the objective of this appraisal being to evaluate treatment rather than setting, we assumed, on the basis of market research evidence[32], that 17% of PEs are treated as outpatients, with sensitivity ranges of 0% to 30%, and the remainder require inpatient care.

Table 47: Summary of resource usage assumptions

Resource item	Point estimate	Sensitivity analyses			Rationale
		Lower	Upper	Distribution	
Acute treatment					
Number of days of acute treatment (ie LMWH) required by a PE patient	[redacted]	[redacted]	[redacted]	Dirichlet (using data presented in Figure 14)	EINSTEIN-PE CSR[73] (Figure 14), SIGN guidelines[9].
Proportion of patients who self-inject LMWH	92%	64%	100%	Beta	The point estimate is taken from the assumptions in NICE CG92 (section 4.7.2).[26] The sensitivity range is an assumption.
Proportion of remaining patients who require nurse assistance at home	80%	56%	100%	Beta	These values are assumptions based on inputs determined for the NICE CG92 model (section 4.7.2).[26]
INR monitoring whilst on LMWH/VKA					
Visits in first 3 months	9	5	15	Gamma	UK observational research[46], BNF[166], SIGN[9].
Visits each 3 months thereafter	5	3	10	Gamma	
Recurrent VTEs: proportion treated as outpatients rather than inpatients					
Recurrent DVT patients	69%	50%	100%	Beta	Bayer Market Research[181]
Incident PE patients	17%	0%	30%	Beta	
Other					
Proportion of patients requiring NHS-funded transportation	8.55%	6%	11%	Beta	Bayer/pH national survey[51]
Proportion of CTEPH patients who require PEA	68.4%	64.2%	72.6%	Beta	321 of 469 patients from Condliffe 2008[143]

Unit costs

Overview

All unit costs assumed in the economic model are listed in Table 23 below, together with the source and rationale for each value.

Where weighted averages of NHS Reference Costs are calculated, the data used for this is shown in Table 49.[164] Upper and lower estimates were derived from the interquartile range (IQR) reported in NHS Reference costs. Where range information was unavailable values were varied by +/- 30% in univariate sensitivity analyses. Probabilistic sensitivity analyses involved sampling each unit cost from a Gamma distribution with a mean equal to the point estimate and standard error calculated from the IQR or in the cases where an IQR was not available the SE was estimated at 30% of the mean.

Unit costs: drug acquisition

The unit cost of rivaroxaban was set-out originally in section 1.10 on a flat, per tablet basis. During the first 21 days of treatment and where the treatment regime is 15 mg bid, two tablets would be required, at a daily cost of £4.20. Subsequently, one 20 mg tablet would be required each day, at a daily cost of £2.10. This acquisition cost may be further enhanced by local rebate agreements between the manufacturer and appropriate NHS budgetholders (as per paragraph 6.45 of the 2009 PPRS).[182]

The daily acquisition cost of each of LMWHs in the treatment of PE is tabulated below (Table 48).

Table 48: Drug acquisition costs of LMWHs

LMWH	Rationale for costing	Daily cost	Source
Clexane® (enoxaparin)	Dose of 1.5 mg/kg required, ie 120 mg at weight of 80 kg. BNF64 indicates 10 x 120 mg / 0.8 mL costs £97.70. Daily cost = £97.70 / 10.	£9.77	BNF 64[166], SmPC[97]
Fragmin® (dalteparin sodium)	BNF64 indicates a dose of 15,000 IU for adults of 69-82 kg weight. 15 000-unit (0.6-mL) syringe = £8.47,	£8.47	BNF 64[166], SmPC[183]
Innohep® (tinzaparin sodium)	BNF64 indicates 14,000 IU at weight of 80 kg. 0.7-mL (14 000-unit) syringe = £11.85	11.85	BNF 64[166], SmPC[184]

The daily cost of enoxaparin was taken as the base case for the daily cost of LMWH in the cost-effectiveness evaluation, as described previously. As with other unit costs in the model this input was varied +/- 30% in sensitivity analyses to £6.84 and £12.70, a range which encompasses the costs of Fragmin® (dalteparin) and Innohep® (tinzaparin).

The BNF indicates the costs for 28 tablets of warfarin are £1.67, £0.86, £0.86 and £0.92 for 0.5 mg, 1.0 mg, 3.0 mg and 5.0 mg tablets respectively. The daily maintenance dose of warfarin is usually 3-9 mg.[166] The daily unit cost for VKA is calculated on the basis of 1 x 5 mg and 1 x 1 mg tablet of warfarin.

Drug monitoring

INR monitoring in primary care was assumed to be delivered by a GP in 50% of cases and by a nurse in the remaining 50% of cases. Additionally, there is the cost of the INR test itself. The cost of monitoring delivered by a GP was taken to be £36.00, based on the consultation costs from the PSSRU.[165] The cost of monitoring delivered by a nurse was taken to be £12.00, according again to PSSRU data.[165] The INR test itself was assumed to cost £3.00, on the basis of the assumptions in the tool provided with the NICE Commissioning Guide for Anticoagulation Services.[173] Overall, the unit cost for INR monitoring delivered in primary care was £26.55 (£3.00+ (£36.00*0.5+(43*(15.5/60))*0.5)).

INR monitoring in secondary care was costed through NHS Reference Costs.[164] The cost of a first attendance visit was taken as the average of consultant and non-consultant led first attendances using NHS Trusts Anticoagulant Services data from the NHS Reference Costs (appendix NSRC01, item 324), weighted by activity (Table 49). This produced a value of

£25.69. Similarly, the cost of a follow-up attendance visit was taken as the average of consultant and non-consultant led visits, again weighted by activity. This produced a value of £21.57.

We described earlier that for INR monitoring, the primary and secondary care setting costs applied for 66.45% and 33.55% of tests/patients respectively.[51] Applying these assumptions to the unit costs above produced a weighted average cost of a first INR monitoring visit of £26.26 and for a subsequent visit was £24.88.

PE and DVT

As noted above in the discussion of resource usage, PEs and DVTs were assumed to be treated either on an inpatient basis, at a composite unit cost, or on an outpatient basis, as the sum of the costs associated with multiple outpatient treatment components as assumed based on expert opinion provided in the development of NICE CG92.[26]

The unit cost of a recurrent DVT treated in an inpatient setting was taken from NHS Reference Costs with HRG code QZ20Z (Deep Vein Thrombosis), as £785.67.[164] The unit cost for a PE in an inpatient setting was taken from NHS Reference Costs as an average across three HRG codes relating to PE, weighted by activity (DZ09A, DZ09B and DZ09C, see Table 49).[164] This yielded a value of £1511.29.

For the index event rivaroxaban was associated with a significantly reduced length of stay. The cost saving achieved from this was estimated using a cost per day for PE hospitalisation derived from a weighted average of relevant NHS reference costs for excess bed-days (£213.16, see Table 49). Excess bed day costs were selected as the cost per day during the later stages of hospitalisation was considered more reflective of inpatient management costs that would be avoided through the use of rivaroxaban. Based on the difference in length of stay between rivaroxaban and LMWH / VKA patients (Table 46[14]) and the proportion of patients treated as inpatients (83%[181]) the cost saving associated with rivaroxaban was calcuated to be £88.46.

The unit costs of each of the items relevant to outpatient care of recurrent PE and DVT were taken from NHS Reference Costs[164] with two exceptions:

- The cost of chest x-rays was taken from a recent diagnostics technology report for NICE.[185]

- The cost of D-dimer tests was taken from a costing in NICE CG92, with appropriate healthcare inflation applied.[26,165]

Bleeding events

Four unit costs were derived:

- major EC bleeding event
- CRNM EC bleeding event
- IC bleeding event
- long-term care following an IC bleeding event (per three months)

Costs associated with major EC bleeds were estimated by averaging the NHS Reference Cost data from ten HRG codes relating to gastrointestinal bleeds with intermediate or major complications, weighted by activity (£929.23, Table 49).[164] It was assumed that there were no further costs associated with this event after three months.

Costs associated with minor extracranial bleeds were modelled by using the NHS Reference Cost data for VB07Z (Accident and Emergency Services: Minor Injury Service: Not Leading to Admitted), which was £128.48.[164] It was assumed that the only costs associated with a minor bleed are those for acute treatment and full recovery was within three months.

Costs associated with IC bleeding events were modelled using the costs for acute care of stroke (£2,605.28) (weighted average of AA23A, B and C) followed by 14 days of rehabilitation. The duration of rehabilitation was modelled on the rehabilitation costs for a major stroke, an assumption that was derived from expert clinical opinion. The cost of rehabilitation was taken from the NHS reference cost of £306.11 per day (weighted average of VC04Z). The cost of the first three months of care for an IC bleed was therefore £6,890.85 (calculated as 2,605.28 + 14 x £306.11).[164]

Follow-on care after an IC bleed was assumed to be identical to the follow-on care for a major ischaemic stroke, which was taken as costing £4826.00 per year for life. This value was taken from a costing by NICE which accounted for the mix of patient dependency that results after a major stroke (38% dependent, 62% independent).[26] The unit cost per 3 month cycle was therefore £1,260.09 after inflation to 2011 prices.[165]

Unit costs: severe PTS

Following the method of Goodacre et al in a recent HTA report, and taking unit costs from NHS Reference Costs, treatment of severe PTS is assumed to require in the first year, three vascular surgery outpatient appointments, and each year thereafter, two GP visits.[152] A first appointment costs £165.00, each follow-up visit costs £123.00 each and a GP visit costs £36.00, according to NHS Reference Costs.[164] This gives a first year cost of £412.06 (£103.02 for each 3 month cycle) and a cost for each subsequent year of £72.00 (£18.00 for each three month cycle). This compares conservatively with a costing of £653 per year in NICE CG92.[26]

Unit costs: CTEPH

Following diagnosis of CTEPH, a PEA may be required.[143,186] The initial cost of a CTEPH was estimated as the weighted average cost of NHS Reference Costs for two relevant HRGs (Table 49), yielding £3,522.38.[45]

The ongoing cost of managing a patient with CTEPH was based on the 2008 estimate of £1219 per month made for NICE CG92, inflated by 3.0% to 2011.[26,165] This yielded a unit cost of £3,844.54 per three month cycle.

Table 49: Weighted averages of NHS Reference Costs by activity

Event	HRG / code	Name	NHS Reference Costs[164]	
			Activity	Unit cost (£)
First INR visit (secondary care)	324	Consultant Led: First Attendance Non-Admitted Face to Face	43,418	49.89
	324	Non-Consultant Led: First Attendance Non-Admitted Face to Face	120,459	16.96
	Total activity and weighted average unit cost		163,877	25.69
Subsequent INR visit (secondary care)		Consultant Led: Follow up Attendance Non-Admitted Face to Face	1,262,317	23.47
		Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face	778,065	18.49
	Total activity and weighted average unit cost		2,040,382	21.57
DVT	QZ20Z	Deep Vein Thrombosis	38,101	785.67
PE	DZ09A	Pulmonary Embolus with Major CC	15,848	1,891
	DZ09B	Pulmonary Embolus with CC	15,441	1,362
	DZ09C	Pulmonary Embolus without CC	6,343	925
	Total activity and weighted average unit cost		37,632	1511.29
Major EC bleed	FZ16Z	Very Major Procedures for Gastrointestinal Bleed	495	4,797.49
	FZ25A	Therapeutic Endoscopic or Intermediate Stomach or Duodenum Procedures 19 years and over	26,301	545.86
	FZ29Z	Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed	22,819	1,056.87
	FZ30Z	Diagnostic Endoscopic or Intermediate Procedures for Gastrointestinal Bleed	19,541	633.13
	FZ38D	Gastrointestinal Bleed with length of stay 2 days or more with Major CC	12,044	2,245.26
	FZ38E	Gastrointestinal Bleed with length of stay 2 days or more without Major CC	14,496	1,404.81

	FZ38F	Gastrointestinal Bleed with length of stay 1 day or less	43,700	433.54
	FZ43A	Non-Malignant Stomach or Duodenum Disorders with length of stay 2 days or more with Major CC	12,915	2,434.66
	FZ43B	Non-Malignant Stomach or Duodenum Disorders with length of stay 2 days or more without Major CC	19,047	1,677.04
	FZ43C	Non-Malignant Stomach or Duodenum Disorders with length of stay 1 day or less	46,146	415.05
	Total activity and weighted average unit cost		217,504	929.23
Minor EC bleed	VB07Z	Category 2 investigation with category 2 treatment	1,590,270	128.48
IC bleed	AA23Z	Haemorrhagic Cerebrovascular Disorders	32,168	2605.28
	VC04Z	Rehabilitation for stroke	599,108	306.11
	Three months of care (1xAA23Z + 14xVC04Z)			6890.85
Elective Excess bed day	DZ09A	Pulmonary Embolus with Major CC	553	204.46
	DZ09B	Pulmonary Embolus with CC	187	206.04
	DZ09C	Pulmonary Embolus without CC	2	407.01
Non-elective Excess bed day	DZ09A	Pulmonary Embolus with Major CC	12,466	213.79
	DZ09B	Pulmonary Embolus with CC	5,189	209.89
	DZ09C	Pulmonary Embolus without CC	774	232.33
	Total activity and weighted average unit cost		19,171	213.16

A summary of all list costs is presented in Table 50.

Table 50. List of all unit costs assumed

Item	Value (£)	Lower (£)	Upper (£)	Source (Range)
Drug acquisition (cost per day whilst on treatment)				
LMWH	£9.77	£6.84	£12.70	BNF 64[166], SmPC[97] (+/- 30%)
VKA	£0.06	£0.04	£0.08	BNF 64[166], SmPC[187] (+/- 30%)
Xarelto® (rivaroxaban)	£2.10	£2.10	£2.10	BNF 64[166]
Inpatient costs				
Diagnosis and treatment of a DVT	£785.67	£568.45	£894.04	NHS Reference Costs 2010-11[164], Table 51 (IQR)
Diagnosis and treatment of a PE	£1,511.29	£876.75	£1,882.92	
Savings due to early discharge for patients treated with Xarelto® (rivaroxaban)	£88.46	£69.07	£104.95	NHS Reference Costs 2010-11: DZ09A, DZ09B, DZ09C.[164] Cost per bed day * (length of stay (VKA) – length of stay (rivaroxaban))* Proportion of patients managed as inpatients = (£213.16*(9.1-8.6)*83% (IQR)
Outpatient treatment items				
Doppler ultrasound	£65.39	£48.85	£73.23	NHS Reference Costs 2010-11: RA24Z Ultrasound scan for less than 20 minutes (IQR)[164]
CT angiography	£95.30	£73.19	£106.32	NHS Reference Costs 2010-11: RA08Z, computed tomography scan, one area, no contrast (IQR)[164]
Chest X-ray	£15.72	£11.01	£20.44	NICE DT1 assessment report (Table 4.17)[185] and PSSRU 2011 (section 13.5)[165]. Calculated from £3.42 for a computed radiography x-ray, £6.16 for a digital radiography + 16 minutes of £41 per hour radiographer = (3.42+6.16)/2+(16/60)*41= 15.72 (+/- 30%)

Item	Value (£)	Lower (£)	Upper (£)	Source (Range)
Electrocardiogram (ECG)	£45.31	£31.72	£58.90	NHS Reference Costs 2010-11: DA13 (+/- 30%)[164]
D-dimer	£12.40	£8.68	£16.13	NICE CG92, PSSRU 2011: £12 from CG92[26] x 1.033 (inflated two years[165]) (+/- 30%)
Emergency admission	£107.02	£47.66	£133.91	NHS Reference Costs 2010-11: service 180: Accident and Emergency (IQR)[164]
Drug monitoring				
INR monitoring in secondary care – first visit	£25.69	£17.98	£33.39	NHS Reference Costs 2010-11[164], Table 51 (+/- 30%. IQR not used due to an error in the NHS reference costs)
INR monitoring in secondary care – each subsequent visit	£21.57	£11.23	£25.95	NHS Reference Costs 2010-11 REF, Table 50 (IQR)
INR monitoring in primary care, per visit	£26.55	£18.59	£34.52	NICE CG36 costing report[175], PSSRU 2011[165] (IQR)
District nurse visit	£37.65	£32.10	£41.69	NHS Reference Costs 2010-11: CN301AF, district nursing services, adult, face to face (IQR)[164]
NHS transportation (where required)	£12.29	£6.61	£14.65	NHS Reference Costs 2010-11 (IQR)[164]
Treatment of bleeds				
CRNM bleed (extracranial)	£128.48	£109.79	£147.48	NHS Reference Costs 2010-11[164], Table 51 (IQR)
Major extracranial bleed	£929.23	£667.41	£1,050.70	
Major intracranial bleed, first 3 months	£6,890.85	£5,635.65	£8,017.51	
Major intracranial bleed, each subsequent 3 months	£1,260.09	£882.06	£1,638.12	
Management of PTS				

Item	Value (£)	Lower (£)	Upper (£)	Source (Range)
Year 1 (3-month cost)	£103.02	£68.76	£122.26	Goodacre 2006[152], NICE CG92[26], NHS Reference Costs 2010-11[164] (IQR, +/- 30% for 2y+)
Year 2+ (3-month cost)	£18.00	£12.60	£23.40	
Management of CTEPH				
PEA	£3,522.38	£1,959.01	£4,338.72	NHS Reference Costs 2010-11[164] (IQR)
Ongoing cost (per 3 months)	£3,844.54	£2,691.17	£4,997.90	NICE CG92[26], PSSRU 2011[165], UK consensus statement[186] (+/- 30%)

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

When resource usage assumptions and unit costs assumptions described in section 7.5.5 are combined, these produce the costs for each model state presented in Table 51.

Table 51: List of health states and associated costs in the economic model

Health states			Value (£)
1	On treatment - rivaroxaban (All costs relate to drug, none to administration.)	Cycle 0 Cycle 1 Cycle 2+	£88.20 £147.63 £191.73
2	On treatment – dual LMWH/VKA	Cycle 0 - drug Cycle 0 - administration Cycle 1 - drug Cycle 1 - administration Cycle 2+ - drug Cycle 2+ - administration	£94.77 £5 £5.18 £228.50 £5.80 £126.18
2	rVTE – DVT		£836.08
3	rVTE – PE		£1,766.25
4	Major bleed - IC		£6,890.85
5	Major bleed - EC		£929.23
6	CRNM bleed		£128.48
7	Off-treatment (post IC bleed)		£1,260.09
8	Off-treatment post iPE		£0.00
9	Off-treatment post DVT		£0.00
10	On-treatment post DVT		£1,766.25

Health states			Value (£)
11	PE post DVT		£1,766.25
12	CTEPH (surgery and on-going)*		£6,255.38
13	CTEPH (on-going)*		£3,844.54
14	Death		£0.00
N/A	PTS severe	Year 1	£103.02
N/A		Year 2+	£18.00

* Ongoing costs apply to each 3 month cycle following CTEPH event.

Cycle 0 corresponds to 21 days treated with rivaroxaban bid for the rivaroxaban arm and 9.7 days of LMWH for the LMWH/VKA arm. Note no monitoring costs were assumed for either treatment arm. Cycle 1 corresponds to the remainder of a 3 month cycle (70 days) treated with rivaroxaban od and the remainder of a 3 month cycle (81.7 days) treated with VKA only. Cycle 2+ corresponds to any subsequent 3 month cycle in which patients are treated either with rivaroxaban or with VKA.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The costing of all items, including bleeding and adverse events, has been covered previously within the model states.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None. The costing of all items has been covered previously.

7.6 Sensitivity analysis

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The uncertainties around model structural assumptions were discussed with clinical experts when finalizing the model structure. Early in model development Professor Bengt Jonsson, Stockholm School of Economics, reviewed the model structure, assumptions and techniques and provided his comments. Subsequent review was provided by Prof. Lieven Annemans, Professor of Health economics at I-CHER (Ghent University and Brussels University). Comments were taken into account during the finalisation of the model structure. Other structural assumptions such as time horizon, inclusion of PTS, CTEPH and discount rates are tested in the one-way sensitivity analyses.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

A range of one way or univariate, deterministic sensitivity analyses (USAs) were performed. Tornado plots are presented according to a net monetary benefit (NMB) or ICER as the outcome, whichever is considered more informative. The rationale for the ranges tested is as follows:

- Probabilities of clinical events on dual LMWH/VKA therapy were varied between 95% CIs. This included:
  - Acute phase probabilities of recurrent VTE, major bleeds, CRNM bleeds, as described in Table 28, Table 30 and Table 31
  - All other clinical events, as outlined in Table 40
- Treatment effects in relation to efficacy and safety variables for rivaroxaban vs dual LMWH/VKA therapy were varied between 95% CI, as described in Table 40.

- Utility, as described in Table 43. (Variations in utility value assumptions were varied between 95% CIs or, where these were not available, the IQR. Assumptions were bounded between 0 and 1.)
- Resource usage, as described in Table 47.
- Unit costs: NHS Reference cost IQR or varied by ±30%, as previously described in section 7.5.5.
- Discounting: A range of 0% to 6% pa was tested, in accordance with the NICE Reference Case.
- The time horizon was varied from lifetime to 5 years
- The setting of care was varied from primary/secondary/hybrid proportions described previously to either 100% primary or 100% secondary
- Mean age at baseline was varied from 58 years to 45 and 75 years

In addition, the USAs also included various additional groupings of parameters, as outlined in Table 52.

Table 52: Grouping of parameters for additional USAs

Group parameters	Individual parameters covered
Cost of ambulatory visits (OPs by different treatment setting plus district nurse)	Cost of all types of monitoring visits for VKA and rivaroxaban; cost of nurse visit
Cost of inpatient treatments	Cost of inpatient treatment for DVT and PE episodes; cost of CTEPH surgery
Cost of outpatient treatment parameters	Doppler ultrasound; CT angiography; Chest X ray; ECG; D-dimer; Emergency admission
Cost of treating bleeds (Major and minor)	Cost of CRNM bleeds and major EC and IC bleeds
Cost of treating PTS (mild/moderate and severe, all years)	Cost of PTS management (mild/moderate and severe) for Yr1 and Yr2+
Cost of treating stroke (initial and subsequent cycles)	Cost of major intra-cranial and post intra-cranial bleeds
Duration of utility impact for VTE and Bleed events	Duration of utility impact for DVT, PE, extra- and intra-cranial bleeds
State-related mortality (all parameters)	All mortality parameters listed under "Probability of death with event" in table above
State-related utility weightings	All utility parameters listed under "utility values" in table

(all parameters)	above
VKA OAC monitoring	The three settings listed under "VKA drug monitoring" in table above

Since the tables referred to in the bullets above (or the bullets themselves) include the point estimates and the USA ranges, no additional table is presented here.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analyses (PSA) were conducted.

This was achieved through repeated sampling of parameter values from a series of assigned distribution types, based on the point estimates and the standard error statistics for each average parameter value. Each set of samples from all the parameters generated a single estimate of expected costs, effects and net benefit generated by the model. The analyses were run over 5,000 iterations, so all the values the parameters are likely to take are represented in a range of outputs.

The following parameters were varied as follows:

- Probabilities of the following clinical events on dual LMWH/VKA therapy:
  - Acute phase probabilities of recurrent VTE, major bleeds, CRNM bleeds, according to Beta distributions as described in Table 28, Table 30 and Table 31.
  - All other clinical events, according to Beta distributions as outlined in Table 40.
- Treatment effects (HR) in relation to efficacy and safety variables (recurrent VTE, major bleeding and CRNM bleeding) according to lognormal distributions for rivaroxaban vs dual LMWH/VKA therapy are described in Table 40.

- Utility, according to Beta distributions as described in Table 43. (Variations in utility value assumptions were varied between 95% CIs or, where these were not available, the IQR. Assumptions were bounded between 0 and 1.)
- Resource usage, according to a variety of distributions as described in Table 47.
- Unit costs, according to Gamma distributions with means equal to the point estimates (given in Table 50) and standard errors informed by interquartlie ranges.

Since the tables referred to in the bullets above (or the bullets themselves) include the statistical distributions, the parameters of those distributions, and their rationale, no additional table is presented here.

7.7 Results

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Outcomes from the economic model and EINSTEIN-PE are compared for the 3, 6 and 12 month treatment duration analyses in Table 53. As the trial period was only 12 months no validation of longterm outcomes can be presented.

VTE (DVT and PE) and bleed (CRNM, intra-cranial and extra-cranial bleed) incidence rates are reported at 3, 6 and 12 months (model cycles 1, 2 and 4). The model was run for a cohort of 100 patients. Clinical trial results for comparison were derived from the EINSTEIN-PE CSR.[73]

Table 53: Incidence of VTE and bleeding in the trial (EINSTEIN-PE) compared with incidence projected from the economic model, by treatment arm and patient group

Patient group	Outcome	Timepoint	Rivaroxaban		LMWH/VKA	
			Model	Trial	Model	Trial
3 months						
	VTE	3 months	1.8%	[redacted]	1.6%	[redacted]
	Bleeding	3 months	8.6%	[redacted]	10.6%	[redacted]
6 months						
	VTE	3 months	1.8%	[redacted]	1.6%	[redacted]
		6 months	0.2%	[redacted]	0.2%	[redacted]
	Bleeding	3 months	7.2%	[redacted]	7.7%	[redacted]
		6 months	2.3%	[redacted]	2.6%	[redacted]
12 months						
	VTE	3 months	1.7%	[redacted]	1.5%	[redacted]
		6 months	0.4%	[redacted]	0.3%	[redacted]
		12 months	0.3%	[redacted]	0.3%	[redacted]
	Bleeding	3 months	6.9%	[redacted]	7.5%	[redacted]
		6 months	2.8%	[redacted]	2.9%	[redacted]
		12 months	2.9%	[redacted]	3.2 %	[redacted]

Overall, differences between model and trial results were modest for both VTE and bleeds. Model results are closer to trial results for the VTE outcome, particularly in the LMWH/VKA arm.

Observations of differences and their possible reasons include:

- in the model, background mortality rates (non-VTE specific) were included;

- estimation of event rates in the rivaroxaban arm of the model through application of the whole study treatment effects rather than period or patient group (intended treatment duration) specifica effects;
- in the model, the inclusion of discontinuation was relatively simple;
- the Markov structure does not allow for the possibility of concurrent events such as bleed and VTE.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 54 shows the proportion of the model cohort occupying each aggregated health state per year for the intervention and the comparator arm, and for each treatment duration (3, 6, 12 months and lifelong). Two aggregated health states are shown:

- VTE: Aggregation of DVT + PE
- Bleeds: Aggregation of CRNM bleeds + major EC + major IC bleeds

For the first year, the probabilities have been detailed for each quarter (i.e. model cycle), to show the impact of each individual treatment duration. The cohort was simulated for a 58 years-old patient over a 40 year lifetime from model entry. Thereafter and for purposes of brevity, the final cycle of each year was reported only.

The eight tables following Table 54 provide the detail of the proportion of the model cohort occupying each individual health state per year for the intervention and the comparator arm, for each treatment duration (3, 6, 12 months and lifelong). For purposes of brevity, the final cycle of each year was reported only.

The health states presented in these tables may be compared with the health states described Table 26 and the structures presented in Figure 12.

Table 54: Proportion of the cohort in each aggregated health state, per treatment arm and treatment duration

	3 months				6 months				12 months				Lifelong			
	Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA	
Years	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	1.836	8.596	1.637	10.640	1.777	7.229	1.584	7.731	1.735	6.873	1.546	7.536	1.735	6.873	1.546	7.536
0.5	1.127	0.000	1.104	0.000	0.179	2.298	0.162	2.629	0.375	2.792	0.335	2.945	0.375	2.820	0.335	2.973
0.75	1.230	0.000	1.225	0.000	1.219	0.000	1.214	0.000	0.133	1.474	0.126	1.598	0.116	1.544	0.110	1.669
1	1.222	0.000	1.217	0.000	1.229	0.000	1.227	0.000	0.161	1.455	0.154	1.577	0.140	1.554	0.134	1.677
2	1.195	0.000	1.190	0.000	1.202	0.000	1.200	0.000	1.206	0.000	1.204	0.000	0.365	1.240	0.348	1.392
3	1.174	0.000	1.168	0.000	1.180	0.000	1.178	0.000	1.185	0.000	1.182	0.000	0.457	1.215	0.442	1.345
4	1.154	0.000	1.148	0.000	1.160	0.000	1.158	0.000	1.164	0.000	1.162	0.000	0.512	1.306	0.511	1.301
5	1.133	0.000	1.128	0.000	1.140	0.000	1.138	0.000	1.144	0.000	1.141	0.000	0.564	1.264	0.562	1.259
6	1.112	0.000	1.107	0.000	1.119	0.000	1.117	0.000	1.123	0.000	1.120	0.000	0.600	1.222	0.598	1.217
7	1.090	0.000	1.086	0.000	1.097	0.000	1.095	0.000	1.101	0.000	1.098	0.000	0.625	1.181	0.623	1.176
8	1.068	0.000	1.063	0.000	1.074	0.000	1.073	0.000	1.078	0.000	1.076	0.000	0.641	1.140	0.638	1.136
9	1.045	0.000	1.041	0.000	1.051	0.000	1.050	0.000	1.055	0.000	1.053	0.000	0.650	1.100	0.647	1.096
10	1.022	0.000	1.017	0.000	1.028	0.000	1.026	0.000	1.031	0.000	1.029	0.000	0.653	1.061	0.650	1.056
11	0.997	0.000	0.993	0.000	1.003	0.000	1.001	0.000	1.006	0.000	1.004	0.000	0.652	1.021	0.648	1.017
12	0.972	0.000	0.967	0.000	0.977	0.000	0.976	0.000	0.981	0.000	0.979	0.000	0.647	0.981	0.643	0.977
13	0.945	0.000	0.941	0.000	0.951	0.000	0.949	0.000	0.954	0.000	0.952	0.000	0.638	0.942	0.635	0.938

	3 months				6 months				12 months				Lifelong			
	Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA	
Years	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds
14	0.918	0.000	0.914	0.000	0.924	0.000	0.922	0.000	0.927	0.000	0.925	0.000	0.628	0.902	0.625	0.899
15	0.890	0.000	0.886	0.000	0.895	0.000	0.894	0.000	0.898	0.000	0.896	0.000	0.615	0.863	0.612	0.859
16	0.861	0.000	0.857	0.000	0.866	0.000	0.864	0.000	0.869	0.000	0.867	0.000	0.600	0.823	0.597	0.820
17	0.830	0.000	0.827	0.000	0.835	0.000	0.834	0.000	0.838	0.000	0.836	0.000	0.584	0.783	0.581	0.780
18	0.798	0.000	0.795	0.000	0.803	0.000	0.802	0.000	0.806	0.000	0.804	0.000	0.566	0.743	0.563	0.740
19	0.765	0.000	0.762	0.000	0.770	0.000	0.768	0.000	0.772	0.000	0.771	0.000	0.546	0.703	0.543	0.700
20	0.731	0.000	0.727	0.000	0.735	0.000	0.734	0.000	0.738	0.000	0.736	0.000	0.525	0.662	0.522	0.660
21	0.695	0.000	0.692	0.000	0.699	0.000	0.697	0.000	0.701	0.000	0.700	0.000	0.502	0.621	0.499	0.619
22	0.657	0.000	0.654	0.000	0.661	0.000	0.660	0.000	0.663	0.000	0.662	0.000	0.478	0.580	0.475	0.578
23	0.618	0.000	0.615	0.000	0.622	0.000	0.620	0.000	0.624	0.000	0.622	0.000	0.452	0.538	0.449	0.536
24	0.577	0.000	0.575	0.000	0.581	0.000	0.580	0.000	0.583	0.000	0.582	0.000	0.424	0.496	0.422	0.494
25	0.536	0.000	0.534	0.000	0.539	0.000	0.538	0.000	0.541	0.000	0.540	0.000	0.396	0.454	0.394	0.453
26	0.494	0.000	0.492	0.000	0.497	0.000	0.496	0.000	0.499	0.000	0.498	0.000	0.367	0.413	0.365	0.412
26	0.451	0.000	0.449	0.000	0.454	0.000	0.453	0.000	0.456	0.000	0.455	0.000	0.337	0.373	0.335	0.371
27	0.408	0.000	0.407	0.000	0.411	0.000	0.410	0.000	0.412	0.000	0.411	0.000	0.306	0.333	0.305	0.331
28	0.366	0.000	0.364	0.000	0.368	0.000	0.367	0.000	0.369	0.000	0.368	0.000	0.276	0.294	0.274	0.293
30	0.324	0.000	0.323	0.000	0.326	0.000	0.325	0.000	0.327	0.000	0.326	0.000	0.245	0.257	0.244	0.256
31	0.284	0.000	0.282	0.000	0.285	0.000	0.285	0.000	0.286	0.000	0.286	0.000	0.216	0.222	0.215	0.221
32	0.246	0.000	0.245	0.000	0.248	0.000	0.247	0.000	0.249	0.000	0.248	0.000	0.189	0.190	0.187	0.189
33	0.212	0.000	0.211	0.000	0.213	0.000	0.212	0.000	0.214	0.000	0.213	0.000	0.163	0.161	0.162	0.161
34	0.180	0.000	0.179	0.000	0.181	0.000	0.180	0.000	0.181	0.000	0.181	0.000	0.139	0.135	0.138	0.135

	3 months				6 months				12 months				Lifelong			
	Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA	
Years	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds
35	0.150	0.000	0.149	0.000	0.151	0.000	0.150	0.000	0.151	0.000	0.151	0.000	0.116	0.111	0.116	0.111
36	0.122	0.000	0.122	0.000	0.123	0.000	0.123	0.000	0.123	0.000	0.123	0.000	0.095	0.090	0.095	0.089
37	0.098	0.000	0.097	0.000	0.099	0.000	0.098	0.000	0.099	0.000	0.099	0.000	0.077	0.071	0.076	0.070
38	0.077	0.000	0.077	0.000	0.077	0.000	0.077	0.000	0.078	0.000	0.077	0.000	0.061	0.055	0.060	0.055
39	0.059	0.000	0.059	0.000	0.060	0.000	0.059	0.000	0.060	0.000	0.060	0.000	0.047	0.042	0.047	0.041
40	0.045	0.000	0.045	0.000	0.045	0.000	0.045	0.000	0.045	0.000	0.045	0.000	0.036	0.031	0.035	0.031

Notes: VTE and Bleed aggregated states as defined above.

Table 55: Markov trace: rivaroxaban arm, 3 months of treatment, aged 58 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	87.133	0.684	1.153	0.420	1.619	6.557	0.000	2.130	0.000	0.000	0.000	0.157	0.000	0.147
0.5	0.000	0.490	0.638	0.000	0.000	0.000	0.236	96.683	0.707	0.000	0.000	0.168	0.153	0.925
0.75	0.000	0.534	0.691	0.000	0.000	0.000	0.236	95.572	1.199	0.000	0.005	0.162	0.313	1.289
1	0.000	0.531	0.683	0.000	0.000	0.000	0.236	94.512	1.731	0.000	0.009	0.161	0.462	1.676
2	0.000	0.519	0.653	0.000	0.000	0.000	0.234	90.345	3.769	0.000	0.023	0.158	1.014	3.285
3	0.000	0.510	0.626	0.000	0.000	0.000	0.233	86.860	5.698	0.000	0.037	0.009	1.079	4.948
4	0.000	0.501	0.602	0.000	0.000	0.000	0.231	83.464	7.513	0.000	0.050	0.009	1.002	6.628
5	0.000	0.492	0.578	0.000	0.000	0.000	0.229	80.154	9.217	0.000	0.063	0.009	0.933	8.327
6	0.000	0.483	0.555	0.000	0.000	0.000	0.227	76.905	10.808	0.000	0.074	0.009	0.869	10.071

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
7	0.000	0.474	0.532	0.000	0.000	0.000	0.225	73.715	12.285	0.000	0.085	0.008	0.810	11.866
8	0.000	0.464	0.509	0.000	0.000	0.000	0.222	70.596	13.653	0.000	0.095	0.008	0.756	13.696
9	0.000	0.454	0.487	0.000	0.000	0.000	0.220	67.534	14.907	0.000	0.104	0.008	0.707	15.580
10	0.000	0.444	0.465	0.000	0.000	0.000	0.217	64.532	16.049	0.000	0.112	0.008	0.661	17.512
11	0.000	0.433	0.444	0.000	0.000	0.000	0.214	61.568	17.074	0.000	0.120	0.008	0.618	19.522
12	0.000	0.422	0.423	0.000	0.000	0.000	0.210	58.652	17.981	0.000	0.127	0.008	0.579	21.599
13	0.000	0.411	0.402	0.000	0.000	0.000	0.207	55.789	18.774	0.000	0.132	0.007	0.542	23.736
14	0.000	0.399	0.382	0.000	0.000	0.000	0.203	52.975	19.449	0.000	0.137	0.007	0.508	25.940
15	0.000	0.387	0.362	0.000	0.000	0.000	0.198	50.200	20.002	0.000	0.141	0.007	0.476	28.226
16	0.000	0.374	0.342	0.000	0.000	0.000	0.194	47.454	20.429	0.000	0.145	0.007	0.446	30.611
17	0.000	0.361	0.323	0.000	0.000	0.000	0.189	44.747	20.730	0.000	0.147	0.006	0.417	33.080
18	0.000	0.347	0.303	0.000	0.000	0.000	0.183	42.073	20.902	0.000	0.148	0.006	0.390	35.647
19	0.000	0.332	0.284	0.000	0.000	0.000	0.177	39.418	20.934	0.000	0.149	0.006	0.364	38.336
20	0.000	0.317	0.265	0.000	0.000	0.000	0.171	36.794	20.831	0.000	0.148	0.006	0.339	41.129
21	0.000	0.302	0.247	0.000	0.000	0.000	0.164	34.197	20.588	0.000	0.146	0.005	0.314	44.036
22	0.000	0.285	0.228	0.000	0.000	0.000	0.157	31.625	20.200	0.000	0.144	0.005	0.291	47.065
23	0.000	0.268	0.210	0.000	0.000	0.000	0.149	29.074	19.663	0.000	0.140	0.005	0.268	50.224
24	0.000	0.251	0.192	0.000	0.000	0.000	0.140	26.560	18.982	0.000	0.135	0.004	0.246	53.490
25	0.000	0.233	0.174	0.000	0.000	0.000	0.132	24.107	18.176	0.000	0.129	0.004	0.224	56.821
26	0.000	0.215	0.157	0.000	0.000	0.000	0.123	21.725	17.253	0.000	0.123	0.004	0.203	60.198
26	0.000	0.196	0.140	0.000	0.000	0.000	0.113	19.402	16.206	0.000	0.115	0.004	0.183	63.642
27	0.000	0.177	0.124	0.000	0.000	0.000	0.103	17.158	15.053	0.000	0.107	0.003	0.163	67.111
28	0.000	0.159	0.108	0.000	0.000	0.000	0.093	15.019	13.822	0.000	0.099	0.003	0.144	70.553

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
30	0.000	0.141	0.094	0.000	0.000	0.000	0.084	13.008	12.544	0.000	0.089	0.003	0.126	73.913
31	0.000	0.123	0.080	0.000	0.000	0.000	0.074	11.133	11.237	0.000	0.080	0.002	0.109	77.162
32	0.000	0.107	0.068	0.000	0.000	0.000	0.065	9.455	9.979	0.000	0.071	0.002	0.094	80.160
33	0.000	0.092	0.057	0.000	0.000	0.000	0.056	7.937	8.750	0.000	0.062	0.002	0.080	82.964
34	0.000	0.078	0.048	0.000	0.000	0.000	0.048	6.589	7.582	0.000	0.054	0.001	0.067	85.532
35	0.000	0.065	0.039	0.000	0.000	0.000	0.041	5.368	6.441	0.000	0.046	0.001	0.056	87.944
36	0.000	0.053	0.031	0.000	0.000	0.000	0.033	4.286	5.359	0.000	0.038	0.001	0.045	90.152
37	0.000	0.043	0.024	0.000	0.000	0.000	0.027	3.355	4.368	0.000	0.031	0.001	0.036	92.115
38	0.000	0.033	0.019	0.000	0.000	0.000	0.021	2.576	3.489	0.000	0.025	0.001	0.028	93.808
39	0.000	0.026	0.014	0.000	0.000	0.000	0.017	1.940	2.732	0.000	0.020	0.000	0.021	95.231
40	0.000	0.019	0.010	0.000	0.000	0.000	0.013	1.434	2.100	0.000	0.015	0.000	0.016	96.392

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death.

Table 56: Markov trace: LMWH/VKA arm, 3 months of treatment, aged 58 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	85.289	0.609	1.027	0.843	3.250	6.548	0.000	2.130	0.000	0.000	0.000	0.157	0.000	0.147
0.5	0.000	0.480	0.624	0.000	0.000	0.000	0.474	96.340	0.630	0.000	0.000	0.166	0.153	1.132
0.75	0.000	0.532	0.688	0.000	0.000	0.000	0.474	95.226	1.113	0.000	0.005	0.161	0.311	1.491
1	0.000	0.529	0.680	0.000	0.000	0.000	0.473	94.170	1.644	0.000	0.008	0.161	0.459	1.877
2	0.000	0.517	0.650	0.000	0.000	0.000	0.470	90.019	3.676	0.000	0.023	0.157	1.009	3.479

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
3	0.000	0.508	0.624	0.000	0.000	0.000	0.467	86.546	5.599	0.000	0.037	0.009	1.073	5.137
4	0.000	0.499	0.600	0.000	0.000	0.000	0.463	83.162	7.409	0.000	0.050	0.009	0.997	6.811
5	0.000	0.490	0.576	0.000	0.000	0.000	0.460	79.864	9.108	0.000	0.062	0.009	0.928	8.504
6	0.000	0.481	0.553	0.000	0.000	0.000	0.455	76.627	10.695	0.000	0.074	0.009	0.864	10.243
7	0.000	0.472	0.530	0.000	0.000	0.000	0.451	73.449	12.169	0.000	0.084	0.008	0.806	12.032
8	0.000	0.462	0.507	0.000	0.000	0.000	0.446	70.341	13.532	0.000	0.094	0.008	0.752	13.856
9	0.000	0.452	0.485	0.000	0.000	0.000	0.441	67.290	14.784	0.000	0.103	0.008	0.703	15.734
10	0.000	0.442	0.464	0.000	0.000	0.000	0.435	64.299	15.923	0.000	0.112	0.008	0.658	17.660
11	0.000	0.431	0.442	0.000	0.000	0.000	0.429	61.346	16.946	0.000	0.119	0.008	0.615	19.664
12	0.000	0.420	0.421	0.000	0.000	0.000	0.422	58.440	17.852	0.000	0.126	0.008	0.576	21.736
13	0.000	0.409	0.401	0.000	0.000	0.000	0.415	55.588	18.643	0.000	0.131	0.007	0.540	23.867
14	0.000	0.397	0.381	0.000	0.000	0.000	0.407	52.784	19.318	0.000	0.136	0.007	0.506	26.065
15	0.000	0.385	0.361	0.000	0.000	0.000	0.398	50.019	19.871	0.000	0.140	0.007	0.474	28.346
16	0.000	0.372	0.341	0.000	0.000	0.000	0.389	47.282	20.298	0.000	0.144	0.007	0.444	30.724
17	0.000	0.359	0.322	0.000	0.000	0.000	0.379	44.586	20.600	0.000	0.146	0.006	0.415	33.188
18	0.000	0.345	0.302	0.000	0.000	0.000	0.368	41.921	20.773	0.000	0.147	0.006	0.388	35.749
19	0.000	0.331	0.283	0.000	0.000	0.000	0.356	39.275	20.808	0.000	0.148	0.006	0.362	38.431
20	0.000	0.316	0.264	0.000	0.000	0.000	0.343	36.661	20.708	0.000	0.147	0.006	0.337	41.218
21	0.000	0.300	0.246	0.000	0.000	0.000	0.329	34.074	20.468	0.000	0.145	0.005	0.313	44.119
22	0.000	0.284	0.227	0.000	0.000	0.000	0.315	31.510	20.084	0.000	0.143	0.005	0.290	47.142
23	0.000	0.267	0.209	0.000	0.000	0.000	0.299	28.969	19.550	0.000	0.139	0.005	0.267	50.295
24	0.000	0.250	0.191	0.000	0.000	0.000	0.282	26.464	18.875	0.000	0.134	0.004	0.245	53.555
25	0.000	0.232	0.173	0.000	0.000	0.000	0.264	24.020	18.075	0.000	0.129	0.004	0.223	56.880

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
26	0.000	0.214	0.156	0.000	0.000	0.000	0.246	21.646	17.158	0.000	0.122	0.004	0.202	60.252
26	0.000	0.195	0.139	0.000	0.000	0.000	0.227	19.332	16.117	0.000	0.115	0.003	0.182	63.689
27	0.000	0.177	0.123	0.000	0.000	0.000	0.207	17.096	14.972	0.000	0.107	0.003	0.162	67.153
28	0.000	0.158	0.108	0.000	0.000	0.000	0.187	14.965	13.748	0.000	0.098	0.003	0.144	70.589
30	0.000	0.140	0.093	0.000	0.000	0.000	0.168	12.961	12.477	0.000	0.089	0.003	0.126	73.944
31	0.000	0.123	0.080	0.000	0.000	0.000	0.148	11.092	11.177	0.000	0.080	0.002	0.109	77.189
32	0.000	0.107	0.068	0.000	0.000	0.000	0.130	9.421	9.926	0.000	0.071	0.002	0.093	80.182
33	0.000	0.092	0.057	0.000	0.000	0.000	0.113	7.908	8.704	0.000	0.062	0.002	0.080	82.983
34	0.000	0.078	0.047	0.000	0.000	0.000	0.097	6.566	7.543	0.000	0.054	0.001	0.067	85.548
35	0.000	0.065	0.039	0.000	0.000	0.000	0.081	5.348	6.408	0.000	0.046	0.001	0.055	87.957
36	0.000	0.053	0.031	0.000	0.000	0.000	0.067	4.271	5.332	0.000	0.038	0.001	0.045	90.162
37	0.000	0.042	0.024	0.000	0.000	0.000	0.054	3.343	4.346	0.000	0.031	0.001	0.036	92.122
38	0.000	0.033	0.019	0.000	0.000	0.000	0.043	2.566	3.471	0.000	0.025	0.001	0.028	93.814
39	0.000	0.026	0.014	0.000	0.000	0.000	0.033	1.933	2.718	0.000	0.019	0.000	0.021	95.235
40	0.000	0.019	0.010	0.000	0.000	0.000	0.026	1.429	2.089	0.000	0.015	0.000	0.016	96.395

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death.

Table 57: Markov trace: rivaroxaban arm, 6 months of treatment, aged 58 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	88.559	0.662	1.115	0.103	0.397	6.729	0.000	2.130	0.000	0.000	0.000	0.157	0.000	0.147

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0.5	90.631	0.068	0.111	0.069	0.266	1.963	0.058	5.188	0.687	0.000	0.000	0.168	0.153	0.637
0.75	0.000	0.530	0.684	0.000	0.000	0.000	0.097	96.600	0.747	0.000	0.005	0.156	0.313	0.868
1	0.000	0.534	0.690	0.000	0.000	0.000	0.097	95.520	1.282	0.000	0.005	0.162	0.457	1.253
2	0.000	0.522	0.660	0.000	0.000	0.000	0.096	91.309	3.352	0.000	0.020	0.159	1.013	2.869
3	0.000	0.513	0.633	0.000	0.000	0.000	0.095	87.786	5.309	0.000	0.034	0.009	1.079	4.541
4	0.000	0.504	0.608	0.000	0.000	0.000	0.095	84.354	7.151	0.000	0.048	0.009	1.002	6.229
5	0.000	0.495	0.584	0.000	0.000	0.000	0.094	81.008	8.881	0.000	0.060	0.009	0.933	7.936
6	0.000	0.486	0.561	0.000	0.000	0.000	0.093	77.725	10.497	0.000	0.072	0.009	0.869	9.689
7	0.000	0.476	0.537	0.000	0.000	0.000	0.092	74.501	11.999	0.000	0.083	0.009	0.811	11.492
8	0.000	0.467	0.515	0.000	0.000	0.000	0.091	71.349	13.389	0.000	0.093	0.008	0.757	13.331
9	0.000	0.457	0.492	0.000	0.000	0.000	0.090	68.254	14.665	0.000	0.102	0.008	0.707	15.224
10	0.000	0.446	0.470	0.000	0.000	0.000	0.089	65.220	15.829	0.000	0.111	0.008	0.662	17.165
11	0.000	0.436	0.449	0.000	0.000	0.000	0.088	62.225	16.873	0.000	0.118	0.008	0.619	19.184
12	0.000	0.425	0.427	0.000	0.000	0.000	0.086	59.277	17.801	0.000	0.125	0.008	0.580	21.271
13	0.000	0.413	0.407	0.000	0.000	0.000	0.085	56.384	18.612	0.000	0.131	0.007	0.543	23.418
14	0.000	0.401	0.386	0.000	0.000	0.000	0.083	53.540	19.304	0.000	0.136	0.007	0.509	25.632
15	0.000	0.389	0.366	0.000	0.000	0.000	0.081	50.736	19.875	0.000	0.140	0.007	0.477	27.929
16	0.000	0.376	0.346	0.000	0.000	0.000	0.079	47.960	20.317	0.000	0.144	0.007	0.447	30.325
17	0.000	0.363	0.326	0.000	0.000	0.000	0.077	45.225	20.633	0.000	0.146	0.006	0.418	32.806
18	0.000	0.349	0.307	0.000	0.000	0.000	0.075	42.522	20.819	0.000	0.148	0.006	0.391	35.384
19	0.000	0.334	0.287	0.000	0.000	0.000	0.073	39.838	20.864	0.000	0.148	0.006	0.365	38.084
20	0.000	0.319	0.268	0.000	0.000	0.000	0.070	37.186	20.774	0.000	0.147	0.006	0.340	40.890
21	0.000	0.304	0.249	0.000	0.000	0.000	0.067	34.562	20.542	0.000	0.146	0.005	0.316	43.810

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
22	0.000	0.287	0.231	0.000	0.000	0.000	0.064	31.962	20.164	0.000	0.143	0.005	0.292	46.852
23	0.000	0.270	0.212	0.000	0.000	0.000	0.061	29.384	19.635	0.000	0.140	0.005	0.269	50.024
24	0.000	0.252	0.194	0.000	0.000	0.000	0.058	26.843	18.964	0.000	0.135	0.005	0.247	53.304
25	0.000	0.234	0.176	0.000	0.000	0.000	0.054	24.364	18.165	0.000	0.129	0.004	0.225	56.649
26	0.000	0.216	0.158	0.000	0.000	0.000	0.050	21.956	17.248	0.000	0.123	0.004	0.204	60.041
26	0.000	0.197	0.141	0.000	0.000	0.000	0.046	19.609	16.206	0.000	0.115	0.004	0.184	63.498
27	0.000	0.178	0.125	0.000	0.000	0.000	0.042	17.341	15.057	0.000	0.107	0.003	0.164	66.981
28	0.000	0.160	0.109	0.000	0.000	0.000	0.038	15.179	13.830	0.000	0.099	0.003	0.145	70.438
30	0.000	0.142	0.095	0.000	0.000	0.000	0.034	13.146	12.553	0.000	0.089	0.003	0.127	73.811
31	0.000	0.124	0.081	0.000	0.000	0.000	0.030	11.251	11.248	0.000	0.080	0.002	0.110	77.074
32	0.000	0.108	0.069	0.000	0.000	0.000	0.027	9.556	9.991	0.000	0.071	0.002	0.094	80.083
33	0.000	0.092	0.058	0.000	0.000	0.000	0.023	8.021	8.762	0.000	0.063	0.002	0.080	82.899
34	0.000	0.079	0.048	0.000	0.000	0.000	0.020	6.660	7.594	0.000	0.054	0.001	0.068	85.477
35	0.000	0.065	0.039	0.000	0.000	0.000	0.017	5.425	6.452	0.000	0.046	0.001	0.056	87.898
36	0.000	0.053	0.031	0.000	0.000	0.000	0.014	4.332	5.370	0.000	0.038	0.001	0.045	90.115
37	0.000	0.043	0.024	0.000	0.000	0.000	0.011	3.391	4.377	0.000	0.031	0.001	0.036	92.085
38	0.000	0.034	0.019	0.000	0.000	0.000	0.009	2.603	3.497	0.000	0.025	0.001	0.028	93.785
39	0.000	0.026	0.014	0.000	0.000	0.000	0.007	1.960	2.739	0.000	0.020	0.000	0.022	95.213
40	0.000	0.020	0.010	0.000	0.000	0.000	0.005	1.450	2.105	0.000	0.015	0.000	0.016	96.378

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death.

Table 58: Markov trace: LMWH/VKA arm, 6 months of treatment, aged 58 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	88.251	0.590	0.994	0.208	0.803	6.719	0.000	2.130	0.000	0.000	0.000	0.157	0.000	0.147
0.5	90.332	0.062	0.100	0.139	0.537	1.953	0.117	5.158	0.613	0.000	0.000	0.167	0.153	0.668
0.75	0.000	0.527	0.682	0.000	0.000	0.000	0.195	96.519	0.667	0.000	0.004	0.156	0.311	0.937
1	0.000	0.533	0.689	0.000	0.000	0.000	0.195	95.439	1.200	0.000	0.005	0.162	0.455	1.321
2	0.000	0.521	0.659	0.000	0.000	0.000	0.194	91.231	3.271	0.000	0.020	0.158	1.010	2.935
3	0.000	0.512	0.633	0.000	0.000	0.000	0.193	87.712	5.227	0.000	0.034	0.009	1.076	4.605
4	0.000	0.503	0.608	0.000	0.000	0.000	0.191	84.282	7.069	0.000	0.047	0.009	1.000	6.291
5	0.000	0.494	0.584	0.000	0.000	0.000	0.190	80.940	8.798	0.000	0.060	0.009	0.931	7.995
6	0.000	0.485	0.560	0.000	0.000	0.000	0.188	77.659	10.414	0.000	0.072	0.009	0.867	9.746
7	0.000	0.476	0.537	0.000	0.000	0.000	0.186	74.438	11.917	0.000	0.082	0.009	0.809	11.547
8	0.000	0.466	0.514	0.000	0.000	0.000	0.184	71.289	13.307	0.000	0.093	0.008	0.755	13.384
9	0.000	0.456	0.492	0.000	0.000	0.000	0.182	68.196	14.584	0.000	0.102	0.008	0.706	15.274
10	0.000	0.446	0.470	0.000	0.000	0.000	0.180	65.165	15.748	0.000	0.110	0.008	0.660	17.214
11	0.000	0.435	0.448	0.000	0.000	0.000	0.177	62.172	16.793	0.000	0.118	0.008	0.618	19.231
12	0.000	0.424	0.427	0.000	0.000	0.000	0.174	59.227	17.721	0.000	0.125	0.008	0.579	21.316
13	0.000	0.412	0.406	0.000	0.000	0.000	0.171	56.336	18.534	0.000	0.131	0.007	0.542	23.460
14	0.000	0.401	0.386	0.000	0.000	0.000	0.168	53.495	19.228	0.000	0.136	0.007	0.508	25.672
15	0.000	0.388	0.366	0.000	0.000	0.000	0.164	50.693	19.799	0.000	0.140	0.007	0.476	27.967
16	0.000	0.375	0.346	0.000	0.000	0.000	0.160	47.919	20.243	0.000	0.143	0.007	0.446	30.361
17	0.000	0.362	0.326	0.000	0.000	0.000	0.156	45.186	20.561	0.000	0.146	0.006	0.417	32.839
18	0.000	0.348	0.306	0.000	0.000	0.000	0.152	42.486	20.748	0.000	0.147	0.006	0.390	35.416

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
19	0.000	0.334	0.287	0.000	0.000	0.000	0.147	39.804	20.796	0.000	0.148	0.006	0.364	38.114
20	0.000	0.319	0.268	0.000	0.000	0.000	0.142	37.155	20.708	0.000	0.147	0.006	0.339	40.917
21	0.000	0.303	0.249	0.000	0.000	0.000	0.136	34.533	20.479	0.000	0.145	0.005	0.315	43.835
22	0.000	0.287	0.230	0.000	0.000	0.000	0.130	31.935	20.104	0.000	0.143	0.005	0.292	46.875
23	0.000	0.270	0.212	0.000	0.000	0.000	0.123	29.359	19.578	0.000	0.139	0.005	0.269	50.046
24	0.000	0.252	0.193	0.000	0.000	0.000	0.116	26.820	18.909	0.000	0.135	0.005	0.246	53.323
25	0.000	0.234	0.176	0.000	0.000	0.000	0.109	24.343	18.114	0.000	0.129	0.004	0.225	56.667
26	0.000	0.216	0.158	0.000	0.000	0.000	0.102	21.938	17.201	0.000	0.122	0.004	0.204	60.056
26	0.000	0.197	0.141	0.000	0.000	0.000	0.094	19.592	16.162	0.000	0.115	0.004	0.183	63.512
27	0.000	0.178	0.125	0.000	0.000	0.000	0.086	17.326	15.018	0.000	0.107	0.003	0.164	66.994
28	0.000	0.160	0.109	0.000	0.000	0.000	0.077	15.166	13.794	0.000	0.098	0.003	0.145	70.448
30	0.000	0.141	0.095	0.000	0.000	0.000	0.069	13.135	12.521	0.000	0.089	0.003	0.127	73.820
31	0.000	0.124	0.081	0.000	0.000	0.000	0.061	11.242	11.219	0.000	0.080	0.002	0.110	77.081
32	0.000	0.107	0.069	0.000	0.000	0.000	0.054	9.548	9.966	0.000	0.071	0.002	0.094	80.089
33	0.000	0.092	0.058	0.000	0.000	0.000	0.047	8.014	8.741	0.000	0.062	0.002	0.080	82.904
34	0.000	0.078	0.048	0.000	0.000	0.000	0.040	6.654	7.576	0.000	0.054	0.001	0.067	85.481
35	0.000	0.065	0.039	0.000	0.000	0.000	0.034	5.421	6.437	0.000	0.046	0.001	0.056	87.902
36	0.000	0.053	0.031	0.000	0.000	0.000	0.028	4.329	5.357	0.000	0.038	0.001	0.045	90.118
37	0.000	0.043	0.024	0.000	0.000	0.000	0.022	3.388	4.367	0.000	0.031	0.001	0.036	92.087
38	0.000	0.034	0.019	0.000	0.000	0.000	0.018	2.601	3.489	0.000	0.025	0.001	0.028	93.787
39	0.000	0.026	0.014	0.000	0.000	0.000	0.014	1.959	2.732	0.000	0.020	0.000	0.021	95.214
40	0.000	0.020	0.010	0.000	0.000	0.000	0.011	1.449	2.100	0.000	0.015	0.000	0.016	96.379

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death.

Table 59: Markov trace: rivaroxaban arm, 12 months of treatment, aged 58 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	88.958	0.646	1.089	0.135	0.522	6.215	0.000	2.130	0.000	0.000	0.000	0.157	0.000	0.147
0.5	89.945	0.141	0.234	0.035	0.134	2.623	0.076	5.170	0.671	0.000	0.000	0.168	0.153	0.649
0.75	88.809	0.054	0.074	0.026	0.100	1.348	0.096	7.329	0.807	0.000	0.005	0.158	0.312	0.882
1	86.488	0.067	0.089	0.026	0.099	1.331	0.110	9.244	0.854	0.000	0.006	0.155	0.458	1.075
2	0.000	0.524	0.668	0.000	0.000	0.000	0.124	92.511	2.487	0.000	0.014	0.159	1.003	2.510
3	0.000	0.515	0.641	0.000	0.000	0.000	0.123	88.943	4.484	0.000	0.029	0.009	1.070	4.186
4	0.000	0.506	0.616	0.000	0.000	0.000	0.122	85.465	6.366	0.000	0.042	0.009	0.995	5.879
5	0.000	0.497	0.592	0.000	0.000	0.000	0.121	82.075	8.134	0.000	0.055	0.009	0.926	7.591
6	0.000	0.488	0.568	0.000	0.000	0.000	0.120	78.749	9.787	0.000	0.067	0.009	0.863	9.349
7	0.000	0.478	0.544	0.000	0.000	0.000	0.119	75.482	11.325	0.000	0.078	0.009	0.806	11.159
8	0.000	0.468	0.521	0.000	0.000	0.000	0.117	72.289	12.751	0.000	0.088	0.008	0.753	13.003
9	0.000	0.458	0.499	0.000	0.000	0.000	0.116	69.153	14.062	0.000	0.098	0.008	0.704	14.902
10	0.000	0.448	0.477	0.000	0.000	0.000	0.115	66.079	15.258	0.000	0.107	0.008	0.658	16.850
11	0.000	0.437	0.455	0.000	0.000	0.000	0.113	63.044	16.336	0.000	0.115	0.008	0.617	18.876
12	0.000	0.426	0.433	0.000	0.000	0.000	0.111	60.058	17.294	0.000	0.122	0.008	0.578	20.971
13	0.000	0.415	0.412	0.000	0.000	0.000	0.109	57.127	18.136	0.000	0.128	0.007	0.541	23.125
14	0.000	0.403	0.391	0.000	0.000	0.000	0.107	54.246	18.859	0.000	0.133	0.007	0.508	25.347

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
15	0.000	0.390	0.371	0.000	0.000	0.000	0.105	51.404	19.458	0.000	0.137	0.007	0.476	27.652
16	0.000	0.377	0.350	0.000	0.000	0.000	0.102	48.592	19.928	0.000	0.141	0.007	0.446	30.057
17	0.000	0.364	0.330	0.000	0.000	0.000	0.100	45.820	20.272	0.000	0.144	0.007	0.417	32.546
18	0.000	0.350	0.311	0.000	0.000	0.000	0.097	43.082	20.484	0.000	0.145	0.006	0.390	35.134
19	0.000	0.336	0.291	0.000	0.000	0.000	0.094	40.363	20.556	0.000	0.146	0.006	0.364	37.845
20	0.000	0.320	0.272	0.000	0.000	0.000	0.090	37.676	20.490	0.000	0.145	0.006	0.339	40.661
21	0.000	0.305	0.253	0.000	0.000	0.000	0.087	35.017	20.283	0.000	0.144	0.005	0.315	43.592
22	0.000	0.288	0.234	0.000	0.000	0.000	0.083	32.383	19.929	0.000	0.142	0.005	0.292	46.645
23	0.000	0.271	0.215	0.000	0.000	0.000	0.079	29.771	19.423	0.000	0.138	0.005	0.269	49.830
24	0.000	0.253	0.196	0.000	0.000	0.000	0.074	27.197	18.773	0.000	0.134	0.005	0.247	53.122
25	0.000	0.235	0.178	0.000	0.000	0.000	0.070	24.685	17.995	0.000	0.128	0.004	0.225	56.480
26	0.000	0.217	0.160	0.000	0.000	0.000	0.065	22.245	17.098	0.000	0.122	0.004	0.204	59.885
26	0.000	0.198	0.143	0.000	0.000	0.000	0.060	19.867	16.075	0.000	0.114	0.004	0.184	63.355
27	0.000	0.179	0.127	0.000	0.000	0.000	0.055	17.569	14.944	0.000	0.106	0.003	0.164	66.852
28	0.000	0.160	0.111	0.000	0.000	0.000	0.049	15.379	13.733	0.000	0.098	0.003	0.145	70.322
30	0.000	0.142	0.096	0.000	0.000	0.000	0.044	13.319	12.472	0.000	0.089	0.003	0.127	73.708
31	0.000	0.124	0.082	0.000	0.000	0.000	0.039	11.399	11.180	0.000	0.080	0.002	0.110	76.983
32	0.000	0.108	0.070	0.000	0.000	0.000	0.034	9.682	9.934	0.000	0.071	0.002	0.095	80.005
33	0.000	0.093	0.059	0.000	0.000	0.000	0.030	8.127	8.716	0.000	0.062	0.002	0.080	82.831
34	0.000	0.079	0.049	0.000	0.000	0.000	0.025	6.747	7.557	0.000	0.054	0.001	0.068	85.420
35	0.000	0.066	0.040	0.000	0.000	0.000	0.021	5.497	6.423	0.000	0.046	0.001	0.056	87.851
36	0.000	0.054	0.032	0.000	0.000	0.000	0.018	4.389	5.347	0.000	0.038	0.001	0.045	90.076
37	0.000	0.043	0.025	0.000	0.000	0.000	0.014	3.436	4.360	0.000	0.031	0.001	0.036	92.054

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
38	0.000	0.034	0.019	0.000	0.000	0.000	0.011	2.637	3.484	0.000	0.025	0.001	0.028	93.761
39	0.000	0.026	0.014	0.000	0.000	0.000	0.009	1.986	2.729	0.000	0.019	0.000	0.022	95.194
40	0.000	0.020	0.011	0.000	0.000	0.000	0.007	1.469	2.098	0.000	0.015	0.000	0.016	96.364

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death.

Table 60: Markov trace: LMWH/VKA arm, 12 months of treatment, aged 58 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	88.483	0.576	0.971	0.274	1.056	6.206	0.000	2.130	0.000	0.000	0.000	0.157	0.000	0.147
0.5	89.787	0.126	0.209	0.070	0.270	2.605	0.154	5.160	0.598	0.000	0.000	0.167	0.153	0.701
0.75	88.630	0.051	0.070	0.052	0.202	1.343	0.193	7.317	0.720	0.000	0.004	0.157	0.311	0.948
1	86.274	0.064	0.085	0.052	0.199	1.326	0.223	9.242	0.765	0.000	0.005	0.155	0.456	1.155
2	0.000	0.523	0.667	0.000	0.000	0.000	0.250	92.392	2.394	0.000	0.013	0.159	1.000	2.601
3	0.000	0.513	0.641	0.000	0.000	0.000	0.248	88.828	4.391	0.000	0.028	0.009	1.067	4.275
4	0.000	0.505	0.616	0.000	0.000	0.000	0.246	85.355	6.271	0.000	0.041	0.009	0.992	5.965
5	0.000	0.496	0.591	0.000	0.000	0.000	0.245	81.970	8.039	0.000	0.054	0.009	0.924	7.673
6	0.000	0.487	0.567	0.000	0.000	0.000	0.242	78.648	9.691	0.000	0.066	0.009	0.861	9.429
7	0.000	0.477	0.544	0.000	0.000	0.000	0.240	75.385	11.229	0.000	0.077	0.009	0.803	11.235
8	0.000	0.467	0.521	0.000	0.000	0.000	0.237	72.196	12.655	0.000	0.088	0.008	0.750	13.077
9	0.000	0.457	0.498	0.000	0.000	0.000	0.235	69.064	13.965	0.000	0.097	0.008	0.702	14.973
10	0.000	0.447	0.476	0.000	0.000	0.000	0.232	65.994	15.162	0.000	0.106	0.008	0.657	16.918

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
11	0.000	0.436	0.454	0.000	0.000	0.000	0.228	62.963	16.240	0.000	0.114	0.008	0.615	18.942
12	0.000	0.425	0.433	0.000	0.000	0.000	0.225	59.981	17.199	0.000	0.121	0.008	0.576	21.033
13	0.000	0.414	0.411	0.000	0.000	0.000	0.221	57.053	18.042	0.000	0.127	0.007	0.540	23.185
14	0.000	0.402	0.391	0.000	0.000	0.000	0.216	54.176	18.766	0.000	0.132	0.007	0.506	25.404
15	0.000	0.389	0.370	0.000	0.000	0.000	0.212	51.338	19.366	0.000	0.137	0.007	0.474	27.706
16	0.000	0.377	0.350	0.000	0.000	0.000	0.207	48.529	19.838	0.000	0.140	0.007	0.445	30.108
17	0.000	0.363	0.330	0.000	0.000	0.000	0.201	45.761	20.184	0.000	0.143	0.006	0.416	32.595
18	0.000	0.349	0.310	0.000	0.000	0.000	0.196	43.027	20.398	0.000	0.145	0.006	0.389	35.180
19	0.000	0.335	0.291	0.000	0.000	0.000	0.189	40.311	20.472	0.000	0.145	0.006	0.363	37.888
20	0.000	0.320	0.271	0.000	0.000	0.000	0.183	37.628	20.409	0.000	0.145	0.006	0.339	40.701
21	0.000	0.304	0.252	0.000	0.000	0.000	0.175	34.972	20.205	0.000	0.143	0.005	0.315	43.629
22	0.000	0.288	0.233	0.000	0.000	0.000	0.167	32.341	19.854	0.000	0.141	0.005	0.291	46.679
23	0.000	0.270	0.214	0.000	0.000	0.000	0.159	29.733	19.352	0.000	0.138	0.005	0.268	49.861
24	0.000	0.253	0.196	0.000	0.000	0.000	0.150	27.162	18.706	0.000	0.133	0.005	0.246	53.150
25	0.000	0.235	0.178	0.000	0.000	0.000	0.141	24.653	17.932	0.000	0.128	0.004	0.225	56.506
26	0.000	0.216	0.160	0.000	0.000	0.000	0.131	22.217	17.039	0.000	0.121	0.004	0.204	59.908
26	0.000	0.198	0.143	0.000	0.000	0.000	0.121	19.841	16.020	0.000	0.114	0.004	0.183	63.376
27	0.000	0.179	0.127	0.000	0.000	0.000	0.110	17.547	14.895	0.000	0.106	0.003	0.164	66.870
28	0.000	0.160	0.111	0.000	0.000	0.000	0.100	15.359	13.688	0.000	0.098	0.003	0.145	70.337
30	0.000	0.142	0.096	0.000	0.000	0.000	0.089	13.302	12.431	0.000	0.089	0.003	0.127	73.722
31	0.000	0.124	0.082	0.000	0.000	0.000	0.079	11.385	11.144	0.000	0.079	0.002	0.110	76.995
32	0.000	0.108	0.070	0.000	0.000	0.000	0.069	9.669	9.903	0.000	0.071	0.002	0.094	80.014
33	0.000	0.093	0.059	0.000	0.000	0.000	0.060	8.116	8.689	0.000	0.062	0.002	0.080	82.839

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
34	0.000	0.079	0.049	0.000	0.000	0.000	0.051	6.739	7.534	0.000	0.054	0.001	0.068	85.426
35	0.000	0.066	0.040	0.000	0.000	0.000	0.043	5.490	6.404	0.000	0.046	0.001	0.056	87.856
36	0.000	0.054	0.032	0.000	0.000	0.000	0.036	4.384	5.331	0.000	0.038	0.001	0.045	90.080
37	0.000	0.043	0.025	0.000	0.000	0.000	0.029	3.431	4.347	0.000	0.031	0.001	0.036	92.057
38	0.000	0.034	0.019	0.000	0.000	0.000	0.023	2.634	3.474	0.000	0.025	0.001	0.028	93.763
39	0.000	0.026	0.014	0.000	0.000	0.000	0.018	1.984	2.721	0.000	0.019	0.000	0.022	95.195
40	0.000	0.020	0.011	0.000	0.000	0.000	0.014	1.467	2.092	0.000	0.015	0.000	0.016	96.365

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death.

Table 61: Markov trace: rivaroxaban arm, lifelong treatment, aged 58 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	88.958	0.646	1.089	0.135	0.522	6.215	0.000	2.130	0.000	0.000	0.000	0.157	0.000	0.147
0.5	90.720	0.141	0.234	0.036	0.137	2.647	0.076	4.368	0.000	0.671	0.000	0.168	0.153	0.649
0.75	89.743	0.046	0.069	0.028	0.108	1.408	0.096	6.333	0.014	0.801	0.000	0.158	0.312	0.883
1	87.495	0.057	0.082	0.029	0.110	1.415	0.112	8.152	0.031	0.829	0.000	0.155	0.458	1.074
2	74.833	0.149	0.214	0.039	0.148	1.053	0.193	18.916	0.157	1.123	0.002	0.154	0.992	2.026
3	64.938	0.190	0.263	0.038	0.145	1.031	0.279	26.997	0.331	1.605	0.004	0.003	1.039	3.137
4	56.771	0.216	0.290	0.063	0.237	1.006	0.408	32.976	0.566	2.144	0.006	0.004	0.946	4.367
5	50.243	0.239	0.316	0.060	0.222	0.982	0.543	37.271	0.865	2.708	0.008	0.004	0.864	5.674
6	44.923	0.255	0.333	0.057	0.209	0.956	0.670	40.228	1.226	3.270	0.012	0.005	0.791	7.065

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
7	40.552	0.267	0.344	0.054	0.198	0.928	0.788	42.135	1.641	3.806	0.015	0.005	0.726	8.540
8	36.933	0.274	0.348	0.052	0.188	0.900	0.900	43.228	2.104	4.302	0.019	0.005	0.668	10.077
9	33.898	0.278	0.349	0.050	0.179	0.871	1.004	43.678	2.604	4.750	0.023	0.005	0.616	11.694
10	31.323	0.280	0.346	0.048	0.170	0.842	1.102	43.629	3.130	5.146	0.027	0.005	0.569	13.383
11	29.099	0.279	0.341	0.047	0.162	0.812	1.193	43.175	3.671	5.486	0.031	0.005	0.526	15.173
12	27.154	0.277	0.334	0.045	0.155	0.781	1.276	42.410	4.216	5.771	0.035	0.005	0.487	17.054
13	25.431	0.274	0.325	0.043	0.148	0.751	1.352	41.406	4.756	6.003	0.039	0.005	0.451	19.015
14	23.879	0.270	0.315	0.042	0.141	0.720	1.421	40.214	5.281	6.184	0.043	0.005	0.419	21.066
15	22.457	0.264	0.304	0.040	0.134	0.689	1.482	38.868	5.783	6.316	0.047	0.005	0.389	23.222
16	21.131	0.258	0.292	0.038	0.127	0.658	1.535	37.393	6.250	6.399	0.051	0.005	0.361	25.502
17	19.885	0.251	0.279	0.037	0.121	0.626	1.578	35.823	6.677	6.437	0.054	0.005	0.335	27.892
18	18.696	0.243	0.266	0.035	0.114	0.594	1.613	34.174	7.057	6.431	0.056	0.004	0.311	30.405
19	17.545	0.235	0.253	0.033	0.108	0.562	1.636	32.448	7.378	6.381	0.059	0.004	0.288	33.070
20	16.428	0.226	0.239	0.031	0.101	0.529	1.650	30.669	7.637	6.290	0.061	0.004	0.267	35.869
21	15.332	0.216	0.224	0.030	0.095	0.496	1.652	28.842	7.828	6.159	0.062	0.004	0.247	38.814
22	14.251	0.205	0.210	0.028	0.089	0.463	1.641	26.974	7.943	5.987	0.063	0.004	0.227	41.914
23	13.178	0.194	0.195	0.026	0.082	0.430	1.618	25.067	7.977	5.776	0.063	0.004	0.208	45.182
24	12.116	0.182	0.180	0.024	0.076	0.396	1.582	23.140	7.928	5.528	0.062	0.003	0.190	48.591
25	11.074	0.170	0.165	0.022	0.069	0.363	1.534	21.217	7.800	5.250	0.061	0.003	0.173	52.099
26	10.052	0.158	0.150	0.020	0.063	0.330	1.474	19.311	7.594	4.944	0.059	0.003	0.157	55.684
26	9.046	0.145	0.135	0.019	0.057	0.297	1.402	17.414	7.305	4.610	0.057	0.003	0.141	59.370
27	8.064	0.132	0.121	0.017	0.051	0.265	1.319	15.549	6.939	4.252	0.054	0.002	0.125	63.111
28	7.116	0.119	0.107	0.015	0.045	0.234	1.226	13.739	6.508	3.878	0.050	0.002	0.110	66.851

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
30	6.214	0.106	0.093	0.013	0.039	0.205	1.127	12.011	6.025	3.498	0.047	0.002	0.097	70.525
31	5.363	0.093	0.081	0.011	0.034	0.177	1.022	10.376	5.500	3.115	0.042	0.002	0.084	74.101
32	4.594	0.081	0.069	0.010	0.029	0.152	0.919	8.894	4.973	2.752	0.038	0.001	0.072	77.418
33	3.889	0.070	0.059	0.008	0.024	0.128	0.816	7.534	4.436	2.401	0.034	0.001	0.061	80.538
34	3.257	0.060	0.049	0.007	0.020	0.108	0.715	6.313	3.907	2.071	0.030	0.001	0.052	83.411
35	2.677	0.050	0.040	0.006	0.017	0.088	0.615	5.189	3.371	1.752	0.026	0.001	0.043	86.125
36	2.156	0.041	0.032	0.005	0.014	0.071	0.518	4.182	2.847	1.452	0.022	0.001	0.035	88.625
37	1.703	0.033	0.026	0.004	0.011	0.056	0.428	3.303	2.354	1.179	0.018	0.001	0.028	90.857
38	1.319	0.026	0.020	0.003	0.008	0.044	0.346	2.558	1.906	0.939	0.015	0.000	0.022	92.795
39	1.002	0.020	0.015	0.002	0.006	0.033	0.274	1.944	1.513	0.733	0.012	0.000	0.017	94.429
40	0.748	0.015	0.011	0.002	0.005	0.025	0.213	1.451	1.177	0.562	0.009	0.000	0.012	95.770

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death.

Table 62: Markov trace: LMWH/VKA arm, lifelong treatment, aged 58 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	88.483	0.576	0.971	0.274	1.056	6.206	0.000	2.130	0.000	0.000	0.000	0.157	0.000	0.147
0.5	90.478	0.126	0.209	0.071	0.273	2.629	0.154	4.441	0.000	0.598	0.000	0.167	0.153	0.701
0.75	89.464	0.044	0.065	0.055	0.211	1.403	0.194	6.420	0.013	0.714	0.000	0.157	0.311	0.949
1	87.183	0.055	0.079	0.055	0.211	1.410	0.224	8.246	0.028	0.742	0.000	0.155	0.456	1.155
2	74.373	0.143	0.204	0.072	0.273	1.048	0.380	19.022	0.141	1.027	0.002	0.154	0.988	2.174

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
3	64.403	0.185	0.254	0.067	0.253	1.025	0.533	27.094	0.302	1.498	0.003	0.003	1.034	3.345
4	56.393	0.216	0.290	0.063	0.236	1.003	0.675	33.015	0.524	2.047	0.005	0.004	0.942	4.587
5	49.924	0.238	0.316	0.059	0.221	0.978	0.808	37.256	0.813	2.623	0.008	0.004	0.861	5.891
6	44.652	0.255	0.333	0.057	0.208	0.952	0.931	40.172	1.165	3.194	0.011	0.005	0.788	7.278
7	40.319	0.266	0.343	0.054	0.197	0.925	1.047	42.049	1.574	3.737	0.014	0.005	0.723	8.748
8	36.730	0.273	0.347	0.052	0.187	0.897	1.155	43.120	2.031	4.239	0.018	0.005	0.665	10.281
9	33.719	0.277	0.348	0.050	0.178	0.868	1.256	43.554	2.527	4.691	0.022	0.005	0.613	11.893
10	31.164	0.278	0.345	0.048	0.170	0.839	1.350	43.493	3.049	5.089	0.026	0.005	0.566	13.577
11	28.957	0.278	0.340	0.046	0.162	0.809	1.436	43.033	3.587	5.431	0.030	0.005	0.524	15.362
12	27.026	0.276	0.333	0.045	0.154	0.778	1.515	42.264	4.130	5.718	0.035	0.005	0.485	17.236
13	25.314	0.273	0.324	0.043	0.147	0.748	1.587	41.259	4.669	5.952	0.039	0.005	0.450	19.192
14	23.772	0.268	0.314	0.041	0.140	0.717	1.651	40.068	5.193	6.134	0.043	0.005	0.417	21.237
15	22.358	0.263	0.303	0.040	0.133	0.686	1.707	38.724	5.693	6.267	0.046	0.005	0.387	23.387
16	21.040	0.257	0.291	0.038	0.127	0.655	1.753	37.253	6.161	6.351	0.050	0.005	0.360	25.661
17	19.800	0.250	0.278	0.036	0.120	0.624	1.791	35.687	6.588	6.390	0.053	0.005	0.334	28.044
18	18.618	0.242	0.265	0.035	0.114	0.592	1.819	34.043	6.967	6.385	0.056	0.004	0.310	30.551
19	17.473	0.233	0.252	0.033	0.107	0.560	1.835	32.322	7.290	6.336	0.058	0.004	0.287	33.209
20	16.360	0.224	0.238	0.031	0.101	0.527	1.841	30.550	7.550	6.247	0.060	0.004	0.266	36.001
21	15.269	0.215	0.224	0.030	0.095	0.494	1.835	28.730	7.743	6.117	0.061	0.004	0.246	38.938
22	14.193	0.204	0.209	0.028	0.088	0.461	1.816	26.869	7.861	5.947	0.062	0.004	0.226	42.032
23	13.125	0.193	0.194	0.026	0.082	0.428	1.784	24.969	7.897	5.738	0.062	0.004	0.207	45.291
24	12.067	0.181	0.179	0.024	0.075	0.395	1.738	23.049	7.851	5.492	0.061	0.003	0.189	48.693
25	11.029	0.169	0.164	0.022	0.069	0.361	1.680	21.133	7.727	5.216	0.060	0.003	0.172	52.193

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14
26	10.012	0.157	0.149	0.020	0.063	0.329	1.610	19.234	7.525	4.913	0.059	0.003	0.156	55.770
26	9.010	0.144	0.135	0.018	0.056	0.296	1.528	17.345	7.240	4.580	0.056	0.003	0.140	59.448
27	8.031	0.131	0.120	0.017	0.050	0.264	1.433	15.487	6.879	4.225	0.053	0.002	0.125	63.181
28	7.087	0.118	0.106	0.015	0.044	0.233	1.329	13.685	6.452	3.854	0.050	0.002	0.110	66.913
30	6.189	0.105	0.093	0.013	0.039	0.204	1.219	11.964	5.975	3.476	0.046	0.002	0.096	70.580
31	5.342	0.092	0.080	0.011	0.034	0.176	1.103	10.335	5.455	3.096	0.042	0.002	0.083	74.149
32	4.575	0.081	0.069	0.010	0.029	0.151	0.990	8.858	4.933	2.735	0.038	0.001	0.072	77.459
33	3.874	0.070	0.058	0.008	0.024	0.128	0.877	7.504	4.401	2.386	0.034	0.001	0.061	80.573
34	3.244	0.059	0.049	0.007	0.020	0.107	0.768	6.288	3.877	2.058	0.030	0.001	0.051	83.440
35	2.666	0.050	0.040	0.006	0.017	0.088	0.660	5.169	3.345	1.741	0.026	0.001	0.042	86.150
36	2.148	0.041	0.032	0.005	0.014	0.071	0.555	4.165	2.826	1.443	0.022	0.001	0.034	88.644
37	1.696	0.033	0.026	0.004	0.011	0.056	0.457	3.290	2.337	1.172	0.018	0.001	0.027	90.873
38	1.313	0.026	0.020	0.003	0.008	0.043	0.369	2.548	1.892	0.933	0.014	0.000	0.021	92.807
39	0.998	0.020	0.015	0.002	0.006	0.033	0.292	1.936	1.502	0.729	0.011	0.000	0.016	94.438
40	0.745	0.015	0.011	0.002	0.005	0.025	0.227	1.445	1.169	0.559	0.009	0.000	0.012	95.777

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The eight tables below show the cumulative QALYs for the two treatment arms analysed when treatment duration is 3, 6, 12 months and lifelong. The values for severe PTS, labelled HS15 are disutilities and do not correspond to any standalone state in the model.

Table 63: QALYs (undiscounted) accrued over time – rivaroxaban arm, 3 months of treatment

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
0.25	15.953	0.136	0.211	0.030	0.299	1.352	0.000	0.439	0.000	0.000	0.000	0.022	0.000	0.000	0.000
0.5	0.000	0.097	0.117	0.000	0.000	0.000	0.042	19.941	0.146	0.000	0.000	0.024	0.021	0.000	0.001
0.75	0.000	0.106	0.126	0.000	0.000	0.000	0.042	19.712	0.247	0.000	0.001	0.023	0.044	0.000	0.001
1	0.000	0.105	0.125	0.000	0.000	0.000	0.042	19.493	0.357	0.000	0.002	0.023	0.065	0.000	0.002
2	0.000	0.103	0.119	0.000	0.000	0.000	0.042	18.634	0.777	0.000	0.004	0.022	0.142	0.000	0.004
3	0.000	0.101	0.115	0.000	0.000	0.000	0.041	17.915	1.175	0.000	0.007	0.001	0.151	0.000	0.007
4	0.000	0.099	0.110	0.000	0.000	0.000	0.041	17.214	1.550	0.000	0.009	0.001	0.140	0.000	0.009
5	0.000	0.098	0.106	0.000	0.000	0.000	0.041	16.532	1.901	0.000	0.012	0.001	0.131	0.000	0.011
6	0.000	0.096	0.102	0.000	0.000	0.000	0.040	15.862	2.229	0.000	0.014	0.001	0.122	0.000	0.013
7	0.000	0.094	0.097	0.000	0.000	0.000	0.040	15.204	2.534	0.000	0.016	0.001	0.113	0.000	0.014
8	0.000	0.092	0.093	0.000	0.000	0.000	0.040	14.560	2.816	0.000	0.017	0.001	0.106	0.000	0.016
9	0.000	0.090	0.089	0.000	0.000	0.000	0.039	13.929	3.075	0.000	0.019	0.001	0.099	0.000	0.017
10	0.000	0.088	0.085	0.000	0.000	0.000	0.039	13.310	3.310	0.000	0.021	0.001	0.093	0.000	0.019
11	0.000	0.086	0.081	0.000	0.000	0.000	0.038	12.698	3.521	0.000	0.022	0.001	0.087	0.000	0.020
12	0.000	0.084	0.077	0.000	0.000	0.000	0.037	12.097	3.709	0.000	0.023	0.001	0.081	0.000	0.021
13	0.000	0.081	0.074	0.000	0.000	0.000	0.037	11.507	3.872	0.000	0.024	0.001	0.076	0.000	0.022
14	0.000	0.079	0.070	0.000	0.000	0.000	0.036	10.926	4.011	0.000	0.025	0.001	0.071	0.000	0.023
15	0.000	0.077	0.066	0.000	0.000	0.000	0.035	10.354	4.125	0.000	0.026	0.001	0.067	0.000	0.023

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
16	0.000	0.074	0.063	0.000	0.000	0.000	0.035	9.787	4.213	0.000	0.026	0.001	0.062	0.000	0.024
17	0.000	0.072	0.059	0.000	0.000	0.000	0.034	9.229	4.276	0.000	0.027	0.001	0.058	0.000	0.024
18	0.000	0.069	0.056	0.000	0.000	0.000	0.033	8.678	4.311	0.000	0.027	0.001	0.055	0.000	0.024
19	0.000	0.066	0.052	0.000	0.000	0.000	0.032	8.130	4.318	0.000	0.027	0.001	0.051	0.000	0.024
20	0.000	0.063	0.049	0.000	0.000	0.000	0.030	7.589	4.296	0.000	0.027	0.001	0.047	0.000	0.024
21	0.000	0.060	0.045	0.000	0.000	0.000	0.029	7.053	4.246	0.000	0.027	0.001	0.044	0.000	0.024
22	0.000	0.057	0.042	0.000	0.000	0.000	0.028	6.523	4.166	0.000	0.026	0.001	0.041	0.000	0.024
23	0.000	0.053	0.038	0.000	0.000	0.000	0.027	5.996	4.055	0.000	0.026	0.001	0.038	0.000	0.023
24	0.000	0.050	0.035	0.000	0.000	0.000	0.025	5.478	3.915	0.000	0.025	0.001	0.034	0.000	0.022
25	0.000	0.046	0.032	0.000	0.000	0.000	0.023	4.972	3.749	0.000	0.024	0.001	0.031	0.000	0.021
26	0.000	0.043	0.029	0.000	0.000	0.000	0.022	4.481	3.558	0.000	0.022	0.001	0.028	0.000	0.020
26	0.000	0.039	0.026	0.000	0.000	0.000	0.020	4.002	3.342	0.000	0.021	0.000	0.026	0.000	0.019
27	0.000	0.035	0.023	0.000	0.000	0.000	0.018	3.539	3.105	0.000	0.020	0.000	0.023	0.000	0.018
28	0.000	0.032	0.020	0.000	0.000	0.000	0.017	3.098	2.851	0.000	0.018	0.000	0.020	0.000	0.016
30	0.000	0.028	0.017	0.000	0.000	0.000	0.015	2.683	2.587	0.000	0.016	0.000	0.018	0.000	0.015
31	0.000	0.024	0.015	0.000	0.000	0.000	0.013	2.296	2.318	0.000	0.015	0.000	0.015	0.000	0.013
32	0.000	0.021	0.012	0.000	0.000	0.000	0.012	1.950	2.058	0.000	0.013	0.000	0.013	0.000	0.012
33	0.000	0.018	0.010	0.000	0.000	0.000	0.010	1.637	1.805	0.000	0.011	0.000	0.011	0.000	0.010
34	0.000	0.015	0.009	0.000	0.000	0.000	0.009	1.359	1.564	0.000	0.010	0.000	0.009	0.000	0.009
35	0.000	0.013	0.007	0.000	0.000	0.000	0.007	1.107	1.328	0.000	0.008	0.000	0.008	0.000	0.008
36	0.000	0.011	0.006	0.000	0.000	0.000	0.006	0.884	1.105	0.000	0.007	0.000	0.006	0.000	0.006
37	0.000	0.008	0.004	0.000	0.000	0.000	0.005	0.692	0.901	0.000	0.006	0.000	0.005	0.000	0.005
38	0.000	0.007	0.003	0.000	0.000	0.000	0.004	0.531	0.720	0.000	0.005	0.000	0.004	0.000	0.004

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
39	0.000	0.005	0.003	0.000	0.000	0.000	0.003	0.400	0.563	0.000	0.004	0.000	0.003	0.000	0.003
40	0.000	0.004	0.002	0.000	0.000	0.000	0.002	0.296	0.433	0.000	0.003	0.000	0.002	0.000	0.002

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death; HS15* : Severe PTS.

Table 64: QALYs (undiscounted) accrued over time – LMWH/VKA arm, 3 months of treatment

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
0.25	15.4283	0.1209	0.1881	0.0604	0.5997	1.3505	0.0000	0.4393	0.0000	0.0000	0.0000	0.0220	0.0000	0.0000	0.0000
0.5	0.0000	0.0951	0.1143	0.0000	0.0000	0.0000	0.0846	19.8702	0.1300	0.0000	0.0000	0.0233	0.0214	0.0000	0.0007
0.75	0.0000	0.1055	0.1260	0.0000	0.0000	0.0000	0.0844	19.6404	0.2295	0.0000	0.0008	0.0225	0.0435	0.0000	0.0013
1	0.0000	0.1048	0.1245	0.0000	0.0000	0.0000	0.0843	19.4226	0.3391	0.0000	0.0015	0.0225	0.0643	0.0000	0.0019
2	0.0000	0.1025	0.1191	0.0000	0.0000	0.0000	0.0838	18.5663	0.7583	0.0000	0.0042	0.0220	0.1412	0.0000	0.0043
3	0.0000	0.1006	0.1143	0.0000	0.0000	0.0000	0.0832	17.8501	1.1549	0.0000	0.0067	0.0013	0.1502	0.0000	0.0065
4	0.0000	0.0989	0.1098	0.0000	0.0000	0.0000	0.0826	17.1521	1.5281	0.0000	0.0091	0.0012	0.1396	0.0000	0.0087
5	0.0000	0.0972	0.1055	0.0000	0.0000	0.0000	0.0819	16.4719	1.8785	0.0000	0.0114	0.0012	0.1299	0.0000	0.0107
6	0.0000	0.0954	0.1012	0.0000	0.0000	0.0000	0.0812	15.8044	2.2058	0.0000	0.0135	0.0012	0.1210	0.0000	0.0125
7	0.0000	0.0935	0.0970	0.0000	0.0000	0.0000	0.0804	15.1488	2.5098	0.0000	0.0154	0.0012	0.1128	0.0000	0.0142
8	0.0000	0.0916	0.0929	0.0000	0.0000	0.0000	0.0795	14.5078	2.7911	0.0000	0.0172	0.0012	0.1053	0.0000	0.0158
9	0.0000	0.0896	0.0889	0.0000	0.0000	0.0000	0.0786	13.8785	3.0491	0.0000	0.0189	0.0011	0.0984	0.0000	0.0173
10	0.0000	0.0876	0.0849	0.0000	0.0000	0.0000	0.0776	13.2616	3.2842	0.0000	0.0204	0.0011	0.0921	0.0000	0.0186
11	0.0000	0.0855	0.0810	0.0000	0.0000	0.0000	0.0764	12.6525	3.4950	0.0000	0.0218	0.0011	0.0861	0.0000	0.0198
12	0.0000	0.0833	0.0772	0.0000	0.0000	0.0000	0.0752	12.0532	3.6819	0.0000	0.0230	0.0011	0.0807	0.0000	0.0209

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
13	0.0000	0.0811	0.0734	0.0000	0.0000	0.0000	0.0739	11.4649	3.8451	0.0000	0.0241	0.0010	0.0755	0.0000	0.0218
14	0.0000	0.0788	0.0697	0.0000	0.0000	0.0000	0.0725	10.8867	3.9842	0.0000	0.0250	0.0010	0.0708	0.0000	0.0226
15	0.0000	0.0763	0.0660	0.0000	0.0000	0.0000	0.0709	10.3164	4.0984	0.0000	0.0257	0.0010	0.0663	0.0000	0.0232
16	0.0000	0.0738	0.0624	0.0000	0.0000	0.0000	0.0693	9.7520	4.1864	0.0000	0.0263	0.0009	0.0621	0.0000	0.0237
17	0.0000	0.0712	0.0589	0.0000	0.0000	0.0000	0.0675	9.1958	4.2487	0.0000	0.0267	0.0009	0.0581	0.0000	0.0241
18	0.0000	0.0685	0.0554	0.0000	0.0000	0.0000	0.0655	8.6463	4.2845	0.0000	0.0270	0.0009	0.0543	0.0000	0.0243
19	0.0000	0.0656	0.0519	0.0000	0.0000	0.0000	0.0634	8.1005	4.2916	0.0000	0.0270	0.0008	0.0507	0.0000	0.0243
20	0.0000	0.0627	0.0484	0.0000	0.0000	0.0000	0.0612	7.5613	4.2709	0.0000	0.0269	0.0008	0.0472	0.0000	0.0242
21	0.0000	0.0596	0.0450	0.0000	0.0000	0.0000	0.0587	7.0277	4.2215	0.0000	0.0266	0.0008	0.0438	0.0000	0.0239
22	0.0000	0.0564	0.0416	0.0000	0.0000	0.0000	0.0561	6.4990	4.1423	0.0000	0.0261	0.0007	0.0406	0.0000	0.0235
23	0.0000	0.0530	0.0383	0.0000	0.0000	0.0000	0.0533	5.9748	4.0323	0.0000	0.0255	0.0007	0.0374	0.0000	0.0229
24	0.0000	0.0495	0.0349	0.0000	0.0000	0.0000	0.0503	5.4582	3.8931	0.0000	0.0246	0.0006	0.0343	0.0000	0.0221
25	0.0000	0.0460	0.0317	0.0000	0.0000	0.0000	0.0471	4.9540	3.7279	0.0000	0.0236	0.0006	0.0312	0.0000	0.0211
26	0.0000	0.0424	0.0286	0.0000	0.0000	0.0000	0.0439	4.4645	3.5388	0.0000	0.0224	0.0005	0.0283	0.0000	0.0201
26	0.0000	0.0387	0.0255	0.0000	0.0000	0.0000	0.0405	3.9871	3.3242	0.0000	0.0210	0.0005	0.0255	0.0000	0.0188
27	0.0000	0.0350	0.0226	0.0000	0.0000	0.0000	0.0370	3.5261	3.0879	0.0000	0.0195	0.0004	0.0227	0.0000	0.0175
28	0.0000	0.0314	0.0198	0.0000	0.0000	0.0000	0.0334	3.0864	2.8356	0.0000	0.0179	0.0004	0.0201	0.0000	0.0161
30	0.0000	0.0278	0.0171	0.0000	0.0000	0.0000	0.0299	2.6731	2.5733	0.0000	0.0163	0.0004	0.0176	0.0000	0.0146
31	0.0000	0.0243	0.0146	0.0000	0.0000	0.0000	0.0264	2.2878	2.3053	0.0000	0.0146	0.0003	0.0152	0.0000	0.0131
32	0.0000	0.0211	0.0124	0.0000	0.0000	0.0000	0.0232	1.9430	2.0473	0.0000	0.0130	0.0003	0.0131	0.0000	0.0116
33	0.0000	0.0181	0.0104	0.0000	0.0000	0.0000	0.0201	1.6310	1.7952	0.0000	0.0114	0.0002	0.0111	0.0000	0.0102
34	0.0000	0.0154	0.0087	0.0000	0.0000	0.0000	0.0172	1.3541	1.5557	0.0000	0.0099	0.0002	0.0094	0.0000	0.0088
35	0.0000	0.0128	0.0071	0.0000	0.0000	0.0000	0.0145	1.1031	1.3216	0.0000	0.0084	0.0002	0.0077	0.0000	0.0075

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
36	0.0000	0.0105	0.0056	0.0000	0.0000	0.0000	0.0120	0.8809	1.0997	0.0000	0.0070	0.0001	0.0063	0.0000	0.0062
37	0.0000	0.0084	0.0044	0.0000	0.0000	0.0000	0.0097	0.6896	0.8964	0.0000	0.0057	0.0001	0.0050	0.0000	0.0051
38	0.0000	0.0066	0.0034	0.0000	0.0000	0.0000	0.0077	0.5293	0.7160	0.0000	0.0045	0.0001	0.0039	0.0000	0.0041
39	0.0000	0.0051	0.0026	0.0000	0.0000	0.0000	0.0060	0.3986	0.5606	0.0000	0.0036	0.0001	0.0030	0.0000	0.0032
40	0.0000	0.0038	0.0019	0.0000	0.0000	0.0000	0.0046	0.2948	0.4309	0.0000	0.0027	0.0000	0.0022	0.0000	0.0024

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death; HS15* : Severe PTS.

Table 65: QALYs (undiscounted) accrued over time – rivaroxaban arm, 6 months of treatment.

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
0.25	16.215	0.131	0.204	0.007	0.073	1.388	0.000	0.439	0.000	0.000	0.000	0.022	0.000	0.000	0.000
0.5	18.693	0.014	0.020	0.005	0.049	0.405	0.010	1.070	0.142	0.000	0.000	0.024	0.021	0.000	0.001
0.75	0.000	0.105	0.125	0.000	0.000	0.000	0.017	19.924	0.154	0.000	0.001	0.022	0.044	0.000	0.001
1	0.000	0.106	0.126	0.000	0.000	0.000	0.017	19.701	0.264	0.000	0.001	0.023	0.064	0.000	0.001
2	0.000	0.104	0.121	0.000	0.000	0.000	0.017	18.832	0.691	0.000	0.004	0.022	0.142	0.000	0.004
3	0.000	0.102	0.116	0.000	0.000	0.000	0.017	18.106	1.095	0.000	0.006	0.001	0.151	0.000	0.006
4	0.000	0.100	0.111	0.000	0.000	0.000	0.017	17.398	1.475	0.000	0.009	0.001	0.140	0.000	0.008
5	0.000	0.098	0.107	0.000	0.000	0.000	0.017	16.708	1.832	0.000	0.011	0.001	0.131	0.000	0.010
6	0.000	0.096	0.103	0.000	0.000	0.000	0.017	16.031	2.165	0.000	0.013	0.001	0.122	0.000	0.012
7	0.000	0.094	0.098	0.000	0.000	0.000	0.016	15.366	2.475	0.000	0.015	0.001	0.113	0.000	0.014
8	0.000	0.093	0.094	0.000	0.000	0.000	0.016	14.716	2.761	0.000	0.017	0.001	0.106	0.000	0.016
9	0.000	0.091	0.090	0.000	0.000	0.000	0.016	14.077	3.025	0.000	0.019	0.001	0.099	0.000	0.017

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
10	0.000	0.089	0.086	0.000	0.000	0.000	0.016	13.452	3.265	0.000	0.020	0.001	0.093	0.000	0.019
11	0.000	0.086	0.082	0.000	0.000	0.000	0.016	12.834	3.480	0.000	0.022	0.001	0.087	0.000	0.020
12	0.000	0.084	0.078	0.000	0.000	0.000	0.015	12.226	3.671	0.000	0.023	0.001	0.081	0.000	0.021
13	0.000	0.082	0.074	0.000	0.000	0.000	0.015	11.629	3.839	0.000	0.024	0.001	0.076	0.000	0.022
14	0.000	0.080	0.071	0.000	0.000	0.000	0.015	11.043	3.982	0.000	0.025	0.001	0.071	0.000	0.023
15	0.000	0.077	0.067	0.000	0.000	0.000	0.014	10.464	4.099	0.000	0.026	0.001	0.067	0.000	0.023
16	0.000	0.075	0.063	0.000	0.000	0.000	0.014	9.892	4.190	0.000	0.026	0.001	0.063	0.000	0.024
17	0.000	0.072	0.060	0.000	0.000	0.000	0.014	9.328	4.256	0.000	0.027	0.001	0.059	0.000	0.024
18	0.000	0.069	0.056	0.000	0.000	0.000	0.013	8.770	4.294	0.000	0.027	0.001	0.055	0.000	0.024
19	0.000	0.066	0.053	0.000	0.000	0.000	0.013	8.217	4.303	0.000	0.027	0.001	0.051	0.000	0.024
20	0.000	0.063	0.049	0.000	0.000	0.000	0.012	7.670	4.285	0.000	0.027	0.001	0.048	0.000	0.024
21	0.000	0.060	0.046	0.000	0.000	0.000	0.012	7.128	4.237	0.000	0.027	0.001	0.044	0.000	0.024
22	0.000	0.057	0.042	0.000	0.000	0.000	0.011	6.592	4.159	0.000	0.026	0.001	0.041	0.000	0.024
23	0.000	0.054	0.039	0.000	0.000	0.000	0.011	6.060	4.050	0.000	0.026	0.001	0.038	0.000	0.023
24	0.000	0.050	0.035	0.000	0.000	0.000	0.010	5.536	3.911	0.000	0.025	0.001	0.035	0.000	0.022
25	0.000	0.046	0.032	0.000	0.000	0.000	0.010	5.025	3.746	0.000	0.024	0.001	0.032	0.000	0.021
26	0.000	0.043	0.029	0.000	0.000	0.000	0.009	4.528	3.557	0.000	0.022	0.001	0.029	0.000	0.020
26	0.000	0.039	0.026	0.000	0.000	0.000	0.008	4.044	3.342	0.000	0.021	0.000	0.026	0.000	0.019
27	0.000	0.035	0.023	0.000	0.000	0.000	0.008	3.577	3.106	0.000	0.020	0.000	0.023	0.000	0.018
28	0.000	0.032	0.020	0.000	0.000	0.000	0.007	3.131	2.852	0.000	0.018	0.000	0.020	0.000	0.016
30	0.000	0.028	0.017	0.000	0.000	0.000	0.006	2.711	2.589	0.000	0.016	0.000	0.018	0.000	0.015
31	0.000	0.025	0.015	0.000	0.000	0.000	0.005	2.321	2.320	0.000	0.015	0.000	0.015	0.000	0.013
32	0.000	0.021	0.013	0.000	0.000	0.000	0.005	1.971	2.061	0.000	0.013	0.000	0.013	0.000	0.012

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
33	0.000	0.018	0.011	0.000	0.000	0.000	0.004	1.654	1.807	0.000	0.011	0.000	0.011	0.000	0.010
34	0.000	0.016	0.009	0.000	0.000	0.000	0.004	1.374	1.566	0.000	0.010	0.000	0.009	0.000	0.009
35	0.000	0.013	0.007	0.000	0.000	0.000	0.003	1.119	1.331	0.000	0.008	0.000	0.008	0.000	0.008
36	0.000	0.011	0.006	0.000	0.000	0.000	0.002	0.894	1.108	0.000	0.007	0.000	0.006	0.000	0.006
37	0.000	0.008	0.004	0.000	0.000	0.000	0.002	0.699	0.903	0.000	0.006	0.000	0.005	0.000	0.005
38	0.000	0.007	0.003	0.000	0.000	0.000	0.002	0.537	0.721	0.000	0.005	0.000	0.004	0.000	0.004
39	0.000	0.005	0.003	0.000	0.000	0.000	0.001	0.404	0.565	0.000	0.004	0.000	0.003	0.000	0.003
40	0.000	0.004	0.002	0.000	0.000	0.000	0.001	0.299	0.434	0.000	0.003	0.000	0.002	0.000	0.002

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death; HS15* : Severe PTS.

Table 66: QALYs (undiscounted) accrued over time – LMWH/VKA arm, 6 months of treatment

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
0.25	15.9642	0.1169	0.1820	0.0149	0.1482	1.3859	0.0000	0.4393	0.0000	0.0000	0.0000	0.0220	0.0000	0.0000	0.0000
0.5	18.4074	0.0123	0.0183	0.0100	0.0991	0.4029	0.0209	1.0639	0.1264	0.0000	0.0000	0.0234	0.0214	0.0000	0.0007
0.75	0.0000	0.1046	0.1249	0.0000	0.0000	0.0000	0.0348	19.9070	0.1376	0.0000	0.0008	0.0218	0.0436	0.0000	0.0008
1	0.0000	0.1057	0.1262	0.0000	0.0000	0.0000	0.0348	19.6842	0.2476	0.0000	0.0009	0.0227	0.0637	0.0000	0.0014
2	0.0000	0.1034	0.1207	0.0000	0.0000	0.0000	0.0346	18.8165	0.6746	0.0000	0.0036	0.0222	0.1414	0.0000	0.0038
3	0.0000	0.1015	0.1158	0.0000	0.0000	0.0000	0.0343	18.0906	1.0781	0.0000	0.0062	0.0013	0.1506	0.0000	0.0061
4	0.0000	0.0998	0.1113	0.0000	0.0000	0.0000	0.0341	17.3832	1.4579	0.0000	0.0087	0.0013	0.1400	0.0000	0.0083
5	0.0000	0.0980	0.1069	0.0000	0.0000	0.0000	0.0338	16.6938	1.8147	0.0000	0.0109	0.0012	0.1303	0.0000	0.0103
6	0.0000	0.0962	0.1025	0.0000	0.0000	0.0000	0.0335	16.0173	2.1480	0.0000	0.0131	0.0012	0.1214	0.0000	0.0122

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
7	0.0000	0.0943	0.0983	0.0000	0.0000	0.0000	0.0332	15.3528	2.4578	0.0000	0.0151	0.0012	0.1132	0.0000	0.0139
8	0.0000	0.0924	0.0941	0.0000	0.0000	0.0000	0.0328	14.7033	2.7446	0.0000	0.0169	0.0012	0.1057	0.0000	0.0156
9	0.0000	0.0904	0.0900	0.0000	0.0000	0.0000	0.0324	14.0655	3.0080	0.0000	0.0186	0.0011	0.0988	0.0000	0.0171
10	0.0000	0.0884	0.0860	0.0000	0.0000	0.0000	0.0320	13.4402	3.2480	0.0000	0.0202	0.0011	0.0924	0.0000	0.0184
11	0.0000	0.0862	0.0821	0.0000	0.0000	0.0000	0.0315	12.8230	3.4637	0.0000	0.0216	0.0011	0.0865	0.0000	0.0196
12	0.0000	0.0840	0.0782	0.0000	0.0000	0.0000	0.0310	12.2156	3.6551	0.0000	0.0228	0.0011	0.0810	0.0000	0.0207
13	0.0000	0.0818	0.0744	0.0000	0.0000	0.0000	0.0305	11.6194	3.8225	0.0000	0.0239	0.0010	0.0759	0.0000	0.0217
14	0.0000	0.0794	0.0706	0.0000	0.0000	0.0000	0.0299	11.0333	3.9657	0.0000	0.0248	0.0010	0.0711	0.0000	0.0225
15	0.0000	0.0770	0.0669	0.0000	0.0000	0.0000	0.0293	10.4553	4.0836	0.0000	0.0256	0.0010	0.0667	0.0000	0.0232
16	0.0000	0.0744	0.0633	0.0000	0.0000	0.0000	0.0286	9.8834	4.1751	0.0000	0.0262	0.0009	0.0624	0.0000	0.0237
17	0.0000	0.0718	0.0597	0.0000	0.0000	0.0000	0.0278	9.3197	4.2407	0.0000	0.0267	0.0009	0.0584	0.0000	0.0240
18	0.0000	0.0691	0.0561	0.0000	0.0000	0.0000	0.0270	8.7628	4.2794	0.0000	0.0269	0.0009	0.0546	0.0000	0.0243
19	0.0000	0.0662	0.0526	0.0000	0.0000	0.0000	0.0262	8.2097	4.2892	0.0000	0.0270	0.0008	0.0510	0.0000	0.0243
20	0.0000	0.0632	0.0491	0.0000	0.0000	0.0000	0.0252	7.6632	4.2710	0.0000	0.0269	0.0008	0.0475	0.0000	0.0242
21	0.0000	0.0601	0.0456	0.0000	0.0000	0.0000	0.0242	7.1223	4.2237	0.0000	0.0266	0.0008	0.0441	0.0000	0.0239
22	0.0000	0.0568	0.0422	0.0000	0.0000	0.0000	0.0231	6.5866	4.1464	0.0000	0.0262	0.0007	0.0408	0.0000	0.0235
23	0.0000	0.0534	0.0388	0.0000	0.0000	0.0000	0.0220	6.0553	4.0380	0.0000	0.0255	0.0007	0.0376	0.0000	0.0229
24	0.0000	0.0499	0.0354	0.0000	0.0000	0.0000	0.0207	5.5317	3.9001	0.0000	0.0246	0.0006	0.0345	0.0000	0.0221
25	0.0000	0.0464	0.0321	0.0000	0.0000	0.0000	0.0194	5.0208	3.7360	0.0000	0.0236	0.0006	0.0315	0.0000	0.0212
26	0.0000	0.0427	0.0290	0.0000	0.0000	0.0000	0.0181	4.5246	3.5476	0.0000	0.0224	0.0005	0.0285	0.0000	0.0201
26	0.0000	0.0391	0.0259	0.0000	0.0000	0.0000	0.0167	4.0408	3.3334	0.0000	0.0211	0.0005	0.0257	0.0000	0.0189
27	0.0000	0.0353	0.0229	0.0000	0.0000	0.0000	0.0153	3.5736	3.0974	0.0000	0.0196	0.0004	0.0229	0.0000	0.0176
28	0.0000	0.0316	0.0200	0.0000	0.0000	0.0000	0.0138	3.1280	2.8450	0.0000	0.0180	0.0004	0.0202	0.0000	0.0161

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
30	0.0000	0.0280	0.0173	0.0000	0.0000	0.0000	0.0123	2.7091	2.5825	0.0000	0.0163	0.0004	0.0177	0.0000	0.0146
31	0.0000	0.0245	0.0148	0.0000	0.0000	0.0000	0.0109	2.3186	2.3140	0.0000	0.0146	0.0003	0.0153	0.0000	0.0131
32	0.0000	0.0213	0.0126	0.0000	0.0000	0.0000	0.0096	1.9692	2.0554	0.0000	0.0130	0.0003	0.0132	0.0000	0.0117
33	0.0000	0.0183	0.0106	0.0000	0.0000	0.0000	0.0083	1.6530	1.8028	0.0000	0.0114	0.0002	0.0112	0.0000	0.0102
34	0.0000	0.0155	0.0088	0.0000	0.0000	0.0000	0.0071	1.3724	1.5625	0.0000	0.0099	0.0002	0.0094	0.0000	0.0089
35	0.0000	0.0130	0.0072	0.0000	0.0000	0.0000	0.0060	1.1180	1.3276	0.0000	0.0084	0.0002	0.0078	0.0000	0.0075
36	0.0000	0.0106	0.0057	0.0000	0.0000	0.0000	0.0049	0.8928	1.1049	0.0000	0.0070	0.0001	0.0063	0.0000	0.0063
37	0.0000	0.0085	0.0045	0.0000	0.0000	0.0000	0.0040	0.6988	0.9007	0.0000	0.0057	0.0001	0.0050	0.0000	0.0051
38	0.0000	0.0067	0.0034	0.0000	0.0000	0.0000	0.0032	0.5364	0.7196	0.0000	0.0046	0.0001	0.0039	0.0000	0.0041
39	0.0000	0.0051	0.0026	0.0000	0.0000	0.0000	0.0025	0.4040	0.5635	0.0000	0.0036	0.0001	0.0030	0.0000	0.0032
40	0.0000	0.0039	0.0019	0.0000	0.0000	0.0000	0.0019	0.2988	0.4332	0.0000	0.0027	0.0000	0.0023	0.0000	0.0025

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death; HS15* : Severe PTS.

Table 67: QALYs (undiscounted) accrued over time – rivaroxaban arm, 12 months of treatment

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
0.25	16.287	0.128	0.199	0.010	0.096	1.282	0.000	0.439	0.000	0.000	0.000	0.022	0.000	0.000	0.000
0.5	18.551	0.028	0.043	0.002	0.025	0.541	0.014	1.066	0.138	0.000	0.000	0.024	0.021	0.000	0.001
0.75	18.317	0.011	0.014	0.002	0.018	0.278	0.017	1.512	0.167	0.000	0.001	0.022	0.044	0.000	0.001
1	17.838	0.013	0.016	0.002	0.018	0.274	0.020	1.907	0.176	0.000	0.001	0.022	0.064	0.000	0.001
2	0.000	0.104	0.122	0.000	0.000	0.000	0.022	19.080	0.513	0.000	0.003	0.022	0.140	0.000	0.003
3	0.000	0.102	0.117	0.000	0.000	0.000	0.022	18.344	0.925	0.000	0.005	0.001	0.150	0.000	0.005

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
4	0.000	0.100	0.113	0.000	0.000	0.000	0.022	17.627	1.313	0.000	0.008	0.001	0.139	0.000	0.007
5	0.000	0.099	0.108	0.000	0.000	0.000	0.022	16.928	1.678	0.000	0.010	0.001	0.130	0.000	0.010
6	0.000	0.097	0.104	0.000	0.000	0.000	0.021	16.242	2.019	0.000	0.012	0.001	0.121	0.000	0.011
7	0.000	0.095	0.100	0.000	0.000	0.000	0.021	15.568	2.336	0.000	0.014	0.001	0.113	0.000	0.013
8	0.000	0.093	0.095	0.000	0.000	0.000	0.021	14.910	2.630	0.000	0.016	0.001	0.105	0.000	0.015
9	0.000	0.091	0.091	0.000	0.000	0.000	0.021	14.263	2.900	0.000	0.018	0.001	0.099	0.000	0.016
10	0.000	0.089	0.087	0.000	0.000	0.000	0.020	13.629	3.147	0.000	0.020	0.001	0.092	0.000	0.018
11	0.000	0.087	0.083	0.000	0.000	0.000	0.020	13.003	3.369	0.000	0.021	0.001	0.086	0.000	0.019
12	0.000	0.084	0.079	0.000	0.000	0.000	0.020	12.387	3.567	0.000	0.022	0.001	0.081	0.000	0.020
13	0.000	0.082	0.075	0.000	0.000	0.000	0.019	11.782	3.741	0.000	0.023	0.001	0.076	0.000	0.021
14	0.000	0.080	0.072	0.000	0.000	0.000	0.019	11.188	3.890	0.000	0.024	0.001	0.071	0.000	0.022
15	0.000	0.077	0.068	0.000	0.000	0.000	0.019	10.602	4.013	0.000	0.025	0.001	0.067	0.000	0.023
16	0.000	0.075	0.064	0.000	0.000	0.000	0.018	10.022	4.110	0.000	0.026	0.001	0.062	0.000	0.023
17	0.000	0.072	0.061	0.000	0.000	0.000	0.018	9.450	4.181	0.000	0.026	0.001	0.058	0.000	0.024
18	0.000	0.069	0.057	0.000	0.000	0.000	0.017	8.886	4.225	0.000	0.027	0.001	0.055	0.000	0.024
19	0.000	0.067	0.053	0.000	0.000	0.000	0.017	8.325	4.240	0.000	0.027	0.001	0.051	0.000	0.024
20	0.000	0.064	0.050	0.000	0.000	0.000	0.016	7.771	4.226	0.000	0.027	0.001	0.048	0.000	0.024
21	0.000	0.060	0.046	0.000	0.000	0.000	0.015	7.222	4.183	0.000	0.026	0.001	0.044	0.000	0.024
22	0.000	0.057	0.043	0.000	0.000	0.000	0.015	6.679	4.110	0.000	0.026	0.001	0.041	0.000	0.023
23	0.000	0.054	0.039	0.000	0.000	0.000	0.014	6.140	4.006	0.000	0.025	0.001	0.038	0.000	0.023
24	0.000	0.050	0.036	0.000	0.000	0.000	0.013	5.609	3.872	0.000	0.024	0.001	0.035	0.000	0.022
25	0.000	0.047	0.033	0.000	0.000	0.000	0.012	5.091	3.711	0.000	0.023	0.001	0.032	0.000	0.021
26	0.000	0.043	0.029	0.000	0.000	0.000	0.012	4.588	3.526	0.000	0.022	0.001	0.029	0.000	0.020

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
26	0.000	0.039	0.026	0.000	0.000	0.000	0.011	4.098	3.315	0.000	0.021	0.000	0.026	0.000	0.019
27	0.000	0.036	0.023	0.000	0.000	0.000	0.010	3.624	3.082	0.000	0.019	0.000	0.023	0.000	0.017
28	0.000	0.032	0.020	0.000	0.000	0.000	0.009	3.172	2.832	0.000	0.018	0.000	0.020	0.000	0.016
30	0.000	0.028	0.018	0.000	0.000	0.000	0.008	2.747	2.572	0.000	0.016	0.000	0.018	0.000	0.015
31	0.000	0.025	0.015	0.000	0.000	0.000	0.007	2.351	2.306	0.000	0.015	0.000	0.015	0.000	0.013
32	0.000	0.021	0.013	0.000	0.000	0.000	0.006	1.997	2.049	0.000	0.013	0.000	0.013	0.000	0.012
33	0.000	0.018	0.011	0.000	0.000	0.000	0.005	1.676	1.798	0.000	0.011	0.000	0.011	0.000	0.010
34	0.000	0.016	0.009	0.000	0.000	0.000	0.005	1.392	1.559	0.000	0.010	0.000	0.009	0.000	0.009
35	0.000	0.013	0.007	0.000	0.000	0.000	0.004	1.134	1.325	0.000	0.008	0.000	0.008	0.000	0.008
36	0.000	0.011	0.006	0.000	0.000	0.000	0.003	0.905	1.103	0.000	0.007	0.000	0.006	0.000	0.006
37	0.000	0.009	0.005	0.000	0.000	0.000	0.003	0.709	0.899	0.000	0.006	0.000	0.005	0.000	0.005
38	0.000	0.007	0.003	0.000	0.000	0.000	0.002	0.544	0.719	0.000	0.005	0.000	0.004	0.000	0.004
39	0.000	0.005	0.003	0.000	0.000	0.000	0.002	0.410	0.563	0.000	0.004	0.000	0.003	0.000	0.003
40	0.000	0.004	0.002	0.000	0.000	0.000	0.001	0.303	0.433	0.000	0.003	0.000	0.002	0.000	0.002

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death; HS15* : Severe PTS.

Table 68: QALYs (undiscounted) accrued over time – LMWH/VKA arm, 12 months of treatment

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
0.25	16.0062	0.1142	0.1777	0.0196	0.1949	1.2800	0.0000	0.4393	0.0000	0.0000	0.0000	0.0220	0.0000	0.0000	0.0000
0.5	18.2964	0.0251	0.0382	0.0050	0.0498	0.5373	0.0275	1.0642	0.1234	0.0000	0.0000	0.0233	0.0214	0.0000	0.0007
0.75	18.0605	0.0102	0.0128	0.0038	0.0373	0.2771	0.0345	1.5092	0.1485	0.0000	0.0008	0.0220	0.0435	0.0000	0.0008

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
1	17.5805	0.0126	0.0156	0.0037	0.0368	0.2735	0.0397	1.9061	0.1578	0.0000	0.0009	0.0217	0.0638	0.0000	0.0009
2	0.0000	0.1037	0.1222	0.0000	0.0000	0.0000	0.0446	19.0559	0.4939	0.0000	0.0025	0.0222	0.1400	0.0000	0.0028
3	0.0000	0.1018	0.1173	0.0000	0.0000	0.0000	0.0443	18.3208	0.9056	0.0000	0.0051	0.0013	0.1494	0.0000	0.0051
4	0.0000	0.1001	0.1127	0.0000	0.0000	0.0000	0.0439	17.6044	1.2935	0.0000	0.0076	0.0013	0.1389	0.0000	0.0073
5	0.0000	0.0983	0.1082	0.0000	0.0000	0.0000	0.0436	16.9063	1.6580	0.0000	0.0099	0.0012	0.1293	0.0000	0.0094
6	0.0000	0.0965	0.1038	0.0000	0.0000	0.0000	0.0432	16.2211	1.9989	0.0000	0.0121	0.0012	0.1205	0.0000	0.0113
7	0.0000	0.0946	0.0995	0.0000	0.0000	0.0000	0.0428	15.5482	2.3161	0.0000	0.0142	0.0012	0.1125	0.0000	0.0131
8	0.0000	0.0927	0.0953	0.0000	0.0000	0.0000	0.0423	14.8904	2.6100	0.0000	0.0161	0.0012	0.1051	0.0000	0.0148
9	0.0000	0.0907	0.0912	0.0000	0.0000	0.0000	0.0418	14.2445	2.8804	0.0000	0.0178	0.0011	0.0982	0.0000	0.0163
10	0.0000	0.0886	0.0871	0.0000	0.0000	0.0000	0.0413	13.6113	3.1272	0.0000	0.0194	0.0011	0.0919	0.0000	0.0177
11	0.0000	0.0865	0.0831	0.0000	0.0000	0.0000	0.0407	12.9862	3.3495	0.0000	0.0209	0.0011	0.0861	0.0000	0.0190
12	0.0000	0.0843	0.0792	0.0000	0.0000	0.0000	0.0400	12.3710	3.5474	0.0000	0.0221	0.0011	0.0806	0.0000	0.0201
13	0.0000	0.0820	0.0753	0.0000	0.0000	0.0000	0.0393	11.7672	3.7212	0.0000	0.0233	0.0010	0.0756	0.0000	0.0211
14	0.0000	0.0797	0.0715	0.0000	0.0000	0.0000	0.0386	11.1737	3.8704	0.0000	0.0242	0.0010	0.0709	0.0000	0.0219
15	0.0000	0.0772	0.0678	0.0000	0.0000	0.0000	0.0378	10.5884	3.9943	0.0000	0.0250	0.0010	0.0664	0.0000	0.0226
16	0.0000	0.0747	0.0641	0.0000	0.0000	0.0000	0.0369	10.0091	4.0916	0.0000	0.0257	0.0009	0.0622	0.0000	0.0232
17	0.0000	0.0720	0.0604	0.0000	0.0000	0.0000	0.0359	9.4383	4.1629	0.0000	0.0262	0.0009	0.0583	0.0000	0.0236
18	0.0000	0.0693	0.0568	0.0000	0.0000	0.0000	0.0349	8.8743	4.2071	0.0000	0.0265	0.0009	0.0545	0.0000	0.0239
19	0.0000	0.0664	0.0532	0.0000	0.0000	0.0000	0.0337	8.3141	4.2224	0.0000	0.0266	0.0008	0.0509	0.0000	0.0239
20	0.0000	0.0634	0.0497	0.0000	0.0000	0.0000	0.0325	7.7607	4.2094	0.0000	0.0265	0.0008	0.0474	0.0000	0.0239
21	0.0000	0.0603	0.0462	0.0000	0.0000	0.0000	0.0312	7.2130	4.1672	0.0000	0.0263	0.0008	0.0440	0.0000	0.0236
22	0.0000	0.0570	0.0427	0.0000	0.0000	0.0000	0.0298	6.6704	4.0949	0.0000	0.0258	0.0007	0.0408	0.0000	0.0232
23	0.0000	0.0536	0.0393	0.0000	0.0000	0.0000	0.0283	6.1323	3.9913	0.0000	0.0252	0.0007	0.0376	0.0000	0.0226

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
24	0.0000	0.0501	0.0359	0.0000	0.0000	0.0000	0.0267	5.6021	3.8581	0.0000	0.0244	0.0006	0.0345	0.0000	0.0219
25	0.0000	0.0465	0.0326	0.0000	0.0000	0.0000	0.0251	5.0847	3.6985	0.0000	0.0234	0.0006	0.0314	0.0000	0.0210
26	0.0000	0.0429	0.0293	0.0000	0.0000	0.0000	0.0233	4.5822	3.5143	0.0000	0.0222	0.0005	0.0285	0.0000	0.0199
26	0.0000	0.0392	0.0262	0.0000	0.0000	0.0000	0.0215	4.0923	3.3042	0.0000	0.0209	0.0005	0.0257	0.0000	0.0187
27	0.0000	0.0354	0.0232	0.0000	0.0000	0.0000	0.0197	3.6190	3.0720	0.0000	0.0194	0.0004	0.0229	0.0000	0.0174
28	0.0000	0.0317	0.0203	0.0000	0.0000	0.0000	0.0178	3.1678	2.8232	0.0000	0.0179	0.0004	0.0202	0.0000	0.0160
30	0.0000	0.0281	0.0176	0.0000	0.0000	0.0000	0.0159	2.7436	2.5640	0.0000	0.0162	0.0004	0.0177	0.0000	0.0145
31	0.0000	0.0246	0.0150	0.0000	0.0000	0.0000	0.0141	2.3481	2.2985	0.0000	0.0145	0.0003	0.0153	0.0000	0.0130
32	0.0000	0.0214	0.0128	0.0000	0.0000	0.0000	0.0123	1.9943	2.0425	0.0000	0.0129	0.0003	0.0132	0.0000	0.0116
33	0.0000	0.0184	0.0107	0.0000	0.0000	0.0000	0.0107	1.6740	1.7922	0.0000	0.0113	0.0002	0.0112	0.0000	0.0102
34	0.0000	0.0156	0.0089	0.0000	0.0000	0.0000	0.0092	1.3899	1.5539	0.0000	0.0098	0.0002	0.0095	0.0000	0.0088
35	0.0000	0.0130	0.0072	0.0000	0.0000	0.0000	0.0077	1.1322	1.3208	0.0000	0.0084	0.0002	0.0078	0.0000	0.0075
36	0.0000	0.0106	0.0058	0.0000	0.0000	0.0000	0.0064	0.9041	1.0996	0.0000	0.0070	0.0001	0.0063	0.0000	0.0062
37	0.0000	0.0085	0.0045	0.0000	0.0000	0.0000	0.0051	0.7077	0.8967	0.0000	0.0057	0.0001	0.0050	0.0000	0.0051
38	0.0000	0.0067	0.0035	0.0000	0.0000	0.0000	0.0041	0.5433	0.7165	0.0000	0.0045	0.0001	0.0039	0.0000	0.0041
39	0.0000	0.0051	0.0026	0.0000	0.0000	0.0000	0.0032	0.4091	0.5613	0.0000	0.0036	0.0001	0.0030	0.0000	0.0032
40	0.0000	0.0039	0.0019	0.0000	0.0000	0.0000	0.0024	0.3026	0.4316	0.0000	0.0027	0.0000	0.0023	0.0000	0.0024

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment – post iPE; HS9: Off-treatment – post DVT; HS10: On-treatment – post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death; HS15* : Severe PTS.

Table 69: QALYs (undiscounted) accrued over time – rivaroxaban arm, lifelong treatment

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
0.25	16.287	0.128	0.199	0.010	0.096	1.282	0.000	0.439	0.000	0.000	0.000	0.022	0.000	0.000	0.000
0.5	18.711	0.028	0.043	0.003	0.025	0.546	0.014	0.901	0.000	0.123	0.000	0.024	0.021	0.000	0.000
0.75	18.510	0.009	0.013	0.002	0.020	0.290	0.017	1.306	0.003	0.147	0.000	0.022	0.044	0.000	0.000
1	18.046	0.011	0.015	0.002	0.020	0.292	0.020	1.681	0.006	0.152	0.000	0.022	0.064	0.000	0.000
2	15.434	0.030	0.039	0.003	0.027	0.217	0.034	3.901	0.032	0.206	0.000	0.022	0.139	0.000	0.000
3	13.393	0.038	0.048	0.003	0.027	0.213	0.050	5.568	0.068	0.294	0.001	0.000	0.145	0.000	0.000
4	11.709	0.043	0.053	0.005	0.044	0.208	0.073	6.801	0.117	0.393	0.001	0.001	0.132	0.000	0.001
5	10.363	0.047	0.058	0.004	0.041	0.202	0.097	7.687	0.178	0.497	0.002	0.001	0.121	0.000	0.001
6	9.265	0.051	0.061	0.004	0.039	0.197	0.119	8.297	0.253	0.600	0.002	0.001	0.111	0.000	0.001
7	8.364	0.053	0.063	0.004	0.037	0.191	0.141	8.690	0.339	0.698	0.003	0.001	0.102	0.000	0.002
8	7.617	0.054	0.064	0.004	0.035	0.186	0.160	8.916	0.434	0.789	0.003	0.001	0.094	0.000	0.002
9	6.991	0.055	0.064	0.004	0.033	0.180	0.179	9.009	0.537	0.871	0.004	0.001	0.086	0.000	0.003
10	6.460	0.055	0.063	0.003	0.031	0.174	0.196	8.998	0.646	0.944	0.005	0.001	0.080	0.000	0.004
11	6.002	0.055	0.062	0.003	0.030	0.167	0.213	8.905	0.757	1.006	0.006	0.001	0.074	0.000	0.004
12	5.601	0.055	0.061	0.003	0.029	0.161	0.227	8.747	0.869	1.058	0.006	0.001	0.068	0.000	0.005
13	5.245	0.054	0.060	0.003	0.027	0.155	0.241	8.540	0.981	1.101	0.007	0.001	0.063	0.000	0.006
14	4.925	0.053	0.058	0.003	0.026	0.149	0.253	8.294	1.089	1.134	0.008	0.001	0.059	0.000	0.006
15	4.632	0.052	0.056	0.003	0.025	0.142	0.264	8.017	1.193	1.158	0.009	0.001	0.054	0.000	0.007
16	4.358	0.051	0.053	0.003	0.023	0.136	0.274	7.712	1.289	1.173	0.009	0.001	0.051	0.000	0.007
17	4.101	0.050	0.051	0.003	0.022	0.129	0.281	7.389	1.377	1.180	0.010	0.001	0.047	0.000	0.008
18	3.856	0.048	0.049	0.003	0.021	0.123	0.287	7.048	1.455	1.179	0.010	0.001	0.044	0.000	0.008
19	3.619	0.047	0.046	0.002	0.020	0.116	0.292	6.692	1.522	1.170	0.011	0.001	0.040	0.000	0.009
20	3.388	0.045	0.044	0.002	0.019	0.109	0.294	6.325	1.575	1.153	0.011	0.001	0.037	0.000	0.009

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
21	3.162	0.043	0.041	0.002	0.018	0.102	0.294	5.949	1.615	1.129	0.011	0.001	0.035	0.000	0.009
22	2.939	0.041	0.038	0.002	0.016	0.096	0.293	5.563	1.638	1.098	0.011	0.001	0.032	0.000	0.009
23	2.718	0.038	0.036	0.002	0.015	0.089	0.288	5.170	1.645	1.059	0.011	0.000	0.029	0.000	0.009
24	2.499	0.036	0.033	0.002	0.014	0.082	0.282	4.773	1.635	1.014	0.011	0.000	0.027	0.000	0.009
25	2.284	0.034	0.030	0.002	0.013	0.075	0.273	4.376	1.609	0.963	0.011	0.000	0.024	0.000	0.009
26	2.073	0.031	0.027	0.001	0.012	0.068	0.263	3.983	1.566	0.907	0.011	0.000	0.022	0.000	0.009
26	1.866	0.029	0.025	0.001	0.010	0.061	0.250	3.592	1.507	0.845	0.010	0.000	0.020	0.000	0.009
27	1.663	0.026	0.022	0.001	0.009	0.055	0.235	3.207	1.431	0.780	0.010	0.000	0.018	0.000	0.008
28	1.468	0.024	0.020	0.001	0.008	0.048	0.219	2.834	1.342	0.711	0.009	0.000	0.015	0.000	0.008
30	1.282	0.021	0.017	0.001	0.007	0.042	0.201	2.477	1.243	0.641	0.009	0.000	0.014	0.000	0.007
31	1.106	0.018	0.015	0.001	0.006	0.036	0.182	2.140	1.134	0.571	0.008	0.000	0.012	0.000	0.006
32	0.947	0.016	0.013	0.001	0.005	0.031	0.164	1.834	1.026	0.505	0.007	0.000	0.010	0.000	0.006
33	0.802	0.014	0.011	0.001	0.005	0.026	0.145	1.554	0.915	0.440	0.006	0.000	0.009	0.000	0.005
34	0.672	0.012	0.009	0.001	0.004	0.022	0.128	1.302	0.806	0.380	0.006	0.000	0.007	0.000	0.005
35	0.552	0.010	0.007	0.000	0.003	0.018	0.110	1.070	0.695	0.321	0.005	0.000	0.006	0.000	0.004
36	0.445	0.008	0.006	0.000	0.003	0.015	0.092	0.862	0.587	0.266	0.004	0.000	0.005	0.000	0.003
37	0.351	0.007	0.005	0.000	0.002	0.012	0.076	0.681	0.486	0.216	0.003	0.000	0.004	0.000	0.003
38	0.272	0.005	0.004	0.000	0.002	0.009	0.062	0.528	0.393	0.172	0.003	0.000	0.003	0.000	0.002
39	0.207	0.004	0.003	0.000	0.001	0.007	0.049	0.401	0.312	0.134	0.002	0.000	0.002	0.000	0.002
40	0.154	0.003	0.002	0.000	0.001	0.005	0.038	0.299	0.243	0.103	0.002	0.000	0.002	0.000	0.001

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death; HS15* : Severe PTS.

Table 70: QALYs (undiscounted) accrued over time – LMWH/VKA arm, lifelong treatment

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
0.25	16.0062	0.1142	0.1777	0.0196	0.1949	1.2800	0.0000	0.4393	0.0000	0.0000	0.0000	0.0220	0.0000	0.0000	0.0000
0.5	18.4371	0.0251	0.0382	0.0051	0.0504	0.5422	0.0275	0.9160	0.0000	0.1087	0.0000	0.0233	0.0214	0.0000	0.0000
0.75	18.2306	0.0088	0.0119	0.0039	0.0389	0.2894	0.0345	1.3240	0.0026	0.1295	0.0000	0.0220	0.0435	0.0000	0.0000
1	17.7657	0.0109	0.0145	0.0040	0.0390	0.2909	0.0400	1.7008	0.0057	0.1345	0.0001	0.0217	0.0638	0.0000	0.0000
2	15.1554	0.0283	0.0373	0.0051	0.0504	0.2161	0.0677	3.9234	0.0292	0.1860	0.0003	0.0215	0.1384	0.0000	0.0002
3	13.1237	0.0366	0.0465	0.0048	0.0466	0.2115	0.0951	5.5881	0.0623	0.2715	0.0006	0.0005	0.1448	0.0000	0.0004
4	11.4915	0.0428	0.0532	0.0045	0.0435	0.2068	0.1204	6.8094	0.1081	0.3709	0.0010	0.0005	0.1319	0.0000	0.0006
5	10.1732	0.0473	0.0578	0.0043	0.0408	0.2017	0.1440	7.6841	0.1676	0.4753	0.0015	0.0006	0.1205	0.0000	0.0010
6	9.0989	0.0505	0.0609	0.0041	0.0385	0.1963	0.1660	8.2855	0.2402	0.5788	0.0020	0.0006	0.1103	0.0000	0.0014
7	8.2160	0.0527	0.0627	0.0039	0.0364	0.1907	0.1866	8.6726	0.3246	0.6771	0.0026	0.0007	0.1013	0.0000	0.0018
8	7.4847	0.0541	0.0636	0.0037	0.0345	0.1849	0.2059	8.8934	0.4189	0.7680	0.0033	0.0007	0.0932	0.0000	0.0024
9	6.8712	0.0549	0.0637	0.0036	0.0329	0.1790	0.2238	8.9830	0.5211	0.8499	0.0041	0.0007	0.0859	0.0000	0.0030
10	6.3505	0.0552	0.0632	0.0034	0.0313	0.1729	0.2406	8.9705	0.6289	0.9221	0.0048	0.0007	0.0793	0.0000	0.0036
11	5.9007	0.0551	0.0623	0.0033	0.0298	0.1668	0.2560	8.8756	0.7398	0.9841	0.0056	0.0007	0.0733	0.0000	0.0042
12	5.5072	0.0547	0.0609	0.0032	0.0285	0.1605	0.2701	8.7170	0.8518	1.0360	0.0063	0.0007	0.0679	0.0000	0.0048
13	5.1583	0.0540	0.0593	0.0031	0.0271	0.1543	0.2828	8.5098	0.9629	1.0784	0.0071	0.0007	0.0629	0.0000	0.0055
14	4.8441	0.0532	0.0575	0.0030	0.0259	0.1479	0.2943	8.2640	1.0710	1.1114	0.0078	0.0007	0.0584	0.0000	0.0061
15	4.5560	0.0521	0.0554	0.0028	0.0246	0.1416	0.3042	7.9869	1.1742	1.1355	0.0085	0.0007	0.0542	0.0000	0.0067
16	4.2875	0.0509	0.0533	0.0027	0.0234	0.1351	0.3125	7.6834	1.2706	1.1507	0.0091	0.0007	0.0503	0.0000	0.0072
17	4.0348	0.0495	0.0510	0.0026	0.0222	0.1286	0.3192	7.3605	1.3587	1.1578	0.0097	0.0006	0.0467	0.0000	0.0077
18	3.7938	0.0480	0.0486	0.0025	0.0210	0.1220	0.3242	7.0213	1.4370	1.1570	0.0102	0.0006	0.0434	0.0000	0.0081
19	3.5605	0.0463	0.0461	0.0024	0.0198	0.1154	0.3272	6.6665	1.5035	1.1481	0.0106	0.0006	0.0402	0.0000	0.0085

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12	HS13	HS14	HS15*
20	3.3337	0.0445	0.0435	0.0022	0.0187	0.1087	0.3282	6.3008	1.5573	1.1319	0.0110	0.0006	0.0372	0.0000	0.0088
21	3.1115	0.0425	0.0409	0.0021	0.0175	0.1020	0.3271	5.9256	1.5970	1.1083	0.0112	0.0005	0.0344	0.0000	0.0091
22	2.8922	0.0405	0.0383	0.0020	0.0163	0.0952	0.3238	5.5417	1.6212	1.0776	0.0113	0.0005	0.0317	0.0000	0.0092
23	2.6745	0.0383	0.0355	0.0019	0.0151	0.0883	0.3180	5.1499	1.6287	1.0397	0.0114	0.0005	0.0290	0.0000	0.0092
24	2.4590	0.0360	0.0328	0.0017	0.0139	0.0814	0.3099	4.7539	1.6193	0.9952	0.0113	0.0005	0.0265	0.0000	0.0092
25	2.2474	0.0336	0.0301	0.0016	0.0127	0.0745	0.2995	4.3587	1.5936	0.9451	0.0110	0.0004	0.0241	0.0000	0.0090
26	2.0402	0.0311	0.0274	0.0015	0.0116	0.0678	0.2871	3.9671	1.5520	0.8901	0.0107	0.0004	0.0218	0.0000	0.0088
26	1.8360	0.0286	0.0247	0.0013	0.0104	0.0611	0.2723	3.5775	1.4932	0.8299	0.0103	0.0004	0.0196	0.0000	0.0085
27	1.6366	0.0260	0.0220	0.0012	0.0093	0.0545	0.2555	3.1942	1.4188	0.7655	0.0098	0.0003	0.0174	0.0000	0.0080
28	1.4442	0.0234	0.0195	0.0011	0.0082	0.0481	0.2370	2.8225	1.3308	0.6983	0.0092	0.0003	0.0154	0.0000	0.0075
30	1.2612	0.0208	0.0170	0.0009	0.0072	0.0421	0.2173	2.4675	1.2323	0.6298	0.0085	0.0003	0.0135	0.0000	0.0070
31	1.0885	0.0183	0.0147	0.0008	0.0062	0.0363	0.1967	2.1315	1.1251	0.5610	0.0077	0.0002	0.0116	0.0000	0.0064
32	0.9323	0.0160	0.0126	0.0007	0.0053	0.0311	0.1765	1.8270	1.0174	0.4955	0.0070	0.0002	0.0100	0.0000	0.0058
33	0.7894	0.0138	0.0107	0.0006	0.0045	0.0264	0.1564	1.5478	0.9077	0.4324	0.0062	0.0002	0.0085	0.0000	0.0051
34	0.6611	0.0118	0.0089	0.0005	0.0038	0.0221	0.1370	1.2968	0.7995	0.3729	0.0055	0.0002	0.0072	0.0000	0.0045
35	0.5433	0.0099	0.0074	0.0004	0.0031	0.0182	0.1176	1.0661	0.6900	0.3155	0.0047	0.0001	0.0059	0.0000	0.0039
36	0.4376	0.0081	0.0059	0.0003	0.0025	0.0146	0.0989	0.8590	0.5828	0.2615	0.0040	0.0001	0.0048	0.0000	0.0033
37	0.3456	0.0065	0.0047	0.0003	0.0020	0.0116	0.0815	0.6786	0.4819	0.2124	0.0033	0.0001	0.0038	0.0000	0.0027
38	0.2676	0.0051	0.0036	0.0002	0.0015	0.0090	0.0658	0.5256	0.3903	0.1691	0.0027	0.0001	0.0030	0.0000	0.0022
39	0.2033	0.0040	0.0028	0.0002	0.0012	0.0068	0.0521	0.3994	0.3097	0.1321	0.0021	0.0001	0.0023	0.0000	0.0018
40	0.1517	0.0030	0.0021	0.0001	0.0009	0.0051	0.0405	0.2980	0.2411	0.1012	0.0016	0.0000	0.0017	0.0000	0.0014

HS1: On-treatment; HS2: rVTE-DVT; HS3: rVTE-PE; HS4: Major bleed – IC; HS5: Major bleed – EC; HS6: CRNM bleed; HS7: Post IC bleed; HS8: Off-treatment - post iPE; HS9: Off-treatment - post DVT; HS10: On-treatment - post DVT; HS11: PE post DVT; HS12: CTEPH; HS13: Long-term CTEPH; HS14: Death; HS15* : Severe PTS.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

There are many states considered in the model and two aggregated clinical outcomes The health states which correspond to VTE are 2, 3, and 11 and those which correspond to bleeding are 4, 5, 6 and 7 (Table 26). Table 71 reports the undiscounted life years (LY) and QALYs accrued for each of the aggregated clinical outcomes (VTE and bleeding) for the intervention (rivaroxaban) and the comparator (LMWH/VKA), differentiated by treatment duration (3, 6, 12 months and lifelong). Undiscounted costs associated with each health state are also provided.

For treatment durations up to 12 months, life years and QALYs accrued are higher for VTE than for the bleeds health state, irrespective of the treatment considered. This relates to the bleed state focusing on adverse events that occur during treatment for the index DVT. The reverse is observed for lifelong treatment as the risk of bleeding exceeds the risk of VTE. Longer treatment durations are associated with lower accrual of LYs and QALYs in the VTE state, reflecting the benefits of continued treatment. The reverse is true for bleeding, reflecting the risks of longer treatment durations.

Table 71: Model outputs by clinical outcomes

	Rivaroxaban			LMWH/VKA		
	LY	QALY	Cost (£)	LY	QALY	Cost (£)
3 months of treatment						
VTE	0.2680	0.2056	2,690.20	0.2692	0.2043	2,769.12
Bleeding	0.0921	0.0588	356.00	0.1449	0.1045	703.29
6 months of treatment						
VTE	0.2669	0.2048	2,684.62	0.2689	0.2041	2,767.63
Bleeding	0.0605	0.0364	159.60	0.0745	0.0553	304.84
12 months of treatment						
VTE	0.2628	0.2017	2,662.46	0.2646	0.2008	2,744.30
Bleeding	0.0748	0.0475	206.76	0.0966	0.0717	390.97
Lifelong treatment						
VTE	0.1677	0.1264	1,973.36	0.1650	0.1251	2,118.29
Bleeding	0.6939	0.5167	2,792.45	0.7630	0.5652	3,131.92

Note: LYs, QALYs and costs are undiscounted; VTE cost includes cost savings associated with early discharge for patients treated with rivaroxaban; PE cost was applied to all patients in the index PE state.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

The requirements of this section are met by providing:

- Disaggregated QALYs by health state
- Disaggregated costs by health state
- Disaggregated costs by category of resource consumed

Results are presented separately for patients of each of the four treatment durations considered.

Disaggregated QALYs by health state

The four tables below (Table 72, Table 73, Table 74 and Table 75) provide the lifetime per patient QALYs gained with rivaroxaban compared with LMWH/VKA as well as the increment, absolute increment and percentage absolute increment (the format specified in the template), for each health state and for each treatment duration.

Table 72: Summary of QALY gain (undiscounted) by health state – 3 months of treatment

Health state	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
On-treatment	0.1595	0.1543	0.0053	0.0053	13.64%
rVTE-DVT	0.0931	0.0926	0.0006	0.0006	1.49%
rVTE-PE	0.0853	0.0847	0.0005	0.0005	1.43%
Major bleed – IC	0.0003	0.0006	-0.0003	0.0003	0.79%
Major bleed – EC	0.0030	0.0060	-0.0030	0.0030	7.82%
CRNM bleed	0.0135	0.0135	0.0000	0.0000	0.05%
Post IC bleed	0.0420	0.0844	-0.0423	0.0423	110.01%
Off-treatment - post iPE	13.0074	12.9605	0.0470	0.0470	122.07%
Off-treatment - post DVT	4.3441	4.3137	0.0303	0.0303	78.74%
On-treatment - post DVT	0.0000	0.0000	0.0000	0.0000	0.00%
PE post DVT	0.0272	0.0270	0.0002	0.0002	0.49%
CTEPH	0.0029	0.0029	0.0000	0.0000	0.04%
Long-term CTEPH	0.0878	0.0874	0.0004	0.0004	1.10%
Death	0.0000	0.0000	0.0000	0.0000	0.00%
PTS severe	-0.0246	-0.0245	-0.0002	0.0002	0.45%
Total	17.8415	17.8030	0.0385	0.0385	100.00%

Table 73: Summary of QALY gain (undiscounted) by health state – 6 months of treatment

Health state	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
On-treatment	0.3491	0.3437	0.0054	0.0054	32.48%
rVTE-DVT	0.0928	0.0925	0.0003	0.0003	1.89%
rVTE-PE	0.0851	0.0848	0.0003	0.0003	1.91%
Major bleed – IC	0.0001	0.0002	-0.0001	0.0001	0.76%
Major bleed – EC	0.0012	0.0025	-0.0012	0.0012	7.57%
CRNM bleed	0.0179	0.0179	0.0000	0.0000	0.25%
Post IC bleed	0.0172	0.0347	-0.0175	0.0175	106.20%
Off-treatment - post iPE	12.9553	12.9443	0.0110	0.0110	66.85%
Off-treatment - post DVT	4.3070	4.2889	0.0181	0.0181	109.86%
On-treatment - post DVT	0.0000	0.0000	0.0000	0.0000	0.00%
PE post DVT	0.0269	0.0268	0.0001	0.0001	0.69%
CTEPH	0.0029	0.0029	0.0000	0.0000	0.04%
Long-term CTEPH	0.0879	0.0877	0.0002	0.0002	1.20%
Death	0.0000	0.0000	0.0000	0.0000	0.00%
PTS severe	-0.0244	-0.0243	-0.0001	0.0001	0.62%
Total	17.9190	17.9025	0.0165	0.0165	100.00%

Table 74: Summary of QALY gain (undiscounted) by health state – 12 months of treatment

Health state	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
On-treatment	0.7099	0.6994	0.0105	0.0105	41.15%
rVTE-DVT	0.0913	0.0909	0.0004	0.0004	1.49%
rVTE-PE	0.0841	0.0837	0.0004	0.0004	1.50%
Major bleed – IC	0.0002	0.0003	-0.0002	0.0002	0.64%
Major bleed – EC	0.0016	0.0032	-0.0016	0.0016	6.31%
CRNM bleed	0.0238	0.0237	0.0001	0.0001	0.29%
Post IC bleed	0.0220	0.0446	-0.0225	0.0225	88.22%
Off-treatment - post iPE	12.7584	12.7420	0.0164	0.0164	64.38%
Off-treatment - post DVT	4.2010	4.1792	0.0218	0.0218	85.31%
On-treatment - post DVT	0.0000	0.0000	0.0000	0.0000	0.00%
PE post DVT	0.0263	0.0261	0.0001	0.0001	0.54%
CTEPH	0.0029	0.0029	0.0000	0.0000	0.03%
Long-term CTEPH	0.0875	0.0873	0.0002	0.0002	0.95%
Death	0.0000	0.0000	0.0000	0.0000	0.00%
PTS severe	-0.0238	-0.0237	-0.0001	0.0001	0.48%
Total	17.9852	17.9597	0.0255	0.0255	100.00%

Table 75: Summary of QALY gain (undiscounted) by health state – lifelong treatment

Health state	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
On-treatment	7.4872	7.3593	0.1279	0.1279	86.81%
rVTE-DVT	0.0563	0.0558	0.0005	0.0005	0.35%
rVTE-PE	0.0597	0.0591	0.0006	0.0006	0.41%
Major bleed – IC	0.0035	0.0038	-0.0003	0.0003	0.23%
Major bleed – EC	0.0307	0.0340	-0.0033	0.0033	2.25%
CRNM bleed	0.1895	0.1887	0.0007	0.0007	0.50%
Post IC bleed	0.2931	0.3387	-0.0456	0.0456	30.92%
Off-treatment - post iPE	7.9981	7.9770	0.0211	0.0211	14.34%
Off-treatment - post DVT	1.4585	1.4394	0.0192	0.0192	13.00%
On-treatment - post DVT	1.1595	1.1334	0.0261	0.0261	17.74%
PE post DVT	0.0103	0.0102	0.0001	0.0001	0.09%
CTEPH	0.0024	0.0024	0.0000	0.0000	0.01%
Long-term CTEPH	0.0761	0.0758	0.0003	0.0003	0.21%
Death	0.0000	0.0000	0.0000	0.0000	0.00%
PTS severe	-0.0083	-0.0082	-0.0001	0.0001	0.07%
Total	18.8168	18.6695	0.1473	0.1473	100.00%

Disaggregated costs by health state

The four tables below (Table 76, Table 77, Table 78 and Table 79) provide the lifetime per patient costs incurred with rivaroxaban compared with LMWH/VKA as well as the increment, absolute increment and percentage absolute increment, for each health state and for each treatment duration.

Table 76: Summary of costs incurred (undiscounted) by health state – 3 months of treatment

Health state		Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
	Index event cost including early discharge saving	1,212.79	1,301.25	-88.46	88.46	17.85%
HS1	On tx	216.74	298.65	-81.90	81.90	16.53%
HS2	rVTE - DVT	392.71	390.30	2.41	2.41	0.49%
HS3	rVTE - PE	822.48	817.18	5.30	5.30	1.07%
HS4	Major bleed -IC	28.93	58.06	-29.13	29.13	5.88%
HS5	Major bleed - EC	15.05	30.20	-15.15	15.15	3.06%
HS6	CRNM bleed	14.87	18.61	-3.74	3.74	0.75%
HS7	Post IC bleed	297.15	596.42	-299.26	299.26	60.39%
HS8	Off Tx - post iPE	0.00	0.00	0.00	0.00	0.00%
HS9	Off tx post DVT	0.00	0.00	0.00	0.00	0.00%
HS10	On tx post DVT	0.00	0.00	0.00	0.00	0.00%
HS11	PE post DVT	262.22	260.39	1.83	1.83	0.37%
HS12	CTEPH	128.06	127.44	0.61	0.61	0.12%
HS13	Long-term CTEPH	2,410.89	2,399.24	11.65	11.65	2.35%
HS14	Death	0.00	0.00	0.00	0.00	0.00%
	PTS severe	46.44	46.13	0.31	0.31	0.06%
	Total	5,848.34	6,343.86	-495.53	495.53	100.00%

Table 77: Summary of costs incurred (undiscounted) by health state – 6 months of treatment

Health state		Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
	Index event cost including early discharge saving	1,212.79	1,301.25	-88.46	88.46	34.74%
HS1	On tx	392.52	424.79	-32.27	32.27	12.67%
HS2	rVTE - DVT	391.16	389.85	1.31	1.31	0.52%
HS3	rVTE - PE	820.71	817.67	3.04	3.04	1.19%
HS4	Major bleed -IC	11.85	23.94	-12.09	12.09	4.75%
HS5	Major bleed - EC	6.16	12.45	-6.29	6.29	2.47%
HS6	CRNM bleed	20.29	23.33	-3.04	3.04	1.19%
HS7	Post IC bleed	121.29	245.12	-123.82	123.82	48.63%
HS8	Off Tx - post iPE	0.00	0.00	0.00	0.00	0.00%
HS9	Off tx post DVT	0.00	0.00	0.00	0.00	0.00%
HS10	On tx post DVT	0.00	0.00	0.00	0.00	0.00%
HS11	PE post DVT	259.96	258.86	1.10	1.10	0.43%
HS12	CTEPH	128.30	128.02	0.28	0.28	0.11%
HS13	Long-term CTEPH	2,414.52	2,409.08	5.44	5.44	2.14%
HS14	Death	0.00	0.00	0.00	0.00	0.00%
	PTS severe	46.10	45.92	0.18	0.18	0.07%
	Total	5,825.67	6,080.28	-254.62	254.62	100.00%

Table 78: Summary of costs incurred (undiscounted) by health state – 12 months of treatment

Health state		Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
	Index event cost including early discharge saving	1,212.79	1,301.25	-88.46	88.46	47.42%
HS1	On tx	727.71	655.44	72.26	72.26	38.74%
HS2	rVTE - DVT	385.07	383.47	1.60	1.60	0.86%
HS3	rVTE - PE	811.10	807.40	3.70	3.70	1.98%
HS4	Major bleed -IC	15.27	30.86	-15.59	15.59	8.36%
HS5	Major bleed - EC	7.94	16.05	-8.11	8.11	4.35%
HS6	CRNM bleed	27.68	29.06	-1.38	1.38	0.74%
HS7	Post IC bleed	155.87	315.00	-159.13	159.13	85.31%
HS8	Off Tx - post iPE	0.00	0.00	0.00	0.00	0.00%
HS9	Off tx post DVT	0.00	0.00	0.00	0.00	0.00%
HS10	On tx post DVT	0.00	0.00	0.00	0.00	0.00%
HS11	PE post DVT	253.50	252.19	1.32	1.32	0.71%
HS12	CTEPH	127.82	127.48	0.35	0.35	0.19%
HS13	Long-term CTEPH	2,403.77	2,397.10	6.67	6.67	3.58%
HS14	Death	0.00	0.00	0.00	0.00	0.00%
	PTS severe	45.09	44.86	0.22	0.22	0.12%
	Total	6,173.61	6,360.15	-186.54	186.54	100.00%

Table 79: Summary of costs incurred (undiscounted) by health state – lifelong treatment

Health state		Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
	Index event cost including early discharge saving	1,212.79	1,301.25	-88.46	88.46	4.50%
HS1	On tx	7,024.42	4,968.81	2,055.60	2,055.60	104.65%
HS2	rVTE - DVT	172.22	197.99	-25.77	25.77	1.31%
HS3	rVTE - PE	501.54	527.96	-26.42	26.42	1.34%
HS4	Major bleed -IC	332.27	364.23	-31.96	31.96	1.63%
HS5	Major bleed - EC	154.47	171.14	-16.67	16.67	0.85%
HS6	CRNM bleed	233.57	202.30	31.27	31.27	1.59%
HS7	Post IC bleed	2,072.15	2,394.26	-322.11	322.11	16.40%
HS8	Off Tx - post iPE	0.00	0.00	0.00	0.00	0.00%
HS9	Off tx post DVT	0.00	0.00	0.00	0.00	0.00%
HS10	On tx post DVT	1,231.14	847.38	383.76	383.76	19.54%
HS11	PE post DVT	86.81	91.09	-4.28	4.28	0.22%
HS12	CTEPH	109.33	108.86	0.46	0.46	0.02%
HS13	Long-term CTEPH	2,090.92	2,082.22	8.70	8.70	0.44%
HS14	Death	0.00	0.00	0.00	0.00	0.00%
	PTS severe	16.48	16.28	0.20	0.20	0.01%
	Total	15,238.11	13,273.78	1,964.33	1,964.33	100.00%

Disaggregated costs by category of resource consumed

Table 80 provides the lifetime per patient costs incurred with rivaroxaban compared with LMWH/VKA as well as the increment, absolute increment and percentage absolute increment, by category of resource consumed and duration of treatment. The categories presented are: drug acquisition costs, monitoring (INR), VTE event costs, bleeding costs and costs associated with PTS or CTEPH.

Table 80: Summary of lifetime costs by category of resource (discounted)

Cost category	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
3 months of treatment					
Drug cost	216.74	99.19	117.55	117.55	29.70%
Monitoring cost	0.00	199.45	-199.45	199.45	50.39%
Event cost	2,204.15	2,285.23	-81.08	81.08	20.48%
Bleeds cost	251.31	493.16	-241.85	241.85	61.10%
PTS/CTEPH	1,839.13	1,830.10	9.03	9.03	2.28%
Total	4,511.33	4,907.14	-395.80	395.80	100.00%
6 months of treatment					
Drug cost	392.52	104.58	287.94	287.94	135.05%
Monitoring cost	0.00	320.20	-320.20	320.20	150.18%
Event cost	2,195.75	2,279.58	-83.83	83.83	39.32%
Bleeds cost	116.69	218.14	-101.44	101.44	47.58%

Cost category	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
PTS/CTEPH	1,840.71	1,836.39	4.33	4.33	2.03%
Total	4,545.68	4,758.89	-213.21	213.21	100.00%
12 months of treatment					
Drug cost	727.71	114.71	612.99	612.99	460.46%
Monitoring cost	0.00	540.73	-540.73	540.73	406.18%
Event cost	2,171.86	2,254.78	-82.93	82.93	62.29%
Bleeds cost	151.44	279.17	-127.73	127.73	95.94%
PTS/CTEPH	1,830.48	1,825.21	5.27	5.27	3.96%
Total	4,881.48	5,014.60	-133.13	133.13	100.00%
Lifetime treatment					
Drug cost	5,969.36	284.15	5,685.21	5,685.21	413.55%
Monitoring cost	0.00	3,962.24	-3,962.24	3,962.24	288.22%
Event cost	1,692.92	1,815.49	-122.57	122.57	8.92%
Bleeds cost	1,593.95	1,826.29	-232.34	232.34	16.90%
PTS/CTEPH	1,611.59	1,604.92	6.67	6.67	0.49%
Total	10,867.82	9,493.09	1,374.73	1,374.73	100.00%

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Results (discounted) are presented separately according to the four groups of patients considered: those requiring lifelong treatment or treatment for 3, 6 or 12 months..

Patients for whom three months of anticoagulation is appropriate

For this group of patients, rivaroxaban was associated with greater LYs, greater QALYs and lower costs, as compared with dual LMWH/VKA therapy. Rivaroxaban was dominant.

Table 81: Base case results for patients requiring 3 months of treatment

Technologies	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£) (QALYs)
Rivaroxaban	4,511	14.571	11.940	-	-	-	-
LMWH/VKA	4,907	14.546	11.912	396	-0.025	-0.027	Dominated

Patients for whom six months of anticoagulation is appropriate

For this group of patients, rivaroxaban was associated with greater LYs, greater QALYs and lower costs, as compared with dual LMWH/VKA therapy. Rivaroxaban was dominant.

Table 82: Base case results for patients requiring 6 months of treatment

Technologies	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£) (QALYs)
Rivaroxaban	4,546	14.630	11.992	-	-	-	-
LMWH/VKA	4,759	14.622	11.979	213	-0.008	-0.013	Dominated

Patients for whom twelve months of anticoagulation is appropriate

For this group of patients, rivaroxaban was associated with greater LYs, greater QALYs and lower costs, as compared with dual LMWH/VKA therapy. Rivaroxaban was dominant.

Table 83: Base case results for patients requiring 12 months of treatment

Technologies	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£) (QALYs)
Rivaroxaban	4,881	14.683	12.035	-	-	-	-
LMWH/VKA	5,015	14.671	12.015	133	-0.011	-0.020	Dominated

Patients for whom lifelong anticoagulation is appropriate

For this group of patients, rivaroxaban was associated with greater LYs, greater QALYs and greater costs, as compared with dual LMWH/VKA therapy. The ICER was £13,252 per QALY gained, so rivaroxaban was cost-effective at a willingness-to-pay (WTP) threshold of £20,000 per QALY.

Table 84: Base case results – lifelong treatment

Technologies	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£) (QALYs)
LMWH/VKA	9,493	15.303	12.375	-	-	-	-
Rivaroxaban	10,868	15.333	12.479	1,375	0.030	0.104	13,252

Conclusion

There was a greater discounted life expectancy and quality-adjusted life expectancy with rivaroxaban compared with LMWH/VKA, irrespective of treatment duration.

For the 3, 6, 12 month and lifelong patient groups, incremental life years gained with rivaroxaban were estimated at 0.025, 0.008, 0.011 and 0.03 and incremental QALYs at 0.027, 0.013, 0.020 and 0.104 respectively.

For patients requiring treatment of up to one year, rivaroxaban was associated with per patient cost savings, which were greatest for the 3 month treatment duration (3 months: £396; 6 months: £213, 12 months: £133). Consequently, for these three treatment durations, rivaroxaban was the dominant treatment option when compared with LMWH/VKA (Table 81, Table 82 and Table 83).

For patients requiring lifelong treatment, additional costs (£1,375) were associated with treatment with rivaroxaban compared with treatment with LMWH/VKA (Table 84). However, the ICER (£13,252/QALY) demonstrated rivaroxaban was cost-effective assuming a £20,000/QALY WTP threshold.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Deterministic sensitivity analysis was performed by means of one-way and multivariate sensitivity analysis, where one parameter or group of related parameters was varied relative to its base case value. The method adopted and the parameters tested were described in section 7.6.2..

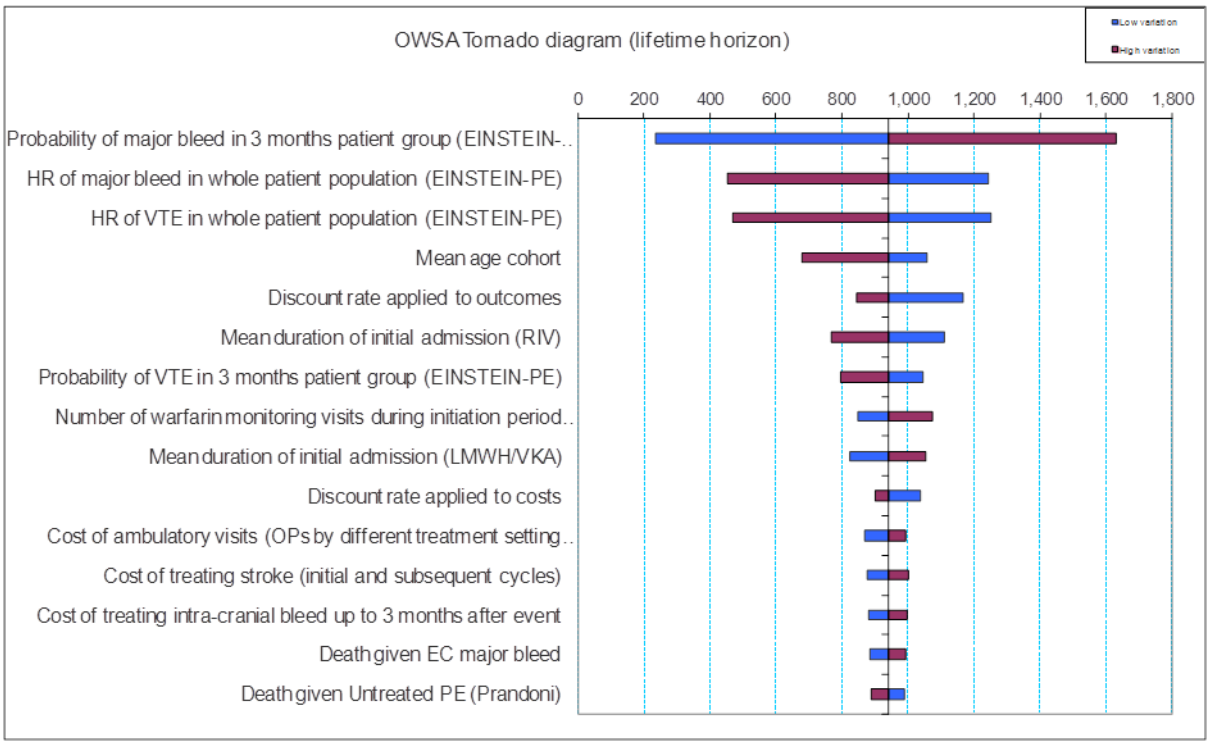
Overall, there were 123 sensitivity analyses conducted for each of the four durations of treatment for which rivaroxaban was evaluated (496 in total). The full set of results can be produced by the MS Excel model accompanying this submission, but is not reproduced here. Instead, tornado plots for the top 15 most sensitive parameters are shown using the net monetary benefit (NMB) measure at a willingness to pay of £20,000 per QALY. Presenting ICER results was less meaningful due to the strong dominance of rivaroxaban for for patients not requiring lifelong treatment..

Results are presented separately according to the four groups of patients considered.

Patients for whom three months of anticoagulation is appropriate

The tornado diagram (Figure 15) shows variation in the NMB from a base case of £939.25. The NMB was positive in all analyses and largely insensitive to variation in the assumptions made, with the exception of the probability of major bleeds and the treatment effect for major bleeds and VTE recurrence.

Figure 15: Tornado plot – net monetary benefit of rivaroxaban vs. LMWH/VKA, 3 months of treatment, lifetime horizon

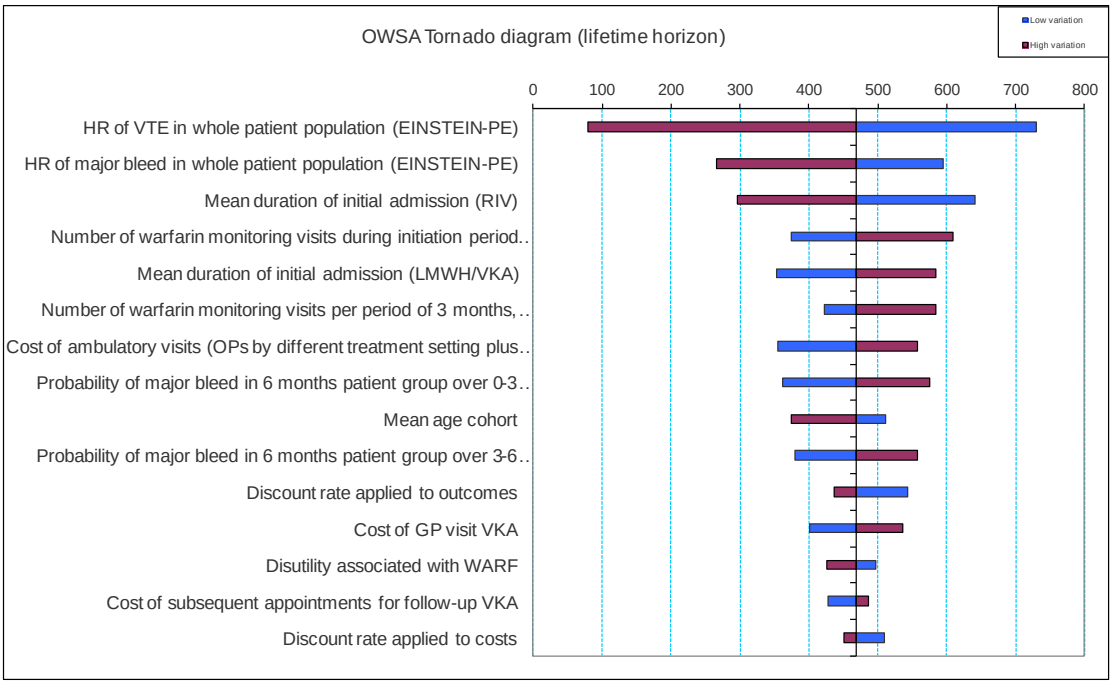


An additional sensitivity analyses was performed setting time horizon at 5 years. Rivaroxaban remains dominant for this time horizon.

Patients for whom six months of anticoagulation is appropriate

The tornado diagram (Figure 16) shows variation in the NMB from a base case of £468.45. The NMB was positive in all analyses; however NMB was sensitive to the assumptions made around the treatment effect for VTE recurrence and to a lesser extent to the treatment effect for major bleeds, number of warfarin monitoring visits in the first 3 months and duration of intital admission for both rivaroxaban and LMWH / VKA patients.

Figure 16: Tornado plot – net monetary benefit of rivaroxaban vs. LMWH/VKA, 6 months of treatment, lifetime horizon

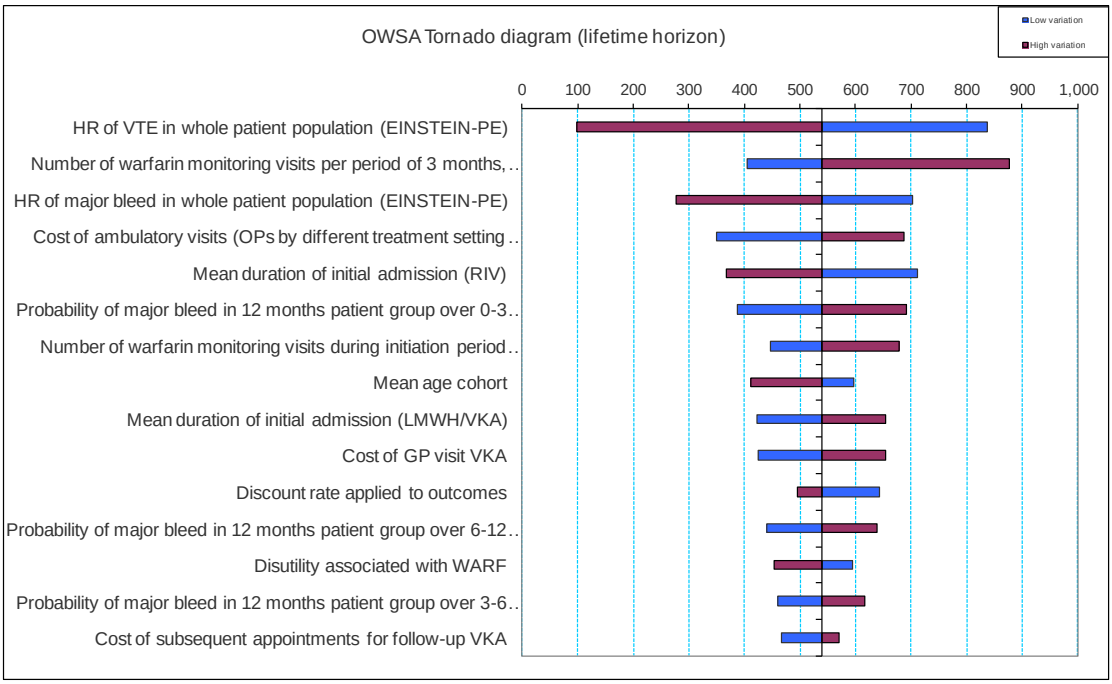


An additional sensitivity analyses was performed setting time horizon at 5 years. Rivaroxaban remains dominant for this time horizon.

Patients for whom twelve months of anticoagulation is appropriate

The tornado diagram (Figure 17) shows variation in the NMB from a base case of £538.88. Whilst the treatment effects for VTE recurrence and bleeds remain important drivers of cost-effectiveness, asssumptions relating to frequency and cost of monitoring visits become more prominent. NMB was positive in all analyses.

Figure 17: Tornado plot – net monetary benefit of rivaroxaban vs. LMWH/VKA, 12 months of treatment

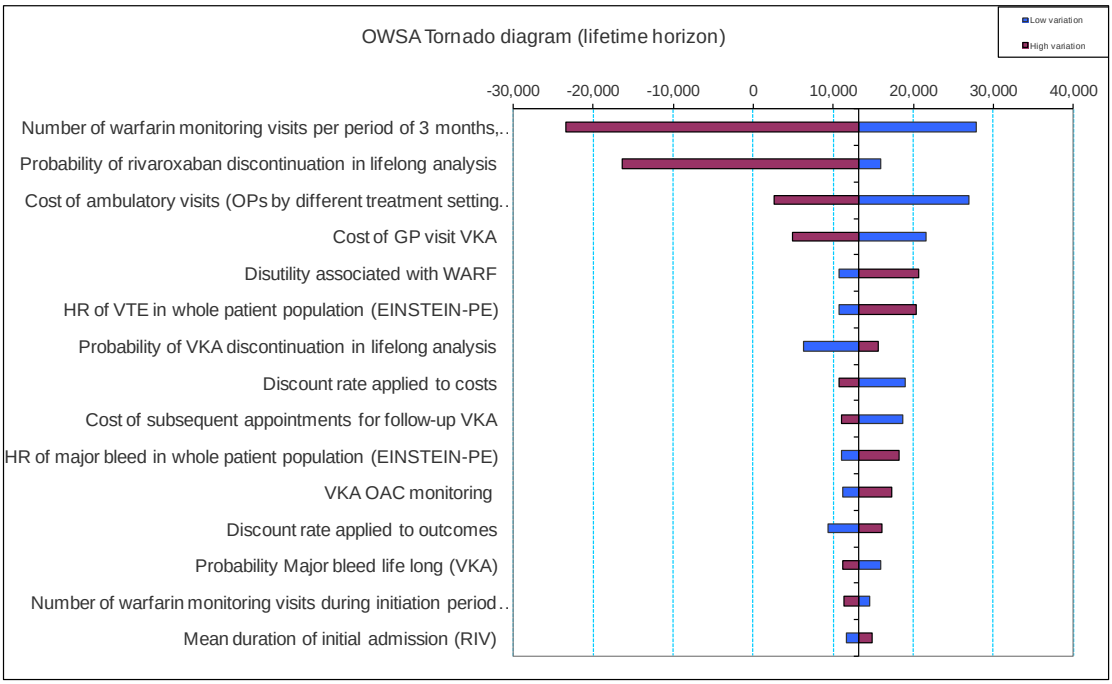


An additional sensitivity analyses was performed setting time horizon at 5 years. Rivaroxaban remains dominant for this time horizon.

Patients for whom lifetime anticoagulation is appropriate

For the lifetime treatment population it is more appropriate to present an ICER based rather than NMB based tornado diagram since rivaroxaban is not dominant in this group (Figure 18). The base case ICER was £13,252. Cost-effectiveness was most sensitive to changes around the frequency of INR monitoring visits, where the ICER reaches £27,914 in the low variation (3 vs 5 visits each quarter after the first), but relatively insensitive to other inputs.

Figure 18: Tornado plot – ICER for rivaroxaban vs. LMWH/VKA, lifetime treatment



An additional sensitivity analyses was performed setting time horizon at 5 years. At this time horizon rivaroxaban has an ICER of £12,282/QALY.

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Overview

Probabilistic sensitivity analyses (PSAs) were run with 5000 simulations in all cases. The probabilities that rivaroxaban is cost-effective in comparison with LMWH/VKA, the current standard of care, at thresholds from £0 to £50,000 are tabulated in Table 85. At a threshold of £20,000 per QALY, the probability of cost-effectiveness was 99.9%, 95.9% and 93.7% for the 3, 6 and 12 month treatment groups. For lifelong anticoagulation therapy this is estimated to be 59.1%.

Greater cost savings and increased incremental QALYs for rivaroxaban were associated with the group of patients requiring shorter durations of therapy. The probability of rivaroxaban being the dominant treatment option was highest in the 3 month treatment group at 99.1% and was 84.9% and 63.9% respectively in patients requiring 6 or 12 months anticoagulation. For the lifelong treatment option this was 19.5%.

The probabilistic mean costs and QALYS are presented separately for patients on each of the four treatment durations considered.

Table 85: Probability that rivaroxaban is cost-effective, by patient group and WTP threshold (£)

WTP per QALY (£)	Patient group (appropriate duration of treatment)			
	3 months	6 months	12 months	Lifelong
0	99.0%	91.2%	66.9%	22.8%
10,000	99.9%	96.2%	89.8%	35.8%
20,000	99.9%	95.9%	93.7%	59.1%
30,000	99.9%	95.5%	94.8%	78.6%
40,000	99.9%	94.9%	95.3%	86.9%
50,000	99.9%	94.6%	95.5%	89.8%

Patients for whom three months of anticoagulation is appropriate

The probabilistic mean costs and QALYs relating to the group of patients for whom three months anticoagulation treatment was appropriate, indicate rivaroxaban was associated with greater LYs, greater QALYs and lower costs, as compared with dual LMWH/VKA therapy (Table 86). Rivaroxaban was dominant. This is consistent with findings from the deterministic base case (Table 81).

Table 86: Probabilistic mean costs and QALYs for patients requiring 3 months of treatment

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£) (QALYs)
Rivaroxaban	4,676.36	13.259	-	-	-
LMWH/VKA	5,061.04	13.221	384.68	-0.038	Dominated

The relevant plots are Figure 19 and Figure 20. The PSA demonstrated a 99.9% probability of rivaroxaban being cost-effectiveness at a threshold of £20,000 per QALY and a 99.1% probability of rivaroxaban being less costly and more effective than LMWH/VKA (dominant).

Figure 19: CE plane for rivaroxaban vs LMWH/VKA - patients requiring 3 months of treatment

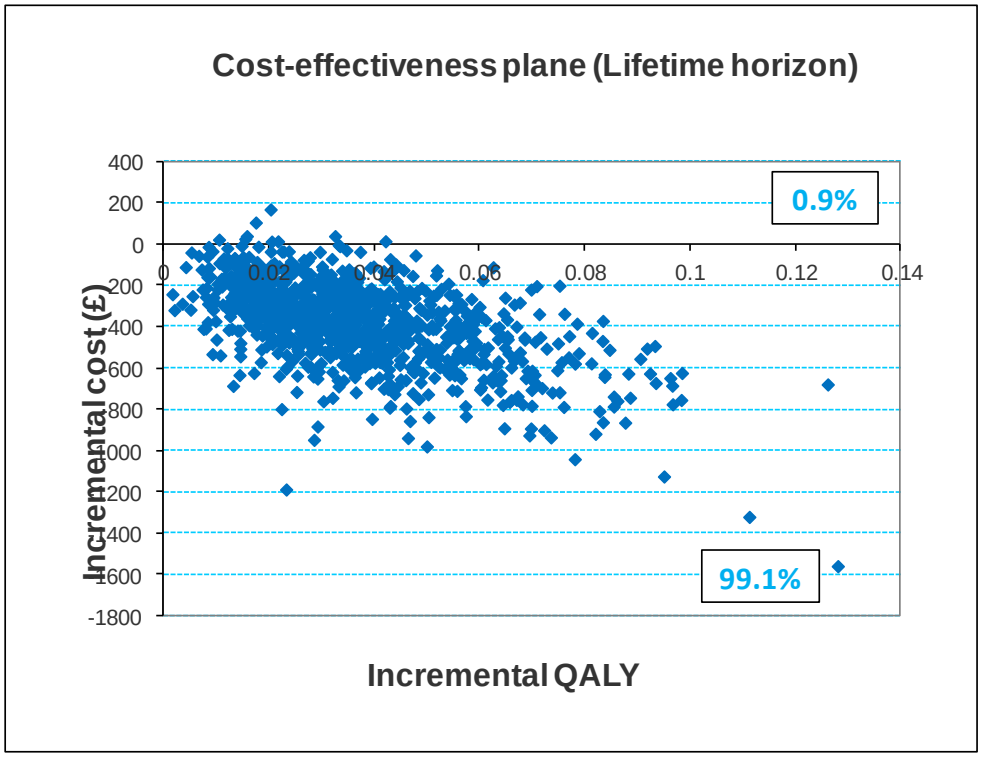
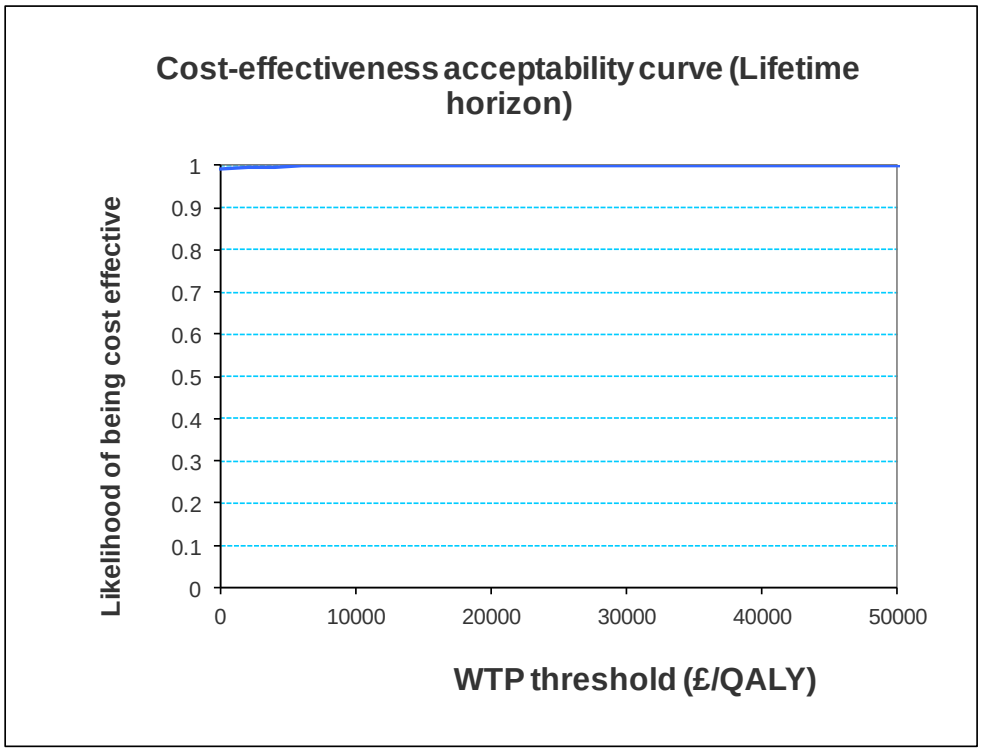


Figure 20: CEAC for rivaroxaban vs LMWH/VKA – patients requiring 3 months of treatment



Patients for whom six months of anticoagulation is appropriate

The probabilistic mean costs and QALYs relating to the group of patients for whom six months anticoagulation treatment was appropriate, indicate rivaroxaban was associated with greater QALYs and lower costs, with respect to dual LMWH/VKA therapy (Table 87). Rivaroxaban was dominant. This is consistent with findings from the deterministic base case (Table 82).

Table 87: Probabilistic mean costs and QALYs – 6 months of treatment

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£) (QALYs)
Rivaroxaban	4,700.66	13.244	-	-	-
LMWH/VKA	4,910.75	13.230	210.08	-0.014	Dominated

The relevant plots are Figure 21 and Figure 22. The PSA demonstrated a 95.9% probability of rivaroxaban being cost-effectivene at a threshold of £20,000 per QALY and a 84.9% probability of rivaroxaban being less costly and more effective than LMWH/VKA (dominant).

Figure 21: CE plane for rivaroxaban vs LMWH/VKA – 6 months of treatment

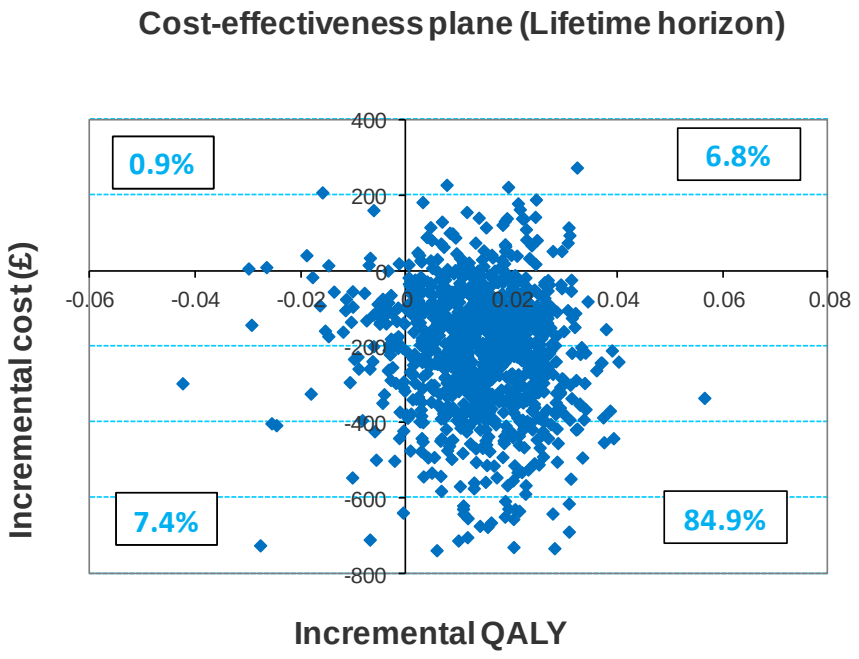
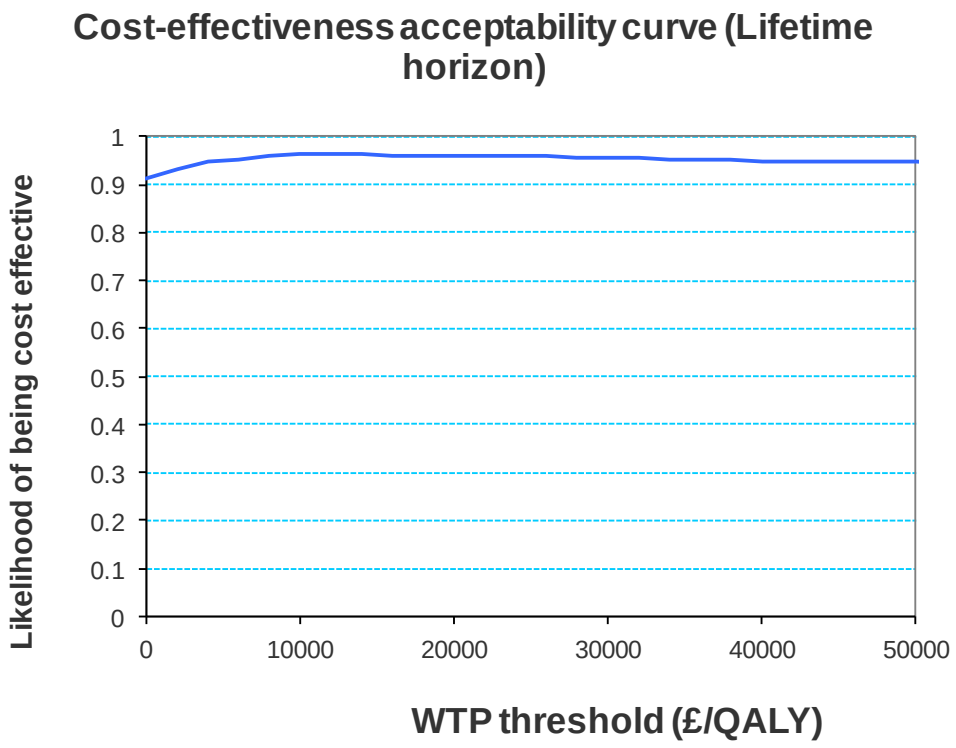


Figure 22: CEAC for rivaroxaban vs LMWH/VKA – 6 months of treatment



Patients for whom twelve months of anticoagulation is appropriate

The probabilistic mean costs and QALYs relating to the group of patients for whom twelve months anticoagulation treatment was appropriate, indicate rivaroxaban was associated with greater LYs, greater QALYs and lower costs, as compared with dual LMWH/VKA therapy (Table 88). Rivaroxaban was dominant. This is consistent with findings from the deterministic base case (Table 83).

Table 88: Probabilistic mean costs and QALYs – 12 months of treatment

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£) (QALYs)
Rivaroxaban	5,025.66	13.232	-	-	-
LMWH/VKA	5,146.66	13.210	121.00	-0.022	Dominated

The relevant plots are Figure 23 and Figure 24. The PSA demonstrated a 93.7% probability of rivaroxaban being cost-effective at a threshold of £20,000 per QALY and a 63.9% probability of rivaroxaban being less costly and more effective than LMWH/VKA (dominant).

Figure 23: CE plane for rivaroxaban vs LMWH/VKA – 12 months of treatment

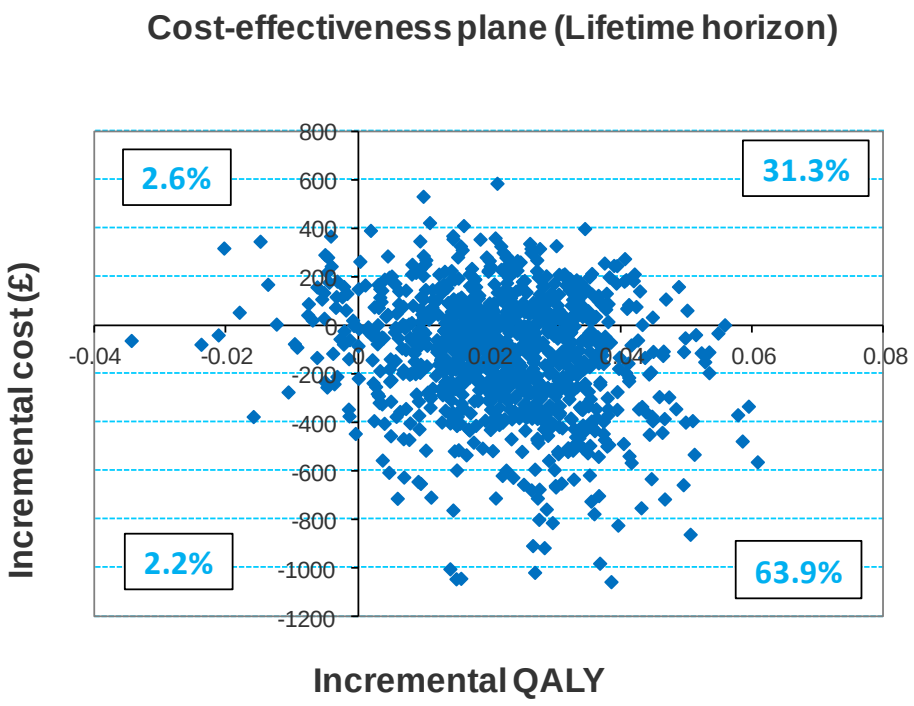
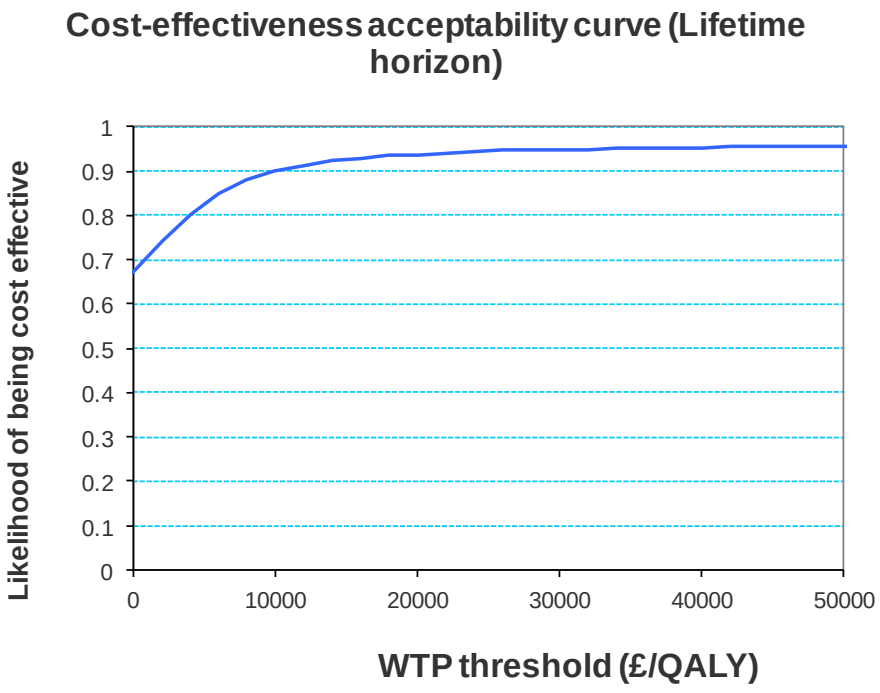


Figure 24: CEAC for rivaroxaban vs LMWH/VKA – 12 months of treatment



Patients for whom lifelong anticoagulation is appropriate

The probabilistic mean costs and QALYs relating to the group of patients for whom lifelong anticoagulation treatment was appropriate, indicate rivaroxaban was associated with greater QALYs and greater costs, as compared with dual LMWH/VKA therapy. The resulting ICER, £13,918 per QALY gained (Table 89), .was consistent with findings from the deterministic base case (ICER of £13,252, Table 84) and indicated cost-effectiveness relative to the willingness to pay threshold of £20,000 per QALY gained.

Table 89: Probabilistic mean costs and QALYs – lifelong treatment

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£) (QALYs)
LMWH/VKA	9,718.55	12.356	-	-	-
Rivaroxaban	11,172.66	12.460	1,454.12	0.104481	13,918

The relevant plots are Figure 25 and Figure 26. The PSA demonstrated a 59.1% probability of rivaroxaban being cost-effective at a threshold of £20,000 per QALY. The PSA also showed a 19.5% probability of rivaroxaban being less costly and more effective than LMWH/VKA (dominant) and a 74.2%

probability of rivaroxaban being more costly and more effective than LMWH/VKA.

Figure 25: CE plane for rivaroxaban vs LMWH/VKA – lifelong treatment

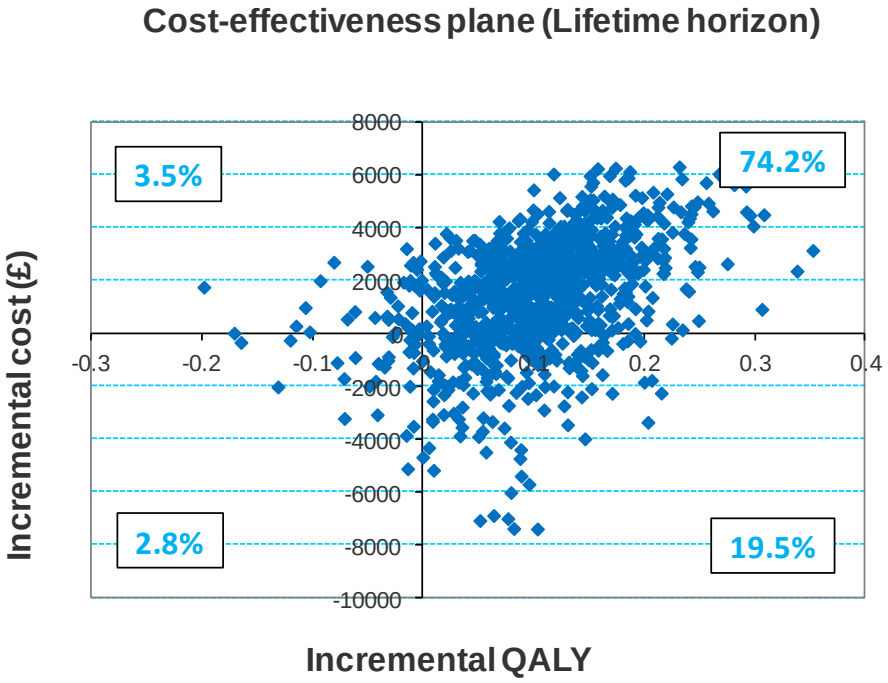
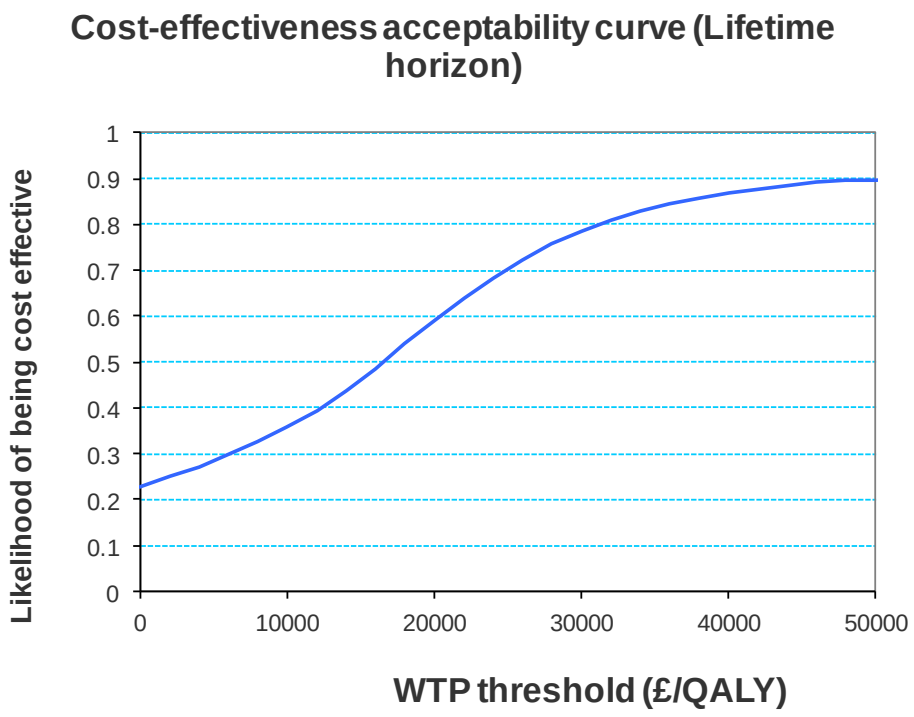


Figure 26: CEAC for rivaroxaban vs LMWH/VKA – lifelong treatment



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

No scenario analyses were conducted other than the time horizon analyses previously described.

7.7.10 What were the main findings of each of the sensitivity analyses?

The dominance of rivaroxaban vs LMWH/VKA was largely insensitive to variation in the assumptions made in all but the lifetime time horizon, whether deterministic or probabilistic. For shorter durations, sensitivity is greatest to the treatment effect parameter but as duration on treatment increases the frequency and cost of INR monitoring become important drivers. Cost-effectiveness in the lifetime treatment population is more sensitive to assumptions made around outpatient care concerning warfarin monitoring visits and the cost of ambulatory visits.

PSA for all of the four analyses also indicated that the model results are robust. The CEAC indicated that the likelihood of rivaroxaban being cost-effective at a threshold of £20,000 per QALY varies between 99.9% and 93.7% for the 3 to 12 months treatment scenarios respectively and is 59.1%

for lifetime anticoagulation. The scatterplots on the cost-effectiveness planes showed that the probability of rivaroxaban being dominant varies between 99.1% and 63.9% for the 3 to 12 months treatment scenarios and is 19.5% for lifetime anticoagulation. Higher probabilities of cost-effectiveness and dominance are recorded in analyses where patients were treated for a shorter durations.

7.7.11 What are the key drivers of the cost-effectiveness results?

The base case results and their insensitivity to deterministic and probabilistic variation in parameter values may be attributed to the clinical and economic value that rivaroxaban may provide the NHS.

- The treatment effect for rivaroxaban vs LMWH/VKA in respect of VTE recurrence in EINSTEIN-PE was a HR of 1.12, 95% CI 0.75 to 1.68).[13]
- Rivaroxaban demonstrated significantly lower rates of major bleeding in the trial (HR for major bleeding of 0.49, 95% CI 0.31 to 0.79)[13].
- Rivaroxaban requires no routine monitoring of coagulation parameters, which can be very costly. The frequency, unit cost and setting of monitoring can affect the apparent cost-effectiveness of rivaroxaban, but only to a limited extent.
- Rivaroxaban requires no LMWH therapy which, aside from being relatively costly to acquire compared to rivaroxaban, requires additional clinical time and resource (eg nurse visits, education).
- Resource use associated with hospitalisation during acute treatment is lower for rivaroxaban patients than for LMWH/VKA patients.[14] This corresponds to a reduced length of stay of 0.5 days (8.6, 95% CI 7.63 to 9.57 vs. 9.1, 95% CI 8.54 to 9.75).

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The economic model has been assured through internal and external validation.

Internal validity assures that outputs are logical and accurate within the framework set by the model. This was ensured by quality control of the model by the model developers (IMS Health), as well as a model audit performed by an external health economic modelling group in addition to Prof. Lieven Annemans, Professor of Health economics at I-CHER (Ghent University and Brussels University.

Extensive external validation was undertaken in consultation with experts in PE treatment, as described below.

- Aside from the systematic review of cost-effectiveness studies updated and reported for this submission, there was an earlier review of key literature in the field of PE economic modeling. This was conducted prior to formulating the model design concept and is referred to briefly in section 7.1.
- The initial design of the cost-effectiveness model was discussed with the involvement of experts in clinical aspects of PE treatment. The assumption of extrapolating the consequences of key outcomes of interest beyond the time horizon of the clinical trials is common practice in the economic modelling of diseases with potential chronic complications and necessary for the NICE Reference Case.[65]
- Comparison of the results from the model over the time horizon of the clinical trial with those directly from EINSTEIN-PE indicated that results from the model were consistent (section 7.7.1).
- Results of the model were compared against other published studies. The results were consistent with the economic analysis of rivaroxaban for the treatment fo DVT presented in TA261.[19] It also captures the key events included in economic analyses for CG144[8] and other published VTE models (section 7.1).

7.9 Subgroup analysis

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost

effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

The Decision Problem (section 5) lists three possible subgroups for consideration: underlying risk of bleeding; provoked or unprovoked venous thromboembolism; presence of active cancer. As outlined in CG144 there are no valid tools for predicting the risk of VTE or bleeding.[8] In EINSTEIN-PE the duration of treatment received by patients was determiend by the physicians assessment of risk. However, as outlined in 6.5, there were no significant interactions between treatment and the risk of bleeding, provoked vs nonprovoked or presence of active of cancer. Therefore, the previously presented treatment duration subgroups are considered representative of the subgroups requested.

The Decision Problem identified LMWH as a comparator for people for whom a vitamin K antagonist is not considered an appropriate treatment, and it is understood that this refers to patients with cancer. Of the 28,623 people diagnosed with PE during 2010/11 in England, 2,519 of them had a secondary diagnosis of cancer (costing template to CG144[8]). This amounts to 8.8% of all PE cases arising in patients with cancer. However, secondary prevention with the standard of care (VKAs) is compromised by issues such as vomiting, malnutrition, liver impairment and drug interactions. Guidelines recommend LMWH as a preferred treatment over VKA for at least the first 3 to 6 months in DVT patients with cancer[8,47] and so, in this subgroup, LMWH is an appropriate comparator.

Whilst dalteparin is currently licensed in the UK for both VTE treatment[188] and extended treatment in oncology[48], other LMWHs have been studied and may be used, a recent Cochrane review found little difference between dalteparin and other LMWHs (see also section 6.7).[77]

Nevertheless, the SMC approved dalteparin in February 2011 with the recommendation reflecting the licensed extended oncology indication.[48,189] In light of this, the specific LMWH to be used as the comparator to rivaroxaban in this subgroup is dalteparin for 6 months.

The relevant treatments considered in this subgroup are therefore:

- Rivaroxaban 15mg bd for 21 days, followed by 20mg od for the remainder of 6 months
- Dalteparin 200 IU/kg total body weight SC od for the first 30 days of treatment (maximum 18,000 IU daily) followed by 150 IU/kg daily, adjusted to reflect fixed doses available.

Given differences in treatment the remainder of section 7.9 considers patients with active cancer.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Patients included in this subgroup in EINSTEIN-PE were those judged at the baseline screening assessment to have active cancer.[13,63]

7.9.3 Please describe how the statistical analysis was undertaken.

Long term LMWH for the secondary prevention of VTE was not included in EINSTEIN-PE and as a consequence an indirect comparison would be required to support an economic analysis of the cancer subgroup. No such analysis has been undertaken. This is in light of the limited evidence base and methodological challenges highlighted during the appraisal of rivaroxaban for DVT in TA261. Please refer to 6.7.1 for further discussion. Nonetheless, TA261 recognised the potential value of rivaroxaban in reducing the monitoring burden on patients with active cancer. Therefore, a cost-minimisation analysis comparing rivaroxaban to LMWH has been undertaken to inform the appraisal.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

The cost minimisation analysis is summarised in Table 90. This table identifies the costs associated with 6 months of PE treatment and secondary prevention with either rivaroxaban or dalteparin in cancer patients. Over this period rivaroxaban was associated with a cost saving of over £900.

Table 90: Cost minimisation of rivaroxaban vs LMWH in the cancer subgroup

Items	Rivaroxaban	Dalteparin	Source
Drug cost	£2.10 per 15 or 20 mg tablet	Month 1: £8.47 per day. Months 2-6: £7.06 per day.	BNF 64[166]

Mean cost of technology treatment			
Initial treatment	£2.10 x 21 x 2 = £88.2	£8.47 x 30 = £254.10	Derived
Extended treatment (remainder of 6 months or 182.5 days)	£2.10 x 161.5 = £339.15	£7.06 x 152.5 = £1,076.65	
Additional cost components			
Monitoring cost:	No monitoring visits	No monitoring visits	Guidelines of the Association for Palliative Medicine for Great Britain and Ireland[47]
Administration	£0	£0	Assumed
Total costs			
Total over 6 months	£427.36	£1,330.75	Derived
Saving associated with rivaroxaban	£903.39		Derived

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Results from EINSTEIN-PE were considered reflective of clinical practice and therefore no further subgroups were considered..

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no published economic literature regarding the cost-effectiveness of rivaroxaban for the treatment of PE, and prevention of recurrent PE and DVT following an acute PE.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes. The EINSTEIN-PE trial included a large proportion of patients with characteristics representative of UK patients requiring treatment for PE as per the Decision Problem. See section 5.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the economic evaluation lies in the comprehensive model structure fed by a robust clinical trial and extensive research to populate it. The model was developed over the course of the EINSTEIN-DVT and PE studies in consultation with UK clinical and health economic experts, ensuring that the model clinical pathway is in line with UK clinical practice. The model developed independently by a NICE Guideline Development Committee for CG 144 included similar key outcome states.[8]

One of the key drivers of this evaluation is the cost of warfarin monitoring. As there is wide variation in the published literature as well as in clinical practice around warfarin monitoring, an extensive research project was undertaken to quantify the costs of warfarin monitoring in the UK. A service evaluation and national survey were conducted to obtain the models of anti-coagulation, quantify its distribution and collect resource use data for each type of model.[46,51] This was combined with NHS Reference Costs[164] for costing purposes (Table 49).[190]

During model development a number of weaknesses were identified. Examination of these issues with sensitivity analysis identified that the majority of weaknesses did not substantially influence findings from the model.

Key limitations were:

Utilities, despite an extensive literature search it was not possible to consistently source utilities elicited using the EQ-5D. Nonetheless, aside from utilities relating to the impact of warfarin on health related quality of life, the findings of the model were stable to variation in utilities.

Non-inferiority trial design. A limitation of the base case deterministic analysis, as with any deterministic analysis, is the dependence on point estimates as model inputs. These point estimates may be uncertain, and this uncertainty is not accounted for in a deterministic analysis. However, clinical and economic decision-making are generally recommended to consider confidence/credible

intervals over p-values, and PSA has accordingly been developed as a method to illustrate the extent of uncertainty in model outputs due to uncertainty in parameter values used as inputs.[65] The PSA results demonstrate high probability for the cost-effectiveness of rivaroxaban in patients appropriate for 3, 6, 12 months or lifelong treatment – a conclusion consistent with the base case deterministic results.

Long term risk of recurrent VTE off treatment, identification of a source suitable for long term recurrence appropriate to the whole trial cohort was challenging. Nonetheless, univariate SA indicated that related inputs were not important drivers

Mortality associated with PE, a search of the literature indicated some variation in estimates of mortality, though this is considered for in SA.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Extensive sensitivity analyses, both one-way and probabilistic, were undertaken to test the robustness of the results. Further evidence generation programmes may improve the overall robustness of the analysis by increasing the accuracy of the input values.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The number of patients eligible for treatment was estimated primarily from a combined analysis of UK hospital and primary care databases (General Practice Research Database, Hospital Episode Statistics database and Office for National Statistics linkage data) for incidence and recurrence of PE. The results of this study are shown in Table 91.

Table 91: Age-specific incidence rates of PE, per 100,000 person-years

Age	PE events*		Person years of follow up		Incidence rate (per 100,000 person-years)	
	First PE	Recurrent PE	First PE	Recurrent PE	First PE	Any PE
18-29	235	50	2,080,517	1,661	11.3	13.7
30-39	391	63	2,134,771	3,071	18.3	21.2
40-49	601	100	2,172,535	4,175	27.7	32.2
50-59	999	148	1,926,861	6,654	51.8	59.3
60-69	1807	221	1,482,445	8,957	121.9	136.0
70-79	2356	303	1,076,374	10,433	218.9	244.7
80-89	1983	202	586,457	5,805	338.1	368.9
90-99	497		118,503	727	419.4	440.3
Total	8,869	5,430	11,578,463	41,483		

Basis of results presented: event rates and person-years of follow-up from from Martinez et al 2011[23], additional data on file from this study[32].

Rates of incidence of any PE were then applied, by age-group, to the principal 2010-based population projections for England and Wales made by the Office of National Statistics.[33] Consequently, we estimate that there would be in the region of 38,612 incident cases of adults with acute PE in 2013 in England

and Wales, including both first and recurrent PEs. The total would rise to a projected 41,276 incident cases in 2017 due to growth and ageing of the population. It was assumed that a total of 15% of PE patients would be unsuitable for rivaroxaban, as described previously in section 2.2. Therefore, we estimate that there would be in the region of 32,821 cases in 2013 potentially treatable with rivaroxaban, rising to approximately 35,085 by 2017, as shown in Table 92.

Table 92: Estimated numbers of PE cases, and patients potentially treatable with rivaroxaban

Year	2013	2014	2015	2016	2017
Population (thousands)	44,654	45,012	45,351	45,676	45,996
Incidence rate (per 100,000)	86.5	87.1	87.8	88.6	89.7
Numbers of cases	38,612	39,207	39,825	40,472	41,276
Potentially treated with rivaroxaban*	32,821	33,326	33,851	34,401	35,085

* Calculated as number of PE cases less 15% assumed not appropriate for rivaroxaban

The time horizon of the model was five years. The model considers each of the four patient groups previously described, as per the decision problem: patients requiring 3 months, 6 months, 12 months or lifelong anticoagulation. The specific duration of `lifelong' treatment was assumed to be at least as long as the (5 year) time horizon of the model.

The proportion of patients requiring lifelong treatment was assumed as 7.5%, following the costing template developed by NICE following the appraisal of rivaroxaban for DVT treatment (though the duration of `lifelong' in this model was assumed to be two years).[19] The remainder of patients (92.5%) were allocated to treatment durations of up to one year based on the distribution of patients in EINSTEIN-PE (Table 10).[13] The full distribution of patients by treatment duration is summarised in Table 93.

Table 93: Distribution of patients by duration of treatment

Appropriate duration of treatment	Percentage of PE patients
3 months	4.8%
6 months	53.1%
12 months	34.6%
Lifelong*	7.5%
Total	100%

* Lifelong patients are patients treated for a minimum of 2 years

Information on the typical treatment duration or persistence of therapy for lifelong patients is limited (as discussed previously in section 7.3.1). The same rate discontinuation was applied to lifelong patients as was assumed in the cost-effectiveness model: 13.5% per year, based on Boggon et al 2011[117].

This annual discontinuation rate was applied to patients after their second year of treatment within the budget impact model i.e to patients that had been in the model for at least 2 years. This approach ensures the proportion of patients receiving 2 years of treatment matches the estimate included in the CG144 costing template.[8]

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

As described in previous sections (eg section 2.5), the standard of care is dual LMWH/VKA therapy. As with the cost-effectiveness modelling in section 7, this is taken to be treatment with enoxaparin for an initial period of [redacted] for a PE event[73] (Figure 14), followed by treatment with warfarin for the remainder of the appropriate treatment duration of 3, 6, 12 months or lifelong, depending on an individual patient risk-benefit.

Monitoring is carried out at a frequency of 9 INR tests in the first three months and 5 INR tests in each quarter thereafter (Table 47).[46,166] We derived in section 7.5 a unit cost for the first INR monitoring visit of £25.69 and for a subsequent visit of £21.57 (Table 50)[164].

8.3 What assumption(s) were made about market share (when relevant)?

The availability of rivaroxaban represents a potentially important change in the approach to the treatment of PE and prevention of recurrent VTE. To help understand the economic impact of rivaroxaban uptake and use, cost savings were estimated under two scenarios; a world with rivaroxaban and a world without rivaroxaban, summarised in Table 94.

In the world without rivaroxaban, it was assumed the only relevant treatment option on the UK market for the general PE population was the dual LMWH/VKA therapy. For the world with rivaroxaban it was anticipated that rivaroxaban would become the treatment of choice for PEs by year 5, with a linear increase from 20% in Year 1 to 80% in Year 5 (with corresponding decrease for dual LMWH/VKA therapy).

Table 94: Market share assumptions in worlds with and without rivaroxaban

	Year 1	Year 2	Year 3	Year 4	Year 5
World without rivaroxaban					
Dual LMWH/VKA therapy	100%	100%	100%	100%	100%
Rivaroxaban	0%	0%	0%	0%	0%
World with rivaroxaban					
Dual LMWH/VKA therapy	80%	65%	50%	35%	20%
Rivaroxaban	20%	35%	50%	65%	80%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

INR monitoring assumptions were previously described in section 8.2.

In addition patient transport, with a unit cost of £12.29, is assumed to be required for 8.55% of patients monitored in secondary care. For patients receiving dual therapy who are unable to self-inject initial LMWH treatment, a cost for a district nurse or clinic visit was also included. This follows the approach adopted for cost-effectiveness modelling in section 7 (Table 50). Patients prescribed rivaroxaban do not require INR monitoring, patient transport or drug administration assistance.

Furthermore, results of the EINSTEIN-PE trial showed a shorter length of hospital stay for hospitalised PE patients receiving rivaroxaban in comparison with dual LMWH/VKA treatment. Cost savings associated with early discharge of patients treated with rivaroxaban were captured in the budget impact by including this saving within monitoring costs in the same fashion as for the cost-effectiveness analyses (see section 7: £88.46 per patient treated with rivaroxaban (see Table 49 and Table 50).[14,164]

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Drug and monitoring costs assumed in this section are identical to those assumed in the cost-effectiveness evaluation in section 7 (see Table 50). The costs per patient for each treatment strategy are shown in Table 95.

Table 95: Cost of treatment per patient

	Drug acquisition cost (£)	Other costs* (£)	Total cost (£)
Dual LMWH/VKA therapy			
3 months	100	233	333
6 months	106	359	465
12 months	117	612	729
Year 2+	23	505	528
Rivaroxaban			
3 months	236	-88	147
6 months	427	-88	339
12 months	811	-88	722
Year 2+	767	0	767

Note: Other costs represents patient transport, drug administration and INR monitoring for patients receiving dual LMWH/VKA, and reflects cost savings from reduced length of hospital for patients receiving rivaroxaban.

The costs of treatment (drug acquisition and monitoring) for the lifelong treatment patients consisted of year 1 costs incurred by patients from the 12 month treatment group. Costs in year 2+ subsequently reduced to reflect the

lower monitoring burden associated with warfarin long term and exclusion of LMWH costs. These costs are summarized in Table 95 above.

8.6 Were there any estimates of resource savings? If so, what were they?

There are four sources of resource savings considered in the budget impact model:

- Reduced duration of hospitalisation with rivaroxaban
- An absence of INR monitoring costs with rivaroxaban
- An absence of a transport costs to attend INR monitoring visits
- Savings in nurse time due to rivaroxaban's oral administration in comparison to the nurse administration required with LMWH for a proportion of patients

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated expenditures for 2013-2017 for worlds with and without rivaroxaban, and the net budget impact, are shown in Table 96. In the first year, additional drug costs of £3.1m were more than offset by savings in monitoring costs of £3.6m, resulting in a net budget impact saving of £0.5m. By year 5, with greater uptake of rivaroxaban, the net budget impact saving was expected to reach £1.3m. Over the five year period, the total additional drug costs were estimated at £46.1m, which were more than offset by total monitoring costs of £50.9m, resulting in a saving to the NHS of £4.8m.

Table 96: Estimated expenditure for NHS in England and Wales in worlds with and without rivaroxaban, and net budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5	Total for years 1-5
World without rivaroxaban						
Drug costs	3,622,259	3,735,112	3,843,429	3,948,502	4,063,330	19,212,633
Monitoring costs	15,082,671	16,557,113	17,892,509	19,111,106	20,281,696	88,925,095
Total costs	18,704,931	20,292,225	21,735,938	23,059,609	24,345,026	108,137,728
World with rivaroxaban						
Drug costs	6,702,891	9,575,102	12,753,662	16,222,498	20,022,024	65,276,176
Monitoring costs	11,485,474	9,916,682	7,960,620	5,648,724	3,008,492	38,019,993
Total costs	18,188,365	19,491,785	20,714,282	21,871,222	23,030,516	103,296,169
Net budget impact (% change)						
Drug costs	3,080,631 (+85%)	5,839,990 (+156%)	8,910,234 (+232%)	12,273,995 (+311%)	15,958,693 (+393%)	46,063,544 (+240%)
Monitoring costs	-3,597,197 (-24%)	-6,640,430 (-40%)	-9,931,890 (-56%)	-13,462,382 (-70%)	-17,273,204 (-85%)	-50,905,102 (-57%)
Total costs	-516,565 (-2.8%)	-800,440 (-3.9%)	-1,021,656 (-4.7%)	-1,188,387 (-5.2%)	-1,314,510 (-5.4%)	-4,841,558 (-4%)

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The budget impact analysis captures the potential for net budgetary savings associated with drug acquisition, reduced length of stay, reduced INR monitoring, transport, self-administration of subcutaneous injections and the need for home visits from community nurses, as described in section 8.6.

However, as with the cost-effectiveness evaluation, no difference in standard disease monitoring and follow-up associated with rivaroxaban was assumed. This simplifying modelling assumption is particularly conservative given the opportunity that rivaroxaban brings, as a once day oral anticoagulant without the need for LMWH bridging therapy or INR monitoring, in providing the scope for redesigning anticoagulation services bringing additional financial savings.

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