NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Rivaroxaban in the treatment of deep vein thrombosis and prevention of recurrent venous thromboembolic events

Bayer plc

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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
CG	Clinical Guideline
CHMP	European Committee for Medical Products for Human Use
CI	Confidence Interval
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
CUS	Compression Ultrasound
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
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
IC	IntraCranial
ICER	Incremental Cost Effectiveness Ratio
INR	International Normalised Range
IQR	InterQuartile Range
ISTH	International Society of Thrombosis and Haematosis
ITT	Intention To Treat
LMWH	Low Molecular Weight Heparin
LYG	Life Years Gained
NHS	(British) National Health Service
NICE	National Institute for health and Clinical Excellence
NPSA	National Patient Safety Agency
OR	Odds Ratio
PE	Pulmonary Embolism
PEA	Pulmonary Endodardectomy
PLS	Perfusion Lung Scan
PP	Per Protocol

PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
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
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

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] It has been evaluated in eight phase III studies with exposure to over 16,000 patients.[2;3]

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 inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.[1]

Rivaroxaban was recommended for approval by the European Committee for Medical Products for Human Use (CHMP) in September 2011 for two indications.[4;5] One indication relates to secondary prevention of atrial fibrillation, and is the subject of another ongoing NICE Single Technology Assessment (STA).[4;6] The other is `treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults' and is the subject of this submission and STA.[2;3] Full UK marketing authorisation for both new indications is anticipated in Q4 2011.

Current treatment of DVT requires initial Low Molecular Weight Heparin (LMWH) therapy (administered by subcutaneous injection) overlapping and followed by therapy with a Vitamin K Antagonist (VKA), typically warfarin. Warfarin has various limitations and requires frequent INR monitoring.[7-10] Rivaroxaban provides a single drug approach for the acute and continued treatment of DVT, and does not require dose adjustment or ongoing monitoring of coagulation parameters.[2;3]

The duration of anticoagulation to be delivered must follow a clinician's assessment of a patient's risk-benefit, reflecting the nature of the index DVT event (eg whether idiopathic or caused by temporary or permanent risk factors) and the patient's characteristics (including age, gender, condition, lifestyle, comorbidities). Generally treatment is recommended for at least 3 months.[9;11;12]

Dosing of LMWH can be dependent on weight and renal function, and this has previously led to safety issues.[13] 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.[7-10]

Rivaroxaban provides a single oral drug approach which avoids the need for bridging therapy with injectables and warfarin dose adjustment. INR monitoring is not only unnecessary but inappropriate and potentially misleading.[2;3;7] See section 2.4.

The indication for rivaroxaban recommends a dosage of 15 mg bid for 21 days followed by 20 mg od thereafter.[2;3] The main comparator for rivaroxaban is the current UK standard of care, dual therapy of LMWH such as enoxaparin (until anticoagulation is established) overlapping with a VKA, typically warfarin.

Evidence as to the safety and effectiveness of rivaroxaban arises primarily from EINSTEIN-DVT, which was a head-to-head RCT of rivaroxaban vs enoxaparin/VKA for 3-12 months of treatment following an acute DVT. This study found a treatment effect in favour of rivaroxaban in time to recurrence of VTE (HR of 0.68, 95% CI 0.44 to 1.04) and comparable rates of bleeding (HR for clinically relevant bleeding of 0.67, 95% CI 0.47 to 0.95, and HR for major bleeding of 0.65, 95% CI 0.33 to 1.28). There was direct measurement of net clinical benefit – the trade-off between VTE recurrence and major bleeding. This outcome was significantly in favour of rivaroxaban (HR of 0.67, 95% CI 0.47 to 0.95, P=0.03).

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).

An indirect comparison is conducted for rivaroxaban vs long-term LMWH in patients with active cancer who experienced an acute DVT, a comparator/subgroup which was highlighted in the Final Scope (section 5.7). Data from across EINSTEIN-DVT and its cancer subgroup were combined, using the mixed treatment comparison techniques recommended by the NICE Decision Support Unit[14], with results from a recent Cochrane review and meta-analysis of long-term LMWH vs dual LMWH/VKA therapy.[15] The Cochrane review had found little apparent difference between LMWHs (Table 24). The indirect comparison results had fairly wide margins of uncertainty for the comparable efficacy and safety of rivaroxaban and long-term LMWH. No non-RCT evidence is presented.

A cost-utility model was developed for this submission using model states relevant to patients with acute DVT and the risk 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-DVT trial[16] and systematic literature reviews[17]. 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.

Regardless of whether patients were appropriate for 3, 6 or 12 months of anticoagulation, rivaroxaban dominated the current standard of care in the base case – rivaroxaban was associated with lower costs and greater QALYs than dual LMWH/VKA therapy (Table 1). This conclusion was robust to the 108 univariate sensitivity analyses conducted at each duration. Probabilistic analysis demonstrated rivaroxaban had greater than 94% probabilities of cost-effectiveness for patients appropriate for 3, 6 or 12 months of treatment respectively at a £20,000 per QALY threshold.

A cost-minimisation analysis was additionally conducted in the cancer subgroup, since indirect comparison had demonstrated broad comparability. Over 6 months of treatment, rivaroxaban was associated with cost savings of over £900 (£909 or 68%) compared to long-term LMWH therapy. See section 6.9.

The oral single drug approach of rivaroxaban can improve patients' satisfaction and experience of treatment.[18] Rivaroxaban is a safe, effective and highly cost-effective option in the treatment of DVT, with built-in simplicity, providing budgetary savings and the opportunity for service redesign.

Table 1: Base case cost-effectiveness results in patients with acute DVT

	Rivaroxaban	Dual LMWH / VKA therapy
Patients appropriate for 3 months of anticoagulation		
Technology acquisition cost	£222	£99
Other costs	£913	£1199
Total costs	£1135	£1298
Difference in total costs	-£163	
LYG	16.274	16.247
LYG difference	+0.027	
QALYs	13.348	13.325
QALY difference	+0.023	
ICER	Dominant	Dominated
Patients appropriate for 6 months of anticoagulation		
Technology acquisition cost	£397	£105
Other costs	£921	£1337
Total costs	£1318	£1442
Difference in total costs	-£124	
LYG	16.294	16.271
LYG difference	+0.023	
QALYs	13.365	13.345
QALY difference	+0.020	
ICER	Dominant	Dominated
Patients appropriate for 12 months of anticoagulation		
Technology acquisition cost	£737	£116
Other costs	£906	£1560
Total costs	£1643	£1676
Difference in total costs	-£33	
LYG	16.309	16.285
LYG difference	+0.024	
QALYs	13.377	13.356
QALY difference	+0.020	
ICER	Dominant	Dominated

Section A – Decision problem

1 Description of technology under assessment

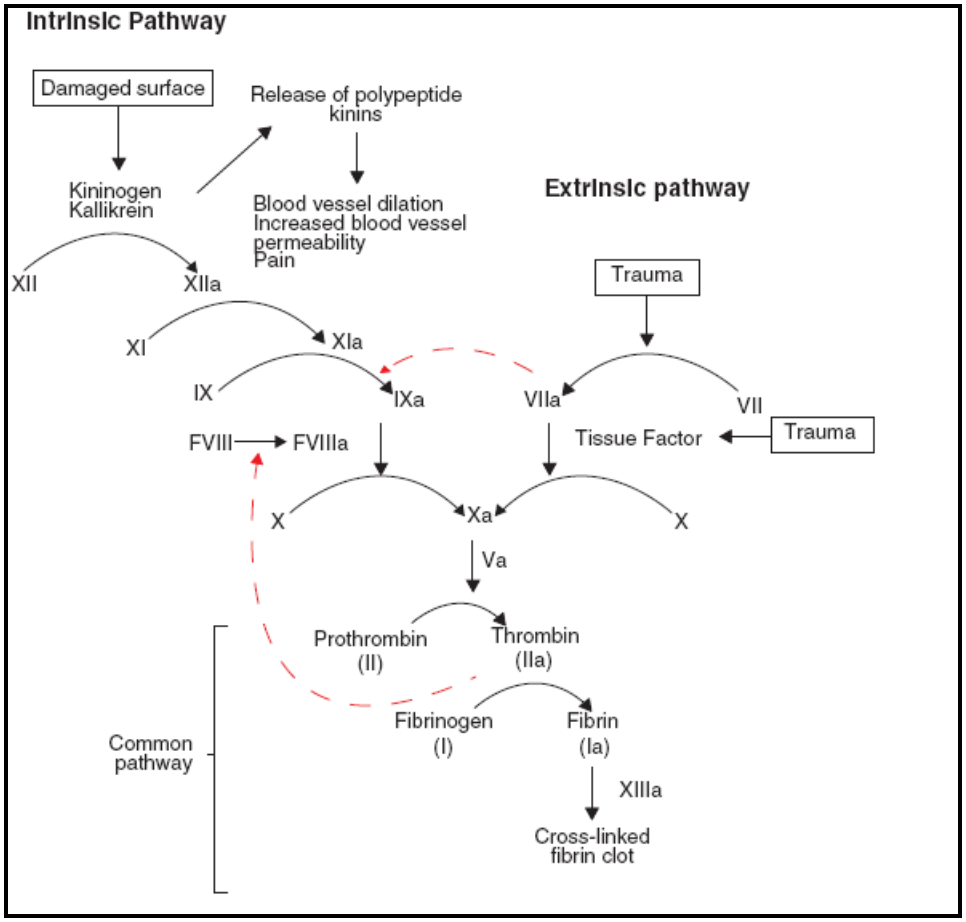
1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

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 inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.[1]

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).

Rivaroxaban holds a UK marketing authorisation for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.[1] Rivaroxaban was submitted for regulatory approval for the indication under appraisal in December 2010 via the EU centralised process. The expected approval date is Q4 2011.

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 licence).

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 anticipated indication is: `Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE), following an acute DVT in adults'. Draft SmPCs are provided.[2;3]

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.

There are three such studies.[16]

1. EINSTEIN-DVT (NCT00440193) – completed

A Prospective, Randomised, Open-Label, Multicentre, Assessor-blind, Event-Driven, Non-inferiority Study Comparing the Efficacy and Safety of Rivaroxaban With standard therapy Enoxaparin and vitamin K antagonist, over a study duration of 3, 6 or 12 months, in patients with confirmed acute symptomatic Deep-Vein Thrombosis without symptomatic Pulmonary Embolism.

2. EINSTEIN-Extension (NCT00439725) – completed

Once - Daily Oral Direct Factor Xa Inhibitor Rivaroxaban In The Long-Term Prevention Of Recurrent Symptomatic Venous Thromboembolism In Patients With Symptomatic Deep-Vein Thrombosis Or Pulmonary Embolism.

This is a multicentre, randomised, double-blind, placebo-controlled, event-driven, superiority study for efficacy. Patients with confirmed symptomatic DVT or PE who completed 6 or 12 months of treatment with rivaroxaban or VKA, and in whom there was clinical equipoise for continuation of treatment for 6 or 12 months, were eligible for this trial.

3. EINSTEIN-PE (NCT00439777) – Ongoing, but not recruiting participants.[19]

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 Q4 2011.

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

Rivaroxaban is yet to gain regulatory approval for this indication in other countries outside the UK.

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. Bayer plc has made a full submission to the Scottish Medicines Consortium (SMC) for rivaroxaban in this indication. The SMC indicates that it will issue its advice in relation to this submission to NHS Scotland and Bayer plc on 13 January 2012, and publicly on 13 February 2012.[20]

This technology is also undergoing a NICE Single Technology Assessment for the prevention of stroke and systemic embolism in people with atrial fibrillation.

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 indicative price is £2.10 per 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[21]).
Method of administration	Oral
Doses	15 mg and 20 mg
Dosing frequency	15 mg twice daily for 21 days, then 20 mg once daily[2;3]
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 draft SmPC advises a reduced dose in patients with moderate or severe renal impairment (ie creatinine clearance < 50 ml/min). The reduced dose would be 15 mg twice daily for 21 days, then 15 mg once daily.[2;3]

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, it is not anticipated that there will be any additional tests or investigations required for selection of patients appropriate for rivaroxaban. There are no particular administration requirements for rivaroxaban.

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 INR monitoring is one of rivaroxaban's advantages.

Rivaroxaban is administered at a fixed dose once daily 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;3]

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 1,000 people per year in the general population presenting with clinical symptoms.[22-24] 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.[22;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), occurring 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 DVT may also be complicated by recurrent episodes of DVT, the development of post-thrombotic syndrome (PTS), as well as chronic thromboembolic pulmonary hypertension (CTEPH).[26]

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.[27] Other risk factors include recent surgery, trauma and immobilisation.

Treatment for venous thromboembolism is usually initiated with anticoagulant drugs, described further in section 2.4. Despite anticoagulation treatment, patients with a DVT or PE 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[28]; a cumulative incidence of 24.6% at two years and 31.8% after ten years has been reported in a large cohort from Vienna.[29]

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 How many patients are assumed to be eligible? How is this figure derived?

We estimate that there would be in the region of 46,300 incident cases of adults with acute DVT in 2012 in England and Wales, of which around 38,600 would be first DVTs. This would rise to a projected 49,100 incident cases in 2016 due to growth and ageing in the population. All but a very small proportion contraindicated for hepatic impairment or very severe renal impairment (creatinine clearance < 15 ml/min), which we estimate to be less than 2%, would be potentially eligible for treatment with interventions considered in this assessment.

These projections are based on DVT 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.[30] The database linkage study has recently been presented at the XXIII Conference of The International Society on Thrombosis and Haematosis (ISTH) by Martinez et al.[22]

For more information on this estimate, please see section 7.1.

2.3 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.

There is no relevant NICE guidance regarding the treatment of DVT. However there is a clinical guideline regarding prophylaxis of VTE in patients admitted to hospital[27] and a clinical guideline in preparation on the management of VTE[31]. The NICE website reports an appraisal in development, of dabigatran etexilate for the treatment of acute venous thromboembolic events.[32] In addition, there are numerous international guidelines which cover the treatment of DVT and prevention of current VTE, summarised in Table 3.

The guidelines are consistent in many areas. All recommend immediate treatment of VTE with heparin, overlapping with vitamin K antagonist (VKA) treatment. Most guidelines recommend use of low molecular weight heparin (LMWH) in preference to

unfractionated heparin (UH). The heparin treatment is to be stopped when an INR of 2.0 has been sustained for >24 hours. VKA treatment should be continued for at least 3 months. There is less clarity around the optimal duration of vitamin K antagonist treatment, discussed further in section 2.5.

There is also general consensus for LMWH to be used in preference to UH or VKA in patients with cancer, with a recommended treatment duration of 3-6 months. Depending on a patient's circumstances and risk factors, this should be continued indefinitely or until the cancer is resolved.[9;11;12;33-35]

Table 3: Summary of international guidelines and recommendations

Organisation	Acute treatment		Longer term
	Heparins	VKA	
British Committee for Standards in Haematology[9;12]	✓LMWH	✓ Calf vein thrombosis: at least 6 weeks treatment. Proximal DVT: at least 3 months. Idiopathic VTE or permanent risk factors: at least 6 months therapy.	
SIGN[11]	✓LMWH – can be continued beyond 5 days if VKA treatment problematic	✓ at least 3 months. >3months depending on individual risk factors	Long term VKA – depending on cause, risks, elapsed time between episodes VTE
ACCP[33]	✓LMWH, UH	✓ at least 3 months. Start with LMWH, UH or fondaparinux, >3 months depending on individual risk factors, especially if first unprovoked VTE	Long term VKA – especially if second episode of unprovoked VTE
ACP / AAFP[35]	✓LMWH in preference to UH	✓3-6 months Idiopathic VTE: consider extended treatment	VKA >12 months
International Consensus Statement[34]	✓LMWH	✓ First episode of VTE and no continuing risk factor: 3-6 months. Idiopathic VTE: consider indefinite treatment.	Long term VKA – depending on cause, risks, elapsed time between episodes VTE

2.4 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.

Current pathway of care

Treatment for DVT is usually initiated with low molecular weight heparins (LMWH) such as enoxaparin, bemiparin, dalteparin or tinzaparin, administered by subcutaneous injection. Oral VKA therapy, usually warfarin, is started at the same time. Parenteral anticoagulant therapy is continued until adequate anticoagulation is established. Thus LMWH is usually required for at least 5 days and until the international normalised ratio (INR) has been in range (equal or above 2.0) for two consecutive days, whichever is the longer.

The duration of anticoagulation treatment varies according to clinical aspects of the case, taking into account whether the DVT was 'provoked' or 'unprovoked', and each individual patient's situation, medical history and risk factors. Most guidelines (UK and internationally) recommend at least 3 months anticoagulant treatment regardless of likely cause of DVT (see summary Table 2, section 2.3). In the case of an idiopathic or 'unprovoked' DVT, or in the presence of permanent risk factors treatment is generally extended to 6 or 12 months.

Anticoagulant services are managed in a number of settings in the UK depending on the locally commissioned arrangements[36], 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

LMWHs are administered by subcutaneous injection. Many patients are managed as outpatients and this typically requires self administration. This can 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.

Warfarin, the oral anticoagulant used most frequently in clinical practice has a number of well reported limitations, 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 elderly 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.

Warfarin management therefore has an infrastructure around it – for blood sampling, testing and dose adjustment.

Clinical pathway for rivaroxaban

Rivaroxaban offers a single drug approach which will increase flexibility of treatment according to the patient and simplify 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 during a secondary care outpatient consultation with follow up in primary care by the GP.

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

In general, a treatment duration of three months is used where patients have only transient risk factors such as recent surgery or trauma, immobilisation, or use of oestrogen-containing drugs (e.g. hormone replacement therapy, combined oral contraceptives). Durations of six or twelve months may be appropriate when patients have had idiopathic VTE or have permanent risk factors such as active cancer, recurrent VTE, or a known thrombophilic condition. Treatment beyond 12 months is rarely appropriate and its benefit is not clearcut, so no duration of treatment beyond 12 months will be evaluated in this submission.

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

The current treatment appropriate to the majority of DVT patients and included in the Final Scope is initial treatment with LMWH, followed by overlapping and continued treatment with a VKA.

UH is generally only used if an alternative to LMWH is required e.g. if thrombolysis is being considered in the immediate postoperative period[11] or in patients with renal failure. The SmPC for enoxaparin recommends a dose adjustment where creatinine clearance is < 30 mL/min.[37] UH is not considered to be a comparator because there is no comparative data with rivaroxaban in such patients, as patients with renal failure (defined again as creatinine clearance < 30 ml/min) were excluded from EINSTEIN-DVT.[16]

The Final Scope lists as a comparator UH or LMWH in people for whom a VKA is not considered an appropriate treatment, and it is understood that this refers to patients with cancer. It is recognised that LMWH is the preferred treatment over VKA for at least the first 3 to 6 months in DVT patients with cancer.[9;11;12;38] In this subgroup, LMWH rather than VKA would be the appropriate comparator. More specifically, dalteparin is currently licensed in the UK for VTE treatment[39] and extended treatment in oncology[40] though other LMWHs have been studied and may be used. The use of LMWH treatment in cancer patients with VTE has been evaluated in two recent Cochrane reviews.[15;41]

The Final Scope also lists `no preventative therapy' as a comparator, whereas all known guidelines on the treatment of VTE / DVT recommend at least 3 months of anticoagulant therapy. Placebo or no treatment is therefore not an appropriate comparison for initial treatment of DVT.

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

The draft SmPC stipulates that, for bleeding complications, usual treatment measures should be considered, including mechanical compression, fluid replacement and hemodynamic support and blood products or platelets. If bleeding cannot be controlled, consideration should be given to the administration of a procoagulant.

2.8 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.

As noted previously, it is anticipated that in the majority of cases, rivaroxaban would be expected to be initiated during a secondary care outpatient consultation with follow-up in primary care by the GP. The unit costs of secondary care outpatient consultations are expected to be taken from NHS Reference Costs 2010-11[42] and of primary care consultations from PSSRU Unit Costs[43].

There are no administration costs specifically associated with use of rivaroxaban and there is no requirement for routine monitoring of coagulation parameters. This is in contrast to LMWHs and warfarin, the main comparators, which are managed within an established infrastructure in the NHS, requiring 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. The prevalence of different models of anticoagulation service in the UK was identified via a UK survey conducted in 2011[36].

Resource use associated with warfarin management, especially in terms of the frequency and nature of appointments, will be informed by sources identified through a systematic review of UK costs and resources in DVT treatment. These should be expected to include relevant UK guidelines (eg BCSH, SIGN), previous guidance from NICE where relevant, product licences and the British National Formulary (BNF). Data sources used will include National Reference Costs and PSSRU Unit Costs.

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

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.

2.10 Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this 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 several health-related benefits provided with rivaroxaban that offers the NHS a step-change in the management of patients with DVT.

Challenges with current therapy

LMWHs are administered by subcutaneous injection. Many patients are managed as outpatients and this therefore requires self administration. This can 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.

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 Rapid Response Report.[13]

Warfarin is an oral anticoagulant that has a number of limitations, 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.

The need for individualised dosing may increase the risk of accidental overdose and requires additional patient education, especially in confused, older people.[7] When warfarin doses are altered, different numbers and strengths of tablets may be required to be taken at different times of day. This may lead to additional anxiety in patients and additional risks of taking inappropriately high or low doses.

The NPSA issued a patient safety alert to healthcare organisations in 2007 regarding best practice actions to make anticoagulation therapy safer.[10]

Warfarin is usually managed within an anticoagulant service. There are several different models of anticoagulant service across the UK ranging from secondary care outpatient clinics to primary care led clinics and many variants in between. Attending such clinics can be difficult for many patients. By contrast, satisfaction with rivaroxaban treatment was high among patients studied in EINSTEIN-DVT.[18]

Advantages that rivaroxaban could offer

The advantages that rivaroxaban could bring to the NHS include:

- 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 heparin 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 and lack of coagulation monitoring requirements.
- 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.

2.11 Do you consider that the use of this technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the 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.[18]
- Reduced fear 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.[7;10;13]

2.12 Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

Statements made in 2.9-2.10 have been referenced to appropriate sources.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

We are not aware of any equity or equality issues.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

We are not aware of any equity or equality issues.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

None identified.

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with confirmed symptomatic DVT	Adults with an acute DVT	To match wording of licensed indication
Intervention	Rivaroxaban	Rivaroxaban	NA
Comparator(s)	Initial treatment with UH or a LMWH (such as enoxaparin) with continued therapy as follows: ▪ VKA (such as warfarin) ▪ UH or LMWH for people for whom a VKA is not considered an appropriate treatment ▪ No preventative therapy	Initial treatment with LMWH with continued VKA therapy for the remainder of 3, 6 or 12 months, followed by no active therapy VKA is not considered an appropriate treatment in patients with cancer, and in this subgroup, the use of LMWH will be evaluated	Guidelines consistently recommend treatment with VKA (or LMWH in cancer patients) for at least 3 months, after initial stabilisation with LMWH. `No therapy' is not a recommended option. Treatment and prevention are recognised as being at alternate ends of a continuum of care. UH is generally only recommended over LMWH if there is severe renal impairment (creatinine clearance < 30 mL/min). Such patients were excluded from the principle phase III trials of rivaroxaban and the use of rivaroxaban in such patients is cautioned against in the draft SmPC.
Outcomes	▪ Mortality ▪ Recurrent VTE ▪ Complications following DVT including post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH) ▪ Adverse events of treatment including bleeding events ▪ Health-related quality of life	As final scope	NA

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
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 (QALY) The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences between the technologies being compared. Costs will be compared from an NHS and Personal Social Services perspective.	As final scope. A lifetime horizon will be used.	NA
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: ▪ Underlying risk of recurrent VTE including the presence of active cancer ▪ Underlying risk of bleeding (for example people over 60 years of age)	Additional analysis will be presented for patients with active cancer. Results will be presented that reflect the duration of treatment received and the characteristics of the population for whom such a duration is appropriate. In doing so, the evaluation will account for such individualised risks.	Risk of bleeding, risk of recurrent VTE and age are among various patient-specific characteristics which influence duration of anticoagulation.
Special considerations, including issues related to equity or equality	None	None	None

Section B – Clinical and cost effectiveness

5 Clinical evidence

5.1 Identification of studies

5.1.1 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 9.2, appendix 2.

A systematic search of the literature was undertaken to identify randomised, placebo or active-controlled, comparative studies investigating the treatment of acute, symptomatic DVT. The searches were undertaken in August 2011 using Medline, Medline in process, EMBASE, and The Cochrane Central Register of Controlled Trials (CENTRAL).

When designing the search strategies, medical subject headings and synonyms were used for the following terms: rivaroxaban in combination with DVT or VTE. RCT study design filters translated from those developed by SIGN were applied to the searches of the MEDLINE and EMBASE databases.[44]

Full details of the literature search strategy including search terms employed are provided in Section 9.2, Appendix 2, as required.

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.

5.2 Study selection

5.2.1 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.

The relevance of each reference identified through the methods described in 5.1 was assessed according to the inclusion and exclusion criteria set out in Table 4. The full-text was reviewed of all references that could not be positively excluded after abstract review. A full-text review against the inclusion/exclusion was conducted on all remaining references by one reviewer and checked by a second reviewer. Where studies were published as abstracts then subsequently as full papers, the abstracts were excluded.

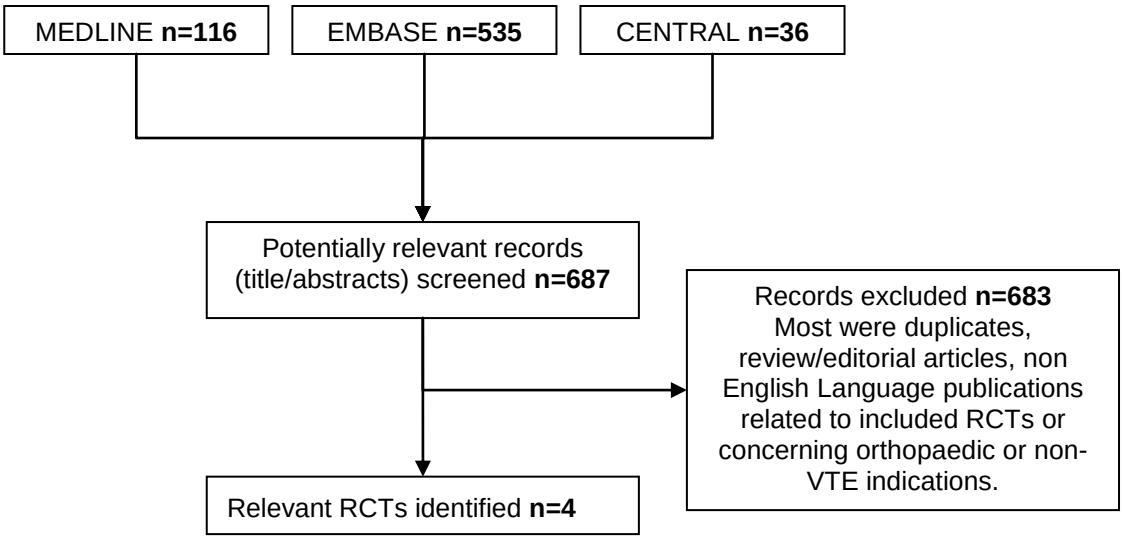
Table 4: Inclusion and exclusion criteria for the systematic search for relevant clinical studies

Inclusion criteria	Population: Interventions: Comparator: Outcomes: Study design: Language restrictions:	Patients with acute, symptomatic DVT Xarelto® (rivaroxaban) Any competitor Efficacy and safety outcomes RCTs English language
Exclusion criteria	Population: Interventions: Comparator: Outcomes: Study design: Language restrictions:	VTE prophylaxis, non VTE indications. Non English language studies

5.2.2 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 5.2.4.

The searches described in 5.1 led to the identification of 687 records, including duplicates. This included only one additional article identified from non literature database sources. From these, 687 were excluded due to duplication or not meeting the inclusion/exclusion in other ways. Many articles were reviews or editorials, concerned other patient populations or treatment settings (eg VTE prophylaxis or prevention of atrial fibrilation), were non-English language or some combination of these factors. In total, four references met the inclusion/exclusion criteria.[16;45-47] A flow diagram is shown in Figure 2.

Figure 2: Study flow diagram for the identification of references relating to RCTs



5.2.3 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.

An overview of all Bayer-sponsored phase 2 and 3 rivaroxaban trials relevant to DVT treatment is provided in Table 5. The publications listed match those four references identified in section 5.2.2.[16;45-47]

The EINSTEIN-Ext study evaluates further treatment in patients some of whom participated in EINSTEIN-DVT or EINSTEIN-PE. The CYP cohort and EINSTEIN-PE studies have not been published at time of writing, so no publications relating to these studies were identified.

Table 5: Overview of rivaroxaban trials

Trial name	Bayer study ID	Phase	Design	Publications
ODIXa-DVT	11223	2	4 x rivaroxaban regimes or enoxaparin/VKA for 12 weeks	Agnelli 2007[45]
EINSTEIN dose ranging	11528	2	3 x rivaroxaban regimes or heparin/VKA for 3 months	Buller 2008[47]
CYP cohort	13238	2	Rivaroxaban single arm	NA
EINSTEIN-DVT	11702a	3	Rivaroxaban vs LMWH/VKA for 3/6/12 months	EINSTEIN investigators 2010[16]
EINSTEIN-PE	11702b	3	Rivaroxaban vs LMWH/VKA for 3/6/12 months	NA
EINSTEIN-Ext	11899	3	Extended treatment of rivaroxaban or placebo for 6/12 months	Buller 2009[46] and EINSTEIN investigators 2010[16]

Complete list of relevant RCTs

5.2.4 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 list of all such RCTs and their three primary references[16;45;47] is shown in Table 6.

Table 6: List of relevant RCTs

Trial name	Intervention	Comparator	Population	Primary reference
ODIXa-DVT Phase II study	Rivaroxaban 10, 20 or 30mg twice daily or 40mg once daily	Enoxaparin (1mg / kg) twice daily overlapping with and followed by VKA	Symptomatic proximal DVT without PE	Agnelli et al 2007[45]
EINSTEIN dose-ranging Phase II study	Rivaroxaban 20, 30 or 40mg once daily	Enoxaparin, tinzaparin or UH overlapping with and followed by VKA	Acute symptomatic DVT without PE	Buller et al 2008[47]
EINSTEIN DVT Phase III study	Rivaroxaban 15mg twice daily for 3 weeks then 20mg once daily for 3,6 or 12 months	Enoxaparin (body weight adjusted) followed by VKA, dose-adjusted to maintain a therapeutic INR (target 2.5, range 2.0-3.0) for 3, 6 or 12 months	Acute symptomatic DVT without any symptoms of PE	Bauersachs et al 2010[16]
EINSTEIN-Extension Phase III study	Rivaroxaban 20mg once daily	Placebo	Objectively confirmed symptomatic DVT or PE that had been treated for 6 to 12 months with warfarin, acenocoumarol or rivaroxaban and equipoise with respect to the need for continued anticoagulation	Bauersachs et al 2010[16]

The list in Table 6 excludes the 2009 abstract by Buller et al[46] because this has been superseded by the New England Journal of Medicine publication by Bauersachs et al[16]. The EINSTEIN-PE and CYP cohort studies are excluded from the list for reasons explained in section 5.2.6.

5.2.5 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.

EINSTEIN-DVT compares rivaroxaban with dual enoxaparin and warfarin therapy in a relevant population and dosing regimen, applicable to the UK population, current decision problem in this submission, and within the marketing approval of rivaroxaban.[16]

EINSTEIN-Ext evaluates rivaroxaban vs placebo as extended treatment beyond an initial 6 or 12 months of anticoagulation following an index VTE, in patients for whom there is clinical equipoise as to extended anticoagulation.[16]

5.2.6 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.

Two studies voluntarily listed in Table 5, CYP cohort and EINSTEIN-PE, were excluded from the list of relevant RCTs in Table 6.

- The CYP cohort study was excluded because it was a single arm study of rivaroxaban and therefore not a RCT. It has not been published and cannot therefore be clearly identified in literature searches.
- The EINSTEIN-PE study was excluded because the study population were patients who had experienced an index PE (with or without a DVT), so will not provide evidence in relation to the treatment of DVT. Also, the study is ongoing and has not been published at time of writing.

Two phase II studies identified in the table of relevant RCTs are also excluded from further discussion since these were proof of concept, dose-ranging studies to inform on dose selection in the larger EINSTEIN phase III study programme. Study endpoints were also not directly comparable. However as they provide supportive evidence on the efficacy and safety of rivaroxaban in a total of 1,156 randomised patients for the treatment of DVT, the studies will be described briefly here. These initial studies explored the safety and efficacy of rivaroxaban at doses of 10 to 30 mg twice-daily (ODIXa study)[45] and 20 to 40 once-daily over 12 weeks (EINSTEIN dose-ranging)[47].

ODIXa-DVT[45]

A total of 613 patients were studied for the primary efficacy endpoint of 'improvement in thrombotic burden at mean day 21 (defined as a 4-point reduction in the thrombus score as measured by CUS examination), without confirmed

symptomatic recurrent VTE or VTE-related death' and the primary safety end point of 'major bleeding' during the 12 weeks of treatment.

At day 21, the primary efficacy end point was achieved in 53.0%, 59.2%, 56.9%, and 43.8% of patients receiving rivaroxaban 10, 20, or 30 mg bd or 40 mg once daily, respectively, compared with 45.9% of patients treated with enoxaparin/VKA (

Table 7). There was no significant trend in the dose–response relationship between rivaroxaban bid and the primary efficacy endpoint (P=0.67). Major bleeding was observed in 1.7%, 1.7%, 3.3%, and 1.7% of patients receiving rivaroxaban 10, 20, or 30 mg bd or 40 mg once daily, respectively while there were no major bleeding events with enoxaparin/VKA.

Table 7: Principal findings of ODIXa-DVT

	Rivaroxaban				**Enoxaparin /VKA**
	10mg bid	20mg bid	30mg bid	40mg od	
Primary efficacy outcome - 21 days	53.0 (42.8 - 63.1)	59.2 (48.8 -69.0)	56.9 (47.0 - 66.3)	43.8 (3.4 - 53.4)	45.9 (36.3 - 55.7)
Primary efficacy outcome - 3 months	71.0	71.4	73.4	68.8	71.6
Major bleeding	1.7 (0.2 -5.9)	1.7 (0.2 - 6.0)	3.3 (0.9 -8.3)	1.7 (0.2 - 5.8)	0 (0.0 - 2.9)

Notes: Table shows proportion of patients with outcome (95% CI) (%).

EINSTEIN-DVT dose-ranging study[47]

In this study, three once-daily doses of rivaroxaban were evaluated in 543 patients with acute symptomatic DVT. The primary efficacy outcome was the composite of symptomatic recurrent DVT, symptomatic fatal or non-fatal PE and asymptomatic deterioration in thrombotic burden, as assessed by CUS and PLS, at baseline and at 12 weeks. Secondary efficacy outcomes were the individual components of the primary efficacy outcome. The principal safety outcome was the combination of major and clinically relevant non-major bleeding.

Each of the 3 dose regimens was shown to be effective and safe compared to standard treatment. Symptomatic recurrent VTE occurred in 2.6%, 3.6% and 1.7% in the once-daily 20, 30 or 40 mg rivaroxaban groups respectively versus 6.9 % in the comparator group (Table 8). Deterioration in thrombotic burden or symptomatic recurrent VTE occurred in 6.1%, 5.4% and 6.6% in the once-daily 20, 30 or 40 mg rivaroxaban groups respectively versus 9.9 % in the comparator group. There was 1 major bleed in the 20 mg group, 2 in the 30 mg and none in the 40 mg group versus 2 in the comparator group. Clinically relevant non-major bleeds occurred in 2.2 to 5.2% in the rivaroxaban groups versus 7.3% in the comparator group.

Table 8: Principal findings from EINSTEIN-DVT dose-ranging study

	Rivaroxaban			Heparin/VKA
	20mg od	30mg od	40mg od	
Primary efficacy outcome	6.1 (2.5 – 12.1)	5.4 (2.0-11.3)	6.6 (2.9 – 12.6)	9.9 (4.9 -17.5)
Major and clinically relevant non-major bleeding	5.9 (2.6 -11.3)	6.0 (2.6 – 11.4)	2.2 (0.5 – 6.3)	8.8 (4.6 -14.8)

Notes: Table shows proportion of patients with outcome (95% CI) (%).

Conclusions from the phase II studies

The phase II studies showed similar efficacy for the twice-daily and once-daily rivaroxaban regimens over 12 weeks. As demonstrated in ODIXa-DVT study, at 3 weeks there was some evidence of a higher improvement rate for the twice-daily arms compared to once-daily dosing. The dose response curves for bleeding were flat. All rivaroxaban regimens were numerically better than heparin / VKA in terms of relative safety (bleeding); however once-daily regimens were better than the twice-daily regimens. The 20 mg once-daily dose of rivaroxaban was the lowest effective dose associated with a safety profile at least as good as standard heparin / VKA treatment and appeared suitable for long-term treatment.

A combined analysis of both dose-finding studies indicated that the optimal regimen consisted of 1) a twice-daily administration of 15 mg of rivaroxaban for the initial 3-week treatment phase, during which a constantly higher C_{trough} level is considered important given the high incidence / risk of recurrent VTE during the first weeks after an acute VTE and 2) followed by once-daily administration of 20 mg of rivaroxaban for the subsequent treatment period - the once-daily regimen appeared to have a more favourable benefit-risk profile and was therefore selected for continued long-term therapy.

Results from phase II studies suggest that this treatment strategy would be at least as good as the current heparin / VKA standard of care in terms of efficacy and safety, hence the selection for investigation in larger patient groups in the EINSTEIN phase III programme, described further in this submission.

List of relevant non-RCTs

5.2.7 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 5.8 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.

5.3 Summary of methodology of relevant RCTs

5.3.1 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.

This section examines the clinical evidence available for rivaroxaban the treatment of DVT and prevention of recurrent DVT and PE.

As highlighted in section 5.2.5, two key studies provide the clinical evidence are EINSTEIN-DVT and EINSTEIN-Ext. These studies are reported alongside each other in order to facilitate data presentation. However, outcomes are not directly comparable or suitable for combining or meta-analysis since they report on the use of rivaroxaban at different timepoints in overlapping populations with differing index events.

The primary study objective of EINSTEIN DVT was to evaluate whether treatment with rivaroxaban is at least as effective as the standard enoxaparin/VKA treatment regimen in patients with acute symptomatic deep-vein thrombosis (DVT) without symptomatic pulmonary embolism, and in the prevention of recurrent venous thromboembolic events.

The primary efficacy objective of EINSTEIN-EXT was to evaluate whether 20 mg od rivaroxaban is superior to placebo in the long-term prevention of recurrent symptomatic VTE in patients:

- with objectively confirmed symptomatic DVT or PE
- who had completed 6 or 12 months of treatment with VKA or rivaroxaban (for example, but not necessarily, due to 6 or 12 months treatment and participation in EINSTEIN-DVT), and
- in whom there was clinical equipoise for continuation of treatment for 6 or 12 months in the secondary prevention of recurrent symptomatic VTE

Patients who clearly did require or did not require further anticoagulation were not eligible for EINSTEIN-Ext, under the clinical equipoise criterion. This provides rationale for the placebo comparator.

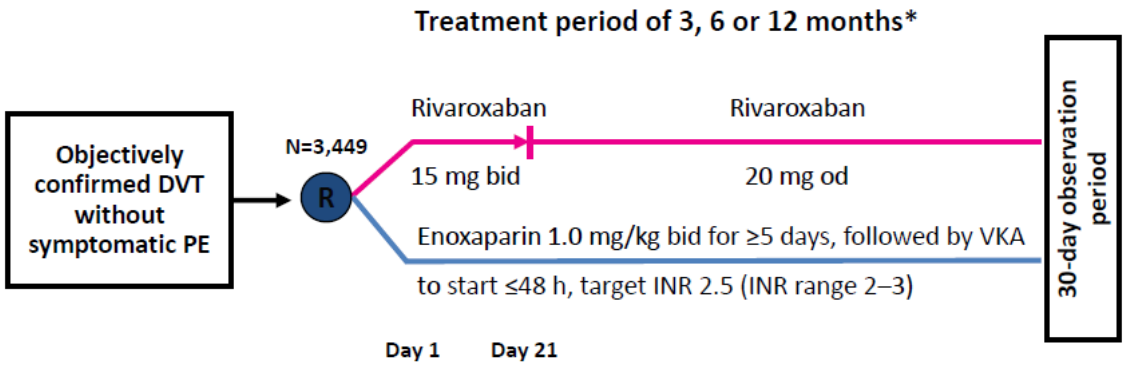
This study was performed because, despite effective treatment strategies to initially treat and prevent recurring VTE in the shorter term in patients with symptomatic DVT, the risk of recurrent VTE persists in many patients with intermediate or permanent risk factors, such as active cancer or factor V Leiden deficiency. However, prolonged use of anticoagulant therapy may increase the risk of bleeding in some of these patients. EINSTEIN-Ext was designed to investigate whether there is a favourable benefit-risk profile with rivaroxaban compared to placebo in this patient group.

Methods

5.3.2 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.

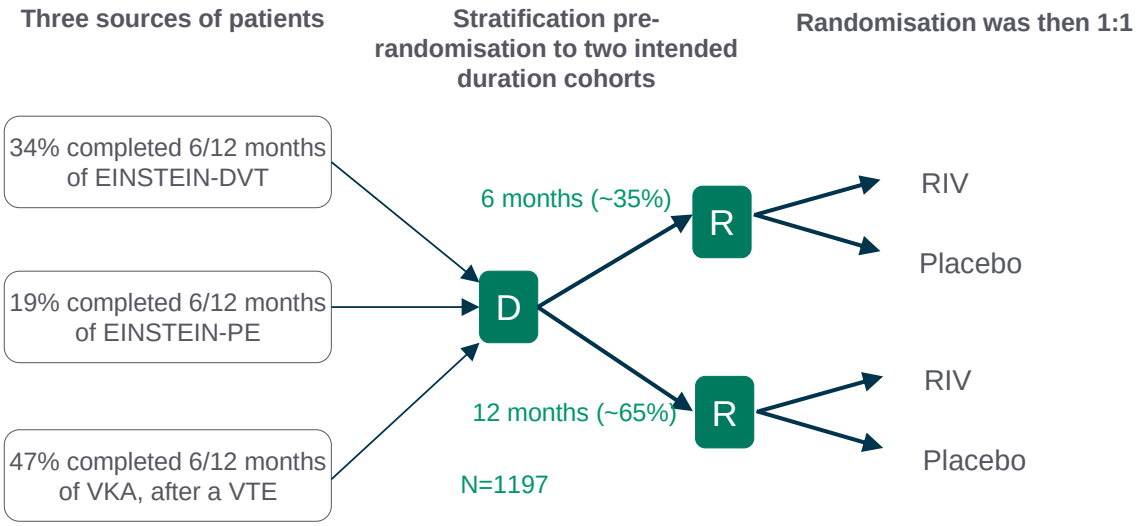
A summary of the design of EINSTEIN-DVT is described in Figure 3 and of EINSTEIN-Ext in Figure 4.

Figure 3: Summary of design of EINSTEIN-DVT



A key feature of the study design was that the intended treatment duration was determined pre-randomisation by the treating physician according to the physician's assessment of the patients' individual risk-benefit. This flexibility in trial design was intended to be reflective of clinical decision-making in real-life practice, respect clinical guidelines especially in terms of length of anticoagulation therapy and allow the trial to include cohorts of patients broad and mixed risk characteristics.

Figure 4: Summary of design of EINSTEIN-Ext



In both studies, patients were followed for the intended treatment duration and seen at fixed intervals that were identical for the rivaroxaban and comparison groups, at which time 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. [redacted]

Table 9: Summary of methodology of relevant RCTs (EINSTEIN-DVT and EINSTEIN-Ext)

	EINSTEIN-DVT	**EINSTEIN-Ext**
Design	International, randomised, event-driven, open-label, assessor-blind, phase III non-inferiority study. Patients were randomised 1:1 into two groups.	International, multicentre, randomised, double-blind, placebo-controlled, event-driven, phase III superiority study. Patients were randomised 1:1 into two groups.
Sites	Australia; Austria; Belgium; Brazil; Canada; China; Czech Republic; Denmark; France; Germany; Hong Kong; Hungary; India; Indonesia; Israel; Italy; Korea; Malaysia; The Netherlands; New Zealand; Norway; Philippines; Poland; Singapore; South Africa; Spain; Sweden; Switzerland; Taiwan; Thailand; UK; USA.	As for EINSTEIN-DVT excluding Canada, Hong Kong, Korea, Taiwan
Duration and recruitment	Study enrolment start: March 2007. Study enrolment stop: September 2009. Study duration = intended treatment duration (3, 6 or 12 months, determined by the clinician pre-randomisation) followed by a 30-day observational period.	Study enrolment start: February 2007 Study enrolment stop: March 2009 Study duration = intended treatment duration (6 or 12 months, determined by the clinician pre-randomisation) followed by a 30 day observational period
Interventions	▪ Rivaroxaban[a] orally: 15mg bid for 21 days then 20mg od for the remainder of the intended duration of treatment. ▪ Enoxaparin 1.0 mg/kg bid subcutaneously until anticoagulation is established[b] plus VKA (warfarin or acenocoumarol)[a], dose-adjusted to maintain the INR within therapeutic range (target 2.5, range 2.0-3.0).	▪ Rivaroxaban 20mg od, orally ▪ Placebo od, orally
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	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, country and previous treatment. The IVRS provided a medication box number. When patients returned for their 3-month visits, medication was re-supplied, the IVRS providing a new medication box number for the same blinded medication.
Method of blinding	This was an open-label study. However, all suspected outcome events were classified by a CIAC whose members were unaware of the treatment assignments. [redacted]	This was a double-blinded study: investigators and patients were blinded. There was a visually matching placebo comparator. All suspected outcome events were classified by a CIAC whose members were unaware of the treatment assignments.

[a] The first tablet of rivaroxaban or VKA was to be taken as soon as possible after randomisation. Tablets taken with food. [redacted]

[b] 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.

5.3.3 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 eligibility criteria for the two trials, EINSTEIN-DVT and EINSTEIN-Ext, and their differences are summarised in Table 10.

Table 10: Eligibility criteria in the EINSTEIN-DVT and EINSTEIN-Ext

	Common to both trials	**Specific to EINSTEIN-DVT**	**Specific to EINSTEIN-Ext**
Inclusion criteria	▪ Male or female ▪ Legal age for consent; ▪ Written consent prior to any study-specific screening procedures	▪ Symptomatic DVT, without symptomatic PE ▪ Adjudicated and objectively confirmed index DVT event, through either a non-compressible proximal vein on CUS or an intraluminal filling defect in the proximal veins on venograph	▪ Confirmed symptomatic PE or DVT which had been treated for 6 or 12 months with VKA (either acenocoumarol or warfarin) or rivaroxaban up to the moment of randomisation ▪ Clinical equipoise as to the risk:benefit of further anticoagulation
Exclusion criteria	▪ 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	▪ Pre-randomisation therapeutic doses of LMWH, fondaparinux or UH for more than 36 hours ▪ >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	▪ Patients in whom anticoagulation treatment for their index DVT or PE should continue

	Common to both trials	Specific to EINSTEIN-DVT	Specific to EINSTEIN-Ext
	screening ▪ Life expectancy of less than 3 months		

5.3.4 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.

The characteristics of patients in EINSTEIN-DVT and EINSTEIN-Ext are described in Table 11 below. No significant differences between the respective treatment groups within each study were noted. Results described here are for the ITT population.

Table 11: Baseline characteristics of EINSTEIN-DVT and EINSTEIN-Ext

	EINSTEIN-DVT		EINSTEIN-Ext	
	Rivaroxaban	LMWH/VKA	Rivaroxaban	LMWH/VKA
ITT population	1731	1718	602	594
Mean (SD) age (years)	55.8 (16.4)	56.4 (16.3)	58.2 (15.6)	58.4 (16)
Number (%) male	993 (57.4)	967 (56.3)	354 (58.8)	339 (57.1)
Weight – number (%)				
<50 kg	37 (2.1)	49 (2.9)	10 (1.7)	5 (0.8)
>50 – 100 kg	1443 (83.4)	1422 (82.8)	491 (81.6)	488 (82.2)
>100 kg	245 (14.2)	246 (14.3)	85 (14.1)	87 (14.6)
Missing data	6 (0.3)	1 (<0.1)	16 (2.7)	14 (2.4)
Creatinine clearance (%)				
<30 mL/min	6 (0.3)	9 (0.5)	0	5 (0.8)
30-49 mL/min	115 (6.6)	120 (7.0)	37 (6.1)	44 (7.4)
50-79 mL/min	393 (22.7)	399 (23.2)	134 (22.3)	122 (20.5)
≥80 mL/min	1193 (68.9)	1170 (68.1)	373 (62.0)	373 (62.8)
Missing data	24 (1.4)	20 (1.2)	58 (9.6)	50 (8.4)
Initial diagnosis				
DVT	1708	1697	386	356
PE	12	11	216	238

	EINSTEIN-DVT		EINSTEIN-Ext	
	Rivaroxaban	**LMWH/VKA**	**Rivaroxaban**	**LMWH/VKA**
Time from onset of symptoms to randomisation				
Median (days)	5	5	204	206
IQR (days)	3-10	3-10	188-302	189-307
Cause of DVT or PE (%)				
Unprovoked	1055 (60.9)	1083 (63.0)	440 (73.1)	441 (74.2)
Recent surgery or trauma	338 (19.5)	335 (19.5)	21 (3.5)	28 (4.7)
Immobilization	265 (15.3)	260 (15.1)	89 (14.8)	77 (13.0)
Estrogen therapy	140 (8.1)	115 (6.7)	23 (3.8)	22 (3.7)
Active cancer	118 (6.8)	89 (5.2)	28 (4.7)	26 (4.4)
Puerperium	6 (0.3)	11 (0.6)	1 (0.2)	0
Known thrombophilic condition (%)	107 (6.2)	116 (6.8)	49 (8.1)	48 (8.1)
Previous VTE (%)	336 (19.4)	330 (19.2)	108 (17.9)	84 (14.1)

Some totals may not add to 100 because of rounding.

Across the EINSTEIN-DVT study:

- the mean (SD) age was 56.1 (16.4) years
- 57% were male and 43% were female
- the racial/ethnic profile was 77% white, 13% asian, 2% black and 8% other, uncodable or not known
- there had been a previous VTE in 19% of patients
- the index VTE was unprovoked in 62% of patients
- the index VTE was provoked by recent surgery or trauma in 20%, immobilisation in 15%, oestrogen therapy in 7%, active cancer in 6% and puerperium in 5%
- Among the ITT population in EINSTEIN-Ext, 53.0% had participated in EINSTEIN-DVT and 27.8% had previously used rivaroxaban.

As shown in Table 10, the 6 month treatment group constituted 63% of the EINSTEIN-DVT trial population. 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 12: Overview of EINSTEIN-DVT patient characteristics

Patients and characteristics	Intended treatment duration			
	3 months	6 months	12 months	Whole study
Number of patients	411	2166	872	3449
Mean (SD) age	[redacted]	[redacted]	[redacted]	56.1 (16.4)
Proportion male	[redacted]	[redacted]	[redacted]	57.5%
Risk factors				
Idiopathic DVT/PE	[redacted]	[redacted]	[redacted]	48.4%
Recent surgery or trauma				19.5%
Immobilisation				15.2%
Use of oestrogen containing drugs				7.4%
Active cancer				6.0%
Previous episodes of DVT/PE				19.3%

Source: [redacted]

Among the patients entered into EINSTEIN-Ext, 59.9% were assigned to 6 months rather than 12 months of randomised treatment, as shown in Table 13. There appeared to be close similarities between the patients in either group.

Table 13: Overview of EINSTEIN-Ext patient characteristics

Patients and characteristics	Intended treatment duration group		
	6 months	12 months	Whole study
Number of patients	717	479	1196
Mean (SD) age (years)	[redacted]	[redacted]	58.3 (15.8)
Number (%) male	[redacted]	[redacted]	693 (57.9)
Previously used rivaroxaban	[redacted]	[redacted]	333 (27.8)
Risk factors			
Idiopathic DVT/PE	[redacted]	[redacted]	711 (59.4)
Recent surgery or trauma			49 (4.1)
Immobilisation			166 (13.9)
Use of oestrogen containing drugs			45 (3.8)
Active cancer	[redacted]	[redacted]	54 (4.5)
Previous episodes of DVT/PE			192 (16.1)
Known thrombophylic condition			97 (8.1)

Source: [redacted]

Outcomes

5.3.5 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, 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 aim of DVT treatment is to prevent extension of the existing thrombus and prevent further, or recurrent DVTs or PE. In line with the aim of therapy, the primary and secondary efficacy outcomes in the EINSTEIN study programme therefore included a wide range of outcomes based on the incidence 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.[4;48] Vascular events were monitored because of a suspected increase in cardiovascular events seen with other novel anticoagulants, including ximelagatran[49], 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. Adverse events were coded using the MedRA dictionary.

A list of key outcomes measured in EINSTEIN-DVT and EINSTEIN-Ext is given in Table 14.

Table 14: List and categorisation of key outcomes measured in EINSTEIN-DVT and EINSTEIN-Ext

	EINSTEIN-DVT	**EINSTEIN-Ext**
Primary efficacy	Symptomatic, recurrent VTE	Symptomatic, recurrent VTE
Primary safety	Clinically relevant bleeding	Major bleeding
Secondary efficacy and safety	▪ Net clinical benefit ▪ Vascular events ▪ All cause mortality ▪ Other adverse events (AEs)	▪ Clinically relevant bleeding ▪ Secondary Outcome 1 ▪ Secondary Outcome 2 ▪ Secondary Outcome 3 ▪ Adverse events ▪ Post hoc: risk-benefit
Treatment satisfaction	▪ Anti Clot Treatment Scale (ACTS) ▪ Treatment Satisfaction Questionnaire (TSQM)	-
Compliance	▪ Discontinuation – rates and reasons ▪ Time in target range (TTR) with enoxaparin/VKA	Discontinuation – rates and reasons
Other	Various healthcare resource utilisation	-

The outcomes selected for both studies are largely consistent, but there is a difference in the composite primary safety outcome between the studies, discussed below. Definitions of each of the outcomes listed above are given in Table 15.

Table 15: 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.
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

ACTS consists of two scales, ACTS Burdens (12 items) and ACTS Benefits (3 items). 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.[18]

The principal safety endpoint of EINSTEIN-DVT was clinically relevant bleeding and of EINSTEIN-Ext was major bleeding. Major bleeding excludes clinically relevant non-major (CRNM) bleeding (Table 15). CRNM bleeding is an outcome that needs to be used differently in various settings. Its importance is less if the assessment is comparing an anticoagulant regimen to placebo as in prolonged duration studies, but this outcome becomes more important in selecting the preferred anticoagulant among two which are equally effective and safe. Since EINSTEIN-Ext aimed to answer the question whether or not the duration of treatment should be extended in the selected population, the analysis of net clinical benefit should be a comparison of the prevention of recurrent symptomatic VTE and VTE-related death with major bleeding. Historically, such an evaluation of the balance of efficacy and safety outcomes has been the basis for the implementation of longer durations of anticoagulant treatment in the field of symptomatic VTE.

Consequently, the outcomes measured in the trials were well-suited to evaluating a treatment in this indication, recommended by relevant and authoritative bodies, measured in appropriate ways so as to assure internal validity and remove potential for bias. Discontinuation and TTR outcomes demonstrate reliability and external validity of outcomes, and relevance of this trial and its data to the decision problem at hand.

Statistical analysis and definition of study groups

5.3.6 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).

A description of the statistical analytic methods employed in EINSTEIN-DVT and EINSTEIN-Ext is given in Table 16.

Table 16: Summary of statistical analyses in EINSTEIN-DVT and EINSTEIN-Ext

	EINSTEIN-DVT	**EINSTEIN-Ext**
Hypothesis objective	▪ A hierarchical procedure was followed, whereby a non-inferiority test was performed first, followed by a test for superiority if found to be significantly non-inferior. ▪ The non-inferiority test had the following hypothesis set. ▪ Null hypothesis: rivaroxaban was inferior to comparator (enoxaparin / VKA). ▪ Alternative hypothesis: rivaroxaban was non-inferior.	▪ This study had a superiority design. ▪ Null hypothesis: there was no treatment effect with rivaroxaban compared to placebo. ▪ Alternative hypothesis: there was a treatment effect with rivaroxaban compared to placebo.
Statistical analysis	▪ Primary efficacy analysis was performed on ITT basis with a supportive analysis of the primary efficacy outcome on the PP population. ▪ A Cox proportional hazard model was used. ▪ The model was pre-specified to be stratified for intended duration of treatment and adjusted for the presence of malignancy at baseline. ▪ Rivaroxaban 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	▪ Primary efficacy analysis was performed on ITT basis with a supportive analysis of the primary efficacy outcome on the PP population. ▪ A Cox proportional hazard model was used. ▪ The model was pre-specified to be adjusted for pre-treatment at baseline (rivaroxaban or VKA). ▪ Unlike EINSTEIN-DVT, there was no stratification for intended treatment duration (in this case 6 or 12 months) and no adjustment for presence of active cancer. However, it was mandated that the analysis should be stratified by intended treatment duration if the proportional hazards assumption failed.

	EINSTEIN-DVT	EINSTEIN-Ext
	comprehensive meta-analysis of historical trials in this indication. ▪ Various secondary and subgroup analyses were conducted of the primary efficacy and other outcomes.	▪ Rivaroxaban considered statistically significantly superior to placebo if the upper limit of the two sided 95% CI for the hazard ratio was below 1.0. ▪ Various secondary and subgroup analyses were conducted of the primary efficacy and other outcomes.
Sample size / power calculation	▪ The sample size was calculated on an event-driven basis ▪ There was assumed to be incidence of 3% and equal efficacy for both treatment arms ▪ A two-sided test was used with a power of 90% and a level of 5%. ▪ This yielded a requirement for a total of 88 events or 3000 patients. ▪ It was specified a priori however, that the steering committee could stop enrolment when it was estimated that 88 events had been reached.	▪ The sample size was calculated on an event-driven basis ▪ There was assumed to be incidence of 3.5% in the placebo group and a 70% risk reduction with rivaroxaban ▪ A two-sided test was used with a power of 90% a level of 5%. ▪ This yielded a requirement for a total of 30 events or 1300 patients. ▪ If the number of patients was reached before all patients completed the intended study duration, then the study was stopped, and the last enrolled patients treated for at least 3 months.
Data management, patient withdrawals	▪ For the ITT analysis, patients were censored at the last recorded day of complete assessment for study outcomes if they did not have a VTE event during the study treatment duration, or were lost to follow-up or died because of other reasons than DVT/PE or withdrew informed consent before the end of the predefined treatment duration and who did not have a primary efficacy outcome. ▪ Supportive analyses on the PP population were performed. ▪ Patients excluded from the analysis populations were listed and summarised by treatment group and reason for exclusion. ▪ The number and percentage of randomised patients who discontinued treatment prematurely were tabulated by main reason for discontinuation and treatment group.	

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

Statistical Analysis Plans (SAPs) were pre-specified for both EINSTEIN-DVT and EINSTEIN-PE and included the following sensitivity analyses.

EINSTEIN-DVT[50]

In addition to [redacted] on the primary efficacy outcome were to be described by calculating adjusted HRs and corresponding 95% CIs. The treatment effect was to be evaluated separately in subgroups of [redacted] Figure 8 and Figure 12 present sensitivity/subgroup analyses that were conducted for primary outcomes.

EINSTEIN-Ext[51]

The impact of [redacted] was to be assessed on the primary efficacy outcome by calculating adjusted HRs and corresponding 95% CIs. Figure 10 and Figure 13 present sensitivity/subgroup analyses that were conducted for primary outcomes.

Participant flow

5.3.8 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.

EINSTEIN-DVT

Over the course of the trial, 3449 patients from 32 countries were randomised to treatment, of whom 3429 patients received treatment. There were 3449 patients valid for the ITT analysis (n=1731 rivaroxaban; n=1718 enoxaparin/VKA) and 3096

patients (n=1525 rivaroxaban; n=1571 enoxaparin/VKA) eligible for the PP population. A CONSORT diagram is shown in Figure 5.

[redacted]

[redacted]

EINSTEIN-Ext

Over the course of the study, 1197 patients from 30 countries were randomised to treatment. As shown in Figure 6, there were 1196 patients included in the ITT

analysis (n=692 rivaroxaban; n=594 placebo) and 1104 patients (n=550 rivaroxaban; n=554 placebo) in the PP population. The study accrued the required efficacy event outcomes sooner than expected leading to fewer patients being randomised than the planned sample size of 1300 patients. A CONSORT diagram is shown in Figure 6.

5.4 Critical appraisal of relevant RCTs

5.4.1 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?

5.4.2 Please provide as an appendix a complete quality assessment for each RCT.

See section 9.3, appendix 3.

5.4.3 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 required information is presented in Table 17. EINSTEIN-DVT has been appraised by the NHS National Prescribing Centre as providing level one evidence.[52] EINSTEIN-DVT and EINSTEIN-Ext have been published in the New England Journal of Medicine.

Table 17: Quality assessment of EINSTEIN-DVT and EINSTEIN-Ext

	EINSTEIN-DVT	EINSTEIN-Ext
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	N/A	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Investigators & Patients were not blinded to treatment. Outcome assessors were blinded to treatment allocation.	Yes, all groups were blinded to treatment allocation.
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	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	Yes

5.5 Results of the relevant RCTs

5.5.1 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.

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

5.5.3 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.

The outcomes specified in the Final Scope and presented in the Decision Problem in chapter 4 were:

- Recurrent VTE
- Mortality
- Complications following DVT including post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH)
- Adverse events of treatment including bleeding events
- Health-related quality of life

We consider each outcome in turn, with additional attention to patients with active cancer, as a subgroup specified in the Decision Problem.

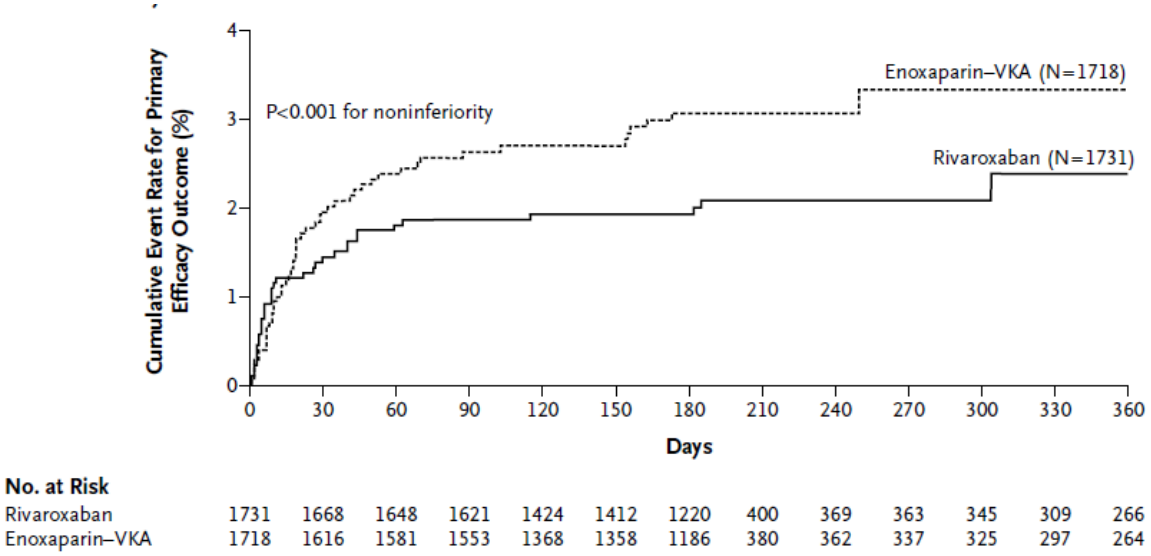
Recurrence of VTE

Recurrence of VTE was the primary efficacy outcome in EINSTEIN-DVT and EINSTEIN-Ext.

EINSTEIN-DVT

In EINSTEIN-DVT, this outcome was confirmed in 36 (2.1%) patients in the rivaroxaban group and 51 (3.0%) patients receiving enoxaparin/VKA. Under the Cox regression model, this produced a hazard ratio of 0.68, favouring rivaroxaban, with a 95% CI of 0.44 to 1.04. There was a P<0.001 for non-inferiority (one-sided test) and P=0.0764 for superiority (two-sided test).

Figure 7: Kaplan-Meier plot for VTE recurrence (primary efficacy outcome) in EINSTEIN-DVT



In both the rivaroxaban and the LMWH/VKA group, most primary efficacy outcome events occurred during the first month of treatment. By day 21 (the end of twice-daily rivaroxaban dosing), the primary efficacy outcome had occurred in 21 patients (1.2%) in the rivaroxaban group and in 29 patients (1.7%) in the standard therapy group. From Month 6 onwards, primary efficacy outcomes occurred infrequently (1 in each group).

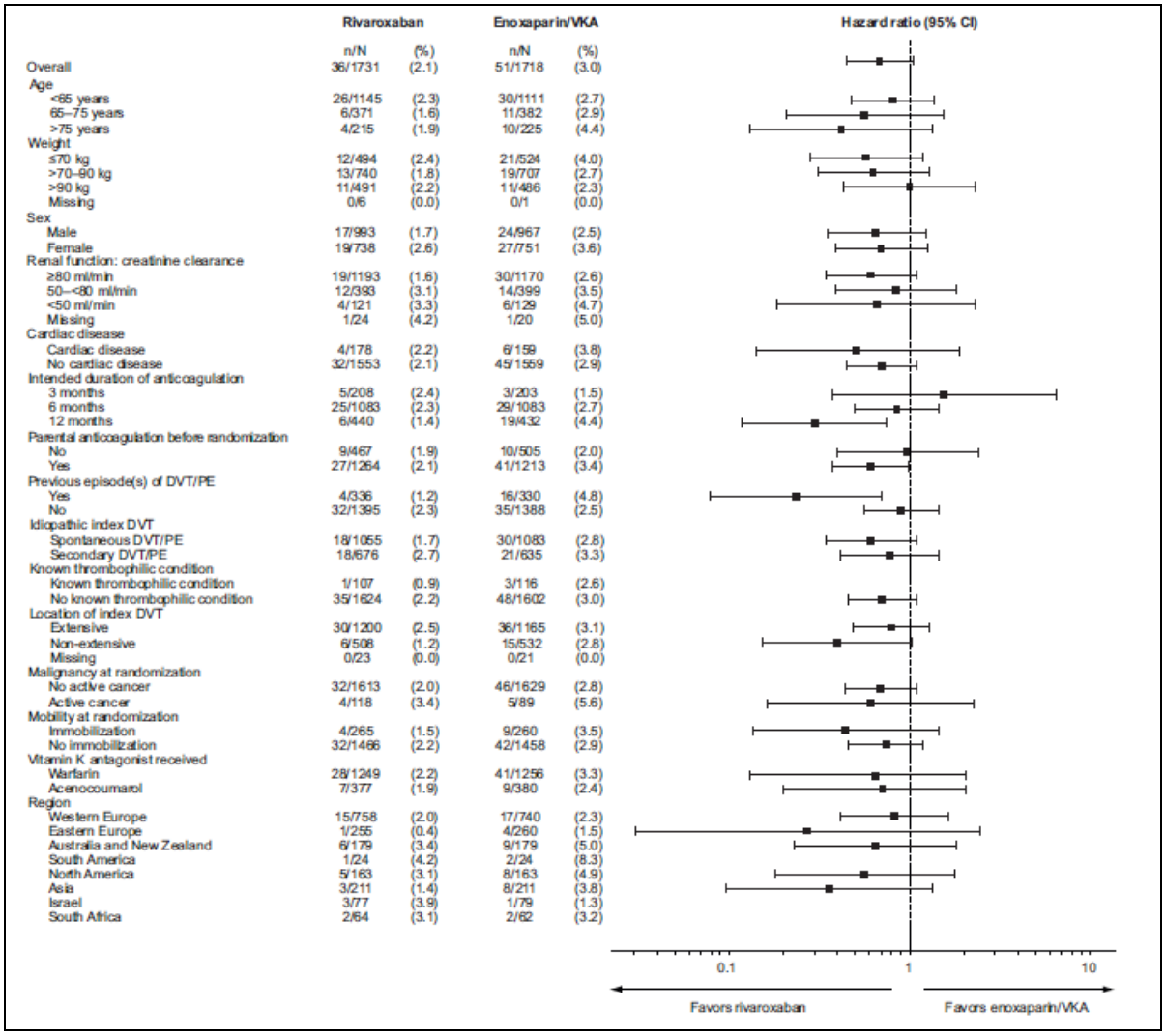
The cumulative event rates in the primary efficacy outcome (comparator minus rivaroxaban) at 3, 6 and 12 months were 0.51%, 0.97% and 0.95%, respectively. This indicates lower event rates in the rivaroxaban group at each of these time points.

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

- HR of 0.68 (95% CI 0.44 to 1.04) in the ITT population
- [redacted]
- [redacted]
- [redacted]

In addition, as shown in Figure 8, the effect size in the primary efficacy outcome was consistent in the wide range of pre-specified subgroups.

Figure 8: Analysis of VTE recurrence (primary efficacy outcome) across the pre-specified subgroups in EINSTEIN-DVT



The primary measure of treatment effect (the HRs described above) have been adjusted for difference in baseline risk due to the presence of active cancer (see Table 16). Patients with active cancer at baseline experienced higher incidence of recurrent VTE than patients without cancer [redacted].

Among the 118 rivaroxaban patients with cancer at baseline, 3% had recurrent VTE, compared with 6% of the 81 in the warfarin group. In this subgroup, the treatment

effect was found to produce a [redacted] The test for interaction of treatment and presence of active cancer was [redacted].

Net clinical benefit was observed in 51 (2.9%) of rivaroxaban patients and 73 (4.2%) of LMWH/VKA patients. This was found to be significantly in favour of rivaroxaban (HR: 0.67, 95% CI 0.47 to 0.95, P=0.03).

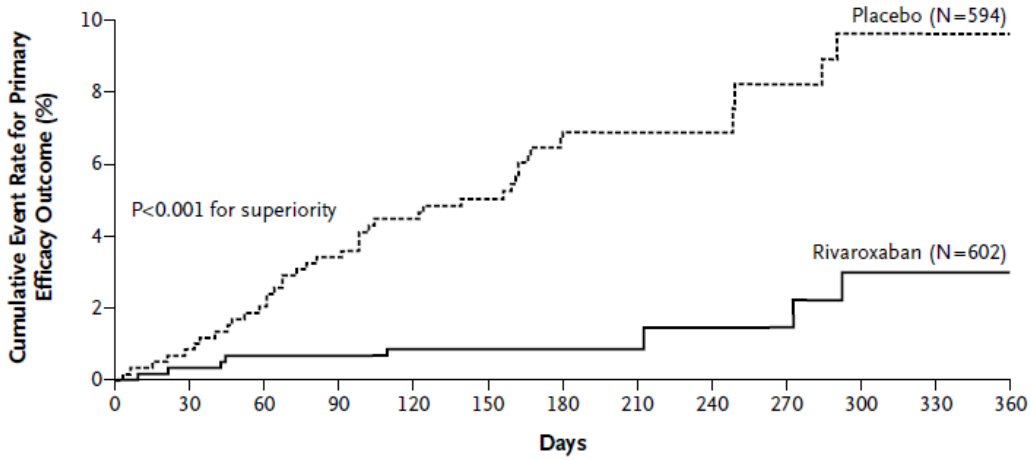
EINSTEIN-Ext

In EINSTEIN-Ext, the primary efficacy outcome of symptomatic recurrent VTE was found in 8 of 602 patients in the rivaroxaban group (1.3%) and 42 of 592 patients receiving placebo (7.1%).

The proportional hazards assumption held, so an analysis stratified by intended treatment duration was not required under the trial protocol. Also, [redacted]

The hazard ratio was 0.18 (95% CI: 0.09 to 0.39, P<0.0001), demonstrating the statistically significant superiority of rivaroxaban to placebo in extended treatment in the study population.

Figure 9: Kaplan-Meier plot for VTE recurrence (primary efficacy outcome) in EINSTEIN-EXT



No. at Risk													
Rivaroxaban	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo	594	582	570	555	522	468	444	164	138	133	110	93	85

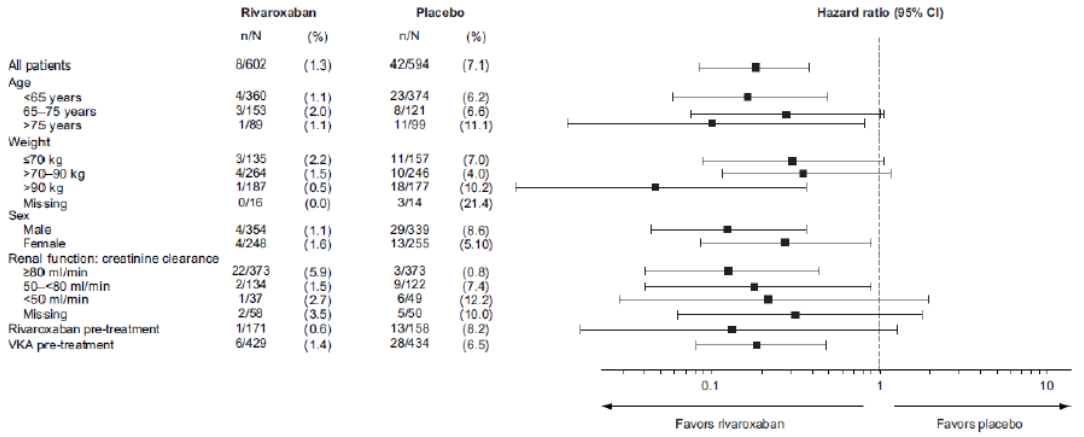
After 6 and 12 months of treatment, the differences in the Kaplan-Meier cumulative event probability rate (placebo minus rivaroxaban) were in favour of rivaroxaban, with a difference of 6.04% at 6 months and 6.65% at 12 months, respectively.

Supportive analyses in the PP and ITT on treatment populations also confirmed the superiority of rivaroxaban:

- HR of 0.18 (95% CI 0.09 to 0.39) in the ITT population, as described
- [redacted]
- [redacted]

In addition, as shown in Figure 10, the effect size in the primary efficacy outcome was consistent in the wide range of pre-specified subgroups.

Figure 10: Analysis of VTE recurrence (primary efficacy outcome) across the pre-specified subgroups in EINSTEIN-Ext



Net clinical benefit was observed in 12 (2.0%) of rivaroxaban patients and 42 (7.1%) of placebo patients. Net clinical benefit was found to be significantly in favour of rivaroxaban (HR: 0.28, 95% CI 0.15 to 0.53, P<0.001).

Mortality

The results described here are also included in Table 18.

EINSTEIN-DVT

All-cause mortality and a composite of all-cause mortality and VTE recurrence were pre-specified secondary outcomes in EINSTEIN-DVT.

All-cause mortality was observed in 38 (2.2%) patients randomised to rivaroxaban and 49 (2.9%) patients randomised to LMWH/VKA, a result numerically in favour of rivaroxaban (HR: 0.67, 95% CI 0.44 to 1.02, P=0.063).

The composite VTE and all-cause mortality outcome was observed in 69 (4.0%) patients randomised to rivaroxaban and 87 (5.1%) patients randomised to

LMWH/VKA, a statistically significant result in favour of rivaroxaban (HR: 0.72, 95% CI 0.53 to 0.99, P=0.044).

There were fewer deaths in the rivaroxaban group than in the placebo group. The three most frequently reported primary causes for death as assigned by the adjudication committee were cancer, unexplained death for which PE could not be ruled out, and infectious disease. One patient from the rivaroxaban treatment group died due to gastrointestinal bleeding and five patients from the enoxaparin/VKA treatment group were also adjudicated with fatal bleeding events (2 gastrointestinal, 1 thoracic and 2 intracranial bleeds).

EINSTEIN-Ext

The composite of all-cause mortality and VTE recurrence was specified as a pre-specified secondary outcome in EINSTEIN-Ext. All-cause mortality was an outcome collected among the AEs.

All-cause mortality was observed in 1 (0.2%) patients randomised to rivaroxaban and 2 (0.3%) patients randomised to LMWH/VKA, a result numerically in favour of rivaroxaban.

The composite VTE and all-cause mortality outcome (Secondary Outcome 1 as per Table 15) was observed in 8 (1.3%) patients randomised to rivaroxaban and 43 (7.2%) patients randomised to LMWH/VKA, a statistically significant result in favour of rivaroxaban (HR: 0.18, 95% CI 0.09 to 0.38, P<0.0001).

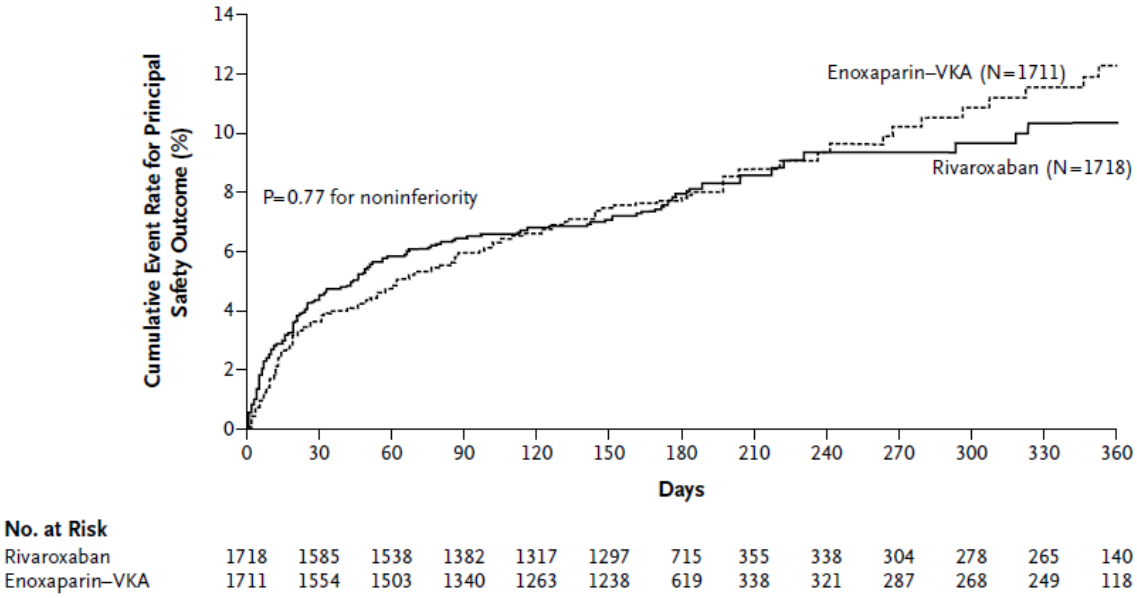
Adverse events of treatment including bleeding events

EINSTEIN-DVT

The primary safety outcome in EINSTEIN-DVT was clinically relevant bleeding. Other AEs, in particular outcomes relating to bleeding, were also recorded (Table 14).

For the primary safety endpoint in EINSTEIN-DVT, results indicated a comparable safety profile of rivaroxaban to enoxaparin / VKA, with no difference between the two treatments (8.1% in both arms to one decimal place; HR: 0.97, 95% CI 0.76 to 1.22, P=0.77 for superiority). A Kaplan-Meier plot is shown in Figure 11.

Figure 11: Kaplan-Meier plot for clinically relevant bleeding (primary safety outcome) in EINSTEIN-DVT



The incidence of major bleeding events was numerically lower in the rivaroxaban treatment group (0.8%) compared to the enoxaparin/VKA treatment group (1.2%) but this did not reach statistical significance (P=0.14). Results for these and other bleeding outcomes are included in Table 18.

Several subgroup analyses were performed on safety outcomes using the safety population, as shown in Figure 12, with consistent results. The treatment by duration interactions had [redacted] Interactions between treatment and presence of active cancer were [redacted]

Figure 12: Analysis of clinically relevant bleeding (primary safety outcome) across the pre-specified subgroups in EINSTEIN-Ext

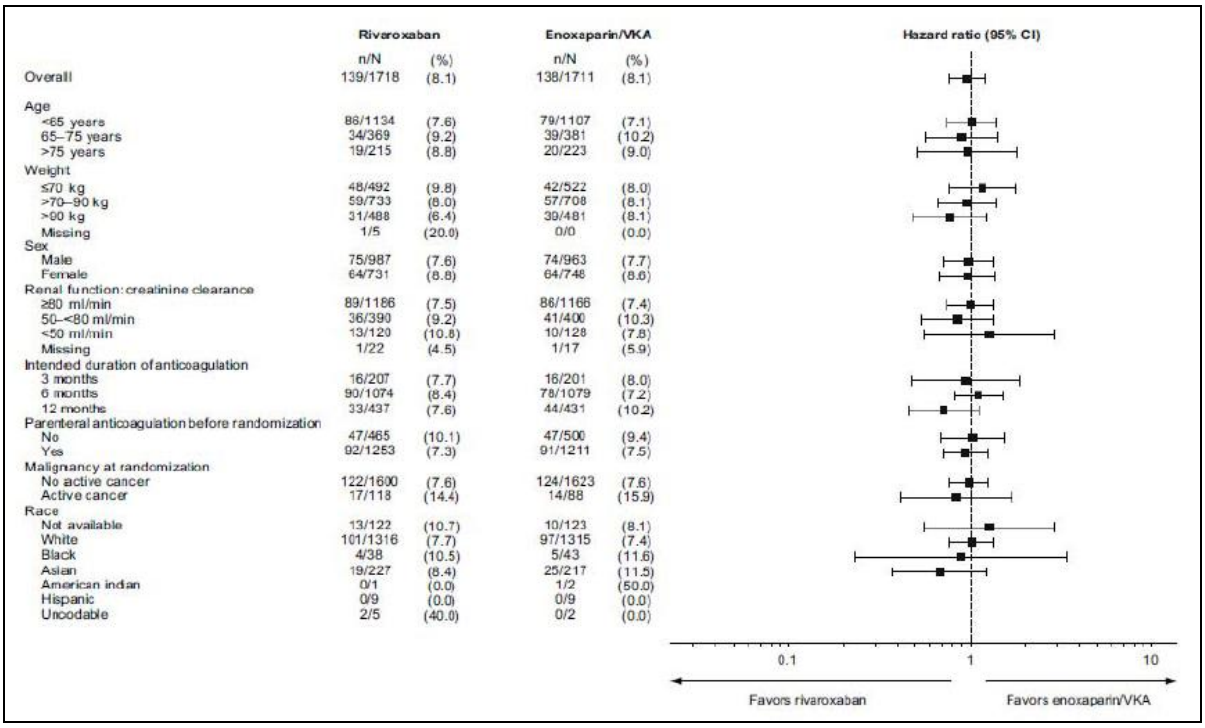


Table 18: Principal bleeding, mortality and vascular event outcomes from EINSTEIN-DVT & EINSTEIN-Ext

	Einstein-DVT						EINSTEIN-Ext					
	Rivaroxaban n	(%)	Comparator n	(%)	Hazard ratio * (95% CI, p-value)		Rivaroxaban n	(%)	Placebo n	(%)	Hazard ratio * (95% CI, p-value)	
Safety population	1718		1711				598		590			
Clinically relevant bleeding	139	(8.1)	138	(8.1)	0.97	(0.76-1.22 P=0.77)	NA		NA		NA	
Major bleeding	14	(0.8)	20	(1.2	0.65	(0.33-1.30 P=0.21)	4	(0.7)	0	(0.0)		P=0.11
Fatal	1	(<0.1)	5	(0.3)			0		0			
Into a critical site	3	(0.2)	3	(0.2)			0		0			
Leading to fall in haemoglobin or transfusion of ≥2 units of blood	10	(0.6)	12	(0.7)			4		0			
Clinically relevant non-major bleeding	126	(7.3)	119	(7.0)			32	(5.4)	7	(1.2)		P<0.001)
First major or clinically relevant non-major bleeding							36	(6.0)	7	(1.2)	5.19	(2.3 to 11.7 P<0.001)
Vascular events												
On treatment	12	(0.7)	14	(0.8)	0.79	(0.36-1.71 P=0.55)	3	(0.5)	4	(0.7)	0.74	(0.17 to 3.3 P=0.69)
Off treatment	1	(<0.01)	4	(0.2)			2	(0.3)	0	(0.0)		
All cause mortality	38	(2.2)	49	(2.9)	0.67	(0.44-1.02 P=0.06)	1	(0.2)	2	(0.3)		
Post thrombotic syndrome (PTS)	[redacted]											
Pulmonary hypertension	[redacted]											

* where available

EINSTEIN-Ext

The primary safety outcome in EINSTEIN-Ext was major bleeding. Other AEs, in particular outcomes relating to bleeding, were also recorded (Table 14).

Four patients in the rivaroxaban group had major bleeding (0.7%), versus none in the placebo group (P=0.11). No Kaplan-Meier plot is shown due to the infrequency of events.

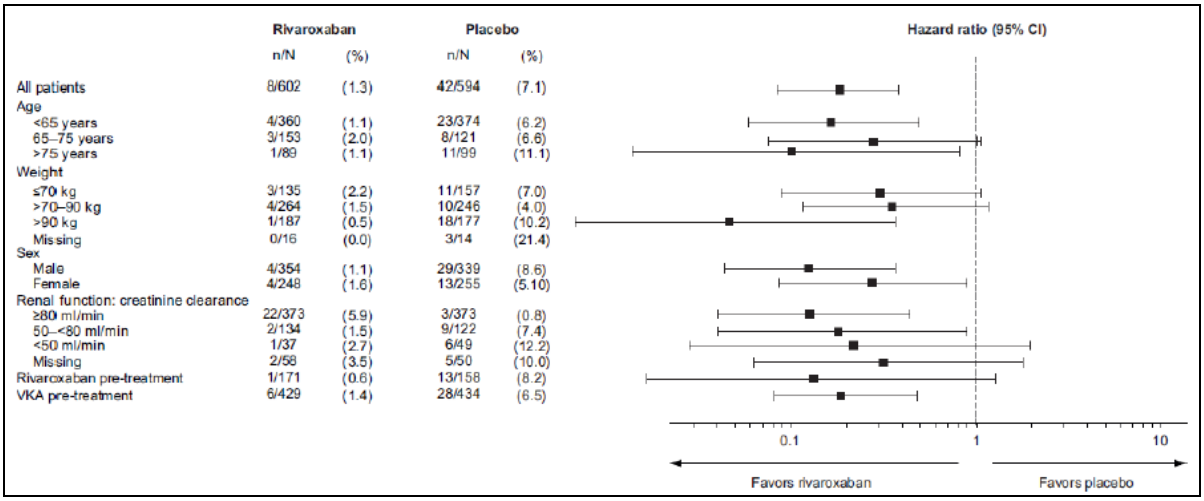
The majority of clinically relevant non-major bleeding was attributed as being due to mucosal bleeding, including urogenital (e.g. vaginal), rectal and nose bleeding. Most patients (81%) resumed or continued the study therapy.

A post hoc analysis was conducted using a composite of the primary efficacy outcome, major bleeding and CRNM bleeding. As described previously, such a composite was the primary safety outcome of EINSTEIN-DVT. It differs from the primary safety outcome of EINSTEIN-Ext by the inclusion of CRNM bleeding. This analysis shows a total event number of 51 (8.6%) in the placebo group (45 primary efficacy outcomes, 0 major bleeds and 10 CRNM bleeds) and 42 (7.0%) in the rivaroxaban group (8 primary efficacy outcomes, 4 major bleeds and 32 CRNM bleeds). While the comparison is nominally in favour of rivaroxaban, the addition of less important bleeding to the analysis, obscures the advantages that rivaroxaban provides over placebo for the most important clinical outcomes.

There was no fatal bleeding event, nor was there bleeding into a critical site. There were three deaths in the trial: two patients had unexplained deaths for which PE could not be ruled-out as a cause (one in each treatment arm) and there was one death due to cancer in the placebo arm.

Several subgroup analyses were performed on safety outcomes using the safety population, which showed consistent results (Figure 13).

Figure 13: Analysis of major bleeding (primary safety outcome) across the pre-specified subgroups in EINSTEIN-Ext



Overall, rivaroxaban showed similar low rates of bleeding compared with enoxaparin/VKA and when treatment was continued, had an acceptable risk of bleeding when compared with placebo. Analyses of the pre-specified subgroups and cohorts also corroborated the results for the principal safety outcomes.

Post thrombotic syndrome (PTS)

Incidence of PTS was recorded among the AEs in both trials. As shown in Table 18, incidence rates were low and similar in both arms of EINSTEIN-DVT (22 cases), and also EINSTEIN-Ext (3 cases).

Chronic thromboembolic pulmonary hypertension (CTEPH)

Incidence of pulmonary hypertension, which includes CTEPH[53], was recorded among the AEs in both trials. As shown in Table 18, incidence rates were low and similar in both arms of EINSTEIN-DVT (3 cases), and also EINSTEIN-Ext (1 case).

Health-related quality of life

EINSTEIN-DVT

Patient-reported satisfaction in EINSTEIN-DVT, as measured by ACTS and TSQM, were recently presented at the International Society on Thrombosis and Haemostasis.[18] No outcomes relating to health preference were recorded, nor any that have been mapped to EQ-5D or other utility measures.[16;54]

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 1472 patients representative of the whole study population. 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 55.2 vs 52.6 ($p<0.0001$) in favour of rivaroxaban with a consistent treatment effect over time and a difference in mean scores ranging from 2.2 at month 2 to 3.2 at month 12.

Mean ACTS Benefits scores were 11.7 vs 11.5 ($p=0.006$); showing an improvement in satisfaction for the rivaroxaban group. The difference in ACTS Benefits scores became apparent from month 2.

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 1472 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 timepoints evaluated.

EINSTEIN-Ext

No outcomes relating to HRQoL were recorded.[16;55] A benefit in HRQoL would nonetheless be expected given the significant reduction in VTE recurrence with rivaroxaban vs placebo, similarity in bleeding outcomes, and convenience of a once-daily oral treatment.

5.6 Meta-analysis

5.6.1 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).

No meta-analysis is presented in this submission, for reasons outlined in section 5.6.2.

5.6.2 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.

Inappropriateness of meta-analysis

Two studies are reported here but no meta-analysis would be appropriate for the following reasons, so none is reported.

- EINSTEIN-DVT evaluates initial treatment (for 3/6/12 months) whereas EINSTEIN-Ext evaluates extended treatment (for 6/12 months following 6/12 months initial anticoagulation).
- The study population of EINSTEIN-DVT is patients with an index DVT whereas the population of EINSTEIN-Ext is patients with an index VTE with clinical equipoise as to the risk-benefit of 6/12 months further anticoagulation.
- The comparator in EINSTEIN-DVT is dual enoxaparin/VKA therapy whereas the comparator in EINSTEIN-Ext is placebo.
- Patients in EINSTEIN-DVT overlap with patients in EINSTEIN-Ext – the study population of EINSTEIN-Ext included patients who had previously participated in EINSTEIN-DVT.

Qualitative overview

Phase II studies provided proof-of-concept evidence on the efficacy and safety of rivaroxaban, relative to enoxaparin / VKA in the treatment of DVT and prevention of recurrent VTE.

In the phase III study, EINSTEIN-DVT:

- The primary efficacy outcome, recurrence of VTE, was in favour of rivaroxaban over LMWH/VKA (HR: 0.68, 95% CI 0.44 to 1.04).

- The primary safety outcome, clinically relevant bleeding, was numerically in favour of rivaroxaban (HR: 0.97, 95% CI 0.76 to 1.22).
- Rates of major bleeding were also comparable (HR: 0.65, 95% CI 0.33 to 1.28).
- There was direct measurement of the net clinical benefit of rivaroxaban vs LMWH/VKA. This outcome was observed in 51 (2.9%) of rivaroxaban patients and 73 (4.2%) of LMWH/VKA patients, which was significantly in favour of rivaroxaban (HR: 0.67, 95% CI 0.47 to 0.95, P=0.03).
- Consistent results were observed across subgroups.

In EINSTEIN-Ext

- The trial population was patients who had received 6/12 months of anticoagulation after an index VTE and who had clinical equipoise in relation to continuing long-term anticoagulation.
- The primary efficacy outcome, recurrence of VTE, was in favour of rivaroxaban over placebo (HR: 0.18; 95% CI 0.09 to 0.39).
- The primary safety outcome, major bleeding, had low incidence in both arms (0.7% with rivaroxaban vs nil with placebo, P=0.11).
- There was direct measurement of the net clinical benefit of rivaroxaban vs placebo. This outcome was observed in 12 (2.0%) of rivaroxaban patients and 42 (7.1%) of placebo patients, which was significantly in favour of rivaroxaban (HR: 0.28, 95% CI 0.15 to 0.53, P<0.001).
- Consistent results were again observed across all important subgroups and cohorts of patients.

The incidence of events in the enoxaparin / VKA treatment arm was comparable to those observed in previous studies, as was the obtained intensity of INR. See also sections 5.10.1-4. This suggests that the trial design, conduct and results provide a fair reflection of the efficacy of rivaroxaban in this patient population.

The positive patient-reported satisfaction measures reported in EINSTEIN-DVT[18] are consistent with 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

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (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.

5.7 Indirect and mixed treatment comparisons

5.7.1 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 9.4, appendix 4.

The Decision Problem states that, if evidence allows, consideration will be given to comparative analyses of rivaroxaban in the subgroup of patients with cancer. Following a systematic review, an indirect comparison was conducted in order to provide evidence as to the clinical effectiveness and cost-effectiveness of rivaroxaban vs long-term LMWH in the cancer subgroup. No indirect or mixed treatment comparison was required for any other reason. This section, together with Appendices 4 and 5 which provide further detail, refers purely to the subgroup of patients with active cancer.

An initial scoping search in the Cochrane Library using the terms 'anticoagulation AND cancer' identified six publications. Four of these publications were immediately discounted:

- Two reviewed the effects of oral or parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation[56;57]
- One study reviewed anticoagulation in patients with cancer and central venous catheters[58]
- Another study was concerned with vena caval filters for the prevention of PE[59]

The two that remained were both reviews of VTE treatment in cancer patients published in June 2011, one for `initial treatment' and the other for `longer term' treatment.[15;41] The `initial treatment' review did not appear to be defined particularly specifically, and only compared agents used in the initial parenteral anticoagulation (typically the first 5-10 days).[41] The `longer term' treatment review however was of clear and direct relevance to the Decision Problem.[15]

Since this systematic review was so recent, included searches of the databases listed above, and appeared to be well-conducted and well-reported, no further searches were undertaken. It is also notable that the studies identified in Akl et al match those studies identified in a previous systematic review conducted for a UK guideline in cancer patients.[38]

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Further information as to the searches and objectives of this systematic review in the publication itself[15] and in Appendices 4 and 5 of this submission, including an overview of the reviewers' study selection criteria in Table 92 and the reviewers' assessment of the quality of included studies, all of them RCTs, in Figure 27.

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[60] 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[61] 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[62;62] 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[63] 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[64] 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.

5.7.3 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.

A summary of the network of RCT evidence used to inform the indirect comparison of rivaroxaban vs long-term LMWH treatment in the subgroup of patients with cancer is presented in Table 19. The network includes the five studies which contributed evidence to the meta-analyses of relevant outcomes in the Akl et al Cochrane review, described above in section 5.7.2, and the EINSTEIN-DVT trial.

Table 19: Summary of the RCTs used to conduct the indirect comparison in the cancer subgroup

Study	Rivaroxaban	Dual heparin / VKA	Long-term LMWH	Other
EINSTEIN-DVT[16]	✓	✓		
Deitcher et al 2006[60]		✓	✓	
Hull et al 2006[61]		✓	✓	✓
Lee et al 2003[62;62]		✓	✓	
Meyer et al 2002[63]		✓	✓	
Romera-Villegas et al 2010[64]		✓	✓	

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

A summary of data to be used in the mixed treatment comparison is provided in the following tables, listed by outcome and method:

- VTE recurrence, measured using time to event methods (hazard ratio), in Table 20;
- VTE recurrence, measured using dichotomous methods (risk ratio), in Table 21;

- Incidence of minor bleeding, measured using dichotomous methods (risk ratio), in Table 23;
- Incidence of major bleeding, measured using dichotomous methods (risk ratio), in Table 22.

Data from the UH arm of Hull et al (`other' in Table 19) is not included in the data to be used, since this does not inform the relative effectiveness of rivaroxaban vs dual heparin / VKA vs long-term LMWH.[61]

Included in the tables are results from the whole trial analysis of EINSTEIN-DVT, as well as the cancer subgroup. As described previously, the Cox regression analysis of VTE recurrence, the primary efficacy outcome, included adjustment for the patient-level presence of active cancer. Additionally, the treatment interaction term for presence of active cancer was [redacted] Consequently, it may be reasonable to assume that the presence of active cancer has no impact on the relative effect of rivaroxaban vs dual LMWH/VKA therapy on the recurrence of VTE or incidence of bleeding outcomes. This is the approach adopted in the primary mixed treatment comparison analysis. A secondary analysis considers the cancer subgroup data alone.

Table 20: Data used in the mixed treatment comparison of VTE recurrence (time to event methods)

Study	Comparison	Point estimate (Log Hazard Ratio)	Standard error of point estimate
EINSTEIN-DVT – whole population[16]	Rivaroxaban vs dual heparin / VKA	-0.3857	0.2194
EINSTEIN-DVT – cancer subgroup[65]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
Deitcher et al 2006[60]	Long-term LMWH vs dual heparin / VKA	NA	NA
Hull et al 2006[61]	Long-term LMWH vs dual heparin VKA	-0.8819	0.455
Lee et al 2003[62;62]	Long-term LMWH vs dual heparin VKA	-0.734	0.24
Meyer et al 2002[63]	Long-term LMWH vs dual heparin VKA	-0.3567	0.9
Romera-Villegas et al 2010[64]	Long-term LMWH vs dual heparin VKA	NA	NA

Source: Analysis 1.5 of Akl et al[15], section 5.5.3 of this submission, and the EINSTEIN-DVT CSR[65].

Table 21: Data used in the mixed treatment comparison of VTE recurrence (dichotomous methods)

Study	Comparison	n/N - intervention 1	n/N - intervention 2
EINSTEIN-DVT – whole population[16]	Rivaroxaban vs dual heparin / VKA	36/1731	51/1718
EINSTEIN-DVT – cancer subgroup[65]	Rivaroxaban vs dual heparin / VKA	4/118	5/89
Deitcher et al 2006[60]	Long-term LMWH vs dual heparin VKA	4/61	3/30
Hull et al 2006[61]	Long-term LMWH vs dual heparin VKA	7/100	16/100
Lee et al 2003[62;62]	Long-term LMWH vs dual heparin VKA	27/336	53/336
Meyer et al 2002[63]	Long-term LMWH vs dual heparin VKA	2/71	3/75
Romera-Villegas et al 2010[64]	Long-term LMWH vs dual heparin VKA	2/36	7/33

Source: Analysis 1.6 of Akl et al[15] and NEJM publication[16].
Abbreviations: n = patients with outcome, N = number of patients in study population.

The data shown in Table 22 imply a risk ratio of 0.68 for rivaroxaban vs LMWH/VKA in the whole trial population. This can be compared with the Cox regression hazard ratio of 0.65 (95% CI 0.83 to 1.34).

Table 22: Data used in the mixed treatment comparison of incidence of major bleeding

Study	Comparison	n/N - intervention 1	n/N - intervention 2
EINSTEIN-DVT – whole population[16]	Rivaroxaban vs dual heparin / VKA	14/1718	20/1711
EINSTEIN-DVT – cancer subgroup[65]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
Deitcher et al 2006[60]	Long-term LMWH vs dual heparin VKA	6/67	1/34
Hull et al 2006[61]	Long-term LMWH vs dual heparin VKA	7/100	7/100
Lee et al 2003[62;62]	Long-term LMWH vs dual heparin VKA	19/338	12/335
Meyer et al 2002[63]	Long-term LMWH vs dual heparin VKA	5/71	12/75
Romera-Villegas et al 2010[64]	Long-term LMWH vs dual heparin VKA	NA	NA

Source: Analysis 1.8 of Akl et al[15], NEJM publication[16] and the EINSTEIN-DVT CSR (safety population). Abbreviations: n = patients with outcome, N = number of patients in study population.

The data shown in Table 23 imply a risk ratio of 1.05 for rivaroxaban vs LMWH/VKA in the whole trial population. This can be compared with the Cox regression hazard ratio of 1.06 (95% CI 0.83 to 1.34).

Table 23: Data used in the mixed treatment comparison of incidence of minor bleeding

Study	Comparison	n/N - intervention 1	n/N - intervention 2
EINSTEIN-DVT – whole population[16]	Rivaroxaban vs dual heparin / VKA	126/1718	119/1711
EINSTEIN-DVT – cancer subgroup[65]	Rivaroxaban vs dual heparin / VKA	[redacted]	[redacted]
Deitcher et al 2006[60]	Long-term LMWH vs dual heparin VKA	39/67	17/34
Hull et al 2006[61]	Long-term LMWH vs dual heparin VKA	20/100	17/100
Lee et al 2003[62;62]	Long-term LMWH vs dual heparin VKA	28/338	51/335
Meyer et al 2002[63]	Long-term LMWH vs dual heparin VKA	5/71	9/75
Romera-Villegas et al 2010[64]	Long-term LMWH vs dual heparin VKA	NA	NA

Source: Analysis 1.7 of Akl et al[15] and Tables 14.3.1/48 and 50 of the EINSTEIN-DVT CSR (safety population). Abbreviations: n = patients with outcome, N = number of patients in study population.

Heterogeneity in the Akl et al meta-analyses

From the five studies of long-term LMWH vs dual heparin / VKA, it can be seen that three[61-63] presented time to event data on recurrence of VTE, which yielded a hazard ratio of 0.47 (95% CI 0.32 to 0.71). Five[60-64] presented risk ratio data on the same outcome, which yielded a risk ratio of 0.49 (95% CI 0.34 to 0.70). Risk ratio data on incidence of minor and major bleeding outcomes was presented by four.[60-63]

The SMC have previously provided advice in this area, apparently based primarily on the evaluation of dalteparin by Lee et al 2003.[62;66] This study contributed 672 (57%) of the 1178 patients included in any of the meta-analyses above. Dalteparin is licensed in the UK for extended treatment in oncology.[40]

Heterogeneity is clearly an important consideration in assessing meta-analyses, so a comparison of the treatment effects from the full meta-analyses with those obtained from the single study by Lee et al is shown in Table 24. It is notable that the results obtained in Lee 2003 for a 6 month regimen of dalteparin were little different from the results shown for other long-term LMWH regimes.

The primary mixed treatment comparison analysis therefore incorporates the relative effectiveness of long-term LMWH vs LMWH/VKA dual therapy obtained in the full Cochrane meta-analysis.[15] A secondary analysis uses data only from Lee et al.[62;62]

Table 24: Relative effectiveness of long-term LMWH vs LMWH/VKA dual therapy in VTE patients with cancer

	Cochrane meta-analysis[15]		Lee 2003[15;62]	
	Point estimate	(95% CI)	Point estimate	(95% CI)
Recurrence of VTE	HR=0.47	(0.32 to 0.71)	HR=0.48	(0.30 to 0.77)
Incidence of minor bleeding	RR=0.85	(0.53 to 1.35)	RR=0.54	(0.35 to 0.84)
Incidence of major bleeding	RR=1.05	(0.53 to 2.10)	RR=1.57	(0.77 to 3.18)

Notes: The Cochrane meta-analysis was conducted under a random effects model.
Abbreviations: HR = hazard ratio, RR = risk ratio.

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

Mixed treatment comparison analyses are conducted using the NICE Decision Support Unit (DSU) recommended approaches and WinBUGS coding for the types of outcomes reported.[14] The aim of this analysis was to synthesise the relative treatment effects of rivaroxaban, dual LMWH/VKA therapy and long-term LMWH therapy for patients with cancer in outcomes relevant to the Decision Problem.

For analysis of VTE recurrence (time to event), we considered the log hazard ratio to be a Normally distributed continuous variable and used an identity link. The data used was presented in Table 20. Comparative effects are presented using a hazard ratio (HR) statistic.

For analysis of VTE recurrence, clinically relevant non-major bleeding and major bleeding (dichotomous data), we considered the arm-specific n/N data as Binomial and used an logit link. The data used was presented in Table 21, Table 23 and Table 22. Comparative effects are presented using an odds ratio (OR) statistic.

A random effects approach was used, as with the Akl meta-analyses. WinBUGS coding (based heavily on the NICE DSU code) is supplied in section 9.6, Appendix 5a. For all analyses, the median is presented as the point estimate of any treatment effect, as this was considered to be a statistic more representative of the central location of the positively skewed posterior distributions of treatment effects than the mean. The 95% Credible Intervals (CrIs) reported are the 2.5th and 97.5th percentiles of the relevant posterior distribution.

As described previously, the primary analysis used data from all studies included in the Akl meta-analyses and data from across the whole of EINSTEIN-DVT. Secondary analyses are presented using data from Lee et al 2003 in place of the full Akl meta-analysis data, and using data from the cancer subgroup of EINSTEIN-DVT rather than the whole trial.

5.7.6 Please present the results of the analysis.

Mixed treatment comparisons of the time to event analyses of the rate of recurrence of VTE are shown in Table 25. Under the primary analysis, the hazard ratio for rivaroxaban vs long-term LMWH was 1.44 (95% CrI 0.07 to 31.4), in a model that appears to fit fairly well. With the reduced dataset of secondary analysis 1, the CrI was much wider but point estimate little different. Secondary analysis 2 produced a similar effect size and CrI as the primary analysis.

Table 25: Results of mixed treatment comparison - VTE recurrence (time to event, hazard ratio)

	Primary	Secondary analysis 1	Secondary analysis 2
Relative effectiveness (median HR, 95% CrI)			
Rivaroxaban vs dual heparin / VKA	0.68 (0.05 to 11.0)	0.68 (0.00 to 335)	0.63 (0.04 to 12.1)
Long-term LMWH vs dual heparin / VKA	0.47 (0.11 to 2.45)	0.49 (0.00 to 213)	0.47 (0.11 to 2.44)
Rivaroxaban vs long-term LMWH	1.44 (0.07 to 31.4)	1.37 (0.00 to 8912)	1.32 (0.06 to 32.3)
Other model statistics			
Tau (mean)	38270	292	38270
Residual deviance (mean)	3.0	2.0	3.0
Number of data points	4	2	4

Using less robust dichotomous methods produces an odds ratio of rivaroxaban vs long-term LMWH in the mixed treatment comparison of 1.59 (95% CrI 0.33 to 7.80), as shown in Table 25. The model appears to fit fairly well. However, the CrI are very wide in the primary analysis, wider in secondary analysis 2, and wider still in the secondary analysis 1.

Table 26: Results of mixed treatment comparison - VTE recurrence (dichotomous methods, odds ratio)

	Primary	Secondary analysis 1	Secondary analysis 2
Relative effectiveness (median odds ratio, 95% CrI)			
Rivaroxaban vs dual heparin / VKA	0.70 (0.17 to 2.69)	0.69 (0.0 to 382)	0.54 (0.08 to 4.0)
Long-term LMWH vs dual heparin / VKA	0.43 (0.20 to 0.91)	0.46 (0.0 to 278)	0.44 (0.18 to 0.96)
Rivaroxaban vs long-term LMWH	1.59 (0.33 to 7.80)	1.52 (0.0 to 10370)	1.29 (0.16 to 10.7)
Other model statistics			
Tau (mean)	2956	28.5	494
Residual deviance (mean)	10.2	4.0	10.3
Number of data points	12	4	12

The primary mixed treatment comparison of major bleeding produced an OR of rivaroxaban vs long-term LMWH of 0.68 (95% CrI 0.02 to 25.8), as shown in Table 27. The model appears to fit fairly well. However, the CrI are very wide in the primary analysis, and even wider in the secondary analyses.

Table 27: Results of mixed treatment comparison – major bleeding (dichotomous methods, odds ratio)

	Primary	Secondary analysis 1	Secondary analysis 2
Relative effectiveness (median odds ratio, 95% CrI)			
Rivaroxaban vs dual heparin / VKA	0.68 (0.02 to 25.8)	0.75 (0.00 to 286)	0.26 (0.01 to 8.31)
Long-term LMWH vs dual heparin / VKA	1.09 (0.20 to 7.5)	1.59 (0.00 to 822)	1.11 (0.24 to 6.59)
Rivaroxaban vs long-term LMWH	0.64 (0.01 to 30.1)	0.44 (0.00 to 2797)	0.24 (0.00 to 9.44)
Other model statistics			
Tau (mean)	802	65	7585
Residual deviance (mean)	10.2	4.1	10.4
Number of data points	10	4	10

The primary mixed treatment comparison of clinically relevant non-major bleeding produced an OR of rivaroxaban vs long-term LMWH of 1.32 (95% CrI 0.09 to 18.7), as shown in Table 28. The model appears to fit fairly well. However, the CrI are very wide in the primary analysis, and even wider in the secondary analyses.

Table 28: Results of mixed treatment comparison – clinically relevant non-major bleeding (dichotomous methods, odds ratio)

	Primary	Secondary analysis 1	Secondary analysis 2
Relative effectiveness (median odds ratio, 95% CrI)			
Rivaroxaban vs dual heparin / VKA	1.07 (0.09 to 12.1)	1.09 (0.00 to 614)	1.29 (0.11 to 16.0)
Long-term LMWH vs dual heparin / VKA	0.81 (0.24 to 3.14)	0.51 (0.00 to 306)	0.80 (0.24 to 2.75)
Rivaroxaban vs long-term LMWH	1.32 (0.09 to 18.7)	2.18 (0.00 to 17420)	1.61 (0.11 to 26.5)
Other model statistics			
Tau (mean)	157	24.9	70.4
Residual deviance (mean)	10.1	4.1	10.0
Number of data points	10	4	10

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

This evidence network, like any other, is not entirely homogeneous. The Akl/Cochrane meta-analysis contains studies of various study populations, with differing cancers and index VTEs, being treated with various LMWH agents and regimes.[15] The EINSTEIN-DVT trial contained patients with and without active cancer, but found that the presence of active cancer had no statistically significant impact on the relative treatment effect for rivaroxaban vs LMWH/VKA in VTE recurrence and bleeding outcomes.[16]

The statistical heterogeneity has been quantified using a parameter denoted tau, the between-trial precision. Greater values for a given scale indicate greater precision and reduced uncertainty.[14] Mean values for tau in primary analyses range from 157 in the clinically relevant non-major bleeding outcome (analysed on a log odds scale) to 38,270 for the recurrence of VTE outcome (analysed on a log hazard scale).

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

There is some uncertainty about the relevance of all long-term LMWH trials other than Lee et al 2003[62], given the licensing status of dalteparin in the UK, the primacy of this trial to the licence,[40] the size of this study and recent SMC advice based around evidence from this trial[66]. Secondary analysis 1 therefore excluded studies by Deichter et al[60], Hull et al[61], Meyer et al[63] and Romera-Villegas et al[64]. Point estimates in secondary analysis 1 were generally similar to the primary analysis, but CrIs were considerably wider.

There is also some uncertainty about the relevance of data relating to patients without cancer from the EINSTEIN-DVT trial. Conventionally, one may wish to exclude data from a group of patients not specific to the population in question. However, the measurement of treatment effect in EINSTEIN-DVT accounted and adjusted for the presence of patients with active cancer and their differential underlying risks. Additionally, analysis of the treatment interaction term with presence of active cancer was non-significant in [redacted] Therefore results from the whole of EINSTEIN-DVT were used in the primary mixed treatment comparison analyses, and data from the cancer subgroup were presented in secondary analysis 2. Point estimates in secondary analysis 2 were generally similar to the primary analysis and CrIs were wider, though not as wide as with secondary analysis 1.

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

As mentioned previously, it is notable that the results obtained in Lee 2003 for a 6 month regimen of dalteparin[62;62] were little different from the results shown for other long-term LMWH regimes. This is apparent when considering differences between trial specific outcomes and the meta-analysis reported in the Akl/Cochrane review (Table 24). It is also apparent when considering differences between the primary analysis and secondary analysis 1 for the mixed treatment comparisons (presented in section 5.7.6).

There appear some minor differences between the direct evidence in relation to the rivaroxaban vs dual LMWH/VKA comparison and the medians of the relevant posterior distributions fitted by the mixed treatment comparisons. Given that there is only one trial of rivaroxaban in the network, such differences may be due to a critical statistical assumption of exchangeability of random (rather than fixed) treatment effects in the evidence synthesis methodology that has been described by the NICE DSU[14] and applied in this appraisal. Various variance modelling approaches may be attempted, but the random effects method employed may be seen as a not unreasonable reflection of the limited evidence network.

5.8 Non-RCT evidence

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 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 9.6 and 9.7, appendices 6 and 7.

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

5.9 Adverse events

5.9.1 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 5.1 to 5.5 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 9.8 and 9.9, appendices 8 and 9.

A systematic review for relevant RCTs has been described in sections 5.1-5.2 (and further in section 9.2, appendix 2). This review did not exclude studies designed primarily for safety. Neither of the main trials identified, EINSTEIN-DVT and EINSTEIN-Ext, were designed primarily for safety.

5.9.2 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.

Section 5.5 contains a description of all outcomes specified in the Decision Problem ocurring in EINSTEIN-DVT and EINSTEIN-Ext (Table 18). This includes mortality, incidence of bleeding, vascular events, PTS and CTEPH and various composite outcomes.

In this section we present aggregate AE data from the two trials and specific AEs which were experienced in at least 4% of any treatment group in Table 29.

Table 29: Most common adverse events in EINSTEIN-DVT and EINSTEIN-Ext

	EINSTEIN-DVT		EINSTEIN-Ext	
	Rivaroxaban (N=1718) n (%)	**LMWH/VKA (N=1711)** n (%)	**Rivaroxaban (N=598)** n (%)	**Placebo (N=590)** n (%)
Treatment-emergent adverse events				
Drug-related				
Serious	201 (12.0)	233 (13.6)		
Drug-related and serious				
Any	1078 (62.7)	1080 (63.1)		
Specific adverse events				
Nasopharyngitis				
Epistaxis				
Headache				
Pain in extremity				
Cough				
Contusion				

Note: The AEs listed are those which were experienced in at least 4% of patients in any treatment group.

The question also requires relative and absolute risk differences. These, calculated post hoc from data in Table 29, are presented in Table 30.

Table 30: Relative and absolute risk differences (%) for the most common adverse events in EINSTEIN-DVT and EINSTEIN-Ext

	EINSTEIN-DVT		EINSTEIN-Ext	
	Risk ratio (95% CI)	**ARD (%)** (95% CI)	**Risk ratio** (95% CI)	**ARD (%)** (95% CI)
Treatment-emergent adverse events				
Drug-related Serious	0.86 (0.72 to 1.02)	-1.9 (-4.1 to 0.3)		
Drug-related and serious Any	0.99 (0.94 to 1.05)	-0.4 (-3.6 to 2.8)		
Specific adverse events				
Nasopharyngitis				
Epistaxis				
Headache				
Pain in extremity				
Cough				
Contusion				

Notes: The AEs listed are those which were experienced in at least 4% of patients in any treatment group. CIs for risk ratios were calculated as per Equation 4.24 of Armitage, Berry and Matthews. CIs for the ARDs were calculated using a Normal approximation to the Binomial.[67]
ARD: absolute risk difference.

In light of the liver function abnormalities produced by ximelagatran, an oral thrombin inhibitor now withdrawn from research[49], liver function was also closely monitored in the EINSTEIN RCTs. Monthly liver function tests did not reveal any signs of impaired liver safety in patients receiving rivaroxaban.

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

The SmPCs note that:

`The safety of rivaroxaban has been evaluated in eight phase III studies including 16,041 patients exposed to rivaroxaban. In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the patients experienced adverse events considered related to treatment as assessed by investigators. …. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients.'[2;3]

Additionally:

- EINSTEIN-DVT showed that acute treatment with rivaroxaban has a similar safety / bleeding profile to comparator LMWH/VKA therapy. The hazard ratio for the primary safety outcome, major bleeding, was 0.97, 95% CI 0.76 to 1.22, P=0.77)
- Continued treatment with rivaroxaban, as demonstrated in EINSTEIN-Ext, also has an acceptable benefit-to-risk profile in terms of the recurrent VTEs prevented and the incidence of bleeding events.
- Safety results were consistent across all studies.
- Despite additional attention on rates of vascular events and adverse events related to liver function, rates of adverse events were low in all studies.
- Discontinuation rates were also low, suggestive of high patient tolerability and satisfaction with rivaroxaban as a once daily oral anticoagulant.

5.10 Interpretation of clinical evidence

5.10.1 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 enoxaparin / VKA regimen in the treatment of DVT and prevention of recurrent VTE events (HR: 0.68; 95% CI 0.44 to 1.04; P<0.001) in EINSTEIN-DVT. Treatment effects with regard to the primary efficacy endpoint were consistent across all pre-specified sub-groups.

EINSTEIN-DVT showed that acute treatment with rivaroxaban has a similar safety / bleeding profile to comparator LMWH/VKA therapy. The hazard ratio for the primary safety outcome, major bleeding, was 0.97, 95% CI 0.76 to 1.22, P=0.77).

Net clinical benefit is a measure of the overall benefit of treatment, offsetting the advantage in terms of reduced occurrence of the primary endpoint against the risk of major bleed events. There was direct measurement of the risk-benefit of rivaroxaban vs comparator in EINSTEIN-DVT and EINSTEIN-Ext. EINSTEIN-DVT demonstrated a significantly positive net clinical benefit vs LMWH/VKA (HR: 0.67; 95% CI 0.47 to 0.95, P=0.03). EINSTEIN-Ext demonstrated a significantly positive net clinical benefit vs placebo (HR: 0.28, 95% CI 0.15 to 0.53, P<0.001).

Clinical superiority of extended treatment for 6/12 months with rivaroxaban compared with placebo was shown in EINSTEIN-Ext (HR: 0.97; 95% CI 0.76 to 1.22, P=0.77), with consistent results again observed across all important subgroups and cohorts of patients, including a broad spectrum of permanent, secondary or transient risk conditions.

Greater satisfaction with treatment was reported with rivaroxaban in EINSTEIN-DVT using the ACTS and TSQM instruments.[18] 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

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

The aim of DVT treatment is to prevent extension of the existing thrombus and prevent further or recurrent DVTs or PE. In line with the aim of therapy, the primary and secondary efficacy outcomes in the EINSTEIN study programme included a wide range of outcomes based on the incidence of DVTs, PE, bleeding and mortality.

One aspect of the design of EINSTEIN-DVT and EINSTEIN-Ext 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, enhances the applicability of trial results to real-life patients and is a strength of the EINSTEIN study programme.

The studies also demonstrated high levels of consistency of efficacy demonstrated across many subgroups including a broad spectrum of permanent, secondary or transient risk conditions.

In addition, the studies showed high compliance rates for rivaroxaban, confirming the simplicity and convenience of rivaroxaban for patients, another important factor in routine clinical practice.

EINSTEIN-DVT

Open-label design and general validity

The EINSTEIN-DVT trial was a randomised controlled trial with an active comparator regimen (LMWH/VKA) of wide international acceptance and use. The trial had a Prospective Randomised Open Blinded Endpoint design, 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 and administration of a placebo in the rivaroxaban group would have required subcutaneous injection of placebo LMWH twice a day for some of the time, unnecessarily increasing 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[4].

Open-label studies may also be validly criticised for their potential for bias arising from 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 pre-defined internationally accepted criteria and are verified centrally by an independent and blinded adjudication panels[68]. EINSTEIN-DVT has these characteristics.

Clinically important, hard outcomes

Outcomes used in EINSTEIN-DVT were indeed clinically important, hard, objective outcomes (DVT, PE, 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), there were fewer confirmed VTE recurrent events in the rivaroxaban arm than in the LMWH/VKA arm. The rate of recurrence seen in the active control group (of around 3%) was also consistent with rates observed in other recent VTE studies.[69;70]

There was low loss to follow-up: 0.9% in the rivaroxaban arm and 1.0% in the LMWH/VKA arm.

We have described previously the baseline characteristics of EINSTEIN-DVT (see Table 11 and Table 12). A substantial proportion of the EINSTEIN-DVT trial population (43%, 1498/3449) were from Western Europe although few were from UK centres.

Use of non-inferiority statistical testing

The EINSTEIN-DVT trial was designed to involve sequential testing of the primary efficacy endpoint for non-inferiority and then, if statistically significant, superiority. As described in section 5.5, the primary efficacy outcome was hazard ratio of 0.68, favouring rivaroxaban, with a 95% CI of 0.44 to 1.04. In terms of the primary efficacy outcome, rivaroxaban was found to be statistically significantly non-inferior to LMWH/VKA (P<0.001) but not statistically significantly superior (P=0.08). As described in section 5.9, the primary safety outcome was a hazard ratio of 0.97 numerically favouring rivaroxaban, with a 95% CI 0.76 to 1.22, P=0.77 for superiority. As described in section 5.5, a pre-specified net clinical benefit outcome, was statistically significantly in favour of rivaroxaban: hazard ratio of 0.67, with a 95% CI of 0.47 to 0.95, P=0.03).

The use of non-inferiority testing may be perceived by some audiences as a limitation. We would draw attention to the confidence intervals (CIs), which may be more meaningful to decision-makers than p-values.[71-73] We would also highlight the consistent effects shown across trial subgroups demonstrated in Figure 4 and Figure 10. Analyses were pre-specified as recommended in EMA guidance[4].

Treatment before randomisation

The EINSTEIN-DVT study was designed to allow a limited amount of treatment before randomisation: up to 48 hours of treatment with LMWH, heparin or fondaparinux were permitted.

There were two main reasons for this. Firstly, this design ensured the study represented current clinical practice, whereby:

- patients presenting with suspected DVT 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 DVT.

A second reason was related to practical and ethical considerations. 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. However, on consideration of the results of the study, [redacted] and baseline characteristics evaluated in subgroup analyses, 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: [redacted]
- The intensity of pre-randomisation anticoagulation was small. Among the subset of patients receiving any pre-randomisation anticoagulation, the treatment was received for just one day in 94% of cases.
- There was no association between duration of pre-randomisation anticoagulation and treatment allocation (P=0.33, post hoc chi-squared test)
- Patients who received pre-randomisation anticoagulants were similar to those who did not in terms of demographics, clinical/risk profile, thrombotic burden and accounting for treatment duration.

- The incidence of the primary efficacy outcome was similar regardless of pre-randomisation anticoagulation:

[redacted]

Time in target range (TTR)

The proportion of time that subjects' INR was in the target range (TTR, ie an INR of 2-3) was lower, at 57.7% across all centres and 59.7% in Western European centres. These trial results can be compared with various external observations:

- In a review for the ACCP guidelines, the mean TTR in RCTs ranged between 42% and 83%, mostly around 60%.[74]
- A recent observational study in UK secondary care anticoagulation services observed TTR of 53% during the first 12 weeks of treatment and 59% thereafter.[75]
- Guideline recommendations from the National Patient Safety Agency and the Scottish Executive Health Department are for TTR of at least 60%.[76;77]

It is important to highlight an observation made in the SmPCs that, after extensive analysis involving ranking centres by TTRs achieved, there was no interaction observed in EINSTEIN-DVT between TTR and treatment effect.[2;3] EINSTEIN-DVT therefore has strong external validity in terms of TTR achieved in the LMWH/VKA arm.

Conclusion

Together this provides evidence of a well-managed trial where therapy was administered to a high standard consistent with standard UK practice. EINSTEIN-DVT has strong external validity with limited risk of bias through its design – a conclusion backed-up by evidence arising from the study's results.

EINSTEIN-Ext study

EINSTEIN-Ext was a large, international, double-blind, placebo-controlled trial with outcomes adjudicated centrally by a blinded panel.

Patient entry criteria and optimal duration of therapy

A further potential limitation arises in the patient inclusion/exclusion criteria for the study. EINSTEIN-Ext was designed to study the efficacy and safety of rivaroxaban in patients who had already undergone at least 6 months anticoagulation treatment and for whom subsequently there was clinical equipoise as to the benefits of continued/extended treatment. Consequently, not all patients from EINSTEIN-DVT were eligible to enter EINSTEIN-Ext; and EINSTEIN-Ext included patients who had not entered EINSTEIN-DVT (see Figure 4). A limitation from this design is therefore that the results of EINSTEIN-Ext do not necessarily extend to the full population of EINSTEIN-DVT, patients with symptomatic DVT. However, EINSTEIN-Ext was designed to permit the applicability of its results to patients within the EINSTEIN-DVT population for whom, after at least 6 months anticoagulation, clinical equipoise remains and for which studies and clinical guidelines suggest may be a common situation.

Appropriate use of placebo control

Criteria for entry to EINSTEIN-Ext are that clinical equipoise must exist as to whether to continue to treat with a thromboprophylactic agent. Hence, as 'no treatment' is a viable management choice for this scenario (i.e. patients who had completed 6 to 12 months of anticoagulation therapy, placebo is an appropriate option and comparator to rivaroxaban in EINSTEIN-Ext.

Differences in prior anticoagulation

It may be suspected that the success of rivaroxaban in extension treatment demonstrated in EINSTEIN-Ext may be attributable, in part at least, to some lack of treatment benefit in earlier, acute treatment. We have noted previously that the EINSTEIN-Ext patient population includes patients with 6 and 12 months prior anticoagulation, and this may be rivaroxaban or dual LMWH/VKA therapy.

However, as previously shown, the effect of rivaroxaban on efficacy and safety outcomes had no apparent statistical association with the type or length of

anticoagulation therapy received prior to entering EINSTEIN-Ext (Figure 8 and Figure 10).

5.10.3 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.

Population - Adults with an acute DVT

Intervention - Rivaroxaban

The results of the EINSTEIN programme are directly applicable to the population defined in the decision problem - patients in England and Wales with an acute DVT.

EINSTEIN-DVT assessed the efficacy and safety of rivaroxaban in the treatment of acute DVT and prevention of recurrent VTE.

EINSTEIN-Ext assessed the efficacy and safety of rivaroxaban as continued anticoagulation for prevention of recurrent VTE in patients who had already received 6 to 12 months of anticoagulation therapy and for whom there was clinical equipoise in continuing therapy.

The data from EINSTEIN-DVT and EINSTEIN-Ext demonstrate robust efficacy and similar comparative safety vs comparators across all important subgroups and cohorts of patients, including a broad spectrum of permanent, secondary or transient risk conditions. It is therefore reasonable to conclude that rivaroxaban would likely provide a favourable benefit-risk profile for patients who require treatment for acute DVT and subsequent prevention of recurrent VTEs. These include patients with an underlying risk of recurrent VTE including the presence of active cancer.

Comparators

EINSTEIN-DVT trial was a randomised controlled trial with an active comparator regimen (LMWH/VKA) of wide international acceptance and use and also in accordance with the decision problem. LMWH and VKA are the anticoagulants used most commonly in England and Wales. Overall TTR in the LMWH/VKA arm of the study was comparable with results from other recent VTE studies[69;70] and demonstrates concordance with UK clinical practice, and thus applicability of results of the study to the Decision Problem.

EINSTEIN-Ext had a placebo control. The criteria for entry to EINSTEIN-Ext were that clinical equipoise must exist as to whether to continue to treat with a thromboprophylactic agent. Hence, as 'no treatment' is a viable management choice

for this scenario, placebo is an appropriate option and comparator to rivaroxaban in EINSTEIN-Ext and also for the decision problem.

There are many challenges with current therapy provided to patients:

LMWHs are administered by subcutaneous injection. Many patients are managed as outpatients and this therefore requires self administration. This can 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.

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 Rapid Response Report[13].

Warfarin is the VKA most commonly used in the UK and has a number of limitations, 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[7].

The NPSA issued a patient safety alert to healthcare organisations in 2007 regarding best practice actions to make anticoagulation therapy safer[10].

Warfarin is usually managed within an anticoagulant service. There are several different models of anticoagulant service across the UK ranging from secondary care outpatient clinics to primary care led clinics and many variants in between. Resources associated with warfarin management are not insignificant.

Patients with cancer

There is general consensus for LMWH to be used in preference to UH or VKA in the treatment of DVT and prevention of recurrent VTEs in patients with cancer, with a

recommended treatment duration of 3-6 months. Depending on a patient's circumstances and risk factors, this may be continued.[9;11;33-35]

In order to compare the use of LMWH with rivaroxaban in this subgroup, comparator data from EINSTEIN-DVT or EINSTEIN-Ext could not be used as LMWH was only administered during the initial stages of treatment in EINSTEIN-DVT. An indirect comparison was therefore made using results from EINSTEIN-DVT and data presented in a Cochrane review and meta-analysis of studies on long-term anticoagulation in patients with cancer.[15;16;65] See section 5.7.

Outcomes

The aim of DVT treatment is to prevent extension of the existing thrombus and prevent further, or recurrent DVTs or PE. A recurrent DVT can lead to re-hospitalisation, a recurrent PE may also lead to patient mortality. After a VTE, a patient is at increased risk of post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). These are all clearly negative health outcomes for patients and can place considerable burden on healthcare systems.

In line with the aim of therapy, the primary and secondary efficacy outcomes in the EINSTEIN study programme therefore included a wide range of outcomes based on the incidence 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 routinely adjudicated by a blinded clinical events committee[4;48]. 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.

The outcomes used in EINSTEIN-DVT and EINSTEIN-Ext have been 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). Vascular events were monitored because of a suspected increase in cardiovascular events seen with other novel anticoagulants, including ximelagatran[49], 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.

5.10.4 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 the EINSTEIN-DVT and EINSTEIN-Ext to be applicable to patients routinely treated in England and Wales, according to the rivaroxaban product licence. We discuss here the 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.

Demographics of trial population

We have described previously the baseline characteristics of EINSTEIN-DVT and EINSTEIN-Ext and other outcomes from EINSTEIN-DVT relevant to considerations of generalisability of the study to real-life outcomes. A substantial proportion of the EINSTEIN-DVT trial population (43%, 1498/3449) were from Western Europe although few were from UK centres. 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-DVT was 56.1 years and not out of line with clinical expectations. The interquartile range of ages at baseline was 44 to 69 years with a full range of 18 to 97 years, supporting broad generalisability.

The proportion of patients in EINSTEIN-DVT describing themselves as white (77%) may be compared with results from data from the 2001 Census, in which 91.31% of people in England and Wales described their ethnic group as white.[78]

The intended duration of treatment selected before randomisation was 3 months in 13% of patients (411/3159), 6 months in 59% of patients (1876/3159) and 12 months in 28% of patients (872/3159) across both arms. This is not inconsistent with international guidelines for the relevant population (see section 2.3).

The gender split of EINSTEIN-DVT (57% male / 43% female) compares favourably with the Martinez et al database linkage study discussed in chapter 7 in which the gender split was 44% male / 56% female[22].

Time to achieve therapeutic INR

Time to therapeutic INR in EINSTEIN-DVT was [redacted] – SIGN guidelines report 6 to 10 days usually being required.[11]

Time in INR range

The proportion of time that subjects' INR was in the target range (TTR, ie an INR of 2-3) was lower, at 57.7% across all centres and 59.7% in Western European centres, as noted previously in section 5.10.2.

These trial results can be compared with various external observations:

- In a review for the ACCP guidelines, the mean TTR in RCTs ranged between 42% and 83%, mostly around 60%[74].
- A recent observational study in UK secondary care anticoagulation services observed TTR of 53% during the first 12 weeks of treatment and 59% thereafter[75].
- Guideline recommendations from the National Patient Safety Agency and the Scottish Executive Health Department are for TTR of at least 60%[76;77].
- It is important to highlight an observation made in the SmPC that, after extensive analysis involving ranking centres by TTRs achieved, there was no interaction observed in EINSTEIN-DVT between TTR and treatment effect[1].

Trial design

The EINSTEIN-DVT trial was a randomised controlled trial with an active comparator regimen (LMWH/VKA) of wide international acceptance and use. One aspect of the design of EINSTEIN-DVT and EINSTEIN-Ext 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.

Enoxaparin regime

EINSTEIN-DVT was designed to require, after entry to the comparator arm of the trials, treatment with enoxaparin at 1.0 mg / kg twice daily 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, EINSTEIN-DVT enabled patients in the comparator arm to be treated according to US Prescribing Information for enoxaparin, which requires enoxaparin to be administered at 1.5 mg / kg once daily (at the same time each day), the EINSTEIN-DVT regime, or 1.0 mg / kg twice daily (without recommendation on timing). 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)[79]. The UK licence for enoxaparin differs in that 1.5 mg / kg once daily is required for at least 5 days and `until adequate oral anticoagulation is established'[37], which can take 6-10 days[11].

It has been suggested that this slight and temporary difference in indications may potentially limit the generalisability of the EINSTEIN programme of studies to practice in England and Wales in the treatment of DVT. We consider this implausible, for various reasons.

1. The two indications 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-DVT 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.[80]
- 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.[81]

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 pre-randomisation medication of any type (Figure 8).

5. The period in which enoxaparin was delivered in EINSTEIN-DVT was very short in comparison to the length of the trial as a whole, over which outcomes are measured and compared between arms. Including pre-randomisation treatment, patients in the LMWH/VKA arm of EINSTEIN-DVT received [redacted] treatment with LMWH[65] (Figure 17). This level of pre-treatment is not inconsistent with recommendations from the British Committee for Standards in Haematology (BCSH)[9] or SIGN guidelines[11].

Compliance

The studies also demonstrated high levels of compliance for rivaroxaban, confirming its simplicity and convenience for patients, another important factor in routine clinical practice. A compliance outcome was calculated as the number of tablets taken divided by the duration of observation from first dispense of study medication up to the last intake of study drug (including those discontinued prematurely). In the ITT population, [redacted]

What proportion of the evidence base is for the dose(s) given in the SPC?

All of the evidence base relates to the standard dose of rivaroxaban (20 mg od for 21 days followed by 15 mg od), as this was the dose of rivaroxaban delivered in EINSTEIN-DVT and EINSTEIN-Ext. EINSTEIN-DVT excluded patients with creatinine clearance less than 30 mL/min.[16] The SmPC recommends a reduced initial dose of rivaroxaban (15 mg bid for 21 days followed by 15 mg od) for patients with creatinine clearance of 30-49 mL/min. Rivaroxaban is contraindicated in patients with creatinine clearance less than 30 mL/min.[2;3]

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 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 9.10, appendix 10.

A literature search was conducted to identify cost-effectiveness studies relevant to this appraisal. The MEDLINE, EMBASE, EconLit and NHS EED databases were used and search strategies are reported in appendix 10, as required, which is section 9.11.

The databases cover a range of relevant medical and economic literature so that all applicable studies are likely be captured in the searches. The search terms were constructed to cover important terms for DVT, treatments and cost-effectiveness analyses. In addition a set of inclusion and exclusion criteria were developed and applied to the search results, after duplicates were removed, shown in Table 32. Abstracts from conference proceedings were not searched and only English language studies were included. The final included studies were extracted and evaluated.

The database searches identified 1479 publications, including 312 duplicates. From these, 1152 publications were excluded after abstract review, leaving 15 publications whose full-text was reviewed. Of these 11 were excluded (due to trial period being less than 3 months or no incremental analysis presented) and 4 were included and fully data extracted. A PRISMA diagram is shown in Figure 14.

Figure 14: PRISMA diagram for the systematic review of cost-effectiveness evaluations

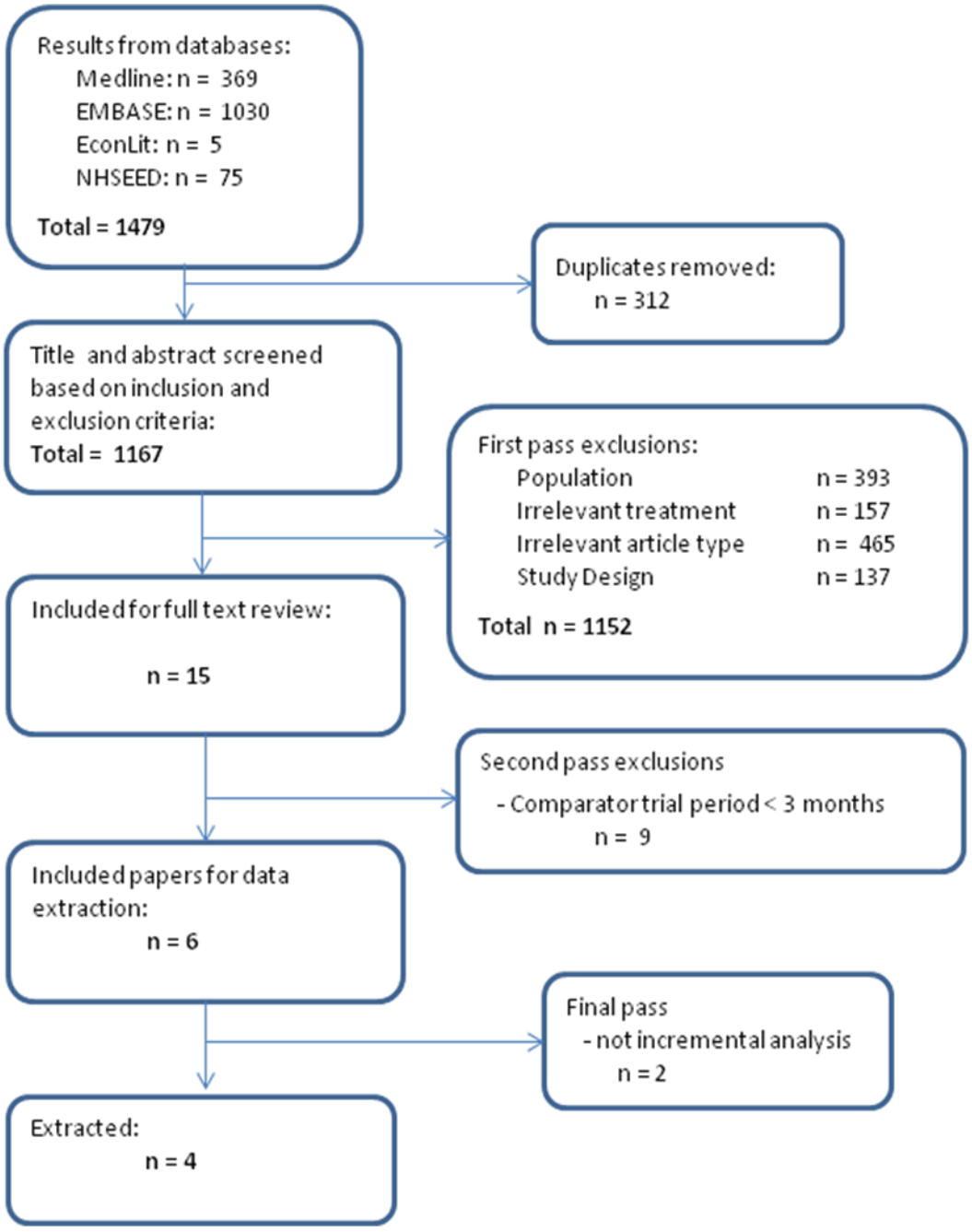


Table 32: Inclusion/exclusion criteria for the systematic review of cost-effectiveness evaluations

Inclusion criteria	Exclusion criteria
▪ Adults ▪ DVT or mix DVT/PE AND treatment (i.e. symptomatic DVT patients presenting for treatment) ▪ Treatment of 3 months or more ▪ Treatment with Warfarin OR other VKA, eg phenprocoumon or acenocoumarol OR	▪ Children OR ▪ Screening OR diagnosis ▪ Prophylaxis OR Prevention (primary & extended)] ▪ PE index event only ▪ Studies evaluating treatments delivered for <3

Inclusion criteria	Exclusion criteria
Rivaroxaban OR LMWH, eg enoxaparin or dalteparin ▪ Published article ▪ Cost-utility OR cost-effectiveness modelling studies OR piggy-back trial evaluations ▪ English language ▪ Human subjects	months ▪ Irrelevant treatments (non-VKA or initial LMWH only), ▪ Dabigatran OR apixaban (not licensed for DVT) ▪ Editorials OR comments OR letters OR general reviews ▪ Articles without cost effectiveness or cost utility ▪ Clinical guidelines OR management OR protocol OR clinical pathway ▪ Articles describing studies reported elsewhere (reviews) ▪ Burden of illness, cost of illness, budget impact, database studies, claims analyses, cost minimisation

Description of identified studies

6.1.2 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.

After full text review a total of four articles were included and extracted into Table 33.[82-85]

One article describes a Markov model and three articles report results of a Decision Tree analysis. Two studies were based in North America, one in Spain and another set in Italy but reporting US costs. One study compares 6 months treatment with warfarin against a single LMWH (dalteparin). Another compares treatment with warfarin against several LMWHs over 3 months. A third study compares the LMWH – bemiparin against UH and/or warfarin over 90 days. The patient populations in these models were over 60 years of age and had suffered with DVT. The final included study compares different durations and intensities of warfarin therapy, reporting modelled results for 3, 6, 12 & 24 months of treatment in addition to an unlimited duration. This study used hypothetical cohorts aged 40, 60 and 80 years of age.

None of the studies identified were directly relevant to the decision problem.

Table 33: Summary of cost-effectiveness evaluations included in the systematic review

Study and year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Aujesky et al, 2005[83]	U.S.	Markov model of 6 treatment strategies to determine the optimal duration and intensity of warfarin therapy after a 1st idiopathic venous thromboembolic event: 1. 3-month conventional intensity 2. 6-month conventional intensity 3. 12-month conventional intensity 4. 24-month conventional intensity 5. Unlimited duration conventional-intensity 6. Unlimited low-intensity	Hypothetical cohorts of 40, 60 and 80 years old Male - 40 Years 1. 3 months 2. 6 months 3. 12 months 4. 24 month 5. Unlimited conventional 6. Unlimited low intensity Male - 60 Years 1. 3 months 2. 6 months 3. 12 months 4. 24 month 5. Unlimited conventional 6. Unlimited low intensity 80 years 1. 3 months 2. 6 months 3. 12 months	Discounted at 3% p.a. 16.566 16.572 16.577 16.587 16.648 16.527 10.088 10.092 10.093 10.089 10.04 9.989 4.487 4.486 4.482	2002 USD ($) discounted at 3% p.a. 23740 23816 24053 24514 32615 33020 17 172 17 284 17 567 18 123 24 314 24 640 10 579 10 764 11 132	 Lowest cost reference $11,618 $48,534 $48,805 $132,396 Dominated by 5 Lowest cost reference $29,878 $225,654 Dominated by 3 Dominated by 3 Dominated by 3 Lowest cost reference Dominated by 1 Dominated by 1

Study and year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			4. 24 month	4.471	11 844	Dominated by 1
			5. Unlimited conventional	4.432	15 094	Dominated by 1
			6. Unlimited low intensity	4.419	15 286	Dominated by 1
			Women			
			40 years			
			1. 3 months	17.546	22 589	Lowest cost reference
			2. 6 months	17.549	22 711	$35,977
			3. 12 months	17.55	23 008	Higher inc'l cost than 4
			4. 24 month	17.551	23 582	$512,337
			5. Unlimited conventional	17.489	33 846	Dominated by 4
			6. Unlimited low intensity	17.356	34 252	Dominated by 4
			60 years			
			1. 3 months	11.335	16 903	Lowest cost reference
			2. 6 months	11.338	17 060	$155,033
			3. 12 months	11.335	17 394	Dominated by 2
			4. 24 month	11.324	18 065	Dominated by 2
			5. Unlimited conventional	11.194	25 932	Dominated by 2
			6. Unlimited low intensity	11.134	26 272	Dominated by 2
			80 years			
			1. 3 months	5.182	10 602	Lowest cost reference
			2. 6 months	5.179	10 828	Dominated by 1
			3. 12 months	5.173	11 250	Dominated by 1
			4. 24 month	5.155	12 071	Dominated by 1
			5. Unlimited conventional	5.087	16 251	Dominated by 1
			6. Unlimited low intensity	5.071	16 461	Dominated by 1

Study and year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Aujesky et al, 2005[82]	U.S.	Decision Analytic model. Decision tree to compare a 6 month course of LMWH with a 6 month course of warfarin in patients with cancer related VTE	65 years. Based on mean age of patients with cancer of between 62 and 66 years as reported in 4 studies	Discounted at 3% p.a. QALYS LMWH - 1.097 Warfarin - 1.046	2002 USD discounted at 3% p.a. LMWH - 15329 Warfarin - 7720	$149,865
Gomez-Outes A et al, 2006[84]	Spain	Decision tree model comparing Bemiparin (LMWH) with UFH in the treatment of DVT in the groups: A. IV infusion of UFH for 7 days, vitamin K antagonist from day 3 to day 90. B. Once daily dose of UFH for 5 to 9 days plus vitamin K antagonist from day 3 to day 90. C. Bemiparin for 90 days	62 years Group A Group B Group C	Undiscounted QALYS: 16.87 18.59 17.61	2002 Euros Undiscounted 4128 3359 3220	 B vs A: Bemiparin dominant C vs A: Bemiparin dominant C vs B: Bemiparin dominant
Marchetti M. et al, 2001[85]	Italy and U,S,	Decision tree model to compare LMWH with warfarin treatment over 3 months for the prevention of DVT recurrence.	Mean 60 (range 56 to 81)	QALYs LMWH = 12.991 Warfarin = 12.985	USD (year not reported) Italian perspective LMWH = 1047 Warfarin = 728 U.S. Perspective	Italian Perspective $53,166 U.S. Perspective

Study and year	Country	Summary of model	Patient population (average age in years)	QALYs/LYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
					LMWH = 1809 Warfarin = 746	$177,166

6.1.3 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 9.11, appendix 11.

The quality assessment table suggested is completed in respect of the four included studies in appendix 11, which is in section 9.12.

Our observations from publications in this area (studies identified in the systematic review and others) were as follows:

- Decision analytic modelling was common, either through markov approaches or others where economic data collection was made alongside clinical trials.
- Outcome measures reported included DVT, PE, VTE, major/minor bleeding. Acute haemorrhagic stroke was reported in one study. Efficacy data were mostly taken from clinical trials or meta-analyses.
- Costs of drugs, blood tests and clinical appointments were included with prices from literature and country-specific standard sources such as the BNF in the UK.
- Warfarin consumption followed country specific licenses. Anticoagulation monitoring included items such as INR tests.
- The time horizons used varied between 3 months and 8 years after the index event.

6.2 De novo analysis

Patients

6.2.1 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 1.4 and 5.3.3, 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 DVT, to match the licensed indication[2;3], EINSTEIN-DVT trial population[16] and stated Decision Problem (chapter 4). Results are presented according to the duration of anticoagulation therapy appropriate to them. The duration of therapy was selected by clinicians to reflect the underlying risks arising from the nature of the index DVT, characteristics of the patient and ongoing risk of recurrent VTE or bleeding[9;11;12]. The characteristics of patients in EINSTEIN-DVT and their index events were summarised in Table 11 and Table 12, in section 5.3.4.

In addition, patients with cancer (a provocation for DVT) are considered in an indirect and mixed treatment comparison analysis in section 5.7, and in a cost minimisation analysis presented in section 6.9.

Model structure

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

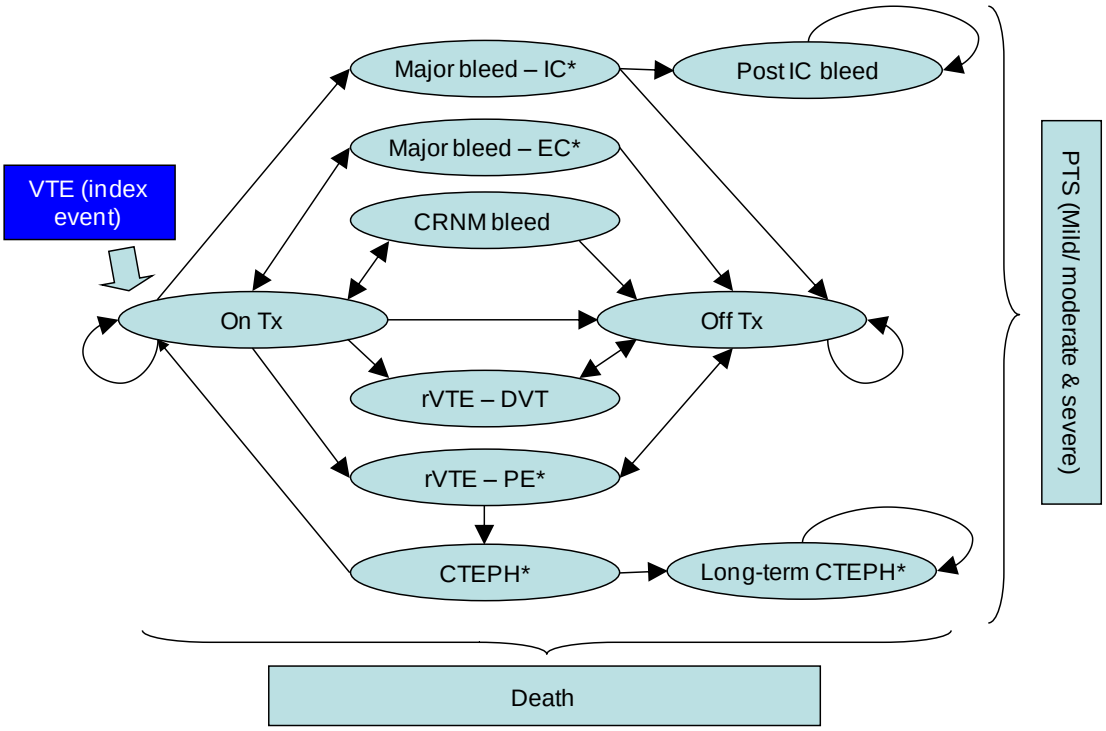
The model was a Markov design comprising ten health and treatment states describing the management and complications of VTE, including:

- On treatment for index event
- Off treatment
- Recurrent event: DVT, PE
- Bleeding event: clinically relevant non-major (CRNM) bleed, intracranial (IC) bleed (all patients discontinue treatment), major extracranial (EC) bleed
- Long-term complications: chronic thromboembolic pulmonary hypertension (CTEPH) (operable and inoperable)
- Post-stroke (an absorbing state for all pts who experience an IC bleed)
- Death

Additionally, all patients 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 the whole surviving cohort.

The detailed model structure is shown in Figure 15.

Figure 15: Structure of the economic model



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

*Additional mortality

Patients enter the model following diagnosis of a DVT 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.

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

Based on the review above 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 trial period, since these were the expected drivers of results. 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 involves initial anticoagulation treatment of the DVT 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 throughout.

This approach therefore captures clinically important stages of a patient's experience of DVT in distinct states. With the assignment of costs and HRQoL to these states, the structure ensures that financially and humanistically important consequences of DVT are captured.

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

The model states referred to in Figure 15 are described in Table 34.

Table 34: Descriptions of modelled health states

Number	State name	Description
1	On tx	Patients who have just experienced an acute DVT, and are receiving one of the acute treatments being evaluated (either 3, 6 or 12 months of 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 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	Patients who have just experienced a recurrent PE. 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 were experiencing an intracranial bleeding event. Therapy was temporarily 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 were experiencing a major bleeding event (e.g. gastrointestinal bleeds). Therapy was temporarily withheld for 1 month 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 were experiencing a CRNM bleeding event. 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. Any assigned therapy still being delivered 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	PTS	Patients incident with CTEPH and who may receive pulmonary endarterectomy (PEA) and incur additional costs.
9	CTEPH	Patients with CTEPH who are exposed to long term management costs
10	Long-term CTEPH	State to which patients with CTEPH transition.
11	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.

6.2.5 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 DVT is associated with both a reduction in recurrent VTEs alongside for the potential for increased risk of bleeding. 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.

6.2.6 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 35.

Table 35: Key features of economic analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (assumed to be 40 years)	NICE Reference Case	NICE Methods Guide[86]
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[86]
Discount of 3.5% for utilities and costs	Yes, 3.5% pa discounting	NICE Reference Case	NICE Methods Guide[86]
Perspective (NHS/PSS)	Yes, NHS/PSS	NICE Reference Case	NICE Methods Guide[86]

Abbreviations: NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years

Technology

6.2.7 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:

- Rivaroxaban (Xarelto®) according to its licence for DVT treatment: 15 mg bid for 21 days followed by 20 mg od for the remaining duration of anticoagulation treatment[2;3]

- 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.[37] VKA overlaps with LMWH and is continued for the full duration of anticoagulation treatment.[87]
- For cancer patients, LMWH therapy at the UK licensed dose for the full duration of anticoagulation treatment.[40]

There are four LMWH treatments licensed for treatment of DVT or PE: Zibor® (bemiparin sodium), Fragmin® (dalteparin sodium), Clexane® (enoxaparin sodium), and Innohep® (tinzaparin sodium). The Patient Information Leaflets for dalteparin, enoxaparin and tinzaparin but not bemiparin refer to the possibility of patient self-administration.[88-91] [redacted] 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,[37] eg 120 mg for an individual of 80 kg.

For the active cancer subgroup analysis, we use the daily cost of Fragmin® (dalteparin) in the cost-minimisation analysis presented in section 6.9. The licensed dose in the extended oncology indication is 15,000 IU per day in month 1 followed by 12,500 IU per day in months 2-6 for an individual of 69-82 kg.[40]

6.2.8 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.

No clinical continuation rule is assumed. The period of anticoagulation is the intended treatment duration from EINSTEIN-DVT.

6.3 Clinical parameters and variables

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

We consider here model inputs relating to:

- Probabilities of bleeding and recurrent VTE 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 associated with particular model events

Probabilities of bleeding and recurrent VTE whilst on treatment

The assumed probabilities of recurrent VTEs, CRNM bleeding and major bleeding occurring in the LMWH/VKA arm are given in Table 36, taken directly from EINSTEIN-DVT trial data. This table also includes the range assumed for these variables for the USA and parameter values for the PSA, assuming a Beta distribution.

Table 36: Incidence of clinical events, range for USA and distributional parameters for PSA

Outcome	Time period (months)	Point estimate (%)	Sensitivity analysis			
			Lower (%)	Upper (%)	Alpha	Beta
Recurrence of VTE						
	0-3 3-6 6-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding						
	0-3 3-6 6-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleeding						
	0-3 3-6 6-12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

The probability of a recurrent VTE in the rivaroxaban arm is calculated by applying the appropriate hazard ratio (the measure of treatment effect pre-specified and then derived from EINSTEIN-DVT) to the probability of recurrent VTE in the LMWH/VKA arm. Equation 1 below was used, to account for the fact that the model inputs required are probabilities rather than rates of VTE occurrence:

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

where:

- $Risk_{LMWH/VKA}$ is the risk (of recurrent VTE in this case) in the LMWH/VKA arm for a particular time period;
- HR is the hazard ratio, specifically 0.68 (95% CI 0.44 to 1.04) for recurrent VTE; and
- $Risk_{RIV}$ is the risk of recurrent VTE in the rivaroxaban arm for that patient group and time period.

The probability that a recurrent VTE is a DVT (conditional on one occurring) was assumed to be [redacted]
Oher VTEs are PEs.

In an analogous fashion, the probability of a major bleed in the rivaroxaban arm was calculated by applying the appropriate hazard ratio to the probability of a major bleed in the LMWH/VKA arm. Equation 1 above was used again, but with major bleed as the outcome and a treatment effect of a HR of 0.65 (95% CI 0.33 to 1.28).

The probability that a major bleeding event was an intracranial (IC) bleed (conditional on occurring) was 12.5%, on the basis of 4 of the 28 major bleeding events which occurred during EINSTEIN-DVT being IC bleeding events.

The probability of a CRNM bleed in the rivaroxaban arm was calculated by applying the appropriate risk ratio to the probability of a major bleed in the LMWH/VKA arm. Risk ratios were used rather than hazard ratios in this case, as hazard ratios were not available or specified in the trial SAP. Equation 2 below was used.

Equation 2: $Risk_{RIV} = RR \times Risk_{LMWH/VKA}$

where:

- $Risk_{LMWH/VKA}$ is the risk of CRNM bleed in the LMWH/VKA arm for a particular time period;
- RR is the risk ratio, specifically 1.05 (95% CI 0.83 to 1.34) for CRNM bleeding; and
- $Risk_{RIV}$ is the risk of recurrent VTE in the rivaroxaban arm for that time period.

Discontinuation

Discontinuation in EINSTEIN-DVT is described in Table 37 and was similar between treatment arms. Consequently, we assume no difference in risk of discontinuation between rivaroxaban and LMWH/VKA.

Table 37: Reasons for discontinuation in EINSTEIN-DVT

[redacted]

This is a conservative assumption because there are significant challenges with use of LMWH and warfarin and substantial potential advantage with rivaroxaban, which mean that real-life 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 with rivaroxaban has been shown to be higher than with LMWH/VKA.[18]

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 bleeding adverse events. The total discontinuation for those reasons was [redacted], which was assumed to be the 6 month probability of discontinuation in the pharmacoeconomic evaluation. This compares

with a trial by Monkman et al which found that voluntary discontinuation occurred in 0.9% of VTE patients in the first three months of VKA treatment.[93]

This 6 month probability from was converted to a 3 month probability of 1.90%, 95% CI of 1.58% to 2.23%. The model additionally assumes that all patients with IC bleeds, 50% of patients with major EC bleeds and 11% of patients with CRNM bleeds discontinue treatment, based on [redacted][65]. These assumptions are included in the summary given in Table 43.

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.[17] Literature searches were first conducted in March 2010 on the MEDLINE, EMBASE and Cochrane Library literature databases (original review) and then updated in July 2011 (update review). In total, before deduplication, 16 795 potentially relevant studies were identified. Following title, abstract and full-text review in comparison with pre-defined but fairly permissive inclusion/exclusion criteria, 129 studies were included. See Table 38.

Table 38: PRISMA-type study flow for systematic review of VTE recurrence

	Original	Update
Database search hits Less: duplicates	15,318 5,145	1,477 370
Available for title/abstract review Less: excluded	10,173 9,962	1,107 1,049
Available for full-text review Less: excluded Plus: articles identified from reference lists	211 114 10	58 45 9
Final included studies	107	22
Combined included studies	129	

Source: Table 8 from systematic review report[17]

Of the 129 included publications, 82 publications considered follow-up of one year or less and a further 31 considered follow-up of no more than five years. This left 16 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.[28]
- 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.[29]

- Two studies which did not report outcomes in the format required.[94;95]
- One study of PE patients only, rather than DVT patients or a mix of VTE types.[96]

The Prandoni and Vienna cohorts produced similar long-term rates of recurrent VTE, shown in Table 39. 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

$$r = 1 - (1 - p_{10}) \text{ ^ } [3/(10x12)]$$

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

Table 39: Risk of recurrent VTE (%, 95% CI) from two long-term cohort studies

Cohort	No. of patients	1 year risk		2 year risk		10 year risk	
		Point estimate	95% CI	Point estimate	95% CI	Point estimate	95% CI
Prandoni[28]	1626	11.0	(9.5, 12.5)	NR	NR	39.9	(35.4, 44.4)
Vienna[29]	929	NR	NR	24.6	(21.6, 28.9)	31.8	(27.6, 37.4)

NR: Not reported

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 Chronic Thromboembolic Pulmonary Hypertension (CTEPH) and Post Thrombotic Syndrome (PTS), in patient populations with index DVTs, PEs or VTEs generally.[17] Literature searches were first conducted in March 2010 on the MEDLINE, EMBASE and Cochrane Library literature databases (original) and then updated in July 2011 (update). In total, before deduplication, 3853 potentially relevant studies were identified. Following title, abstract and full-text review in comparison with pre-defined inclusion/exclusion criteria, 42 studies were included. Among the included studies, three considered incidence of CTEPH.[97-99] See Table 40.

Table 40: PRISMA-type study flow for systematic review of complications of VTEs

	Original	Update
Database search hits Less: duplicates	3429 3288	424 97
Available for title/abstract review Less: excluded	141 25	327 319
Available for full-text review Less: excluded Plus: articles identified from reference lists	116 93 12	8 7 6
Final included studies	35	7
Combined included studies	42	

Source: Table 34 from systematic review report[17]

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. The recent NICE VTE prophylaxis guideline development[27;100] cited the study by Miniati et al[97], which appeared to present rates in line with the other two sources, so this was the source chosen for use in the model. Among 320 patients with confirmed PE, four subsequently developed CTEPH. It was therefore assumed that 1.25% (95% CI 0.03% to 2.46%) of incident 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 of incidence of PTS.[17] Of the 42 studies included in that review, 39 provided data on incidence of PTS. Among these studies, the longest and most robust prospective cohort studies were in two papers authored by Prandoni et al.[26;101]

Our literature review of utility studies found evidence to suggest that mild PTS was of little detrimental effect on quality of life,[102] so the pharmacoeconomic evaluation is focussed on incidence of severe PTS.

Prandoni et al followed-up consecutive patients with diagnosed, symptomatic DVT and recorded incidence of PTS by severity. In 1996, it was reported that the cumulative incidence of severe PTS was 2.6% after one year and 9.3% after 5 years among 355 patients.[26] In 1997, it was reported that the cumulative incidence was 2.7% after one year and 8.1% after five years in 528 patients.[101]

The three month probability of severe PTS in the first (r1) and subsequent (r2) years were calculated from the one and five year risks above from the 1997 paper, as follows:

$$r_1 = 1 - (1 - p_1) \text{ ^ } (3/12)$$

$$r_2 = 1 - [(1 - p_5)/ (1 - p_1)] \text{ ^ } [3/(4x12)]$$

where p_1 and p_5 were the one and five year risks respectively which were reported in Prandoni et al.[101]

Risk of mortality for the patient population, associated with age

General all-cause mortality was based on UK life tables.[103]

Risk of mortality associated with particular model events

In addition to the general risk of mortality associated with age, the pharmacoeconomic model accounts for additional risks of mortality in respect of the specific events, namely

- PE, during acute treatment phase
- PE, after acute treatment phase
- Major IC bleed
- Major EC bleed
- CTEPH

The inputs and their rationale are discussed below. Other than the risk for CTEPH mortality, which is presented as an ongoing risk per 3 month period (to fit the model cycle lengths), each mortality risk is applied once in the model, at the time of the event.

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.[17] Literature searches were first conducted in April 2010 on the MEDLINE, EMBASE, Econ Lit and Cochrane Library literature databases (original review) and then updated in July 2011 (update review). In total, before deduplication, 2755 potentially relevant studies were identified. Following title, abstract and full-text review in comparison with pre-defined inclusion/exclusion criteria, 17 studies were included. See Table 41.

Table 41: PRISMA-type study flow for systematic review of case fatality

	Original	Update
Database search hits Less: duplicates	2436 1081	319 123
Available for title/abstract review Less: excluded	1355 1286	196 181
Available for full-text review Less: excluded Plus: articles identified from reference lists	69 64 4	15 9 2
Final included studies	9	8
Combined included studies	17	

Source: Table 27 from systematic review report[17]

Within the included studies was a 2010 systematic review of mortality from VTE trials by Carrier et al[104], several individual VTE trials reporting mortality associated with bleeding and recurrent VTEs, a study of survival with CTEPH[105], and two relevant analyses of the RIETE database[106;107]. Outwith the included studies (due to indexing issues) was a more recent systematic review by Linkins et al[108] which provided evidence on mortality associated with bleeding. Due to the availability of published reviews and meta-analyses, notably Linkins et al[108], the individual trials identified were not considered further.

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-DVT 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,[106;107] and through this, the potential for missing sudden, relevant deaths.

There were few PEs in either EINSTEIN-DVT or EINSTEIN-Ext and even fewer deaths potentially attributable to PE. The base case assumption was that 20.4% of PEs occurring in the acute phase would lead to death, based on 10 deaths occurring across both treatment arms in EINSTEIN-DVT either attributed to PE or for which PE could not be ruled-out as an underlying cause, in comparison with 49 PEs.

The study used to provide the model inputs in relation to VTE recurrence also presented information on the incidence of mortality among patients with recurrent PEs.[28] 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%).

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.[108] 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.[109] 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.

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.[105] 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 centers, but there are significant improvements in pulmonary hemodynamics and self-reported functional class. 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 (ie 26% mortality). The 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.

6.3.2 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 6.3.1 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 42. Each transition matrix used is visible within the economic model.

- 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.

Table 42: 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

6.3.3 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 6.3.2. 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 either duration.[85]

6.3.4 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.

6.3.5 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
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality 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 from the trial or a systematic literature review and therefore expert opinion was not sought for these values.

Summary of selected values

6.3.6 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 36 in section 6.3.1, so are not repeated here.

All other clinical parameters are listed in Table 43. 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 43, 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 43: Overview of assumed clinical parameters

Event / outcome	Point estimate	Sensitivity range		Source
		Lower	Upper	
Treatment effect for rivaroxaban vs dual LMWH/VKA therapy				
Incidence of recurrent VTE (hazard ratio)	0.68	0.44	1.04	EINSTEIN-DVT[16]
Incidence of major bleed (hazard ratio)	0.65	0.33	1.28	
Incidence of CRNM bleed (risk ratio)	1.05	0.83	1.34	
Disambiguation of composite endpoints				
Probability that a recurrent VTE is a DVT	[redacted]	[redacted]	[redacted]	EINSTEIN-DVT[16]
Probability that a major bleed is a (major) IC bleed				
Discontinuation from treatment (per 3 month timestep)				
Patients with IC bleeds	[redacted]	[redacted]	[redacted]	EINSTEIN-DVT[16]
Patients with major EC bleeds				
Patients with IC bleeds				
For any other reason (additional)				
Risks of subsequent morbidities				
Recurrent VTE, per 3 month timestep	1.26%	1.09%	1.46%	Prandoni 2007[28]
Progression to CTEPH after a PE	1.25%	0.03%	2.46%	Miniati 2006[97]
Cumulative incidence of severe PTS – to 1 year	2.7%	1.3%	4.1%	Prandoni 1997[101]
Cumulative incidence of severe PTS – to 5 years	8.1%	5.8%	10.4%	
Mortality associated with another model event				
PE, during acute treatment phase	[redacted]	[redacted]	[redacted]	EINSTEIN-DVT[16]
PE, after acute treatment phase	33.1%	25.0%	41.2%	Prandoni 1997[101]
Major IC bleed	43.6%	36.5%	50.7%	Linkins 2010[108]
Major EC bleed	3.9%	2.5%	5.4%	Linkins 2010[108]
CTEPH (per three month cycle)	2.48%	2.05%	2.93%	Condliffe 2008[105]

6.3.7 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-DVT was one year and data on VTE recurrence is available to ten years.[28] In contrast, the time horizon for the economic model is a patient's lifetime, as per the Decision Problem, so extrapolation has been necessary.

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 6.3.1, and the values used in the model were included in Table 43.

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-DVT trial data (and previously described in section 6.3.1) rather than epidemiological literature identified in systematic reviews.

6.3.8 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 (eg Table 34, Table 36, Table 43, Table 47).

1. Characterisation of DVT 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 DVT. 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-DVT 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-DVT 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).

4. Representativeness of EINSTEIN-DVT to UK practice and patients. The features of EINSTEIN-DVT have been discussed previously (including in section 5.10).

5. Cessation of treatment effect on cessation of acute treatment. DVT 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. No difference in standard disease monitoring and follow-up associated with rivaroxaban. This simplifying modelling assumption is a particularly conservative assumption 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 to make them more efficient, bringing additional treatment satisfaction

- A significant reduction in hospital length of stay observed in rivaroxaban patients vs dual LMWH/VKA patients in EINSTEIN-DVT. [redacted]

6.4 Measurement and valuation of health effects

Patient experience

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

A DVT is an unpleasant experience in itself, its current treatment detracts from QoL, patients live with the risk and fear of a recurrent VTE, and the risk and fear of complications of these and the original DVT.

The impact of the DVT itself

In a long-term outcomes study of DVT, it was shown that symptoms in the leg, such as pain, swelling, ulceration and discoloration, affected patients' perception of health-related Quality of life (HRQL) as measured by the Short Form Health Survey (SF-36).[110;111] Exploratory factor analysis as part of a quality of life validation study in patients with DVT yielded six distinct factors denoting emotional distress: symptoms; limitation in physical activity; hassle with coagulation monitoring; sleep disturbance; and dietary problems.[112]

Patients have reported significantly decreased HRQoL compared to the general population as measured by the SF-36, regardless of gender and age. This was in agreement with findings from a previous study where patients reported poorer perception of health, lower levels of physical functioning and more severe role limitations due to DVT.[110]

The impact of current therapy for DVT

As well as the impact of the disease per se, the mode of therapy can also have negative effects on patients' perceptions of their HRQoL.[110;112;113] There are a number of characteristics of current oral anticoagulation therapies that can potentially induce dissatisfaction and reduce HRQoL. 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.[112]

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 DVT. 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 DVT, difficulties with current treatment modalities, and the underlying fear of a recurrent VTE.[114-117]

The detrimental HRQoL measured in patients with DVT may be attributable in part to the risk and fear of recurrent VTE.[110-112]

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 DVT and PE, but the development of PTS and CTEPH.[97;101]

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.[101]

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 pulmonary embolism.[97] 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.[105]

6.4.2 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.[97;101]

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

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (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-DVT or 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-DVT as described previously. These demonstrated greater satisfaction with rivaroxaban than with dual LMWH/VKA therapy.[18]

Mapping

6.4.4 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

6.4.5 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 9.12, appendix 12.

A systematic literature review was conducted for relevant HRQoL data.[17] The systematic review conducted for this purpose had the broad objective of finding evidence on utility associated with VTEs, including events such as DVT, PE, bleeding, CTEPH and PTS, in patient populations with index DVTs, PEs 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 appendix 12, as required (which is in section 9.13), 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 in July 2011 (update review). In total, before deduplication, 2811 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.[85;102;118-121] See Table 41.

Table 44: PRISMA-type study flow for systematic review of HRQoL studies

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

Source: Table 44 from systematic review report[17]

6.4.6 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 yielded six studies.[85;102;118-121] Additionally section 6.4.7 will describe how two further studies were used for the population baseline[122] and for the post IC bleed state[123]. One of these eight studies (Goodacre et al, 2006[118]) 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 6.5. Seven studies were left to be extracted into Table 45.[85;102;119-123]

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Table 45: Extraction 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[122]	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 HRQoL assessment
Lenert 1997[102]	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 death.	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
Locadia 2004[119]	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[121]	General medicine patients	Random selection of 36 patients	20 patients had experience of DVT, 16 did	Pre-defined states: good health, mild postphlebitic	Bleeding was a state	Standard gamble.	Mean (95% CI) values were: 1	Not appropriate	Not appropriate

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
		attending general medicine appointments	not. No further information.	syndrome, severe postphlebitic syndrome, central nervous system bleeding, and death.	considered.		(NA), 0.995 (0.990-1), 0.982 (0.962-1), 0.290 (0.127-0.453) and 0 (NA) respectively.		
Marchetti 2001[85]	Patients attending a local anticoagulation clinic	NA	Sample of 48	QoL related to taking warfarin, or taking LMWH according to description of hypothetical patients taking either	NA	Time trade off.	Mean (SD) reported. Warfarin = 0.988 (0.016). LMWH = 0.992 (0.024).	Appropriate. These results were used in a cost-effectiveness analysis.	Appropriate – for treatment related disutility.
Meads 2008[120]	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[123]	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								

6.4.7 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-DVT.

Adverse events

6.4.8 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 34.[102;119;120;122;123]

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

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. 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[122], 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, but is highlighted in Table 45 as the only study considered that was appropriate for baseline HRQoL assessment.

The most appropriate evidence on the disutility relative to this anchor point for DVT, PE, major EC bleed (assumed to match the disutility reported for GI bleed), major IC bleed (assumed to match the disutility report for haemorrhagic stroke) was an evaluation of patient preferences in VTE by Locadia et al.[119] Although there were limitations in this study due, for example, to its elicitation of preferences from patients rather than the general public, this study provided time trade-off utilities for various states considered in the economic model.

The HRQoL relating to PTS was measured in at least three studies[102;119;121] but severe PTS specifically, the state in the economic model to be valued, was measured in only one, a study of the general public and physicians by Lenert et al[102]. 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. 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).[120] 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. No other studies provided EQ-5D utility specific to CTEPH.

The systematic review described here did not yield a source for utility following an IC bleed, but a large and relevant health preference study was identified in work connected with a separate indication.[123] 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. Since functional outcomes after stroke have been found to be not significantly different to outcomes after IC bleed,[109] this value was used as the valuation of the post IC bleed state.

Only one study shown in Table 45 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 0.989 (SD=0.016) for warfarin and 0.993 (SD=0.024) for LMWH.[85] Whilst it may be reasonable to assumed that LMWH/VKA treatment may be associated with a disutility, no such assumption was made in the base case. All utility assumptions were made independent of treatment arm.

The values adopted for the cost-effectiveness analysis are summarised in Table 46.

Table 46: Utility values assumed in the cost-effectiveness evaluation

Model state	Point estimate	Sensitivity analyses Lower	Upper	Notes	Source
Population norm	0.825	0.819	0.831		Kind 1998[122]
Post IC bleed	0.71	0.70	0.72		Rivero-Arias 2010[123]
CTEPH	0.56	0.53	0.59		Meads 2008[120]
Adjustments to utility norm due to modelled events					
DVT	0.84	0.64	0.98		Locadia 2004[119]
PE	0.63	0.36	0.86		Locadia 2004[119]
EC bleed	0.65	0.49	0.86	GI bleed was the disease state valued	Locadia 2004[119]
IC bleed	0.33	0.14	0.53	Haemorrhagic stroke was the disease state valued	Locadia 2004[119]
PTS	0.93	0.91	1.00	Serious PTS was the disease state valued	Lenert 1997[102]

Notes to table:
- Locadia quoted a population norm (own health) as 0.95 (95% CI 0.81-1.00).[119]
- Lower and Upper values are estimates of 95% CIs from data presented (eg sample population size, n, and SD) in the source literature.
- The 95% CI for DVT, PE, EC bleed and IC bleed adjustments to utility norms have been assumed to equal the IQR due to the absence of further information and the size of the sample in Locadia et al.[119]
- 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.

6.4.10 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 speciality 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 health related quality of life values for this STA.

6.4.11 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 development of the cost-effectiveness model for NICE CG92.[27;100] 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.

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

1. The economic model dose not assume any detrimental impact on HRQoL associated with treatment with warfarin, despite a study identified in the systematic review quantifying some detriment,[85] and additional evidence suggesting greater patient satisfaction with rivaroxaban treatment than dual LMWH/VKA therapy.[18] This was a conservative approach.

2. Healthcare resource usage outcomes in EINSTEIN-DVT have indicated that it is likely that rivaroxaban will reduce the length of stay for patients admitted with DVT. As noted in section 6.3.8, [redacted] A reduced stay in hospital with rivaroxaban may attract further HRQoL gains. These have not been included, following a conservative approach.

3. 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,[102] so the cost-effectiveness evaluation focussed on severe PTS.

4. 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.

6.4.13 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.[122] Quality of life was modelled relative to this baseline for DVT, PE, IC bleed, EC bleed and PTS.[119] 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.[120;123] See section 6.4.9.

6.4.14 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 46). Due to recurrence of VTE and incidence of post-VTE complications over time, the model projects a gradual deterioration in average HRQL over a patient cohort lifecourse.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

There are no such amendments.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 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, DVT 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, the Personal Social Services Research Unit and MIMS. There is one HRG for DVT (QZ20Z) and three HRGs relating to PE (DZ09A, DZ90B and DZ09C).

6.5.2 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 weighed 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

6.5.3 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 9.13, 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.

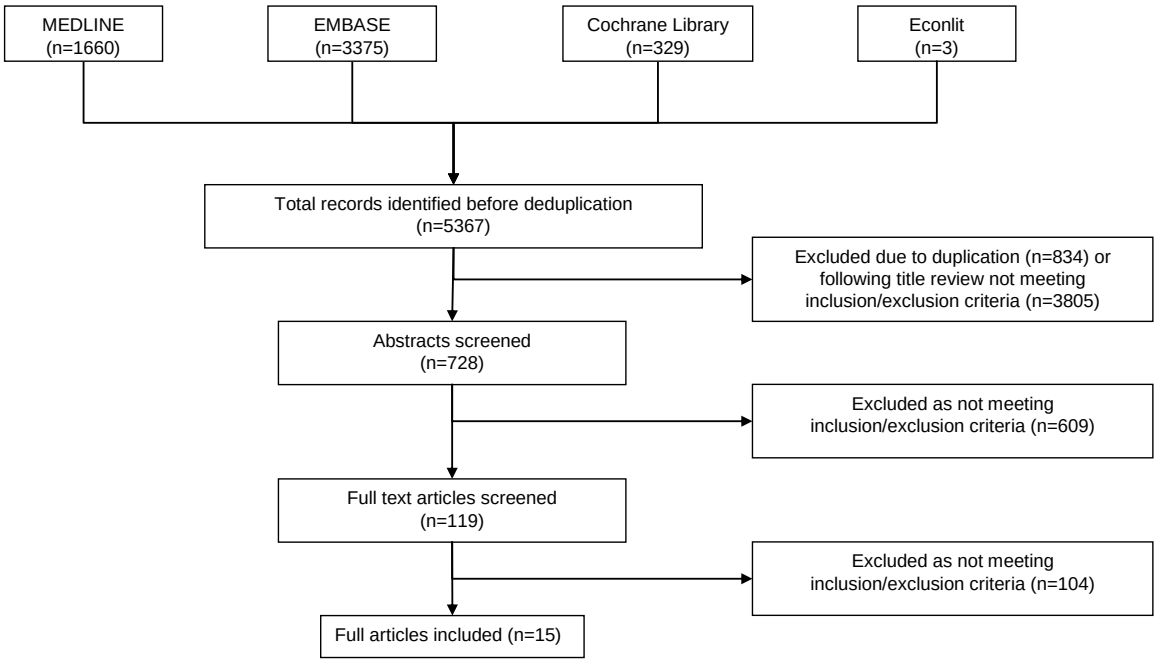
A systematic search of the literature was performed to identify all resource and cost data associated with the treatment of venous thromboembolism (VTE) and any associated published UK costings or cost analyses.

Searches were kept 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 appendix 13, as required, which is in section 9.14.

The searches identified 5,367 hits of potential relevance, from which 4,639 were excluded at title review (including due to duplication), 609 were excluded at abstract review and 104 after reviewing full publications. A PRISMA diagram is shown in Figure 16.

Figure 16: PRISMA diagram for systematic review for cost and resource literature



This left 15 included publications, of which:

- seven studies contained data reporting on the resource / costs involved in anticoagulation for the treatment of DVT or PE[118;124-129]
- seven contained data on the provision and monitoring of anticoagulation, thromboprophylaxis, stroke and any adverse consequences[8;27;130-134]
- and one was a commissioning and benchmarking tool[135].

A summary of the characteristics of these included studies is given in Table 47.

Table 47: Summary of the characteristics of resourcing studies

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Number of patients	Follow-up

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Number of patients	Follow-up
Anderson et al 2002[124]	UK	2000-2001	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[125]	UK	1991 / 1992	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[8]	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
Davies et al 2000[130]	UK	1997-1998	Cost-effectiveness study based on UK costs and practice. NB. This study modeled cost-effectiveness of thromboprophyl axis 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 thromboprophyl axis for hip surgery	Acute and subsequent treatment of VTE

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Number of patients	Follow-up
Goodacre et al 2006[118]	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[126]	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
National Audit Office 2010[134]	UK	2008	Yes resource and unit costs based upon UK practice[131;132]	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)[132]	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 Costing report to CG 68, 2008[131]	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	-
NICE CG92, 2010[27]	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	-

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Number of patients	Follow-up
NICE Anticoagulation Service Commissioning and Benchmarking tool[135]	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	-
Reeves et al 2004[127]	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[133]	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
Simpson et al 2009[128]	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

Reference	Country	Date of study	Applicability to UK practice	Cost valuations used in study	Number of patients	Follow-up
Valette et al 1995[129]	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)

6.5.4 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 speciality 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-DVT. 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

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, 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 6.2.2.

We discuss resource usage and unit costs separately. Resource usage assumptions are summarised in Table 48 and unit cost assumptions in Table 51 (to meet the stated requirements). When resource usage assumptions and unit costs assumptions are combined, these produce the costs for each model state presented in the following section, 6.5.6.

To avoid duplication in later sections, we 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

Resource usage: overview

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

1. Standard disease monitoring. This refers to existing monitoring of patients' disease and the index event, 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. This is conservative in that the potential for savings associated with shorter inpatient admissions for patients on rivaroxaban is not included.

2. 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 DVT and incident bleeds, PE, PTS and CTEPH. A summary of all resource usage assumptions is provided in Table 48.

Resource usage: 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 6.2.7, four LMWH treatments are licensed for the treatment of DVT or PE, 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-DVT was discussed in chapter 5. 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. Differences between the trial dosage and UK licensed dosage (1.5 mg/kg/day in UK licence vs 2 mg/kg/day in EINSTEIN-DVT) and impact on trial validity, which is expected to be minimal, are discussed in chapter 5 (in particular section 5.10.4, enoxaparin regime). The UK dose has lower drug acquisition cost, so leads to a conservative evaluation of the cost-effectiveness of rivaroxaban. Patients in the LMWH/VKA arm of EINSTEIN-DVT received [redacted] treatment with LMWH, including pre-randomisation treatment (Figure 17). Some skewness is apparent.

[redacted]

[redacted]

We assume that patient education would be successfully delivered to 92% of patients, an assumption guided by evidence submitted in the development of NICE CG92.[27;100] These patients would take Clexane® (enoxaparin) pre-filled syringes in their own homes at the UK licensed dose of 1.5 mg/kg/day for 9.6 days. This input was assumed to vary in the PSA according to a Dirichlet distribution with parameters informed by data illustrated in Figure 13. In the univariate analyses, we also vary this parameter between 6 and 10 days, reflecting the duration in SIGN guidelines over which patients are expected to discontinue LMWH.[11]

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 conducted by pH Associates.[36] 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, 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.[36]

Resource usage: longer term care with VKA

Patients in the LMWH/VKA arm of the model subsequently require longer term treatment with VKA. The MHRA commented in the development of the Scope for this appraisal that warfarin was the VKA primarily used in the UK, and it was also the VKA used by the large majority of patients in the LMWH/VKA arm of the EINSTEIN-DVT trial. Among the 1718 patients in the ITT population of the LMWH/VKA arm of EINSTEIN-DVT, 1256 (73%) were treated in centres which exclusively used warfarin as the VKA and 380 (22%) were treated in centres which exclusively used acenocoumarol as the VKA.[65] 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,[9;12] SIGN guidelines,[11] an observational research study of UK anticoagulation services[75] and information in the BNF[136], 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.

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.[36] 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:

- [redacted]
- [redacted]
- [redacted]

Furthermore, [redacted] 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.[8] 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

See section 6.2.7.

Resource usage: other

In addition to treatment of the original index event, the economic model also accounts for resource usage associated with bleeding (of various types/severities), recurrent DVTs, and incident PEs, 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.[105]

Recurrent DVTs and incident PEs 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 in NICE CG92.

BCSH guidelines recommend that `Outpatient therapy of DVT may be considered for selected patients with appropriate support services in place'. Patients not suited for outpatient treatment include those with co-existent serious medical pathology, those with significant risk of bleeding or those with poor social circumstances.[12] SIGN guidelines note that `The widespread use of LMWH (administered subcutaneously once daily and without requirement for laboratory monitoring) in the initial treatment of VTE has led to the increasing practice of managing acute DVT, or even PE, in the community setting'.[11]

A recent survey suggested that 69% of patients with a DVT would be treated as an outpatient with no admission related to the index event.[137] This is the value we select for economic modelling of recurrent DVTs, with sensitivity ranges of 50% to 100%.

The British Thoracic Society has recommended that the current arrangements for outpatient management of DVT should be extended to include stable patients with PE.[138;139] However, there are no widely accepted criteria for defining PE patients who

can be deemed eligible for outpatient treatment. SIGN recommends `Validated prognostic models to identify patients at low risk of adverse outcomes may be incorporated into treatment algorithms for the management of patients with PE, to identify those suitable for outpatient management or early discharge.'[11] PE therefore appears to be mainly treated in hospital. The same survey referred to with DVT suggested that 17% of patients with a PE would be treated as an outpatient with no admission related to the index event.[137] We assume for the purposes of economic modelling that 17% of PEs are treated as outpatients, with sensitivity ranges of 0% to 30%.

Patients with DVTs who were managed on an outpatient basis were assumed to require one of each of the following resources: emergency admission, Doppler ultrasound, and D-dimer. PEs managed on an outpatient basis were assumed to require one of each of: emergency admission, CT angiography, chest x-ray, electrocardiogram, D-dimer.

Table 48: 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 DVT patient	9.6	6	10	Dirichlet (using data presented in Figure 17)	EINSTEIN-DVT (see Figure 13). SIGN guidelines.[11]
Proportion of patients who self-inject LMWH	92%	80%	100%	Beta	The point estimate is taken from the assumptions in NICE CG92 (section 4.7.2).[27] The sensitivity range is an assumption.
Proportion of remaining patients who require nurse assistance at home	80%	60%	100%	Beta	These values are assumptions based on inputs determined for the NICE CG92 model (section 4.7.2).[27]
INR monitoring whilst on LMWH/VKA					
Visits in first 3 months	9	5	15	Gamma	EINSTEIN-DVT (see Figure 13). SIGN guidelines.[11] UK observational research.[36] BNF.[136]
Visits each 3 months thereafter	5	2.5	10	Gamma	
Recurrent VTEs: proportion treated as outpatients rather than inpatients					
Recurrent DVT patients	69%	50%	100%	Beta	SIGN guidelines[11], Bayer Market Research[137]
Incident PE patients	17%	0%	30%	Beta	
Other					
Proportion of patients requiring NHS-funded transportation	8.55%	6%	11%	Beta	Bayer/pH national survey[36]
Proportion of CTEPH patients who require PEA	68.4%	64.2%	72.6%	Beta	321 of 469 patients from Condliffe 2008[105]

Unit costs

Unit costs: overview

All unit costs assumed in the economic model are listed in Table 51 below, together with the source and rationale for each value. Where weighted averages of NHS Reference Costs are taken[42], the data used for this is shown in Table 50.

In univariate sensitivity analyses, values were varied +/- 30%. Probabilistic sensitivity analyses involved sampling each unit cost from a Gamma distribution with a mean equal to the point estimate and standard error equal to 30% of the mean.

Unit costs: drug acquisition

The unit cost of rivaroxaban was set-out originally in section 1(h) on a flat, per tablet. 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 PPRS21).

We present in Table 49 the daily acquisition cost of each of LMWHs in the treatment of DVT.

MIMS indicates the costs of 28 tablets of warfarin are £1.49, £0.93, £0.95 and £1.03 for 0.5 mg, 1.0 mg, 3.0 mg and 5.0 mg tablets respectively. The BNF indicates the daily maintenance dose of warfarin is usually 3-9 mg. The daily unit cost for VKA is calculated on the basis of 1 x 5 mg and 1 x 1 mg tablet of warfarin.

Table 49: 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. MIMS indicates 10 x 120 mg / 0.8 mL costs £97.70. Daily cost = £97.70 / 10.	£9.77	MIMS[140], SmPC[37]
Fragmin® (dalteparin sodium)	Dose of 15,000 IU required if 69-82 kg weight. MIMS indicates 5 x 0.6 mL of 25,000 IU/ml (ie 5 x 15,000 IU) costs £42.34. Daily cost = £42.34 / 5.	£8.47	MIMS[140], SmPC[39]
	Extended oncology treatment: Dose of 15,000 IU required in month 1 and 12,500 IU in months 2-6. First month costed above. MIMS indicates 5 x 0.5 ml of 25,000 IU/ml (ie 5 x 12,500 IU) costs £35.29. Daily cost = £35.29 / 5.	£8.47 in month 1, £7.06 thereafter	MIMS[140], SmPC[40]
Innohep® (tinzaparin sodium)	Dose of 175 IU/kg required, ie 14,000 IU at weight of 80 kg. MIMS indicates 6 x 0.7 mL of 20,000 IU/ml (ie 6 x 14,000 IU) costs £71.08. Daily cost = £71.08 / 6.	£11.85	MIMS[140], SmPC[141]
Zibor® (bemiparin sodium)	Dose of 115 units/kg required, ie 9200 units at weight of 80 kg. MIMS indicates 10 x 0.4 mL / 10 000 unit pre-filled syringes costs £43.84. Daily cost = £43.84 / 10.	£4.38	MIMS[140], SmPC[142]

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).

Unit costs: 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, according to PSSRU data, which assumes a surgery consultation lasting 11.7 minutes.[43] The cost of monitoring delivered by a nurse was taken to be £12.00, according again to PSSRU data.[43] 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.[135] Overall, the unit cost for INR monitoring delivered in primary care was £27.00 (ie £3.00 + 0.5 x £36.00 + 0.5 x £12.00).

INR monitoring in secondary care was costed through NHS Reference Costs.[42] 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 50). This produced a value of £47.19. 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 £24.69.

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.[36] Applying these

assumptions to the unit costs above produced a weighted average cost of a first INR monitoring visit was £33.77 and for a subsequent visit was £26.23.

Unit costs: Recurrent DVT and PE

As noted above in the discussion of resource usage, recurrent DVTs and incident PEs 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 in NICE CG92[27;100].

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 £814.39.[42] 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 50).[42] This yielded a value of £1584.68.

The unit costs of each of the items relevant to outpatient care of recurrent DVT and PE were taken from NHS Reference Costs[42] with two exceptions:

- The cost of chest x-rays was taken from a recent diagnostics technology report for NICE.[143]
- The cost of D-dimer tests was taken from a costing in NICE CG92, with appropriate healthcare inflation added.[27;43;100]

Unit costs: 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 extracranial 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 (see Table 50).[42] It was assumed that there were no further costs associated with this event after three months. The weighted average cost was £942.05.

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 £126.34.[42] 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 intracranial bleeding events were modelled using the costs for acute care of stroke (£2,580.99) (AA23Z) followed by 14 days of rehabilitation.[42] 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 £308.94 per day (VC04Z). The cost of the first three months of care for an intracranial bleed was therefore £6906.13 (calculated as £2072.72 + 14 x £308.94)

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).[27;100] The unit cost per 3 month timestep was therefore £1,206.50.

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.[118] A first appointment costs £161.98, each follow-up visit costs £111.03 each and a GP visit costs £36.00, according to NHS Reference Costs.[42] This gives a first year cost of £384.04 (£96.01 each 3 months) and a cost for each subsequent year of £72.00 (£18.00 each three months). This compares conservatively with a costing of £653 per year in NICE CG92.[27;100]

Unit costs: CTEPH

Following diagnosis of CTEPH, a PEA may be required.[53] This was estimated from the weighted average cost of NHS Reference Costs for two relevant HRGs (see Table 50), yielding £6109.86.[42]

The ongoing cost of managing a patient with CTEPH was based on the estimate of £1219 per month made for NICE CG92, inflated by 1.7% to 2010.[27;43] This yielded a unit cost of £3719.17 per three month timestep.

Table 50: Weighted averaging of NHS Reference Costs by activity

Event	HRG / code	Name	NHS Reference Costs	
			Activity	Unit cost (£)
First INR visit (secondary care)	324	Consultant Led: First Attendance Non-Admitted Face to Face	71,646	£47.30
	324	Non-Consultant Led: First Attendance Non-Admitted Face to Face	24,700	£46.87
	Total activity and weighted average unit cost		96,346	£47.19
Subsequent INR visit (secondary care)		Consultant Led: Follow up Attendance Non-Admitted Face to Face	1,201,276	£29.35
		Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face	790,414	£17.61
	Total activity and weighted average unit cost		1,991,690	£24.69
DVT	QZ20Z	Deep Vein Thrombosis	38,521	814.39
PE	DZ09A	Pulmonary Embolus with Major CC	14,278	1978.26
	DZ09B	Pulmonary Embolus with CC	13,906	1470.08
	DZ09C	Pulmonary Embolus without CC	6,637	978.13
	Total activity and weighted average unit cost		34,821	1584.68
Major EC bleed	FZ16Z	Very Major Procedures for Gastrointestinal Bleed	589	4604.98
	FZ25A	Therapeutic Endoscopic or Intermediate Stomach or Duodenum Procedures 19 years and over	23,852	592.21
	FZ29Z	Major or Therapeutic Endoscopic Procedures for Gastrointestinal Bleed	22,385	1073.13
	FZ30Z	Diagnostic Endoscopic or Intermediate Procedures for Gastrointestinal Bleed	8,807	586.95
	FZ38D	Gastrointestinal Bleed with length of stay 2 days or more with Major CC	10,175	2186.07
	FZ38E	Gastrointestinal Bleed with length of stay 2 days or more without Major CC	13,377	1366.50
	FZ38F	Gastrointestinal Bleed with length of stay 1 day or less	40,083	434.18
	FZ43A	Non-Malignant Stomach or Duodenum Disorders with length of stay 2 days or more with Major CC	12,195	2406.91
	FZ43B	Non-Malignant Stomach or Duodenum Disorders with length of stay 2 days or more without Major CC	20,400	1656.05
	FZ43C	Non-Malignant Stomach or Duodenum Disorders with length of stay 1 day or less	45,720	416.51
	Total activity and weighted average unit cost		197,583	942.05
Minor EC bleed	VB07Z	Category 2 investigation with category 2 treatment	1,417,141	126.34
IC bleed	AA23Z	Haemorrhagic Cerebrovascular Disorders	32,268	2580.99
	VC04Z	Rehabilitation for stroke	540,021	308.94
	Three months of care (1xAA23Z + 14xVC04Z)			6906.13

Source: NHS National Schedule of Reference Costs 2009/10 for NHS Trusts and PCTs Combined[42]

Table 51: List of all unit costs assumed

Item		Value (£)	Source
Drug acquisition (cost per day whilst on treatment)			
	LMWH	9.77	MIMS[140], SmPC[37]
	VKA	0.07	BNF[136], MIMS[140], SmPC[87]
	Xarelto® (rivaroxaban)	2.10	Section 1(h)
Inpatient costs			
	Diagnosis and treatment of a DVT	£814.39	NHS Reference Costs 2009-10[42], Table 50
	Diagnosis and treatment of a PE	£1584.68	
Outpatient treatment items			
	Doppler ultrasound	69.46	NHS Reference Costs 2009-10[42]: RA24Z, ultrasound scan for less than 20 minutes
	CT angiography	100.38	NHS Reference Costs 2009-10[42]: RA08Z, computed tomography scan, one area, no contrast
	Chest X-ray	12.26	NICE DT1 assessment report (Table 4.17)[143] and PSSRU 2010 (section 13.5)[43]. Calculated from £3.42 for a computed radiography x-ray, £6.16 for a digital radiography + 16 minutes of £28 per hour radiographer = (3.42+6.16)/2+16x28/60 = £12.26
	Electrocardiogram (ECG)	33.27	NHS Reference Costs 2009-10[42]: DA01 (other currencies: ECG, 12 lead)
	D-dimer	12.20	NICE CG92[27;100], PSSRU 2010[43]: £12 from CG92 x 1.017 (inflated one year)
	Emergency admission	113.18	NHS Reference Costs 2009-10[42]. Service 180: Accident and Emergency
Drug monitoring			
	INR monitoring in secondary care – first visit	47.19	NHS Reference Costs 2009-10[42], Table 50
	INR monitoring in secondary care – each subsequent visit	24.69	NHS Reference Costs 2009-10[42], Table 50
	INR monitoring in primary care, per visit	27.00	NICE CG36 costing report[132], PSSRU 2010[43]
	District nurse visit	38.57	NHS Reference Costs 2009-10[42]: CN301AF, district nursing services, adult, face to face
	NHS transportation (where required)	30.96	NHS Reference Costs 2009-10[42]
Treatment of bleeds			
	CRNM bleed (extracranial)	£126.34	NHS Reference Costs 2009-10[42], Table 50
	Major extracranial bleed	£942.05	
	Major intracranial bleed, first 3 months	£6906.13	
	Major intracranial bleed, each subsequent 3 months	£1206.50	
Management of PTS			
	Year 1 (3-month cost)	£96.01	Goodacre 2006[118], NICE CG92[27;100], NHS Reference Costs 2009-10[42]
	Year 2+ (3-month cost)	£18.00	
Management of CTEPH			
	PEA	£6109.86	NHS Reference Costs 2009-10[42]
	Ongoing cost (per 3 months)	£3719.17	NICE CG92[27;100], PSSRU 2010[43], UK consensus statement[53]

Health-state costs

6.5.6 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 6.2.4.

When resource usage assumptions and unit costs assumptions described in section 6.5.5 are combined, these produce the costs for each model state presented in Table 52.

Table 52: List of health states and associated costs in the economic model

Health states			**Value**
0	On treatment - rivaroxaban (All costs relate to drug, none to administration.)	Cycle 0 Cycle 1 Cycle 2+	£88.20 £147.53 £191.63
0	On treatment – dual LMWH/VKA	Cycle 0 - drug Cycle 0 - administration Cycle 1 - drug Cycle 1 - administration Cycle 2+ - drug Cycle 2+ - administration	£93.79 £0 £5.72 £250.58 £6.39 £135.02
1	DVT		£899.81
2	PE		£1,873.31
3	Minor bleed		£126.34
4	Extra-cranial bleed		£942.05
5	Intra-cranial bleed		£6,906.13
6	Off-treatment		£0
7	Off-treatment (post IC bleed)		£1,206.50
8	CTEPH (surgery and on-going)*		£7,900.97
9	CTEPH (on-going)*		£3,119.17
10	Death		£0
11	PTS mild		£0
12	PTS severe		£96.01

* 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 9.6 days of LMWH for the LMWH/VKA arm. Note no monitoring costs were assumed for either treatment arm. Cycle 1 corresponds to the remaining 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

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. 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 6.2.2.

The costing of all items, including bleeding and adverse events, has been covered previously within the model states.

Miscellaneous costs

6.5.8 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.

6.6 Sensitivity analysis

6.6.1 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 uncertainty 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. These comments were taken into account for the finalisation of the model structure. Other structural assumptions such as time horizon and discount rates are tested in the one-way sensitivity analyses.

6.6.2 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 6.3.6 (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. 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 36

  - All other clinical events, as outlined in Table 43
- Treatment effects in relation to efficacy and safety variables for rivaroxaban vs dual LMWH/VKA therapy were varied between 95% CI, specifically:
  - HR of 0.68 (95% CI 0.44 to 1.04) for recurrent VTE;
  - HR of 0.65 (95% CI 0.33 to 1.28) for major bleeding;
  - RR of 1.05 (95% CI 0.83 to 1.34) for CRNM bleeding.
- Utility, as described in Table 46. (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 48.
- Unit costs: Values were varied by ±30%, as previously described in section 6.5.5.
- 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 56 years to 46 and 66 years

In addition, the USAs also included various additional groupings of parameters, as outlined in Table 53.

Table 53: 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 parameters)	All utility parameters listed under "utility values" in table 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.

6.6.3 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 6.3.6, 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 in the model to take account of the simultaneous effect of uncertainty relating to model parameter values. This was achieved through repeated sampling of mean 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 1,000 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 36

- All other clinical events, according to Beta distributions as outlined in Table 43

- Treatment effects in relation to efficacy and safety variables for rivaroxaban vs dual LMWH/VKA therapy:
  - HR for recurrent VTE sampled from a Lognormal distribution to fit a point estimate of 0.68 and 95% CI of 0.44 to 1.04;
  - HR for major bleeding sampled from a Lognormal distribution to fit a point estimate of 0.65 and 95% CI 0.33 to 1.28;
  - RR for CRNM bleeding sampled from a Lognormal distribution to fit a point estimate of 1.05 and 95% CI 0.83 to 1.34.
- Utility, according to Beta distributions as described in Table 46. (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 48.
- Unit costs, according to Gamma distributions with means equal to the point estimates (given in Table 51) and standard errors equal to 30% of those means.

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.

6.7 Results

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), 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-DVT are compared in Table 54.

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 were derived from the EINSTEIN-DVT CSR ([redacted]).[65]

Table 54: Summary of model results compared with trial outcomes from EINSTEIN-DVT

	Rivaroxaban		LMWH/VKA	
Outcome	**Clinical trial result**	**Model result**	**Clinical trial result**	**Model result**
VTE				
3 months	[redacted]	1.7%	[redacted]	2.6%
6 months	[redacted]	0.3%	[redacted]	0.4%
12 months	[redacted]	0.3%	[redacted]	0.4%
Bleeds				
3 months	[redacted]	5.7%	[redacted]	5.8%
6 months	[redacted]	1.7%	[redacted]	1.7%
12 months	[redacted]	2.6%	[redacted]	2.4%

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. The differences observed for bleeding relate to slight differences in risk over time for the two trial arms. In the trial rivaroxaban was associated with a marginally greater risk of CRNM bleeding than LMWH/VKA during months 0-3. However, in the 6-12 month period this trend was reversed. Since in the model the risk of bleeding for rivaroxaban is derived using the respective HR in comparison to LMWH/VKA, this trend is not observed in model outputs.

Further reasons for the small differences observed are:

- in the model, background mortality rates (non-VTE specific) were included;
- in the model, rivaroxaban event rates were derived from the trial event rates for the LMWH/VKA arm to which an HR were applied;
- 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.

6.7.2 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 55 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 and 12 months). 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 56 years-old patient over a 40 year lifetime from model entry.

The six tables following Table 55 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 and 12 months). For purposes of brevity, the final cycle of each year was reported only. The eleven individual health states presented are:

- HS1: On-treatment
- HS2: DVT
- HS3: PE
- HS4: CRNM bleeds
- HS5: IC bleeds
- HS6: Major EC bleeds
- HS7: Off-treatment
- HS8: Off-treatment post IC bleed
- HS9: Acute CTEPH
- HS10: Long term CTEPH
- HS11: Death

The health states presented in these tables may be compared with the health states described in Table 34 and the model structure presented in Figure 15.

Table 55: Proportion of the cohort in each aggregated health state, per treatment arm and treatment duration

	3 months				6 months				12 months			
	Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA	
Years	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds
0	0.000	0.000	0.000	0.000	0	0	0	0	0.000	0.000	0.000	0.000
0.25	1.746	5.729	2.558	5.778	1.746	5.729	2.558	5.778	1.746	5.729	2.558	5.778
0.5	1.167	0.000	1.156	0.000	0.292	1.686	0.414	1.689	0.292	1.686	0.414	1.689
0.75	1.240	0.000	1.237	0.000	1.231	0.000	1.228	0.000	0.155	1.314	0.201	1.232
1	1.236	0.000	1.234	0.000	1.238	0.000	1.235	0.000	0.180	1.288	0.227	1.208
2	1.051	0.000	1.049	0.000	1.053	0.000	1.051	0.000	1.054	0.000	1.052	0.000
3	1.044	0.000	1.042	0.000	1.045	0.000	1.043	0.000	1.046	0.000	1.044	0.000
4	1.036	0.000	1.034	0.000	1.037	0.000	1.035	0.000	1.038	0.000	1.036	0.000
5	1.027	0.000	1.025	0.000	1.028	0.000	1.026	0.000	1.029	0.000	1.027	0.000
6	1.017	0.000	1.015	0.000	1.018	0.000	1.016	0.000	1.019	0.000	1.017	0.000
7	1.006	0.000	1.004	0.000	1.007	0.000	1.005	0.000	1.008	0.000	1.006	0.000
8	0.994	0.000	0.993	0.000	0.996	0.000	0.994	0.000	0.997	0.000	0.995	0.000
9	0.982	0.000	0.980	0.000	0.983	0.000	0.981	0.000	0.984	0.000	0.982	0.000
10	0.968	0.000	0.967	0.000	0.970	0.000	0.968	0.000	0.970	0.000	0.969	0.000
11	0.954	0.000	0.952	0.000	0.955	0.000	0.953	0.000	0.956	0.000	0.954	0.000
12	0.938	0.000	0.937	0.000	0.939	0.000	0.938	0.000	0.940	0.000	0.939	0.000
13	0.922	0.000	0.920	0.000	0.923	0.000	0.921	0.000	0.924	0.000	0.922	0.000
14	0.904	0.000	0.902	0.000	0.905	0.000	0.903	0.000	0.906	0.000	0.904	0.000
15	0.885	0.000	0.883	0.000	0.886	0.000	0.884	0.000	0.886	0.000	0.885	0.000
16	0.864	0.000	0.862	0.000	0.865	0.000	0.863	0.000	0.865	0.000	0.864	0.000
17	0.841	0.000	0.839	0.000	0.842	0.000	0.840	0.000	0.843	0.000	0.841	0.000
18	0.817	0.000	0.815	0.000	0.818	0.000	0.816	0.000	0.818	0.000	0.817	0.000
19	0.790	0.000	0.789	0.000	0.791	0.000	0.790	0.000	0.792	0.000	0.791	0.000
20	0.762	0.000	0.761	0.000	0.763	0.000	0.762	0.000	0.764	0.000	0.763	0.000
21	0.732	0.000	0.731	0.000	0.733	0.000	0.732	0.000	0.734	0.000	0.732	0.000
22	0.700	0.000	0.698	0.000	0.701	0.000	0.699	0.000	0.701	0.000	0.700	0.000
23	0.666	0.000	0.664	0.000	0.666	0.000	0.665	0.000	0.667	0.000	0.666	0.000

	3 months				6 months				12 months			
	Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA		Rivaroxaban		LMWH/VKA	
Years	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds	VTE	Bleeds
24	0.630	0.000	0.628	0.000	0.630	0.000	0.629	0.000	0.631	0.000	0.630	0.000
25	0.592	0.000	0.591	0.000	0.593	0.000	0.592	0.000	0.593	0.000	0.592	0.000
26	0.553	0.000	0.552	0.000	0.554	0.000	0.553	0.000	0.554	0.000	0.553	0.000
26	0.513	0.000	0.512	0.000	0.513	0.000	0.513	0.000	0.514	0.000	0.513	0.000
27	0.472	0.000	0.471	0.000	0.472	0.000	0.471	0.000	0.473	0.000	0.472	0.000
28	0.430	0.000	0.429	0.000	0.431	0.000	0.430	0.000	0.431	0.000	0.430	0.000
30	0.390	0.000	0.389	0.000	0.390	0.000	0.389	0.000	0.390	0.000	0.390	0.000
31	0.349	0.000	0.349	0.000	0.350	0.000	0.349	0.000	0.350	0.000	0.349	0.000
32	0.310	0.000	0.309	0.000	0.310	0.000	0.310	0.000	0.310	0.000	0.310	0.000
33	0.270	0.000	0.269	0.000	0.270	0.000	0.270	0.000	0.271	0.000	0.270	0.000
34	0.232	0.000	0.231	0.000	0.232	0.000	0.232	0.000	0.232	0.000	0.232	0.000
35	0.197	0.000	0.196	0.000	0.197	0.000	0.197	0.000	0.197	0.000	0.197	0.000
36	0.164	0.000	0.164	0.000	0.165	0.000	0.164	0.000	0.165	0.000	0.164	0.000
37	0.135	0.000	0.135	0.000	0.135	0.000	0.135	0.000	0.136	0.000	0.135	0.000
38	0.109	0.000	0.109	0.000	0.110	0.000	0.109	0.000	0.110	0.000	0.109	0.000
39	0.087	0.000	0.087	0.000	0.087	0.000	0.087	0.000	0.087	0.000	0.087	0.000
40	0.068	0.000	0.068	0.000	0.068	0.000	0.068	0.000	0.068	0.000	0.068	0.000

Notes: VTE and Bleed aggregated states as defined above.

Table 56: Markov trace: rivaroxaban arm, 3 months of treatment, aged 56 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	90.485	0.843	0.903	5.163	0.071	0.496	1.900	0.000	0.000	0.000	0.139
0.5	0.000	0.942	0.224	0.000	0.000	0.000	98.155	0.040	0.011	0.000	0.627
0.75	0.000	1.001	0.238	0.000	0.000	0.000	97.867	0.040	0.003	0.011	0.840
1	0.000	0.998	0.238	0.000	0.000	0.000	97.651	0.040	0.003	0.013	1.057
2	0.000	0.992	0.059	0.000	0.000	0.000	97.108	0.040	0.001	0.019	1.781
3	0.000	0.985	0.059	0.000	0.000	0.000	96.411	0.039	0.001	0.020	2.486
4	0.000	0.977	0.058	0.000	0.000	0.000	95.660	0.039	0.001	0.020	3.244
5	0.000	0.969	0.058	0.000	0.000	0.000	94.827	0.039	0.001	0.021	4.086
6	0.000	0.960	0.057	0.000	0.000	0.000	93.918	0.038	0.001	0.022	5.004
7	0.000	0.949	0.057	0.000	0.000	0.000	92.922	0.038	0.001	0.022	6.011
8	0.000	0.939	0.056	0.000	0.000	0.000	91.856	0.038	0.001	0.022	7.089
9	0.000	0.927	0.055	0.000	0.000	0.000	90.696	0.037	0.001	0.023	8.262
10	0.000	0.914	0.054	0.000	0.000	0.000	89.453	0.037	0.001	0.023	9.519
11	0.000	0.900	0.054	0.000	0.000	0.000	88.116	0.036	0.001	0.023	10.871
12	0.000	0.886	0.053	0.000	0.000	0.000	86.677	0.036	0.001	0.023	12.326
13	0.000	0.870	0.052	0.000	0.000	0.000	85.129	0.035	0.001	0.023	13.891
14	0.000	0.853	0.051	0.000	0.000	0.000	83.483	0.034	0.001	0.022	15.556
15	0.000	0.835	0.050	0.000	0.000	0.000	81.708	0.034	0.001	0.022	17.351
16	0.000	0.815	0.049	0.000	0.000	0.000	79.775	0.033	0.001	0.022	19.306
17	0.000	0.794	0.047	0.000	0.000	0.000	77.678	0.032	0.001	0.022	21.426
18	0.000	0.771	0.046	0.000	0.000	0.000	75.439	0.031	0.001	0.021	23.691
19	0.000	0.746	0.044	0.000	0.000	0.000	73.013	0.030	0.001	0.021	26.145
20	0.000	0.719	0.043	0.000	0.000	0.000	70.412	0.029	0.001	0.020	28.776
21	0.000	0.691	0.041	0.000	0.000	0.000	67.622	0.028	0.001	0.019	31.598
22	0.000	0.660	0.039	0.000	0.000	0.000	64.640	0.027	0.000	0.019	34.614

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
23	0.000	0.628	0.037	0.000	0.000	0.000	61.478	0.025	0.000	0.018	37.813
24	0.000	0.594	0.035	0.000	0.000	0.000	58.160	0.024	0.000	0.017	41.169
25	0.000	0.559	0.033	0.000	0.000	0.000	54.696	0.023	0.000	0.016	44.673
26	0.000	0.522	0.031	0.000	0.000	0.000	51.090	0.021	0.000	0.015	48.321
26	0.000	0.484	0.029	0.000	0.000	0.000	47.369	0.020	0.000	0.014	52.084
27	0.000	0.445	0.027	0.000	0.000	0.000	43.575	0.018	0.000	0.013	55.922
28	0.000	0.406	0.024	0.000	0.000	0.000	39.735	0.017	0.000	0.012	59.806
30	0.000	0.368	0.022	0.000	0.000	0.000	35.992	0.015	0.000	0.011	63.593
31	0.000	0.330	0.020	0.000	0.000	0.000	32.268	0.013	0.000	0.010	67.359
32	0.000	0.292	0.017	0.000	0.000	0.000	28.614	0.012	0.000	0.008	71.055
33	0.000	0.255	0.015	0.000	0.000	0.000	24.936	0.010	0.000	0.007	74.776
34	0.000	0.219	0.013	0.000	0.000	0.000	21.402	0.009	0.000	0.006	78.351
35	0.000	0.186	0.011	0.000	0.000	0.000	18.163	0.008	0.000	0.005	81.627
36	0.000	0.155	0.009	0.000	0.000	0.000	15.184	0.006	0.000	0.005	84.641
37	0.000	0.128	0.008	0.000	0.000	0.000	12.495	0.005	0.000	0.004	87.361
38	0.000	0.103	0.006	0.000	0.000	0.000	10.107	0.004	0.000	0.003	89.776
39	0.000	0.082	0.005	0.000	0.000	0.000	8.039	0.003	0.000	0.002	91.868
40	0.000	0.064	0.004	0.000	0.000	0.000	6.273	0.003	0.000	0.002	93.654

HS1: on-treatment; HS2: DVT (ipsilateral); HS3: DVT (contralateral); HS4: PE; HS5: minor bleeds; HS6: intra-cranial bleeds; HS7: extra-cranial bleeds; HS8: off-treatment; HS9: off-treatment (post-IC bleed); HS10: acute CTEPH: HS11: long-term CTEPH; HS12: death

Table 57: Markov trace: LMWH/VKA arm, 3 months of treatment, aged 56 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	89.625	1.235	1.323	4.903	0.109	0.766	1.900	0.000	0.000	0.000	0.139
0.5	0.000	0.934	0.222	0.000	0.000	0.000	97.973	0.062	0.017	0.000	0.793
0.75	0.000	0.999	0.238	0.000	0.000	0.000	97.677	0.062	0.003	0.016	1.005
1	0.000	0.996	0.237	0.000	0.000	0.000	97.461	0.061	0.003	0.018	1.222
2	0.000	0.990	0.059	0.000	0.000	0.000	96.920	0.061	0.001	0.023	1.945
3	0.000	0.983	0.059	0.000	0.000	0.000	96.224	0.061	0.001	0.024	2.649
4	0.000	0.976	0.058	0.000	0.000	0.000	95.474	0.060	0.001	0.024	3.407
5	0.000	0.967	0.058	0.000	0.000	0.000	94.643	0.060	0.001	0.024	4.247
6	0.000	0.958	0.057	0.000	0.000	0.000	93.736	0.059	0.001	0.024	5.164
7	0.000	0.948	0.056	0.000	0.000	0.000	92.742	0.059	0.001	0.025	6.170
8	0.000	0.937	0.056	0.000	0.000	0.000	91.678	0.058	0.001	0.025	7.246
9	0.000	0.925	0.055	0.000	0.000	0.000	90.520	0.057	0.001	0.025	8.417
10	0.000	0.912	0.054	0.000	0.000	0.000	89.280	0.057	0.001	0.024	9.672
11	0.000	0.899	0.053	0.000	0.000	0.000	87.945	0.056	0.001	0.024	11.022
12	0.000	0.884	0.053	0.000	0.000	0.000	86.509	0.055	0.001	0.024	12.475
13	0.000	0.868	0.052	0.000	0.000	0.000	84.964	0.054	0.001	0.024	14.038
14	0.000	0.851	0.051	0.000	0.000	0.000	83.321	0.053	0.001	0.024	15.699
15	0.000	0.833	0.050	0.000	0.000	0.000	81.550	0.052	0.001	0.023	17.491
16	0.000	0.814	0.048	0.000	0.000	0.000	79.621	0.051	0.001	0.023	19.443
17	0.000	0.792	0.047	0.000	0.000	0.000	77.528	0.049	0.001	0.022	21.560
18	0.000	0.769	0.046	0.000	0.000	0.000	75.293	0.048	0.001	0.022	23.821
19	0.000	0.745	0.044	0.000	0.000	0.000	72.871	0.047	0.001	0.021	26.271
20	0.000	0.718	0.043	0.000	0.000	0.000	70.275	0.045	0.001	0.020	28.898
21	0.000	0.690	0.041	0.000	0.000	0.000	67.491	0.043	0.001	0.020	31.715
22	0.000	0.659	0.039	0.000	0.000	0.000	64.515	0.041	0.000	0.019	34.726
23	0.000	0.627	0.037	0.000	0.000	0.000	61.359	0.039	0.000	0.018	37.919
24	0.000	0.593	0.035	0.000	0.000	0.000	58.047	0.037	0.000	0.017	41.270

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
25	0.000	0.558	0.033	0.000	0.000	0.000	54.590	0.035	0.000	0.016	44.767
26	0.000	0.521	0.031	0.000	0.000	0.000	50.991	0.033	0.000	0.015	48.409
26	0.000	0.483	0.029	0.000	0.000	0.000	47.278	0.030	0.000	0.014	52.166
27	0.000	0.444	0.026	0.000	0.000	0.000	43.490	0.028	0.000	0.013	55.998
28	0.000	0.405	0.024	0.000	0.000	0.000	39.658	0.026	0.000	0.012	59.875
30	0.000	0.367	0.022	0.000	0.000	0.000	35.922	0.023	0.000	0.011	63.655
31	0.000	0.329	0.020	0.000	0.000	0.000	32.205	0.021	0.000	0.010	67.415
32	0.000	0.292	0.017	0.000	0.000	0.000	28.559	0.018	0.000	0.009	71.105
33	0.000	0.254	0.015	0.000	0.000	0.000	24.888	0.016	0.000	0.007	74.819
34	0.000	0.218	0.013	0.000	0.000	0.000	21.361	0.014	0.000	0.006	78.388
35	0.000	0.185	0.011	0.000	0.000	0.000	18.128	0.012	0.000	0.005	81.659
36	0.000	0.155	0.009	0.000	0.000	0.000	15.154	0.010	0.000	0.005	84.667
37	0.000	0.127	0.008	0.000	0.000	0.000	12.471	0.008	0.000	0.004	87.382
38	0.000	0.103	0.006	0.000	0.000	0.000	10.088	0.007	0.000	0.003	89.794
39	0.000	0.082	0.005	0.000	0.000	0.000	8.023	0.005	0.000	0.002	91.882
40	0.000	0.064	0.004	0.000	0.000	0.000	6.261	0.004	0.000	0.002	93.665

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH, HS10: long-term CTEPH; HS11: death.

Table 58: Markov trace: rivaroxaban arm, 6 months of treatment, aged 56 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	90.485	0.843	0.903	5.163	0.071	0.496	1.900	0.000	0.000	0.000	0.139
0.5	91.559	0.149	0.143	1.510	0.022	0.154	5.900	0.040	0.011	0.000	0.513
0.75	0.000	0.994	0.237	0.000	0.000	0.000	97.989	0.052	0.002	0.011	0.715
1	0.000	1.000	0.238	0.000	0.000	0.000	97.763	0.052	0.003	0.012	0.931
2	0.000	0.993	0.059	0.000	0.000	0.000	97.220	0.052	0.001	0.018	1.656
3	0.000	0.986	0.059	0.000	0.000	0.000	96.522	0.052	0.001	0.019	2.362
4	0.000	0.979	0.058	0.000	0.000	0.000	95.770	0.051	0.001	0.020	3.121
5	0.000	0.970	0.058	0.000	0.000	0.000	94.936	0.051	0.001	0.020	3.964
6	0.000	0.961	0.057	0.000	0.000	0.000	94.027	0.050	0.001	0.021	4.883
7	0.000	0.951	0.057	0.000	0.000	0.000	93.030	0.050	0.001	0.021	5.891
8	0.000	0.940	0.056	0.000	0.000	0.000	91.962	0.049	0.001	0.022	6.970
9	0.000	0.928	0.055	0.000	0.000	0.000	90.801	0.049	0.001	0.022	8.145
10	0.000	0.915	0.054	0.000	0.000	0.000	89.556	0.048	0.001	0.022	9.403
11	0.000	0.901	0.054	0.000	0.000	0.000	88.218	0.047	0.001	0.022	10.757
12	0.000	0.887	0.053	0.000	0.000	0.000	86.777	0.047	0.001	0.022	12.214
13	0.000	0.871	0.052	0.000	0.000	0.000	85.227	0.046	0.001	0.022	13.781
14	0.000	0.854	0.051	0.000	0.000	0.000	83.579	0.045	0.001	0.022	15.448
15	0.000	0.836	0.050	0.000	0.000	0.000	81.803	0.044	0.001	0.022	17.245
16	0.000	0.816	0.049	0.000	0.000	0.000	79.867	0.043	0.001	0.022	19.203
17	0.000	0.795	0.047	0.000	0.000	0.000	77.768	0.042	0.001	0.021	21.326
18	0.000	0.772	0.046	0.000	0.000	0.000	75.527	0.041	0.001	0.021	23.593
19	0.000	0.747	0.044	0.000	0.000	0.000	73.097	0.040	0.001	0.020	26.051
20	0.000	0.720	0.043	0.000	0.000	0.000	70.493	0.038	0.001	0.020	28.685
21	0.000	0.692	0.041	0.000	0.000	0.000	67.700	0.037	0.001	0.019	31.510
22	0.000	0.661	0.039	0.000	0.000	0.000	64.715	0.035	0.000	0.018	34.530
23	0.000	0.629	0.037	0.000	0.000	0.000	61.549	0.033	0.000	0.018	37.733
24	0.000	0.595	0.035	0.000	0.000	0.000	58.227	0.032	0.000	0.017	41.094

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
25	0.000	0.560	0.033	0.000	0.000	0.000	54.759	0.030	0.000	0.016	44.602
26	0.000	0.523	0.031	0.000	0.000	0.000	51.149	0.028	0.000	0.015	48.255
26	0.000	0.485	0.029	0.000	0.000	0.000	47.424	0.026	0.000	0.014	52.022
27	0.000	0.446	0.027	0.000	0.000	0.000	43.625	0.024	0.000	0.013	55.866
28	0.000	0.406	0.024	0.000	0.000	0.000	39.781	0.022	0.000	0.012	59.755
30	0.000	0.368	0.022	0.000	0.000	0.000	36.034	0.020	0.000	0.011	63.546
31	0.000	0.330	0.020	0.000	0.000	0.000	32.305	0.018	0.000	0.010	67.318
32	0.000	0.293	0.017	0.000	0.000	0.000	28.647	0.016	0.000	0.008	71.018
33	0.000	0.255	0.015	0.000	0.000	0.000	24.965	0.014	0.000	0.007	74.743
34	0.000	0.219	0.013	0.000	0.000	0.000	21.427	0.012	0.000	0.006	78.323
35	0.000	0.186	0.011	0.000	0.000	0.000	18.184	0.010	0.000	0.005	81.604
36	0.000	0.155	0.009	0.000	0.000	0.000	15.201	0.008	0.000	0.005	84.621
37	0.000	0.128	0.008	0.000	0.000	0.000	12.509	0.007	0.000	0.004	87.345
38	0.000	0.103	0.006	0.000	0.000	0.000	10.119	0.006	0.000	0.003	89.763
39	0.000	0.082	0.005	0.000	0.000	0.000	8.048	0.004	0.000	0.002	91.858
40	0.000	0.064	0.004	0.000	0.000	0.000	6.281	0.003	0.000	0.002	93.646

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH, HS10: long-term CTEPH; HS11: death.

Table 59: Markov trace: LMWH/VKA arm, 6 months of treatment, aged 56 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	89.625	1.235	1.323	4.903	0.109	0.766	1.900	0.000	0.000	0.000	0.139
0.5	90.516	0.208	0.206	1.418	0.034	0.236	6.678	0.062	0.017	0.000	0.626
0.75	0.000	0.992	0.236	0.000	0.000	0.000	97.817	0.081	0.003	0.016	0.857
1	0.000	0.998	0.238	0.000	0.000	0.000	97.590	0.080	0.003	0.018	1.073
2	0.000	0.992	0.059	0.000	0.000	0.000	97.048	0.080	0.001	0.023	1.798
3	0.000	0.985	0.059	0.000	0.000	0.000	96.351	0.079	0.001	0.024	2.503
4	0.000	0.977	0.058	0.000	0.000	0.000	95.600	0.079	0.001	0.024	3.261
5	0.000	0.968	0.058	0.000	0.000	0.000	94.768	0.078	0.001	0.024	4.103
6	0.000	0.959	0.057	0.000	0.000	0.000	93.860	0.078	0.001	0.024	5.021
7	0.000	0.949	0.056	0.000	0.000	0.000	92.865	0.077	0.001	0.024	6.028
8	0.000	0.938	0.056	0.000	0.000	0.000	91.799	0.076	0.001	0.025	7.106
9	0.000	0.926	0.055	0.000	0.000	0.000	90.639	0.075	0.001	0.024	8.279
10	0.000	0.913	0.054	0.000	0.000	0.000	89.397	0.074	0.001	0.024	9.536
11	0.000	0.900	0.054	0.000	0.000	0.000	88.061	0.073	0.001	0.024	10.888
12	0.000	0.885	0.053	0.000	0.000	0.000	86.623	0.072	0.001	0.024	12.343
13	0.000	0.869	0.052	0.000	0.000	0.000	85.076	0.071	0.001	0.024	13.908
14	0.000	0.853	0.051	0.000	0.000	0.000	83.431	0.069	0.001	0.024	15.572
15	0.000	0.834	0.050	0.000	0.000	0.000	81.657	0.068	0.001	0.023	17.367
16	0.000	0.815	0.048	0.000	0.000	0.000	79.726	0.066	0.001	0.023	19.322
17	0.000	0.793	0.047	0.000	0.000	0.000	77.630	0.065	0.001	0.022	21.442
18	0.000	0.770	0.046	0.000	0.000	0.000	75.392	0.063	0.001	0.022	23.706
19	0.000	0.746	0.044	0.000	0.000	0.000	72.967	0.061	0.001	0.021	26.160
20	0.000	0.719	0.043	0.000	0.000	0.000	70.368	0.059	0.001	0.020	28.791
21	0.000	0.691	0.041	0.000	0.000	0.000	67.580	0.057	0.001	0.020	31.611
22	0.000	0.660	0.039	0.000	0.000	0.000	64.600	0.054	0.000	0.019	34.627
23	0.000	0.628	0.037	0.000	0.000	0.000	61.440	0.052	0.000	0.018	37.825
24	0.000	0.594	0.035	0.000	0.000	0.000	58.123	0.049	0.000	0.017	41.181

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
25	0.000	0.559	0.033	0.000	0.000	0.000	54.662	0.046	0.000	0.016	44.684
26	0.000	0.522	0.031	0.000	0.000	0.000	51.058	0.043	0.000	0.015	48.331
26	0.000	0.484	0.029	0.000	0.000	0.000	47.340	0.040	0.000	0.014	52.093
27	0.000	0.445	0.026	0.000	0.000	0.000	43.547	0.037	0.000	0.013	55.931
28	0.000	0.406	0.024	0.000	0.000	0.000	39.710	0.033	0.000	0.012	59.814
30	0.000	0.368	0.022	0.000	0.000	0.000	35.970	0.030	0.000	0.011	63.600
31	0.000	0.330	0.020	0.000	0.000	0.000	32.248	0.027	0.000	0.010	67.366
32	0.000	0.292	0.017	0.000	0.000	0.000	28.596	0.024	0.000	0.009	71.061
33	0.000	0.255	0.015	0.000	0.000	0.000	24.921	0.021	0.000	0.007	74.781
34	0.000	0.219	0.013	0.000	0.000	0.000	21.389	0.018	0.000	0.006	78.355
35	0.000	0.185	0.011	0.000	0.000	0.000	18.152	0.015	0.000	0.005	81.631
36	0.000	0.155	0.009	0.000	0.000	0.000	15.174	0.013	0.000	0.005	84.644
37	0.000	0.128	0.008	0.000	0.000	0.000	12.487	0.011	0.000	0.004	87.363
38	0.000	0.103	0.006	0.000	0.000	0.000	10.101	0.009	0.000	0.003	89.778
39	0.000	0.082	0.005	0.000	0.000	0.000	8.034	0.007	0.000	0.002	91.870
40	0.000	0.064	0.004	0.000	0.000	0.000	6.269	0.005	0.000	0.002	93.655

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH, HS10: long-term CTEPH; HS11: death.

Table 60: Markov trace: rivaroxaban arm, 12 months of treatment, aged 56 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	90.485	0.843	0.903	5.163	0.071	0.496	1.900	0.000	0.000	0.000	0.139
0.5	91.559	0.149	0.143	1.510	0.022	0.154	5.900	0.040	0.011	0.000	0.513
0.75	89.728	0.099	0.056	1.314	0.000	0.000	8.042	0.052	0.002	0.011	0.696
1	87.699	0.120	0.060	1.288	0.000	0.000	9.922	0.052	0.001	0.012	0.847
2	0.000	0.994	0.059	0.000	0.000	0.000	97.312	0.052	0.001	0.016	1.566
3	0.000	0.987	0.059	0.000	0.000	0.000	96.613	0.052	0.001	0.017	2.272
4	0.000	0.980	0.058	0.000	0.000	0.000	95.861	0.051	0.001	0.018	3.032
5	0.000	0.971	0.058	0.000	0.000	0.000	95.026	0.051	0.001	0.019	3.875
6	0.000	0.962	0.057	0.000	0.000	0.000	94.116	0.050	0.001	0.020	4.795
7	0.000	0.951	0.057	0.000	0.000	0.000	93.118	0.050	0.001	0.020	5.803
8	0.000	0.941	0.056	0.000	0.000	0.000	92.049	0.049	0.001	0.021	6.884
9	0.000	0.929	0.055	0.000	0.000	0.000	90.886	0.049	0.001	0.021	8.059
10	0.000	0.916	0.055	0.000	0.000	0.000	89.641	0.048	0.001	0.021	9.318
11	0.000	0.902	0.054	0.000	0.000	0.000	88.301	0.047	0.001	0.022	10.673
12	0.000	0.888	0.053	0.000	0.000	0.000	86.859	0.047	0.001	0.022	12.132
13	0.000	0.872	0.052	0.000	0.000	0.000	85.308	0.046	0.001	0.022	13.700
14	0.000	0.855	0.051	0.000	0.000	0.000	83.658	0.045	0.001	0.022	15.369
15	0.000	0.837	0.050	0.000	0.000	0.000	81.880	0.044	0.001	0.022	17.167
16	0.000	0.817	0.049	0.000	0.000	0.000	79.943	0.043	0.001	0.021	19.127
17	0.000	0.795	0.047	0.000	0.000	0.000	77.842	0.042	0.001	0.021	21.252
18	0.000	0.772	0.046	0.000	0.000	0.000	75.598	0.041	0.001	0.021	23.522
19	0.000	0.748	0.045	0.000	0.000	0.000	73.166	0.040	0.001	0.020	25.981
20	0.000	0.721	0.043	0.000	0.000	0.000	70.560	0.038	0.001	0.020	28.618
21	0.000	0.692	0.041	0.000	0.000	0.000	67.764	0.037	0.001	0.019	31.446
22	0.000	0.662	0.039	0.000	0.000	0.000	64.776	0.035	0.000	0.018	34.469
23	0.000	0.630	0.037	0.000	0.000	0.000	61.607	0.033	0.000	0.018	37.674
24	0.000	0.596	0.035	0.000	0.000	0.000	58.282	0.032	0.000	0.017	41.039

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
25	0.000	0.560	0.033	0.000	0.000	0.000	54.811	0.030	0.000	0.016	44.550
26	0.000	0.523	0.031	0.000	0.000	0.000	51.197	0.028	0.000	0.015	48.206
26	0.000	0.485	0.029	0.000	0.000	0.000	47.469	0.026	0.000	0.014	51.977
27	0.000	0.446	0.027	0.000	0.000	0.000	43.666	0.024	0.000	0.013	55.824
28	0.000	0.407	0.024	0.000	0.000	0.000	39.818	0.022	0.000	0.012	59.717
30	0.000	0.369	0.022	0.000	0.000	0.000	36.068	0.020	0.000	0.011	63.511
31	0.000	0.330	0.020	0.000	0.000	0.000	32.336	0.018	0.000	0.010	67.287
32	0.000	0.293	0.017	0.000	0.000	0.000	28.674	0.016	0.000	0.008	70.991
33	0.000	0.255	0.015	0.000	0.000	0.000	24.989	0.014	0.000	0.007	74.719
34	0.000	0.219	0.013	0.000	0.000	0.000	21.447	0.012	0.000	0.006	78.303
35	0.000	0.186	0.011	0.000	0.000	0.000	18.201	0.010	0.000	0.005	81.586
36	0.000	0.155	0.009	0.000	0.000	0.000	15.216	0.008	0.000	0.005	84.606
37	0.000	0.128	0.008	0.000	0.000	0.000	12.521	0.007	0.000	0.004	87.333
38	0.000	0.103	0.006	0.000	0.000	0.000	10.128	0.006	0.000	0.003	89.753
39	0.000	0.082	0.005	0.000	0.000	0.000	8.056	0.004	0.000	0.002	91.850
40	0.000	0.064	0.004	0.000	0.000	0.000	6.286	0.003	0.000	0.002	93.640

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH, HS10: long-term CTEPH; HS11: death.

Table 61: Markov trace: LMWH/VKA arm, 12 months of treatment, aged 56 years at baseline

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
0	100.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.25	89.625	1.235	1.323	4.903	0.109	0.766	1.900	0.000	0.000	0.000	0.139
0.5	90.516	0.208	0.206	1.418	0.034	0.236	6.678	0.062	0.017	0.000	0.626
0.75	88.718	0.124	0.077	1.232	0.000	0.000	8.920	0.081	0.003	0.016	0.831
1	86.681	0.146	0.081	1.208	0.000	0.000	10.800	0.080	0.001	0.018	0.985
2	0.000	0.993	0.059	0.000	0.000	0.000	97.136	0.080	0.001	0.021	1.710
3	0.000	0.985	0.059	0.000	0.000	0.000	96.439	0.079	0.001	0.022	2.415
4	0.000	0.978	0.058	0.000	0.000	0.000	95.687	0.079	0.001	0.023	3.174
5	0.000	0.969	0.058	0.000	0.000	0.000	94.854	0.078	0.001	0.023	4.017
6	0.000	0.960	0.057	0.000	0.000	0.000	93.945	0.078	0.001	0.023	4.936
7	0.000	0.950	0.057	0.000	0.000	0.000	92.949	0.077	0.001	0.023	5.943
8	0.000	0.939	0.056	0.000	0.000	0.000	91.883	0.076	0.001	0.024	7.022
9	0.000	0.927	0.055	0.000	0.000	0.000	90.722	0.075	0.001	0.024	8.196
10	0.000	0.914	0.054	0.000	0.000	0.000	89.479	0.074	0.001	0.024	9.454
11	0.000	0.901	0.054	0.000	0.000	0.000	88.141	0.073	0.001	0.024	10.807
12	0.000	0.886	0.053	0.000	0.000	0.000	86.702	0.072	0.001	0.024	12.264
13	0.000	0.870	0.052	0.000	0.000	0.000	85.154	0.071	0.001	0.023	13.830
14	0.000	0.853	0.051	0.000	0.000	0.000	83.507	0.069	0.001	0.023	15.496
15	0.000	0.835	0.050	0.000	0.000	0.000	81.732	0.068	0.001	0.023	17.292
16	0.000	0.815	0.049	0.000	0.000	0.000	79.798	0.066	0.001	0.022	19.248
17	0.000	0.794	0.047	0.000	0.000	0.000	77.701	0.065	0.001	0.022	21.370
18	0.000	0.771	0.046	0.000	0.000	0.000	75.461	0.063	0.001	0.022	23.637
19	0.000	0.746	0.044	0.000	0.000	0.000	73.034	0.061	0.001	0.021	26.093
20	0.000	0.720	0.043	0.000	0.000	0.000	70.432	0.059	0.001	0.020	28.726
21	0.000	0.691	0.041	0.000	0.000	0.000	67.642	0.057	0.001	0.020	31.549
22	0.000	0.661	0.039	0.000	0.000	0.000	64.659	0.054	0.000	0.019	34.568
23	0.000	0.628	0.037	0.000	0.000	0.000	61.496	0.052	0.000	0.018	37.768
24	0.000	0.594	0.035	0.000	0.000	0.000	58.176	0.049	0.000	0.017	41.128

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11
25	0.000	0.559	0.033	0.000	0.000	0.000	54.712	0.046	0.000	0.016	44.633
26	0.000	0.522	0.031	0.000	0.000	0.000	51.104	0.043	0.000	0.015	48.284
26	0.000	0.484	0.029	0.000	0.000	0.000	47.383	0.040	0.000	0.014	52.050
27	0.000	0.445	0.027	0.000	0.000	0.000	43.587	0.037	0.000	0.013	55.891
28	0.000	0.406	0.024	0.000	0.000	0.000	39.746	0.033	0.000	0.012	59.778
30	0.000	0.368	0.022	0.000	0.000	0.000	36.002	0.030	0.000	0.011	63.567
31	0.000	0.330	0.020	0.000	0.000	0.000	32.277	0.027	0.000	0.010	67.336
32	0.000	0.292	0.017	0.000	0.000	0.000	28.622	0.024	0.000	0.009	71.035
33	0.000	0.255	0.015	0.000	0.000	0.000	24.944	0.021	0.000	0.007	74.758
34	0.000	0.219	0.013	0.000	0.000	0.000	21.408	0.018	0.000	0.006	78.335
35	0.000	0.186	0.011	0.000	0.000	0.000	18.168	0.015	0.000	0.005	81.614
36	0.000	0.155	0.009	0.000	0.000	0.000	15.188	0.013	0.000	0.005	84.630
37	0.000	0.128	0.008	0.000	0.000	0.000	12.498	0.011	0.000	0.004	87.352
38	0.000	0.103	0.006	0.000	0.000	0.000	10.110	0.009	0.000	0.003	89.769
39	0.000	0.082	0.005	0.000	0.000	0.000	8.041	0.007	0.000	0.002	91.862
40	0.000	0.064	0.004	0.000	0.000	0.000	6.275	0.005	0.000	0.002	93.650

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH, HS10: long-term CTEPH; HS11: death.

6.7.3 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 six tables below show the cumulative QALYs for the two treatments arms analysed when treatment duration is 3, 6, and 12 months. Note the values associated with mild/moderate PTS (HS12) are 0 as this state is inactive in the present analysis. The values for severe PTS (HS13) are disutilities.

Table 62: 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*
0.25	18.6625	0.1672	0.1654	1.0648	0.0051	0.0915	0.3919	0.0000	0.0000	0.0000	0.0000	0.0000	0.0098
0.5	0.0000	0.1869	0.0411	0.0000	0.0000	0.0000	20.2445	0.0071	0.0016	0.0000	0.0000	0.0000	0.0196
0.75	0.0000	0.1986	0.0437	0.0000	0.0000	0.0000	20.1850	0.0071	0.0004	0.0015	0.0000	0.0000	0.0293
1	0.0000	0.1980	0.0435	0.0000	0.0000	0.0000	20.1404	0.0071	0.0004	0.0019	0.0000	0.0000	0.0390
2	0.0000	0.1968	0.0108	0.0000	0.0000	0.0000	20.0286	0.0070	0.0001	0.0026	0.0000	0.0000	0.0589
3	0.0000	0.1953	0.0107	0.0000	0.0000	0.0000	19.8847	0.0070	0.0001	0.0028	0.0000	0.0000	0.0784
4	0.0000	0.1938	0.0107	0.0000	0.0000	0.0000	19.7298	0.0070	0.0001	0.0029	0.0000	0.0000	0.0977
5	0.0000	0.1921	0.0106	0.0000	0.0000	0.0000	19.5580	0.0069	0.0001	0.0030	0.0000	0.0000	0.1164
6	0.0000	0.1903	0.0105	0.0000	0.0000	0.0000	19.3706	0.0068	0.0001	0.0030	0.0000	0.0000	0.1153
7	0.0000	0.1883	0.0103	0.0000	0.0000	0.0000	19.1653	0.0068	0.0001	0.0031	0.0000	0.0000	0.1141
8	0.0000	0.1861	0.0102	0.0000	0.0000	0.0000	18.9453	0.0067	0.0001	0.0031	0.0000	0.0000	0.1128
9	0.0000	0.1838	0.0101	0.0000	0.0000	0.0000	18.7060	0.0066	0.0001	0.0032	0.0000	0.0000	0.1114
10	0.0000	0.1812	0.0100	0.0000	0.0000	0.0000	18.4497	0.0065	0.0001	0.0032	0.0000	0.0000	0.1098
11	0.0000	0.1785	0.0098	0.0000	0.0000	0.0000	18.1739	0.0064	0.0001	0.0032	0.0000	0.0000	0.1082
12	0.0000	0.1756	0.0097	0.0000	0.0000	0.0000	17.8770	0.0063	0.0001	0.0032	0.0000	0.0000	0.1064
13	0.0000	0.1725	0.0095	0.0000	0.0000	0.0000	17.5578	0.0062	0.0001	0.0032	0.0000	0.0000	0.1045
14	0.0000	0.1691	0.0093	0.0000	0.0000	0.0000	17.2184	0.0061	0.0001	0.0031	0.0000	0.0000	0.1025
15	0.0000	0.1656	0.0091	0.0000	0.0000	0.0000	16.8523	0.0060	0.0001	0.0031	0.0000	0.0000	0.1003
16	0.0000	0.1616	0.0089	0.0000	0.0000	0.0000	16.4536	0.0059	0.0001	0.0031	0.0000	0.0000	0.0980
17	0.0000	0.1574	0.0087	0.0000	0.0000	0.0000	16.0212	0.0057	0.0001	0.0030	0.0000	0.0000	0.0954

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12*	HS13*
18	0.0000	0.1529	0.0084	0.0000	0.0000	0.0000	15.5594	0.0055	0.0001	0.0030	0.0000	0.0000	0.0926
19	0.0000	0.1479	0.0081	0.0000	0.0000	0.0000	15.0589	0.0054	0.0001	0.0029	0.0000	0.0000	0.0897
20	0.0000	0.1427	0.0078	0.0000	0.0000	0.0000	14.5224	0.0052	0.0001	0.0028	0.0000	0.0000	0.0865
21	0.0000	0.1370	0.0075	0.0000	0.0000	0.0000	13.9471	0.0050	0.0001	0.0027	0.0000	0.0000	0.0830
22	0.0000	0.1310	0.0072	0.0000	0.0000	0.0000	13.3321	0.0048	0.0001	0.0026	0.0000	0.0000	0.0794
23	0.0000	0.1246	0.0068	0.0000	0.0000	0.0000	12.6798	0.0045	0.0001	0.0025	0.0000	0.0000	0.0755
24	0.0000	0.1178	0.0065	0.0000	0.0000	0.0000	11.9954	0.0043	0.0001	0.0024	0.0000	0.0000	0.0714
25	0.0000	0.1108	0.0061	0.0000	0.0000	0.0000	11.2811	0.0040	0.0001	0.0022	0.0000	0.0000	0.0672
26	0.0000	0.1035	0.0057	0.0000	0.0000	0.0000	10.5372	0.0038	0.0001	0.0021	0.0000	0.0000	0.0627
26	0.0000	0.0960	0.0053	0.0000	0.0000	0.0000	9.7699	0.0035	0.0001	0.0019	0.0000	0.0000	0.0582
27	0.0000	0.0883	0.0049	0.0000	0.0000	0.0000	8.9873	0.0032	0.0000	0.0018	0.0000	0.0000	0.0535
28	0.0000	0.0805	0.0044	0.0000	0.0000	0.0000	8.1953	0.0029	0.0000	0.0016	0.0000	0.0000	0.0488
30	0.0000	0.0729	0.0040	0.0000	0.0000	0.0000	7.4233	0.0027	0.0000	0.0015	0.0000	0.0000	0.0442
31	0.0000	0.0654	0.0036	0.0000	0.0000	0.0000	6.6553	0.0024	0.0000	0.0013	0.0000	0.0000	0.0396
32	0.0000	0.0580	0.0032	0.0000	0.0000	0.0000	5.9017	0.0021	0.0000	0.0012	0.0000	0.0000	0.0351
33	0.0000	0.0505	0.0028	0.0000	0.0000	0.0000	5.1431	0.0019	0.0000	0.0010	0.0000	0.0000	0.0306
34	0.0000	0.0434	0.0024	0.0000	0.0000	0.0000	4.4142	0.0016	0.0000	0.0009	0.0000	0.0000	0.0263
35	0.0000	0.0368	0.0020	0.0000	0.0000	0.0000	3.7461	0.0014	0.0000	0.0008	0.0000	0.0000	0.0223
36	0.0000	0.0308	0.0017	0.0000	0.0000	0.0000	3.1317	0.0011	0.0000	0.0006	0.0000	0.0000	0.0186
37	0.0000	0.0253	0.0014	0.0000	0.0000	0.0000	2.5771	0.0009	0.0000	0.0005	0.0000	0.0000	0.0153
38	0.0000	0.0205	0.0011	0.0000	0.0000	0.0000	2.0846	0.0008	0.0000	0.0004	0.0000	0.0000	0.0124
39	0.0000	0.0163	0.0009	0.0000	0.0000	0.0000	1.6580	0.0006	0.0000	0.0003	0.0000	0.0000	0.0099
40	0.0000	0.0127	0.0007	0.0000	0.0000	0.0000	1.2939	0.0005	0.0000	0.0003	0.0000	0.0000	0.0077

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH; HS10: long-term CTEPH; HS11: death; HS12: mild/moderate PTS; HS13: severe PTS. * Disutilities

Table 63: 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*
0.25	18.4852	0.2448	0.2422	1.0112	0.0078	0.1414	0.3919	0.0000	0.0000	0.0000	0.0000	0.0000	0.0098
0.5	0.0000	0.1851	0.0407	0.0000	0.0000	0.0000	20.2069	0.0110	0.0023	0.0000	0.0000	0.0000	0.0195
0.75	0.0000	0.1982	0.0436	0.0000	0.0000	0.0000	20.1459	0.0110	0.0004	0.0023	0.0000	0.0000	0.0292
1	0.0000	0.1976	0.0434	0.0000	0.0000	0.0000	20.1014	0.0110	0.0004	0.0026	0.0000	0.0000	0.0389
2	0.0000	0.1964	0.0108	0.0000	0.0000	0.0000	19.9898	0.0109	0.0001	0.0033	0.0000	0.0000	0.0588
3	0.0000	0.1950	0.0107	0.0000	0.0000	0.0000	19.8462	0.0108	0.0001	0.0033	0.0000	0.0000	0.0783
4	0.0000	0.1934	0.0106	0.0000	0.0000	0.0000	19.6916	0.0107	0.0001	0.0034	0.0000	0.0000	0.0975
5	0.0000	0.1918	0.0105	0.0000	0.0000	0.0000	19.5201	0.0107	0.0001	0.0034	0.0000	0.0000	0.1162
6	0.0000	0.1899	0.0104	0.0000	0.0000	0.0000	19.3331	0.0106	0.0001	0.0034	0.0000	0.0000	0.1151
7	0.0000	0.1879	0.0103	0.0000	0.0000	0.0000	19.1281	0.0105	0.0001	0.0034	0.0000	0.0000	0.1139
8	0.0000	0.1858	0.0102	0.0000	0.0000	0.0000	18.9086	0.0103	0.0001	0.0034	0.0000	0.0000	0.1126
9	0.0000	0.1834	0.0101	0.0000	0.0000	0.0000	18.6698	0.0102	0.0001	0.0034	0.0000	0.0000	0.1112
10	0.0000	0.1809	0.0099	0.0000	0.0000	0.0000	18.4139	0.0101	0.0001	0.0034	0.0000	0.0000	0.1097
11	0.0000	0.1782	0.0098	0.0000	0.0000	0.0000	18.1387	0.0100	0.0001	0.0034	0.0000	0.0000	0.1080
12	0.0000	0.1753	0.0096	0.0000	0.0000	0.0000	17.8424	0.0098	0.0001	0.0034	0.0000	0.0000	0.1063
13	0.0000	0.1721	0.0095	0.0000	0.0000	0.0000	17.5238	0.0096	0.0001	0.0033	0.0000	0.0000	0.1044
14	0.0000	0.1688	0.0093	0.0000	0.0000	0.0000	17.1850	0.0095	0.0001	0.0033	0.0000	0.0000	0.1023
15	0.0000	0.1652	0.0091	0.0000	0.0000	0.0000	16.8197	0.0093	0.0001	0.0033	0.0000	0.0000	0.1002
16	0.0000	0.1613	0.0089	0.0000	0.0000	0.0000	16.4217	0.0090	0.0001	0.0032	0.0000	0.0000	0.0978
17	0.0000	0.1571	0.0086	0.0000	0.0000	0.0000	15.9901	0.0088	0.0001	0.0031	0.0000	0.0000	0.0952
18	0.0000	0.1526	0.0084	0.0000	0.0000	0.0000	15.5292	0.0086	0.0001	0.0031	0.0000	0.0000	0.0925
19	0.0000	0.1476	0.0081	0.0000	0.0000	0.0000	15.0297	0.0083	0.0001	0.0030	0.0000	0.0000	0.0895
20	0.0000	0.1424	0.0078	0.0000	0.0000	0.0000	14.4943	0.0080	0.0001	0.0029	0.0000	0.0000	0.0863
21	0.0000	0.1367	0.0075	0.0000	0.0000	0.0000	13.9200	0.0077	0.0001	0.0028	0.0000	0.0000	0.0829
22	0.0000	0.1307	0.0072	0.0000	0.0000	0.0000	13.3062	0.0074	0.0001	0.0027	0.0000	0.0000	0.0792
23	0.0000	0.1243	0.0068	0.0000	0.0000	0.0000	12.6553	0.0070	0.0001	0.0025	0.0000	0.0000	0.0754
24	0.0000	0.1176	0.0065	0.0000	0.0000	0.0000	11.9722	0.0066	0.0001	0.0024	0.0000	0.0000	0.0713
25	0.0000	0.1106	0.0061	0.0000	0.0000	0.0000	11.2592	0.0063	0.0001	0.0023	0.0000	0.0000	0.0671

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12*	HS13*
26	0.0000	0.1033	0.0057	0.0000	0.0000	0.0000	10.5168	0.0058	0.0001	0.0021	0.0000	0.0000	0.0626
26	0.0000	0.0958	0.0053	0.0000	0.0000	0.0000	9.7510	0.0054	0.0001	0.0020	0.0000	0.0000	0.0581
27	0.0000	0.0881	0.0048	0.0000	0.0000	0.0000	8.9698	0.0050	0.0000	0.0018	0.0000	0.0000	0.0534
28	0.0000	0.0804	0.0044	0.0000	0.0000	0.0000	8.1795	0.0046	0.0000	0.0017	0.0000	0.0000	0.0487
30	0.0000	0.0728	0.0040	0.0000	0.0000	0.0000	7.4090	0.0041	0.0000	0.0015	0.0000	0.0000	0.0441
31	0.0000	0.0653	0.0036	0.0000	0.0000	0.0000	6.6424	0.0037	0.0000	0.0013	0.0000	0.0000	0.0396
32	0.0000	0.0579	0.0032	0.0000	0.0000	0.0000	5.8902	0.0033	0.0000	0.0012	0.0000	0.0000	0.0351
33	0.0000	0.0504	0.0028	0.0000	0.0000	0.0000	5.1332	0.0029	0.0000	0.0010	0.0000	0.0000	0.0306
34	0.0000	0.0433	0.0024	0.0000	0.0000	0.0000	4.4056	0.0025	0.0000	0.0009	0.0000	0.0000	0.0262
35	0.0000	0.0367	0.0020	0.0000	0.0000	0.0000	3.7389	0.0021	0.0000	0.0008	0.0000	0.0000	0.0223
36	0.0000	0.0307	0.0017	0.0000	0.0000	0.0000	3.1256	0.0018	0.0000	0.0006	0.0000	0.0000	0.0186
37	0.0000	0.0253	0.0014	0.0000	0.0000	0.0000	2.5721	0.0014	0.0000	0.0005	0.0000	0.0000	0.0153
38	0.0000	0.0204	0.0011	0.0000	0.0000	0.0000	2.0806	0.0012	0.0000	0.0004	0.0000	0.0000	0.0124
39	0.0000	0.0163	0.0009	0.0000	0.0000	0.0000	1.6548	0.0009	0.0000	0.0003	0.0000	0.0000	0.0099
40	0.0000	0.0127	0.0007	0.0000	0.0000	0.0000	1.2914	0.0007	0.0000	0.0003	0.0000	0.0000	0.0077

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH; HS10: long-term CTEPH; HS11: death; HS12: mild/moderate PTS; HS13: severe PTS. * Disutilities

Table 64: 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*
0.25	18.6625	0.1672	0.1654	1.0648	0.0051	0.0915	0.3919	0.0000	0.0000	0.0000	0.0000	0.0000	0.0098
0.5	18.8840	0.0295	0.0262	0.3113	0.0016	0.0285	1.2168	0.0071	0.0016	0.0000	0.0000	0.0000	0.0196
0.75	0.0000	0.1971	0.0433	0.0000	0.0000	0.0000	20.2103	0.0093	0.0003	0.0015	0.0000	0.0000	0.0293
1	0.0000	0.1982	0.0436	0.0000	0.0000	0.0000	20.1637	0.0093	0.0004	0.0017	0.0000	0.0000	0.0390
2	0.0000	0.1970	0.0108	0.0000	0.0000	0.0000	20.0517	0.0092	0.0001	0.0025	0.0000	0.0000	0.0589
3	0.0000	0.1956	0.0107	0.0000	0.0000	0.0000	19.9077	0.0092	0.0001	0.0027	0.0000	0.0000	0.0785
4	0.0000	0.1940	0.0107	0.0000	0.0000	0.0000	19.7526	0.0091	0.0001	0.0028	0.0000	0.0000	0.0978
5	0.0000	0.1924	0.0106	0.0000	0.0000	0.0000	19.5807	0.0090	0.0001	0.0029	0.0000	0.0000	0.1166
6	0.0000	0.1905	0.0105	0.0000	0.0000	0.0000	19.3930	0.0090	0.0001	0.0029	0.0000	0.0000	0.1155
7	0.0000	0.1885	0.0104	0.0000	0.0000	0.0000	19.1874	0.0089	0.0001	0.0030	0.0000	0.0000	0.1142
8	0.0000	0.1863	0.0102	0.0000	0.0000	0.0000	18.9672	0.0088	0.0001	0.0031	0.0000	0.0000	0.1129
9	0.0000	0.1840	0.0101	0.0000	0.0000	0.0000	18.7276	0.0087	0.0001	0.0031	0.0000	0.0000	0.1115
10	0.0000	0.1815	0.0100	0.0000	0.0000	0.0000	18.4710	0.0086	0.0001	0.0031	0.0000	0.0000	0.1100
11	0.0000	0.1787	0.0098	0.0000	0.0000	0.0000	18.1949	0.0084	0.0001	0.0031	0.0000	0.0000	0.1083
12	0.0000	0.1758	0.0097	0.0000	0.0000	0.0000	17.8977	0.0083	0.0001	0.0031	0.0000	0.0000	0.1066
13	0.0000	0.1727	0.0095	0.0000	0.0000	0.0000	17.5781	0.0082	0.0001	0.0031	0.0000	0.0000	0.1047
14	0.0000	0.1693	0.0093	0.0000	0.0000	0.0000	17.2383	0.0080	0.0001	0.0031	0.0000	0.0000	0.1026
15	0.0000	0.1657	0.0091	0.0000	0.0000	0.0000	16.8718	0.0079	0.0001	0.0031	0.0000	0.0000	0.1005
16	0.0000	0.1618	0.0089	0.0000	0.0000	0.0000	16.4726	0.0077	0.0001	0.0031	0.0000	0.0000	0.0981
17	0.0000	0.1576	0.0087	0.0000	0.0000	0.0000	16.0397	0.0075	0.0001	0.0030	0.0000	0.0000	0.0955
18	0.0000	0.1530	0.0084	0.0000	0.0000	0.0000	15.5774	0.0073	0.0001	0.0029	0.0000	0.0000	0.0928
19	0.0000	0.1481	0.0081	0.0000	0.0000	0.0000	15.0763	0.0070	0.0001	0.0029	0.0000	0.0000	0.0898
20	0.0000	0.1428	0.0079	0.0000	0.0000	0.0000	14.5392	0.0068	0.0001	0.0028	0.0000	0.0000	0.0866
21	0.0000	0.1372	0.0075	0.0000	0.0000	0.0000	13.9632	0.0065	0.0001	0.0027	0.0000	0.0000	0.0831
22	0.0000	0.1311	0.0072	0.0000	0.0000	0.0000	13.3475	0.0063	0.0001	0.0026	0.0000	0.0000	0.0795
23	0.0000	0.1247	0.0069	0.0000	0.0000	0.0000	12.6945	0.0060	0.0001	0.0025	0.0000	0.0000	0.0756
24	0.0000	0.1180	0.0065	0.0000	0.0000	0.0000	12.0093	0.0056	0.0001	0.0024	0.0000	0.0000	0.0715
25	0.0000	0.1110	0.0061	0.0000	0.0000	0.0000	11.2941	0.0053	0.0001	0.0022	0.0000	0.0000	0.0673
26	0.0000	0.1036	0.0057	0.0000	0.0000	0.0000	10.5494	0.0050	0.0001	0.0021	0.0000	0.0000	0.0628

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12*	HS13*
26	0.0000	0.0961	0.0053	0.0000	0.0000	0.0000	9.7812	0.0046	0.0001	0.0019	0.0000	0.0000	0.0582
27	0.0000	0.0884	0.0049	0.0000	0.0000	0.0000	8.9976	0.0042	0.0000	0.0018	0.0000	0.0000	0.0536
28	0.0000	0.0806	0.0044	0.0000	0.0000	0.0000	8.2048	0.0039	0.0000	0.0016	0.0000	0.0000	0.0489
30	0.0000	0.0730	0.0040	0.0000	0.0000	0.0000	7.4319	0.0035	0.0000	0.0015	0.0000	0.0000	0.0443
31	0.0000	0.0655	0.0036	0.0000	0.0000	0.0000	6.6630	0.0031	0.0000	0.0013	0.0000	0.0000	0.0397
32	0.0000	0.0580	0.0032	0.0000	0.0000	0.0000	5.9085	0.0028	0.0000	0.0012	0.0000	0.0000	0.0352
33	0.0000	0.0506	0.0028	0.0000	0.0000	0.0000	5.1491	0.0024	0.0000	0.0010	0.0000	0.0000	0.0307
34	0.0000	0.0434	0.0024	0.0000	0.0000	0.0000	4.4193	0.0021	0.0000	0.0009	0.0000	0.0000	0.0263
35	0.0000	0.0368	0.0020	0.0000	0.0000	0.0000	3.7505	0.0018	0.0000	0.0008	0.0000	0.0000	0.0223
36	0.0000	0.0308	0.0017	0.0000	0.0000	0.0000	3.1353	0.0015	0.0000	0.0006	0.0000	0.0000	0.0187
37	0.0000	0.0253	0.0014	0.0000	0.0000	0.0000	2.5800	0.0012	0.0000	0.0005	0.0000	0.0000	0.0154
38	0.0000	0.0205	0.0011	0.0000	0.0000	0.0000	2.0870	0.0010	0.0000	0.0004	0.0000	0.0000	0.0124
39	0.0000	0.0163	0.0009	0.0000	0.0000	0.0000	1.6599	0.0008	0.0000	0.0003	0.0000	0.0000	0.0099
40	0.0000	0.0127	0.0007	0.0000	0.0000	0.0000	1.2954	0.0006	0.0000	0.0003	0.0000	0.0000	0.0077

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH; HS10: long-term CTEPH; HS11: death; HS12: mild/moderate PTS; HS13: severe PTS. * Disutilities

Table 65: 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*
0.25	18.4852	0.2448	0.2422	1.0112	0.0078	0.1414	0.3919	0.0000	0.0000	0.0000	0.0000	0.0000	0.0098
0.5	18.6689	0.0412	0.0378	0.2926	0.0024	0.0436	1.3773	0.0110	0.0023	0.0000	0.0000	0.0000	0.0196
0.75	0.0000	0.1966	0.0432	0.0000	0.0000	0.0000	20.1747	0.0144	0.0004	0.0023	0.0000	0.0000	0.0293
1	0.0000	0.1979	0.0435	0.0000	0.0000	0.0000	20.1279	0.0143	0.0004	0.0025	0.0000	0.0000	0.0390
2	0.0000	0.1966	0.0108	0.0000	0.0000	0.0000	20.0161	0.0143	0.0001	0.0032	0.0000	0.0000	0.0588
3	0.0000	0.1952	0.0107	0.0000	0.0000	0.0000	19.8723	0.0142	0.0001	0.0033	0.0000	0.0000	0.0784
4	0.0000	0.1937	0.0106	0.0000	0.0000	0.0000	19.7176	0.0141	0.0001	0.0033	0.0000	0.0000	0.0976
5	0.0000	0.1920	0.0106	0.0000	0.0000	0.0000	19.5459	0.0140	0.0001	0.0034	0.0000	0.0000	0.1164
6	0.0000	0.1902	0.0105	0.0000	0.0000	0.0000	19.3586	0.0138	0.0001	0.0034	0.0000	0.0000	0.1153
7	0.0000	0.1882	0.0103	0.0000	0.0000	0.0000	19.1533	0.0137	0.0001	0.0034	0.0000	0.0000	0.1141
8	0.0000	0.1860	0.0102	0.0000	0.0000	0.0000	18.9335	0.0135	0.0001	0.0034	0.0000	0.0000	0.1128
9	0.0000	0.1836	0.0101	0.0000	0.0000	0.0000	18.6944	0.0134	0.0001	0.0034	0.0000	0.0000	0.1113
10	0.0000	0.1811	0.0100	0.0000	0.0000	0.0000	18.4382	0.0132	0.0001	0.0034	0.0000	0.0000	0.1098
11	0.0000	0.1784	0.0098	0.0000	0.0000	0.0000	18.1626	0.0130	0.0001	0.0034	0.0000	0.0000	0.1082
12	0.0000	0.1755	0.0096	0.0000	0.0000	0.0000	17.8659	0.0128	0.0001	0.0034	0.0000	0.0000	0.1064
13	0.0000	0.1724	0.0095	0.0000	0.0000	0.0000	17.5469	0.0126	0.0001	0.0033	0.0000	0.0000	0.1045
14	0.0000	0.1690	0.0093	0.0000	0.0000	0.0000	17.2076	0.0124	0.0001	0.0033	0.0000	0.0000	0.1025
15	0.0000	0.1654	0.0091	0.0000	0.0000	0.0000	16.8419	0.0121	0.0001	0.0033	0.0000	0.0000	0.1003
16	0.0000	0.1615	0.0089	0.0000	0.0000	0.0000	16.4434	0.0118	0.0001	0.0032	0.0000	0.0000	0.0979
17	0.0000	0.1573	0.0086	0.0000	0.0000	0.0000	16.0112	0.0115	0.0001	0.0031	0.0000	0.0000	0.0954
18	0.0000	0.1528	0.0084	0.0000	0.0000	0.0000	15.5497	0.0112	0.0001	0.0030	0.0000	0.0000	0.0926
19	0.0000	0.1478	0.0081	0.0000	0.0000	0.0000	15.0495	0.0109	0.0001	0.0030	0.0000	0.0000	0.0896
20	0.0000	0.1426	0.0078	0.0000	0.0000	0.0000	14.5134	0.0105	0.0001	0.0029	0.0000	0.0000	0.0864
21	0.0000	0.1369	0.0075	0.0000	0.0000	0.0000	13.9384	0.0101	0.0001	0.0028	0.0000	0.0000	0.0830
22	0.0000	0.1309	0.0072	0.0000	0.0000	0.0000	13.3238	0.0096	0.0001	0.0027	0.0000	0.0000	0.0794
23	0.0000	0.1245	0.0068	0.0000	0.0000	0.0000	12.6720	0.0092	0.0001	0.0025	0.0000	0.0000	0.0755
24	0.0000	0.1178	0.0065	0.0000	0.0000	0.0000	11.9880	0.0087	0.0001	0.0024	0.0000	0.0000	0.0714
25	0.0000	0.1108	0.0061	0.0000	0.0000	0.0000	11.2741	0.0082	0.0001	0.0023	0.0000	0.0000	0.0672

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12*	HS13*
26	0.0000	0.1035	0.0057	0.0000	0.0000	0.0000	10.5307	0.0076	0.0001	0.0021	0.0000	0.0000	0.0627
26	0.0000	0.0959	0.0053	0.0000	0.0000	0.0000	9.7639	0.0071	0.0001	0.0020	0.0000	0.0000	0.0582
27	0.0000	0.0882	0.0048	0.0000	0.0000	0.0000	8.9817	0.0065	0.0000	0.0018	0.0000	0.0000	0.0535
28	0.0000	0.0805	0.0044	0.0000	0.0000	0.0000	8.1902	0.0060	0.0000	0.0017	0.0000	0.0000	0.0488
30	0.0000	0.0729	0.0040	0.0000	0.0000	0.0000	7.4187	0.0054	0.0000	0.0015	0.0000	0.0000	0.0442
31	0.0000	0.0653	0.0036	0.0000	0.0000	0.0000	6.6511	0.0049	0.0000	0.0013	0.0000	0.0000	0.0396
32	0.0000	0.0579	0.0032	0.0000	0.0000	0.0000	5.8980	0.0043	0.0000	0.0012	0.0000	0.0000	0.0351
33	0.0000	0.0505	0.0028	0.0000	0.0000	0.0000	5.1399	0.0038	0.0000	0.0010	0.0000	0.0000	0.0306
34	0.0000	0.0433	0.0024	0.0000	0.0000	0.0000	4.4114	0.0032	0.0000	0.0009	0.0000	0.0000	0.0263
35	0.0000	0.0368	0.0020	0.0000	0.0000	0.0000	3.7438	0.0027	0.0000	0.0008	0.0000	0.0000	0.0223
36	0.0000	0.0307	0.0017	0.0000	0.0000	0.0000	3.1297	0.0023	0.0000	0.0006	0.0000	0.0000	0.0186
37	0.0000	0.0253	0.0014	0.0000	0.0000	0.0000	2.5755	0.0019	0.0000	0.0005	0.0000	0.0000	0.0153
38	0.0000	0.0205	0.0011	0.0000	0.0000	0.0000	2.0833	0.0015	0.0000	0.0004	0.0000	0.0000	0.0124
39	0.0000	0.0163	0.0009	0.0000	0.0000	0.0000	1.6570	0.0012	0.0000	0.0003	0.0000	0.0000	0.0099
40	0.0000	0.0127	0.0007	0.0000	0.0000	0.0000	1.2931	0.0010	0.0000	0.0003	0.0000	0.0000	0.0077

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH; HS10: long-term CTEPH; HS11: death; HS12: mild/moderate PTS; HS13: severe PTS. * Disutilities

Table 66: 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*
0.25	18.6625	0.1672	0.1654	1.0648	0.0051	0.0915	0.3919	0.0000	0.0000	0.0000	0.0000	0.0000	0.0098
0.5	18.8840	0.0295	0.0262	0.3113	0.0016	0.0285	1.2168	0.0071	0.0016	0.0000	0.0000	0.0000	0.0196
0.75	18.5063	0.0196	0.0102	0.2710	0.0000	0.0000	1.6587	0.0093	0.0003	0.0015	0.0000	0.0000	0.0293
1	18.0879	0.0238	0.0110	0.2656	0.0000	0.0000	2.0463	0.0093	0.0001	0.0017	0.0000	0.0000	0.0390
2	0.0000	0.1972	0.0108	0.0000	0.0000	0.0000	20.0707	0.0092	0.0001	0.0022	0.0000	0.0000	0.0590
3	0.0000	0.1958	0.0108	0.0000	0.0000	0.0000	19.9265	0.0092	0.0001	0.0024	0.0000	0.0000	0.0786
4	0.0000	0.1942	0.0107	0.0000	0.0000	0.0000	19.7713	0.0091	0.0001	0.0025	0.0000	0.0000	0.0979
5	0.0000	0.1925	0.0106	0.0000	0.0000	0.0000	19.5991	0.0090	0.0001	0.0026	0.0000	0.0000	0.1167
6	0.0000	0.1907	0.0105	0.0000	0.0000	0.0000	19.4113	0.0090	0.0001	0.0027	0.0000	0.0000	0.1156
7	0.0000	0.1887	0.0104	0.0000	0.0000	0.0000	19.2055	0.0089	0.0001	0.0028	0.0000	0.0000	0.1144
8	0.0000	0.1865	0.0103	0.0000	0.0000	0.0000	18.9851	0.0088	0.0001	0.0029	0.0000	0.0000	0.1130
9	0.0000	0.1841	0.0101	0.0000	0.0000	0.0000	18.7453	0.0087	0.0001	0.0030	0.0000	0.0000	0.1116
10	0.0000	0.1816	0.0100	0.0000	0.0000	0.0000	18.4884	0.0086	0.0001	0.0030	0.0000	0.0000	0.1101
11	0.0000	0.1789	0.0098	0.0000	0.0000	0.0000	18.2120	0.0084	0.0001	0.0030	0.0000	0.0000	0.1084
12	0.0000	0.1760	0.0097	0.0000	0.0000	0.0000	17.9146	0.0083	0.0001	0.0030	0.0000	0.0000	0.1067
13	0.0000	0.1728	0.0095	0.0000	0.0000	0.0000	17.5947	0.0082	0.0001	0.0030	0.0000	0.0000	0.1048
14	0.0000	0.1695	0.0093	0.0000	0.0000	0.0000	17.2545	0.0080	0.0001	0.0030	0.0000	0.0000	0.1027
15	0.0000	0.1659	0.0091	0.0000	0.0000	0.0000	16.8877	0.0079	0.0001	0.0030	0.0000	0.0000	0.1006
16	0.0000	0.1620	0.0089	0.0000	0.0000	0.0000	16.4882	0.0077	0.0001	0.0030	0.0000	0.0000	0.0982
17	0.0000	0.1577	0.0087	0.0000	0.0000	0.0000	16.0548	0.0075	0.0001	0.0029	0.0000	0.0000	0.0956
18	0.0000	0.1532	0.0084	0.0000	0.0000	0.0000	15.5921	0.0073	0.0001	0.0029	0.0000	0.0000	0.0928
19	0.0000	0.1482	0.0081	0.0000	0.0000	0.0000	15.0905	0.0070	0.0001	0.0028	0.0000	0.0000	0.0899
20	0.0000	0.1430	0.0079	0.0000	0.0000	0.0000	14.5529	0.0068	0.0001	0.0028	0.0000	0.0000	0.0867
21	0.0000	0.1373	0.0075	0.0000	0.0000	0.0000	13.9764	0.0065	0.0001	0.0027	0.0000	0.0000	0.0832
22	0.0000	0.1312	0.0072	0.0000	0.0000	0.0000	13.3601	0.0063	0.0001	0.0026	0.0000	0.0000	0.0796
23	0.0000	0.1248	0.0069	0.0000	0.0000	0.0000	12.7065	0.0060	0.0001	0.0025	0.0000	0.0000	0.0757
24	0.0000	0.1181	0.0065	0.0000	0.0000	0.0000	12.0206	0.0056	0.0001	0.0023	0.0000	0.0000	0.0716
25	0.0000	0.1111	0.0061	0.0000	0.0000	0.0000	11.3048	0.0053	0.0001	0.0022	0.0000	0.0000	0.0673

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12*	HS13*
26	0.0000	0.1037	0.0057	0.0000	0.0000	0.0000	10.5594	0.0050	0.0001	0.0021	0.0000	0.0000	0.0629
26	0.0000	0.0962	0.0053	0.0000	0.0000	0.0000	9.7905	0.0046	0.0001	0.0019	0.0000	0.0000	0.0583
27	0.0000	0.0885	0.0049	0.0000	0.0000	0.0000	9.0061	0.0042	0.0000	0.0018	0.0000	0.0000	0.0536
28	0.0000	0.0807	0.0044	0.0000	0.0000	0.0000	8.2126	0.0039	0.0000	0.0016	0.0000	0.0000	0.0489
30	0.0000	0.0731	0.0040	0.0000	0.0000	0.0000	7.4389	0.0035	0.0000	0.0015	0.0000	0.0000	0.0443
31	0.0000	0.0655	0.0036	0.0000	0.0000	0.0000	6.6692	0.0031	0.0000	0.0013	0.0000	0.0000	0.0397
32	0.0000	0.0581	0.0032	0.0000	0.0000	0.0000	5.9141	0.0028	0.0000	0.0012	0.0000	0.0000	0.0352
33	0.0000	0.0506	0.0028	0.0000	0.0000	0.0000	5.1539	0.0024	0.0000	0.0010	0.0000	0.0000	0.0307
34	0.0000	0.0435	0.0024	0.0000	0.0000	0.0000	4.4235	0.0021	0.0000	0.0009	0.0000	0.0000	0.0263
35	0.0000	0.0369	0.0020	0.0000	0.0000	0.0000	3.7540	0.0018	0.0000	0.0008	0.0000	0.0000	0.0224
36	0.0000	0.0308	0.0017	0.0000	0.0000	0.0000	3.1383	0.0015	0.0000	0.0006	0.0000	0.0000	0.0187
37	0.0000	0.0254	0.0014	0.0000	0.0000	0.0000	2.5825	0.0012	0.0000	0.0005	0.0000	0.0000	0.0154
38	0.0000	0.0205	0.0011	0.0000	0.0000	0.0000	2.0890	0.0010	0.0000	0.0004	0.0000	0.0000	0.0124
39	0.0000	0.0163	0.0009	0.0000	0.0000	0.0000	1.6615	0.0008	0.0000	0.0003	0.0000	0.0000	0.0099
40	0.0000	0.0127	0.0007	0.0000	0.0000	0.0000	1.2966	0.0006	0.0000	0.0003	0.0000	0.0000	0.0077

HS1: on-treatment; HS2: DVT; HS3: PE; HS4: CRNM bleeds; HS5: intra-cranial bleeds; HS6: extra-cranial bleeds; HS7: off-treatment; HS8: off-treatment (post-IC bleed); HS9: acute CTEPH; HS10: long-term CTEPH; HS11: death; HS12: mild/moderate PTS; HS13: severe PTS. * Disutilities

Table 67: 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*
0.25	18.4852	0.2448	0.2422	1.0112	0.0078	0.1414	0.3919	0.0000	0.0000	0.0000	0.0000	0.0000	0.0098
0.5	18.6689	0.0412	0.0378	0.2926	0.0024	0.0436	1.3773	0.0110	0.0023	0.0000	0.0000	0.0000	0.0196
0.75	18.2980	0.0247	0.0140	0.2542	0.0000	0.0000	1.8397	0.0144	0.0004	0.0023	0.0000	0.0000	0.0293
1	17.8780	0.0290	0.0148	0.2491	0.0000	0.0000	2.2275	0.0143	0.0001	0.0025	0.0000	0.0000	0.0390
2	0.0000	0.1968	0.0108	0.0000	0.0000	0.0000	20.0344	0.0143	0.0001	0.0030	0.0000	0.0000	0.0589
3	0.0000	0.1954	0.0107	0.0000	0.0000	0.0000	19.8904	0.0142	0.0001	0.0031	0.0000	0.0000	0.0785
4	0.0000	0.1939	0.0107	0.0000	0.0000	0.0000	19.7355	0.0141	0.0001	0.0032	0.0000	0.0000	0.0977
5	0.0000	0.1922	0.0106	0.0000	0.0000	0.0000	19.5637	0.0140	0.0001	0.0032	0.0000	0.0000	0.1165
6	0.0000	0.1903	0.0105	0.0000	0.0000	0.0000	19.3762	0.0138	0.0001	0.0033	0.0000	0.0000	0.1154
7	0.0000	0.1883	0.0104	0.0000	0.0000	0.0000	19.1708	0.0137	0.0001	0.0033	0.0000	0.0000	0.1142
8	0.0000	0.1862	0.0102	0.0000	0.0000	0.0000	18.9508	0.0135	0.0001	0.0033	0.0000	0.0000	0.1129
9	0.0000	0.1838	0.0101	0.0000	0.0000	0.0000	18.7114	0.0134	0.0001	0.0033	0.0000	0.0000	0.1114
10	0.0000	0.1813	0.0100	0.0000	0.0000	0.0000	18.4550	0.0132	0.0001	0.0033	0.0000	0.0000	0.1099
11	0.0000	0.1786	0.0098	0.0000	0.0000	0.0000	18.1791	0.0130	0.0001	0.0033	0.0000	0.0000	0.1083
12	0.0000	0.1757	0.0097	0.0000	0.0000	0.0000	17.8822	0.0128	0.0001	0.0033	0.0000	0.0000	0.1065
13	0.0000	0.1725	0.0095	0.0000	0.0000	0.0000	17.5629	0.0126	0.0001	0.0033	0.0000	0.0000	0.1046
14	0.0000	0.1692	0.0093	0.0000	0.0000	0.0000	17.2233	0.0124	0.0001	0.0032	0.0000	0.0000	0.1026
15	0.0000	0.1656	0.0091	0.0000	0.0000	0.0000	16.8572	0.0121	0.0001	0.0032	0.0000	0.0000	0.1004
16	0.0000	0.1617	0.0089	0.0000	0.0000	0.0000	16.4584	0.0118	0.0001	0.0031	0.0000	0.0000	0.0980
17	0.0000	0.1574	0.0087	0.0000	0.0000	0.0000	16.0258	0.0115	0.0001	0.0031	0.0000	0.0000	0.0955
18	0.0000	0.1529	0.0084	0.0000	0.0000	0.0000	15.5639	0.0112	0.0001	0.0030	0.0000	0.0000	0.0927
19	0.0000	0.1480	0.0081	0.0000	0.0000	0.0000	15.0633	0.0109	0.0001	0.0029	0.0000	0.0000	0.0897
20	0.0000	0.1427	0.0078	0.0000	0.0000	0.0000	14.5266	0.0105	0.0001	0.0028	0.0000	0.0000	0.0865
21	0.0000	0.1371	0.0075	0.0000	0.0000	0.0000	13.9511	0.0101	0.0001	0.0027	0.0000	0.0000	0.0831
22	0.0000	0.1310	0.0072	0.0000	0.0000	0.0000	13.3359	0.0096	0.0001	0.0026	0.0000	0.0000	0.0794
23	0.0000	0.1246	0.0068	0.0000	0.0000	0.0000	12.6835	0.0092	0.0001	0.0025	0.0000	0.0000	0.0755
24	0.0000	0.1179	0.0065	0.0000	0.0000	0.0000	11.9989	0.0087	0.0001	0.0024	0.0000	0.0000	0.0715
25	0.0000	0.1109	0.0061	0.0000	0.0000	0.0000	11.2844	0.0082	0.0001	0.0022	0.0000	0.0000	0.0672

Years	HS1	HS2	HS3	HS4	HS5	HS6	HS7	HS8	HS9	HS10	HS11	HS12*	HS13*
26	0.0000	0.1035	0.0057	0.0000	0.0000	0.0000	10.5403	0.0076	0.0001	0.0021	0.0000	0.0000	0.0628
26	0.0000	0.0960	0.0053	0.0000	0.0000	0.0000	9.7728	0.0071	0.0001	0.0020	0.0000	0.0000	0.0582
27	0.0000	0.0883	0.0049	0.0000	0.0000	0.0000	8.9899	0.0065	0.0000	0.0018	0.0000	0.0000	0.0535
28	0.0000	0.0805	0.0044	0.0000	0.0000	0.0000	8.1977	0.0060	0.0000	0.0016	0.0000	0.0000	0.0488
30	0.0000	0.0729	0.0040	0.0000	0.0000	0.0000	7.4255	0.0054	0.0000	0.0015	0.0000	0.0000	0.0442
31	0.0000	0.0654	0.0036	0.0000	0.0000	0.0000	6.6572	0.0049	0.0000	0.0013	0.0000	0.0000	0.0397
32	0.0000	0.0580	0.0032	0.0000	0.0000	0.0000	5.9034	0.0043	0.0000	0.0012	0.0000	0.0000	0.0352
33	0.0000	0.0505	0.0028	0.0000	0.0000	0.0000	5.1446	0.0038	0.0000	0.0010	0.0000	0.0000	0.0306
34	0.0000	0.0434	0.0024	0.0000	0.0000	0.0000	4.4155	0.0032	0.0000	0.0009	0.0000	0.0000	0.0263
35	0.0000	0.0368	0.0020	0.0000	0.0000	0.0000	3.7472	0.0027	0.0000	0.0008	0.0000	0.0000	0.0223
36	0.0000	0.0308	0.0017	0.0000	0.0000	0.0000	3.1326	0.0023	0.0000	0.0006	0.0000	0.0000	0.0187
37	0.0000	0.0253	0.0014	0.0000	0.0000	0.0000	2.5778	0.0019	0.0000	0.0005	0.0000	0.0000	0.0154
38	0.0000	0.0205	0.0011	0.0000	0.0000	0.0000	2.0852	0.0015	0.0000	0.0004	0.0000	0.0000	0.0124
39	0.0000	0.0163	0.0009	0.0000	0.0000	0.0000	1.6585	0.0012	0.0000	0.0003	0.0000	0.0000	0.0099
40	0.0000	0.0127	0.0007	0.0000	0.0000	0.0000	1.2942	0.0010	0.0000	0.0003	0.0000	0.0000	0.0077

HS1: on-treatment; HS2: DVT (ipsilateral); HS3: DVT (contralateral); HS4: PE; HS5: CRNM bleeds; HS6: intra-cranial bleeds; HS7: extra-cranial bleeds; HS8: off-treatment; HS9: off-treatment (post-IC bleed); HS10: acute CTEPH: HS11: long-term CTEPH; HS12: death; HS13: mild/moderate PTS; HS14: severe PTS. * Disutilities

6.7.4 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. Table 68 reports the 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 and 12 months). Costs associated with each health state are also provided.

Overall, life years and QALYs accrued are higher for the 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. 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 68: Model outputs by clinical outcomes

	Rivaroxaban			LMWH/VKA		
	LY	QALY	Cost (£)	LY	QALY	Cost (£)
3 months of treatment						
VTE	0.2712	0.2140	1,047.11	0.2727	0.2151	1,056.42
Bleeding	0.0244	0.0188	69.87	0.0300	0.0227	104.63
6 months of treatment						
VTE	0.2693	0.2125	1,039.51	0.2712	0.2139	1,050.80
Bleeding	0.0317	0.0244	91.71	0.0390	0.0295	135.36
12 months of treatment						
VTE	0.2646	0.2088	1,020.73	0.2667	0.2104	1,033.24
Bleeding	0.0383	0.0298	98.33	0.0451	0.0345	140.75

Note: LYs, QALYs and costs are undiscounted.

6.7.5 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 three treatment durations considered.

Disaggregated QALYs by health state

The three tables below (Table 69, Table 70 and Table 71) provide the lifetime per patient QALYs gained 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 69: 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	0.1866	0.1849	0.0018	0.0018	4.94%
Off-treatment	20.2498	20.2106	0.0392	0.0392	109.26%
DVT	0.2004	0.2008	-0.0004	0.0004	1.05%
PE	0.0135	0.0143	-0.0007	0.0007	2.07%
CRNM bleeds	0.0106	0.0101	0.0005	0.0005	1.50%
Extra-cranial bleeds	0.0009	0.0014	-0.0005	0.0005	1.39%
Intra-cranial bleeds	0.0001	0.0001	0.0000	0.0000	0.08%
Acute CTEPH	0.0001	0.0001	0.0000	0.0000	0.02%
Long term CTEPH	0.0035	0.0037	-0.0002	0.0002	0.68%
Post-IC bleed	0.0072	0.0111	-0.0039	0.0039	10.94%
Death	0.0000	0.0000	0.0000	0.0000	0.00%
Mild/moderate PTS	0.0000	0.0000	0.0000	0.0000	0.00%
Severe PTS	0.1119	0.1117	0.0002	0.0002	0.53%
Total	**20.7848**	**20.7489**	**0.0359**	**0.0359**	**100.00%**

Table 70: 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	0.3755	0.3715	0.0039	0.0039	12.52%
Off-treatment	20.0827	20.0487	0.0340	0.0340	108.54%
DVT	0.1991	0.1996	-0.0005	0.0005	1.73%
PE	0.0134	0.0143	-0.0009	0.0009	2.75%
CRNM bleeds	0.0138	0.0130	0.0007	0.0007	2.31%
Extra-cranial bleeds	0.0012	0.0018	-0.0007	0.0007	2.08%
Intra-cranial bleeds	0.0001	0.0001	0.0000	0.0000	0.12%
Acute CTEPH	0.0001	0.0001	0.0000	0.0000	0.03%
Long term CTEPH	0.0035	0.0037	-0.0003	0.0003	0.90%
Post-IC bleed	0.0094	0.0145	-0.0051	0.0051	16.30%
Death	0.0000	0.0000	0.0000	0.0000	0.00%
Mild/moderate PTS	0.0000	0.0000	0.0000	0.0000	0.00%
Severe PTS	0.1120	0.1119	0.0002	0.0002	0.52%
Total	**20.8108**	**20.7794**	**0.0314**	**0.0314**	**100.00%**

Table 71: 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	0.7414	0.7333	0.0081	0.0081	25.35%
Off-treatment	19.7344	19.7040	0.0303	0.0303	94.88%
DVT	0.1957	0.1964	-0.0006	0.0006	2.02%
PE	0.0130	0.0140	-0.0009	0.0009	2.93%
CRNM bleeds	0.0191	0.0181	0.0011	0.0011	3.31%
Extra-cranial bleeds	0.0012	0.0018	-0.0007	0.0007	2.03%
Intra-cranial bleeds	0.0001	0.0001	0.0000	0.0000	0.11%
Acute CTEPH	0.0001	0.0001	0.0000	0.0000	0.03%
Long term CTEPH	0.0033	0.0037	-0.0003	0.0003	0.95%
Post-IC bleed	0.0094	0.0145	-0.0051	0.0051	15.97%
Death	0.0000	0.0000	0.0000	0.0000	0.00%
Mild/moderate PTS	0.0000	0.0000	0.0000	0.0000	0.00%
Severe PTS	0.1121	0.1120	0.0002	0.0002	0.52%
Total	**20.8300**	**20.7980**	**0.0320**	**0.0320**	**100.00%**

Disaggregated costs by health state

The three tables below (Table 72, Table 73, Table 74) 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 72: Summary of costs incurred (undiscounted) by health state – 3 months of treatment

Health state	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
On-treatment	221.69	98.91	122.77	122.77	170.19%
Off-treatment	0.00	0.00	0.00	0.00	0.00%
DVT	908.57	910.28	-1.71	1.71	2.37%
PE	138.54	146.14	-7.59	7.59	10.53%
CRNM bleeds	11.60	14.57	-2.97	2.97	4.12%
Extra-cranial bleeds	4.67	7.22	-2.55	2.55	3.53%
Intra-cranial bleeds	4.89	7.56	-2.67	2.67	3.70%
Acute CTEPH	7.24	7.64	-0.40	0.40	0.55%
Long term CTEPH	93.15	99.60	-6.44	6.44	8.93%
Post-IC bleed	48.71	75.29	-26.58	26.58	36.84%
Death	0.00	0.00	0.00	0.00	0.00%
Mild/moderate PTS	0.00	0.00	0.00	0.00	0.00%
Severe PTS	165.14	164.86	0.28	0.28	0.39%
Total	**1,604.21**	**1,532.07**	**72.14**	**72.14**	**100.00%**

Table 73: Summary of costs incurred (undiscounted) by health state – 6 months of treatment

Health state	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
On-treatment	397.14	104.70	292.44	292.44	127.26%
Off-treatment	0.00	0.00	0.00	0.00	0.00%
DVT	902.39	904.85	-2.45	2.45	1.07%
PE	137.12	145.95	-8.83	8.83	3.84%
CRNM bleeds	15.44	17.70	-2.26	2.26	0.99%
Extra-cranial bleeds	6.12	9.44	-3.32	3.32	1.45%
Intra-cranial bleeds	6.41	9.89	-3.48	3.48	1.51%
Acute CTEPH	7.17	7.63	-0.46	0.46	0.20%
Long term CTEPH	91.93	99.41	-7.48	7.48	3.25%
Post-IC bleed	63.75	98.33	-34.58	34.58	15.05%
Death	0.00	0.00	0.00	0.00	0.00%
Mild/moderate PTS	0.00	0.00	0.00	0.00	0.00%
Severe PTS	165.35	165.11	0.24	0.24	0.10%
Total	**1,792.82**	**1,563.01**	**229.81**	**229.81**	**100.00%**

Table 74: Summary of costs incurred (undiscounted) by health state – 12 months of treatment

Health state	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
On-treatment	737.13	115.90	621.23	621.23	111.35%
Off-treatment	0.00	0.00	0.00	0.00	0.00%
DVT	887.24	890.17	-2.93	2.93	0.53%
PE	133.49	143.08	-9.59	9.59	1.72%
CRNM bleeds	22.05	23.08	-1.04	1.04	0.19%
Extra-cranial bleeds	6.12	9.44	-3.32	3.32	0.60%
Intra-cranial bleeds	6.41	9.89	-3.48	3.48	0.62%
Acute CTEPH	6.98	7.48	-0.50	0.50	0.09%
Long term CTEPH	88.86	96.98	-8.11	8.11	1.45%
Post-IC bleed	63.75	98.33	-34.58	34.58	6.20%
Death	0.00	0.00	0.00	0.00	0.00%
Mild/moderate PTS	0.00	0.00	0.00	0.00	0.00%
Severe PTS	165.50	165.25	0.25	0.25	0.04%
Total	**2,117.52**	**1,559.60**	**557.92**	**557.92**	**100.00%**

Disaggregated costs by category of resource consumed

Table 75 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 75: Summary of lifetime costs by category of resource

Cost category	Rivaroxaban arm	LMWH/VKA arm	Increment	Absolute increment	% absolute increment
3 months of treatment					
Drug cost	221.69	98.91	122.77	122.77	75.39%
Monitoring cost	0.00	245.00	-245.00	245.00	150.44%
Event cost	687.88	697.89	-10.00	10.00	6.14%
Bleeds cost	52.53	77.83	-25.30	25.30	15.54%
PTS/CTEPH	173.14	178.46	-5.32	5.32	3.27%
Total	1,135.24	1,298.09	-162.85	162.85	100.00%
6 months of treatment					
Drug cost	397.14	104.70	292.44	292.44	235.43%
Monitoring cost	0.00	367.21	-367.21	367.21	295.62%
Event cost	679.87	691.79	-11.92	11.92	9.60%
Bleeds cost	68.97	100.27	-31.31	31.31	25.20%
PTS/CTEPH	172.23	178.45	-6.22	6.22	5.01%
Total	1,318.20	1,442.42	-124.22	124.22	100.00%
12 months of treatment					
Drug cost	737.13	115.90	621.23	621.23	1894.26%
Monitoring cost	0.00	604.03	-604.03	604.03	1841.81%
Event cost	660.64	673.81	-13.17	13.17	40.16%
Bleeds cost	75.58	105.66	-30.08	30.08	91.71%
PTS/CTEPH	169.73	176.48	-6.75	6.75	20.57%
Total	1,643.08	1,675.88	-32.80	32.80	100.00%

Base-case analysis

6.7.6 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 are presented separately for patients of each of the three treatment durations considered.

Patients for whom three months of anticoagulation is appropriate

In the base case analysis relating to the group of patients for whom three months anticoagulation treatment was appropriate, rivaroxaban was associated with greater LYs, greater QALYs and lower costs, as compared with dual LMWH/VKA therapy. Rivaroxaban was dominant.

Table 76: Base case results – 3 months of treatment

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£) (QALYs)
Rivaroxaban	1,135.24	16.274	13.348				
LMWH/VKA	1,298.09	16.247	13.325	-162.85	0.027	0.023	Dominated

Patients for whom six months of anticoagulation is appropriate

In the base case analysis relating to the group of patients for whom six months anticoagulation treatment was appropriate, rivaroxaban was associated with greater LYs, greater QALYs and lower costs, as compared with dual LMWH/VKA therapy. Rivaroxaban was dominant.

Table 77: Base case results – 6 months of treatment

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£) (QALYs)
Rivaroxaban	1,318.20	16.294	13.365				
LMWH/VKA	1,442.42	16.271	13.345	-124.22	0.023	0.020	Dominated

Patients for whom twelve months of anticoagulation is appropriate

In the base case analysis relating to the group of patients for whom twelve months anticoagulation treatment was appropriate, rivaroxaban was associated with greater LYs, greater QALYs and lower costs, as compared with dual LMWH/VKA therapy. Rivaroxaban was dominant.

Table 78: Base case results – 12 months of treatment

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	ICER (£) (QALYs)
Rivaroxaban	1,643.08	16.309	13.377				
LMWH/VKA	1,675.88	16.285	13.356	-32.80	0.024	0.020	Dominated

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 and 12 month patient groups, incremental life years gained were estimated at 0.027, 0.023 and 0.024 and incremental QALYs at 0.023, 0.020 and 0.020 respectively. Rivaroxaban was associated with per patient cost-savings, which were greatest for the 3 month treatment duration (3 months: £162.85; 6 months: £124.22 and 12 months: £32.80). Consequently, rivaroxaban was the dominant treatment option when compared with LMWH/VKA for all treatment durations (Table 76, Table 77 and Table 78).

Sensitivity analyses

6.7.7 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 6.6.2.

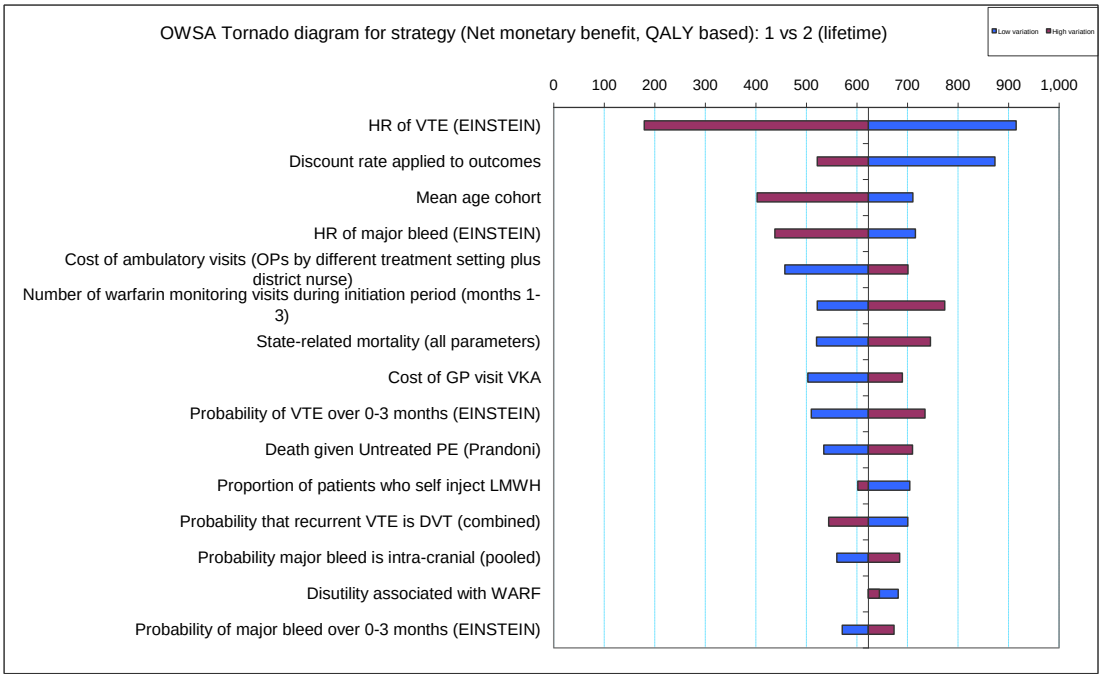
Overall, there were 101 sensitivity analyses conducted for each of the three durations of treatment for which rivaroxaban was evaluated. The full set of results can be produced by the MS Excel model accompanying this submission, but is not reproduced here. Instead, tornado plots for the top 15 most sensitive 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).

Results are presented separately for patients of each of the three treatment durations considered.

Patients for whom three months of anticoagulation is appropriate

The tornado diagram (Figure 18) shows variation in the NMB from a base case of £622.40. The cost-effectiveness of rivaroxaban vs LMWH/VKA for 3 months of treatment was largely insensitive to variation in the assumptions made, with the exception of the treatment effect for VTE recurrence. The higher treatment effect variation leads to a QALY gain close to zero but still a negative incremental cost. Net monetary benefit was positive in all analyses.

Figure 18: Tornado plot – net monetary benefit of rivaroxaban vs. LMWH/VKA, 3 months of treatment, lifetime horizon

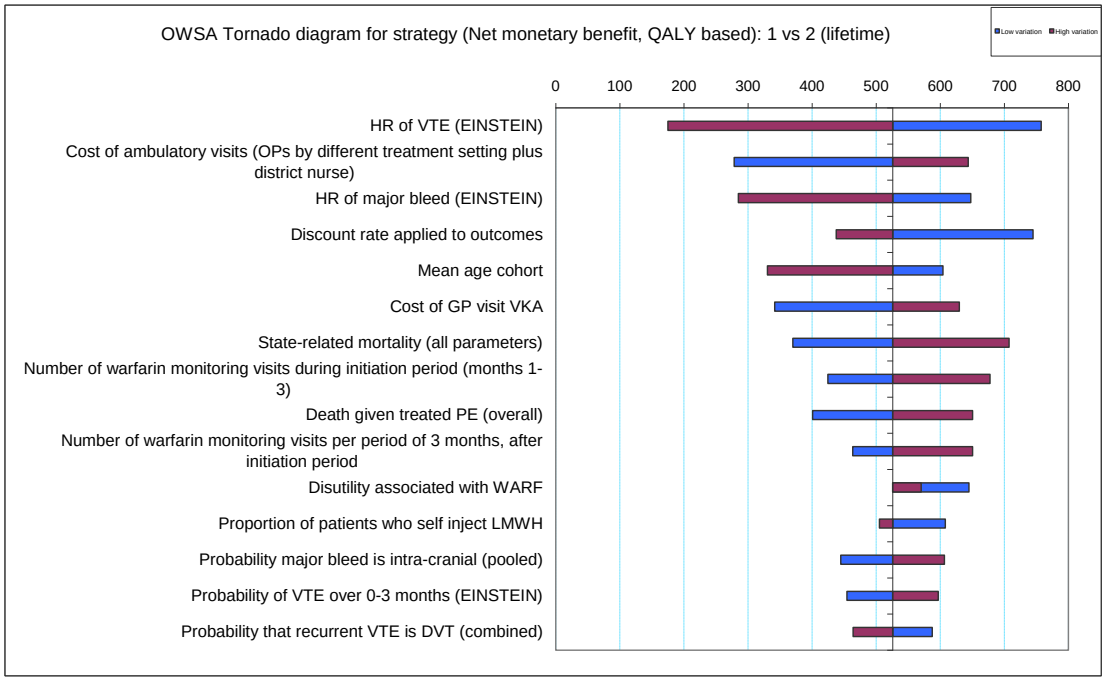


Additional sensitivity analyses were performed setting time horizon at 5 years. Rivaroxaban remains dominant for this time horizon.

Patients for whom six months of anticoagulation is appropriate

The tornado diagram (Figure 19) shows variation in the NMB from a base case of £525.76. The cost-effectiveness of rivaroxaban vs LMWH/VKA for 6 months of treatment was also largely insensitive to variation in the assumptions made. Net monetary benefit was positive in all analyses.

Figure 19: Tornado plot – net monetary benefit of rivaroxaban vs. LMWH/VKA, 6 months of treatment, lifetime horizon

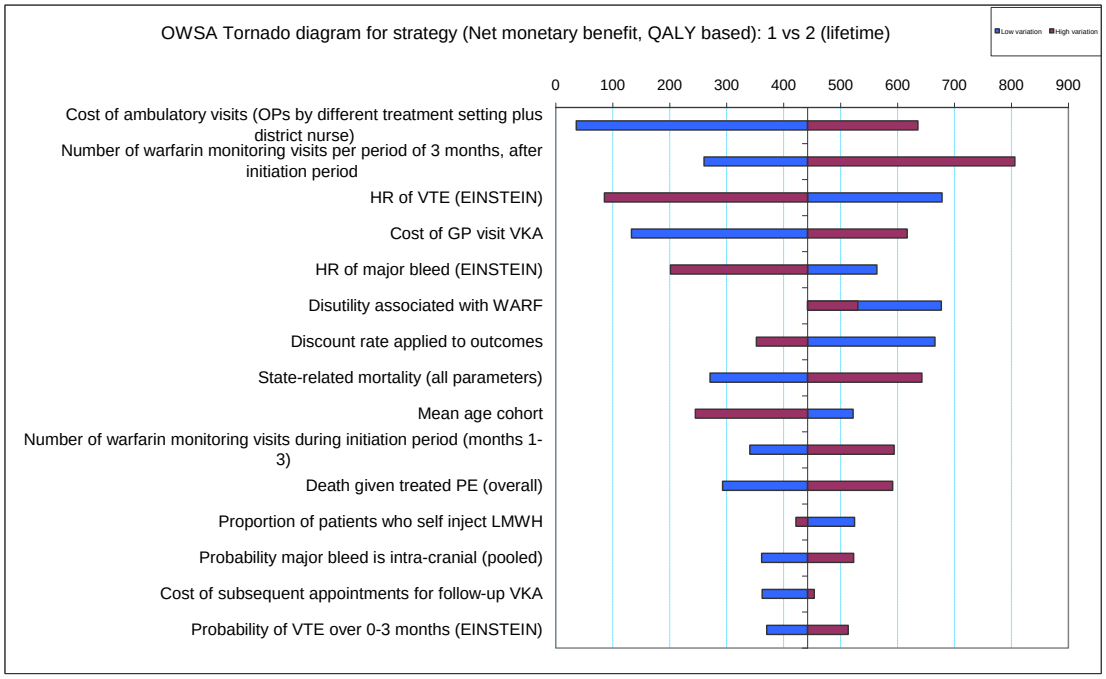


Additional sensitivity analyses were performed setting time horizon at 5 years. Rivaroxaban remains dominant for this time horizon.

Patients for whom twelve months of anticoagulation is appropriate

The tornado diagram (Figure 20) shows variation in the NMB from a base case of £442.16. The cost-effectiveness of rivaroxaban was still largely insensitive to variation in the assumptions made. Assumptions relating to frequency and cost of monitoring visits become more prominent than treatment effect assumptions, to which there was more sensitivity in shorter durations of treatment. Net monetary benefit was positive in all analyses.

Figure 20: Tornado plot – net monetary benefit of rivaroxaban vs. LMWH/VKA, 12 months of treatment



Additional sensitivity analyses were performed setting time horizon at 5 years. Rivaroxaban remained dominant.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Results are presented separately for patients of each of the three treatment durations considered as Cost-Effectiveness Planes (CE Planes) and Cost-Effectiveness Acceptability Curves (CEACs).

Patients for whom three months of anticoagulation is appropriate

The relevant plots are Figure 21 and Figure 22. The PSA demonstrated a 98.9% probability of rivaroxaban being cost-effectiveness at a threshold of £20,000 per QALY and a 97.1% probability of rivaroxaban being less costly and more effective than LMWH/VKA (dominant).

Patients for whom six months of anticoagulation is appropriate

The relevant plots are Figure 23 and Figure 24. The PSA demonstrated a 97.1% probability of rivaroxaban being cost-effectiveness at a threshold of £20,000 per QALY and a 83.9% probability of rivaroxaban being less costly and more effective than LMWH/VKA (dominant).

Patients for whom twelve months of anticoagulation is appropriate

The relevant plots are Figure 25 and Figure 26. The PSA demonstrated a 94.2% probability of rivaroxaban being cost-effective at a threshold of £20,000 per QALY and a 53.0% probability of rivaroxaban being less costly and more effective than LMWH/VKA (dominant).

Overview

The PSAs demonstrated that at a threshold of £20,000 per QALY, the probability of rivaroxaban being cost-effective in comparison with LMWH/VKA, the current standard of care was greater than 94% whether a patient required 3, 6 or 12 months of anticoagulation therapy.

The probability of rivaroxaban being the dominant treatment option was 97.1%, 83.9% and 53.0% in patients requiring 3, 6 or 12 months of anticoagulation respectively.

Greater cost savings and increased incremental QALYs for rivaroxaban were associated with the group of patients requiring shorter durations of therapy.

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Figure 21: CE plane for rivaroxaban vs LMWH/VKA - 3 months of treatment

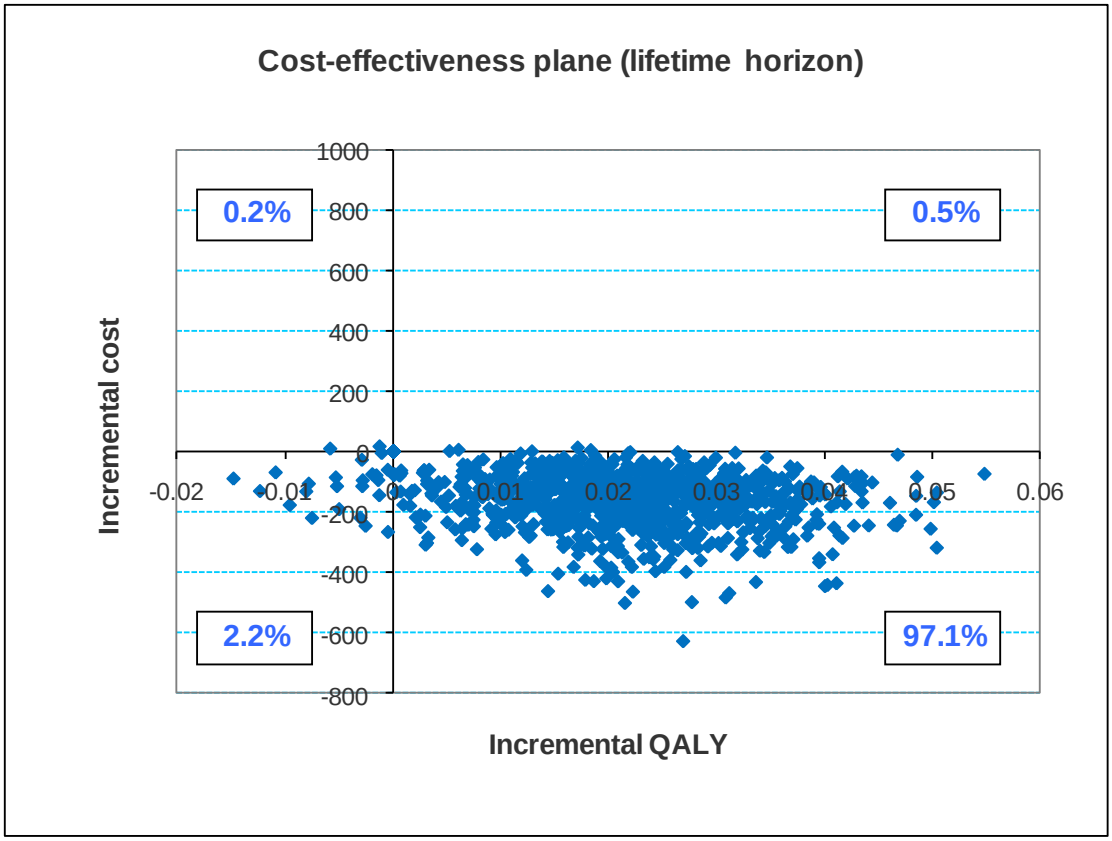


Figure 22: CEAC for rivaroxaban vs LMWH/VKA - 3 months of treatment

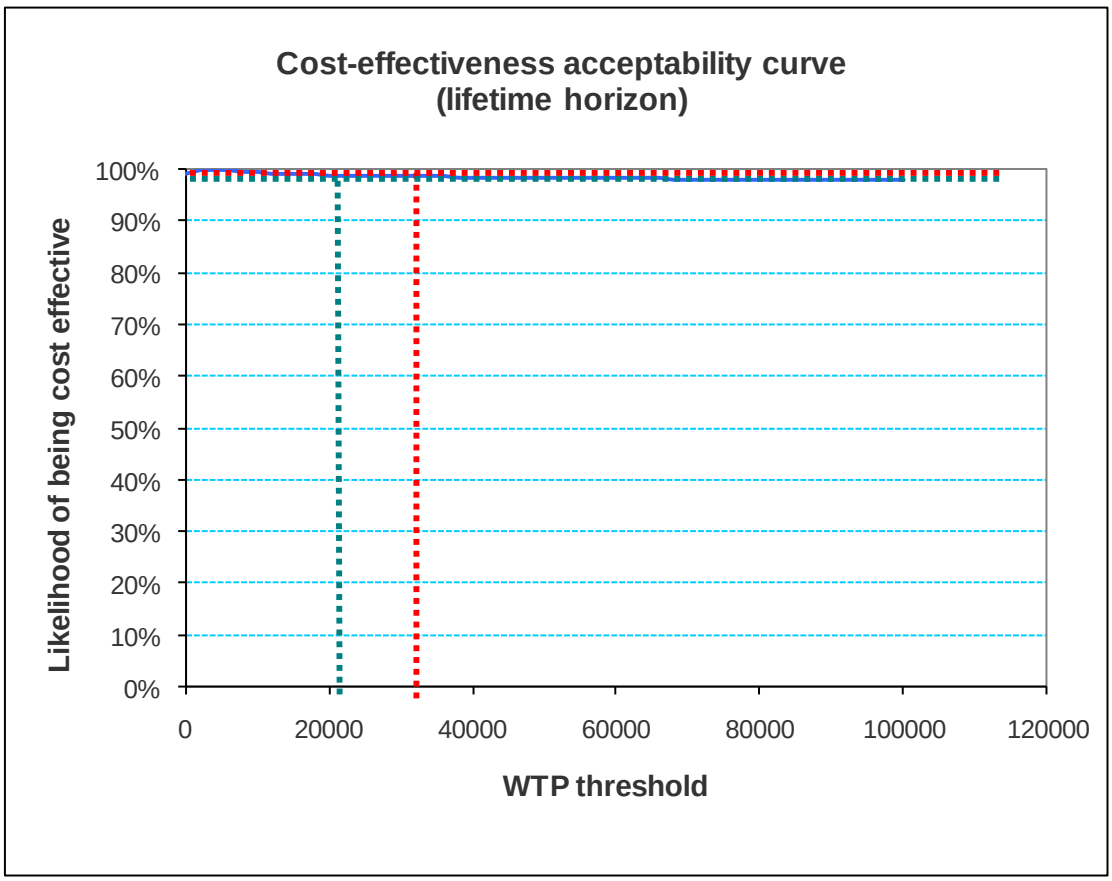


Figure 23: CE plane for rivaroxaban vs LMWH/VKA - 6 months of treatment

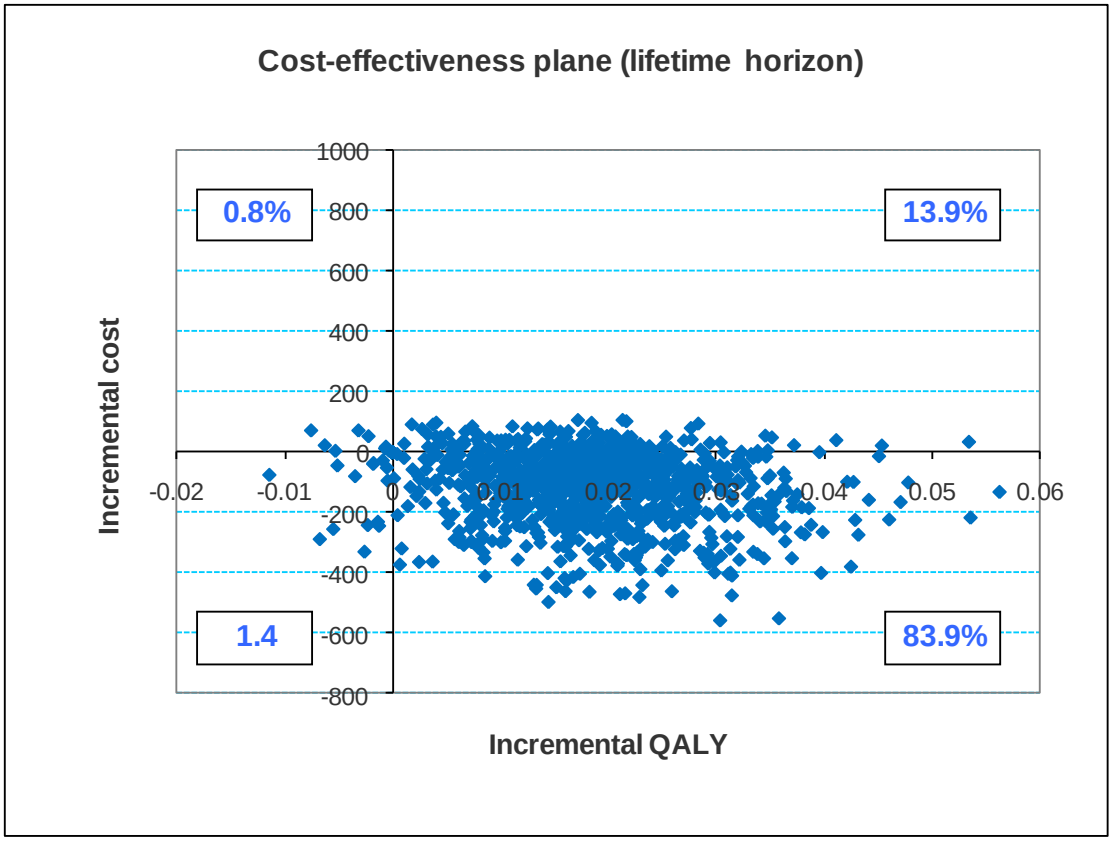


Figure 24: CEAC for rivaroxaban vs LMWH/VKA - 6 months of treatment

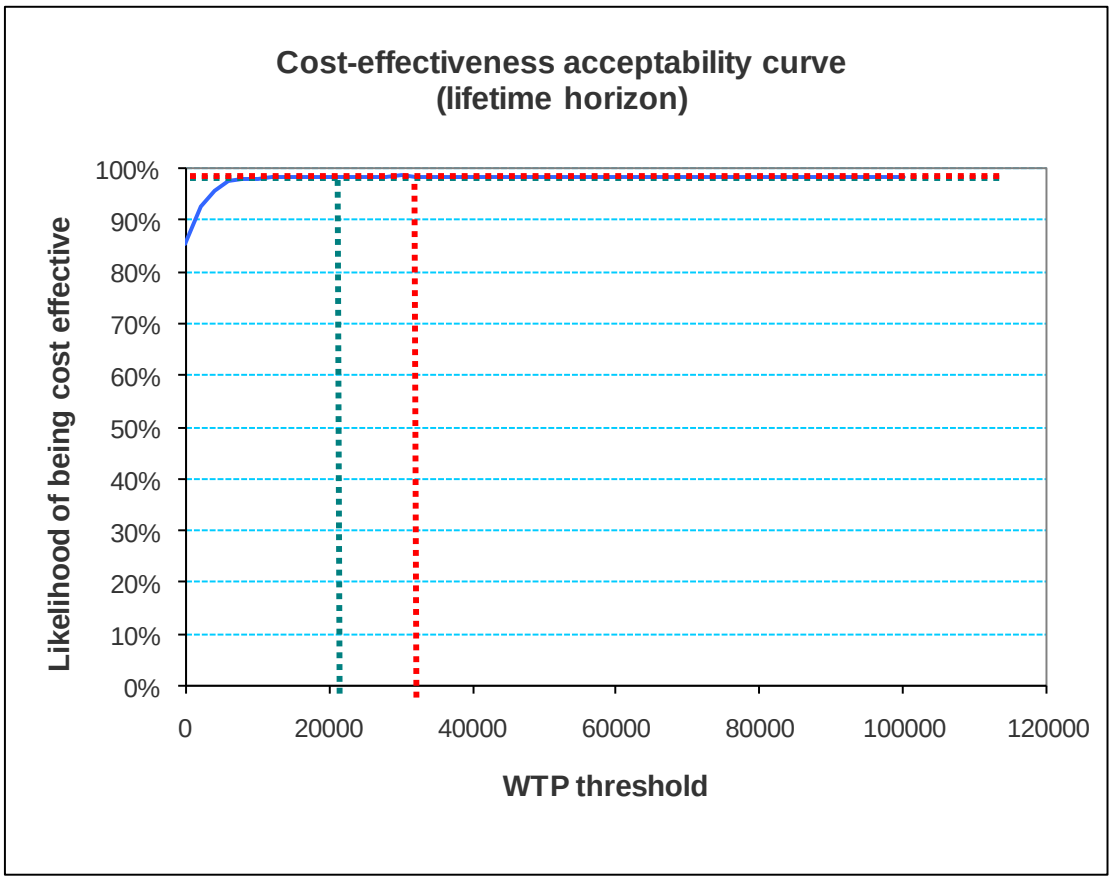


Figure 25: CE plane for rivaroxaban vs LMWH/VKA - 12 months of treatment

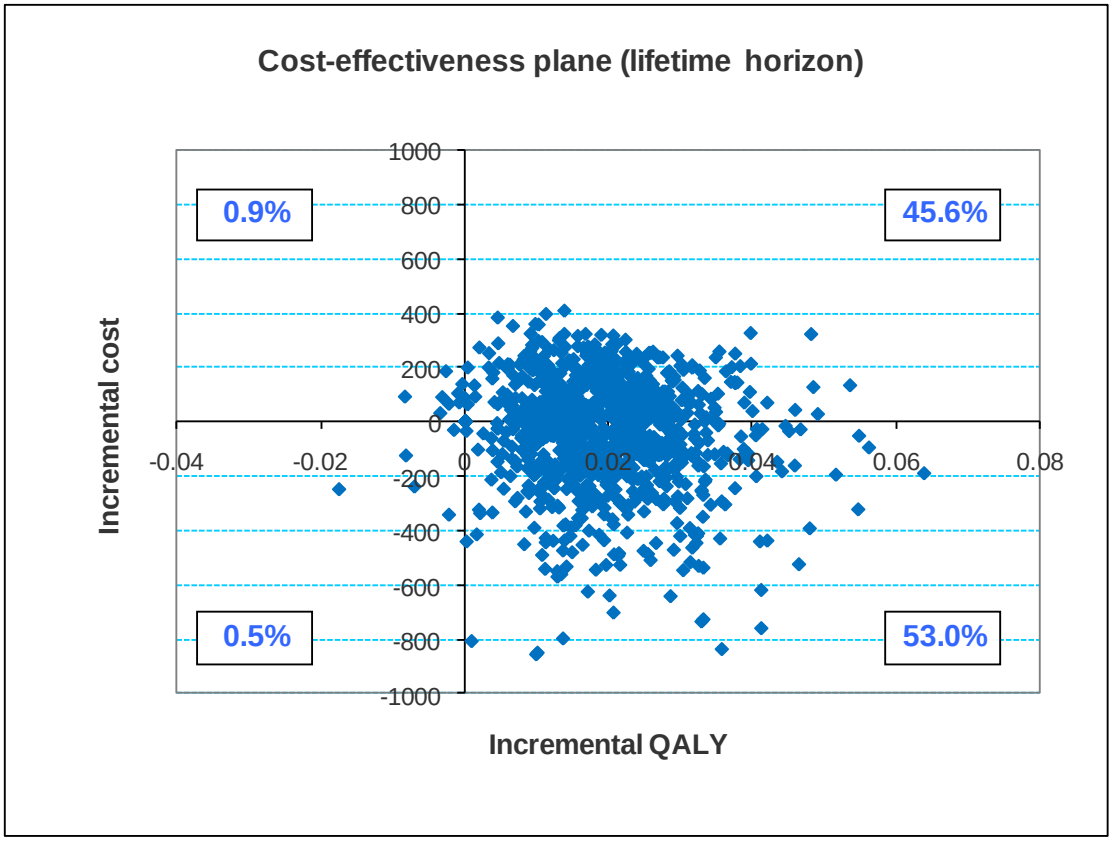
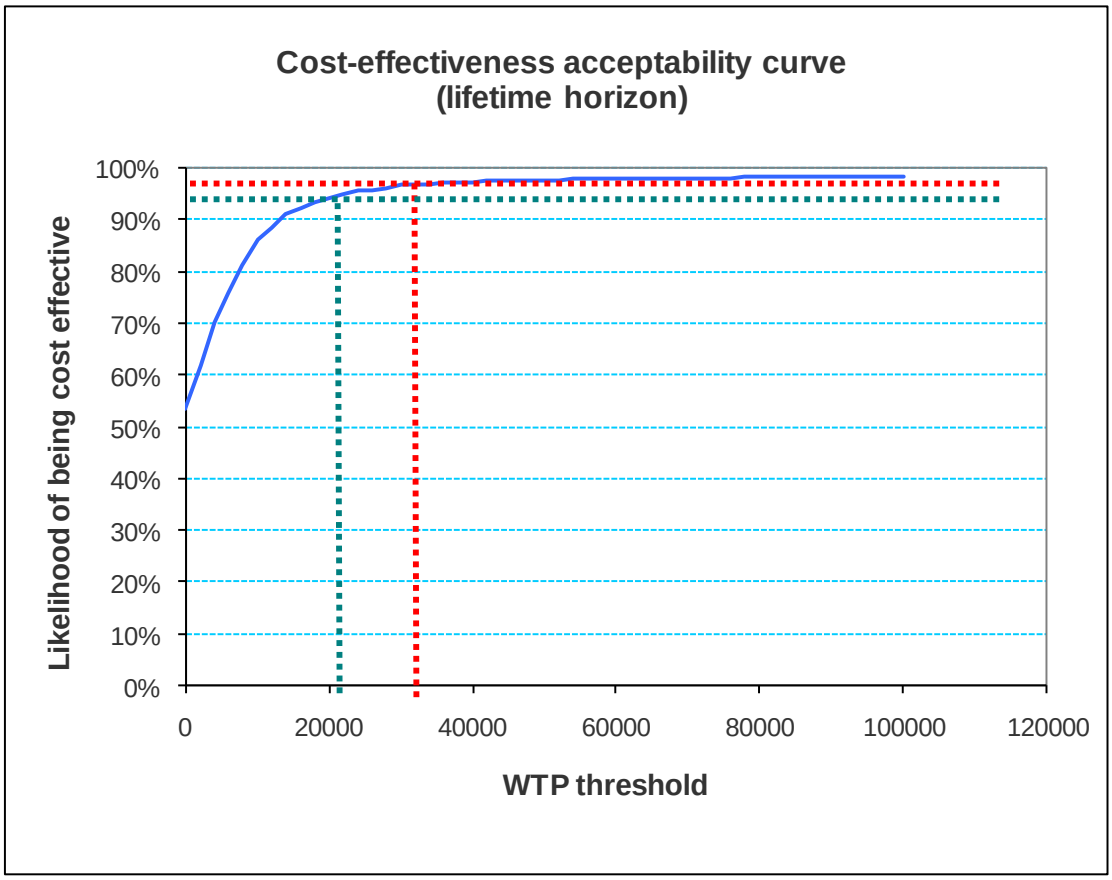


Figure 26: CEAC for rivaroxaban vs LMWH/VKA - 12 months of treatment



6.7.9 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.

6.7.10 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, whether deterministic or probabilistic. For shorter durations, sensitivity was greatest to the treatment effect parameter but for longer durations, sensitivity was greatest to the frequency and cost of INR monitoring.

PSA for all of the three analyses also indicated that the model results are robust. The CEAC indicated that the likelihood of rivaroxaban being cost-effectiveness at a threshold of £20,000 per QALY varies between 98.9% and 94.2%, with a shorter treatment duration associated with higher probability. The scatterplots on the cost-effectiveness planes showed that the probability of rivaroxaban being dominant varies between varied between 97.1% and 53.0%, with a higher probability in analyses where patients were treated for a shorter duration.

6.7.11 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 the reduction of VTE recurrence was in favour of rivaroxaban in EINSTEIN-DVT (HR of 0.68, 95% CI 0.44 to 1.04).
- Rivaroxaban demonstrated comparable rates of major and CRNM bleeding in that trial (HR for major bleeding of 0.65, 95% CI 0.33 to 1.28; RR for CRNM bleeding of 1.05, 95% CI 0.83 to 1.34).
- 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 not so as to eliminate the net health benefit demonstrated.

- 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).

6.8 Validation

6.8.1 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, as well as a model audit performed by an external health economist (Peter Lindgren of i3 Innovus).

Extensive external validation was undertaken in consultation with experts in DVT treatment, as described below.

- Aside from the systematic review of cost-effectiveness studies reported in this submission, there was an earlier review of key literature in the field of DVT economic modeling. This was conducted prior to formulating the model design concept and is referred to briefly in section 6.1.
- The initial design of the cost-effectiveness model was discussed with the involvement of key experts in clinical aspects of DVT 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.
- Comparison of the results from the model over the time horizon of the clinical trial with those directly from EINSTEIN-DVT indicated that results from the model were representative of those from EINSTEIN-DVT (section 6.7.1)
- Results of the model were compared against other published studies and found to be comparable.

6.9 Subgroup analysis

6.9.1 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 due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

The Decision Problem (section 4) lists as a comparator UH or LMWH in people for whom a VKA is not considered an appropriate treatment, and it is understood that this refers to patients with cancer. It has been estimated that 12.2% of all DVT cases in the UK arise in patients with cancer.[22] 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[9;11;33;34] and so, in this subgroup, LMWH is an appropriate comparator.

Whilst dalteparin is currently licensed in the UK for both VTE treatment[39] and extended treatment in oncology[40], other LMWHs have been studied and may be used, a recent Cochrane review found little difference between dalteparin and other LMWHs (Table 24).[15]

Nevertheless, the SMC approved dalteparin in February 2011 with the recommendation reflecting the licensed extended oncology indication.[40;66] 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.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

Patients included in this subgroup in EINSTEIN-DVT were those judged at the baseline screening assessment to have active cancer.[16;54]

6.9.3 Please describe how the statistical analysis was undertaken.

An indirect comparison was undertaken to examine the relative efficacy and safety of rivaroxaban and LMWH in DVT patients with cancer in section 5.7. In the absence of significant differences and recognising the presence of statistical and clinical heterogeneity (in study populations and designs), a cost minimisation analysis was considered appropriate and is presented here.

Given that cancer patients are likely to be closely monitored, undergoing frequent full blood count tests and in many cases frequent home and clinic visits it was considered unlikely that administration of dalteparin would impose substantial additional burden outside of drug costs. There is a reduced need for frequent INR monitoring with long-term LMWH compared with warfarin treatment in cancer patients due to a more predictable pharmacokinetic profile.[38] No INR monitoring is accounted for in the cost minimisation, nor is any potential improved length of hospital stay with rivaroxaban, both being conservative assumptions in the evaluation of rivaroxaban.

The dosing of dalteparin was described in section 6.9.1 and costed in Table 49 as £8.47 per day in the first month and £7.06 per day thereafter. Costs for rivaroxaban are as described in 6.5.5.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

The cost minimisation analysis is summarised in Table 79. This table identifies the costs associated with 6 months of DVT 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 (£909).

Table 79: Cost minimisation of rivaroxaban vs LMWH in the cancer subgroup

Items	Rivaroxaban	Dalteparin	Reference
Technology cost	£2.10 per tablet	Month 1: £8.47 per day. Months 2-6: £7.06 per day.	See Table 49
Mean cost of technology treatment			
Initial treatment	£2.10 x 21 x 2 = £88.2	£8.47 x 30 = £254.10	
Extended treatment (remainder of 6 months – 180 days)	£333.90	£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[38]
Administration	£0	£0	Assumed
Total over 6 months	£427.36	£1,330.75	Derived
Saving associated with rivaroxaban	£903.39		Derived

6.9.5 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 4.

There are no other such subgroups. Results from EINSTEIN-DVT were considered reflective of clinical practice and therefore no further subgroups were considered. It may be helpful to refer to Figure 8 and Figure 10.

6.10 Interpretation of economic evidence

6.10.1 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 DVT, and prevention of recurrent DVT and PE following an acute DVT.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes. The EINSTEIN-DVT trial included a large proportion of patients with characteristics representative of UK patients requiring treatment for DVT as per the Decision Problem. See section 5.10.

6.10.3 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 study in consultation with UK clinical and health economic experts, ensuring that the model clinical pathway is in line with UK clinical practice.

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.

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 CIs over p-values,[71-73] and PSA has been developed as a method to illustrate the extent of uncertainty in model outputs due to uncertainty in parameter values used as inputs. The PSA results demonstrate high probability for the cost-effectiveness of rivaroxaban in patients appropriate for 3, 6 or 12 months of treatment – a conclusion consistent with the base case deterministic results.

In the cancer subgroup, there is strong evidence that rivaroxaban would be associated with lower costs than long-term LMWH. An indirect analysis was necessary due to the absence of head-to-head trials in this subgroup. The indirect analysis conducted suggested comparable efficacy and safety between rivaroxaban and long-term LMWH in terms of recurrence of VTE and incidence of minor or major bleeding. However, the uncertainty intervals (95% CrIs) in relative efficacy and safety were wide.

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.

Discussion with clinical experts and evidence from healthcare resource usage outcomes in EINSTEIN-DVT have indicated that it is likely that rivaroxaban will reduce the length of stay for patients admitted with DVT. As noted in section 6.3.8,

[redacted]

[redacted] However, given the novel nature of the technology this cannot be estimated at this stage. It is therefore likely that the potential cost savings associated with rivaroxaban have been underestimated.

6.10.4 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

7 Assessment of factors relevant to the NHS and other parties

7.1 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 DVT and PE. The database linkage study has recently been presented at the XXIII Conference of The International Society on Thrombosis and Haematosis (ISTH) by Martinez et al. These plus additional data are summarised in Table 80.[22;144] The same study reported that 12.2% of first DVT cases were identified in patients with active cancer.

Table 80: Age-specific incidence rates of DVT, per 100,000 person-years

Age	DVT events		Person years of follow-up	Incidence rate (per 100,000 person-years)	
	First	Any		First DVT	Any DVT
0-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70-79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80-89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]		

Rates of incidence of DVT were then applied, by age-group, to the principal 2008-based population projections for England and Wales made by the Office of National Statistics.[30] The results of this calculation are shown in Table 81.

Table 81: Estimated numbers of cases, and patients potentially treatable with rivaroxaban

Year		2012	2013	2014	2015	2016
Population (thousands)		44,304	44,650	44,992	45,334	45,659
Incidence rates (per 100,000)	First DVT	87.2	87.7	88.4	89.1	89.8
	Any DVT	104.6	105.2	105.9	106.7	107.6
Numbers of cases	First DVT	38,620	39,171	39,757	40,373	41,013
	Subsequent DVT	7,708	7,803	7,905	8,009	8,115
	All DVTs	46,328	46,974	47,662	48,382	49,128
Potentially treated with rivaroxaban*		45,402	46,035	46,709	47,414	48,146

* Calculated as number of first DVT cases less 2% estimated to be specifically contraindicated

Consequently, we estimate that there would be in the region of 46,300 incident cases of adults with acute DVT in 2012 in England and Wales, of which approximately 38,600 would be first DVTs. The total would rise to a projected 49,100 incident cases in 2016 due to growth and ageing in the population.

Our budget impact estimate is based on all patients with DVTs being potentially treated with rivaroxaban, other than 2% with specific contraindications.

The assumption about frequency of contraindications is based on:

- 1.6% of patients contraindicated due to hepatic impairment, from a US study of VTE prophylaxis among over 30,000 patients with total hip or knee replacements[145]; and
- Approximately 0.2% of patients contraindicated with very severe renal impairment (creatinine clearance < 15 mL/min). This assumption is consistent with 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[146].

Therefore, we estimate that there would be in the region of 45,400 incident cases of adults with acute DVT in 2012 in England and Wales potentially treatable with rivaroxaban, rising to approximately 48,100 in 2016.

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

As described in previous sections, the standard of care is dual LMWH/VKA therapy. This is taken to be treatment with enoxaparin for an initial period of 9.6 days, followed by treatment with warfarin for the remainder of the appropriate treatment duration of 3, 6 or 12 months, depending on an individual patient risk assessment. Following the EINSTEIN-DVT duration stratification (Table 12), 12% of patients without cancer were assumed to have 3 months of treatment, 63% were assumed to

have 6 months of treatment and 25% were assumed to have 12 months of treatment. Monitoring is then carried out at a frequency of 9 INR tests in the first three months and 5 INR tests in each quarter thereafter. We derived in section 6.5.5 a unit cost for the first INR monitoring visit of £33.77 and for a subsequent visit of £26.23. See also Table 48 and Table 51.

Patients with cancer have a different current standard of care. Cancer patients with DVT were expected to be managed with dalteparin for six months, without warfarin or any VKA and without INR monitoring. See section 6.9.

The assumptions adopted are summarised in Table 82.

Table 82: Current treatment received in population potentially treatable with rivaroxaban

	Patients without cancer	Patients with cancer
Proportion of all patients eligible for treatment	87.8%	12.2%
Appropriate duration of treatment		
3 months	12%	0%
6 months	63%	100%
12 months	25%	0%
Total	100%	100%

7.3 What assumption(s) were made about market share (when relevant)?

The availability of the rivaroxaban represents a potentially important change in the approach to the treatment of DVT. 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. The market share of rivaroxaban was assumed to [redacted]

World without rivaroxaban

The estimated market share for a world without rivaroxaban is reported in Table 83.

Table 83: Market share assumptions - world without rivaroxaban

	Year 1	Year 2	Year 3	Year 4	Year 5
3 months duration (10.5% of all patients)					
Dual LMWH/VKA therapy	100%	100%	100%	100%	100%
Dalteparin	0%	0%	0%	0%	0%
Rivaroxaban	0%	0%	0%	0%	0%
6 months duration (67.5% of all patients)					
Dual LMWH/VKA therapy	82%	82%	82%	82%	82%
Dalteparin	18%	18%	18%	18%	18%
Rivaroxaban	0%	0%	0%	0%	0%
12 months duration (22.0% of all patients)					
Dual LMWH/VKA therapy	100%	100%	100%	100%	100%
Dalteparin	0%	0%	0%	0%	0%
Rivaroxaban	0%	0%	0%	0%	0%

World with rivaroxaban

For the world with rivaroxaban it was anticipated that rivaroxaban would become the treatment of choice for DVTs by [redacted]

Table 84: Market share assumptions - world with rivaroxaban

[redacted]

7.4 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).

Patients receiving dual LMWH/VKA therapy require monitoring at a frequency of 9 INR tests in the first three months and 5 INR tests in each quarter thereafter. We derived in section 6.5.5 a unit cost for the first INR monitoring visit of £33.77 and for a subsequent visit of £26.23. In addition patient transport, with a unit cost of £30.96, is 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. See also Table 48 and Table 51. Patients prescribed rivaroxaban do not require INR monitoring, patient transport or drug administration assistance. These additional costs were not explicitly modelled for cancer patients on long-term LMWH in cancer patients, as discussed in section 6.9.

7.5 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 6. Unit costs were sourced as described in section 6.5.5 and 6.9. The costs per patient for each type of therapy, and the corresponding cost with rivaroxaban, is shown in Table 85.

Table 85: Cost of treatment, per patient

Current care				Rivaroxaban
	Drug acquisition cost (£)	Monitoring cost (£)	Total cost (£)	Total cost
Dual LMWH/VKA therapy				
3 months	100	251	350	236
6 months	106	386	491	427
12 months	119	656	774	811
Long-term LMWH therapy (6 months)	1331	0	1331	427

Note: For dual therapy this includes costs for patient transport and drug administration in a proportion of patients

7.6 Were there any estimates of resource savings? If so, what were they?

Displacement of warfarin by rivaroxaban will be associated with a reduction in INR monitoring costs in both primary and secondary care. There will also be a transport cost saving amongst those patients whose INR was monitored in secondary care and require NHS transport to attend appointments.[65]

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated expenditure for 2012-2016 for worlds with and without rivaroxaban, and the net budget impact, is shown in Table 86. In the first year, additional drug costs of £2.6m more than offset savings in monitoring costs of £3.4m, resulting in a net budget impact of saving of £0.8m. By year 5, the impact on drug costs and monitoring costs is higher, with greater assumed use of rivaroxaban in the world with rivaroxaban. Over the five year period, additional drug costs of £34.0m more than offset savings in monitoring costs of £44.7m, resulting in a net budget impact of a saving to the NHS of £10.7m.

Table 86: 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	9,271,214	9,400,569	9,538,135	9,682,199	9,831,600	47,723,717
Monitoring costs	17,197,416	17,437,360	17,692,534	17,959,763	18,236,891	88,523,963
Total costs	26,468,630	26,837,928	27,230,669	27,641,961	28,068,491	136,247,680
World with rivaroxaban						
Drug costs	11,887,890	14,043,642	16,268,161	18,563,379	20,930,949	81,694,021
Monitoring costs	13,757,933	11,334,284	8,846,267	6,285,917	3,647,378	43,871,779
Total costs	25,645,823	25,377,925	25,114,428	24,849,296	24,578,328	125,565,800
Net budget impact (% change)						
Drug costs	2,616,676 (+28%)	4,643,073 (+49%)	6,730,026 (+71%)	8,881,180 (+92%)	11,099,349 (+113%)	33,970,304 (+71%)
Monitoring costs	-3,439,483 (-20%)	-6,103,076 (-35%)	-8,846,267 (-50%)	-11,673,846 (-65%)	-14,589,513 (-80%)	-44,652,185 (-50%)
Total costs	-822,807 (-3%)	-1,460,003 (-5%)	-2,116,241 (-8%)	-2,792,666 (-10%)	-3,490,164 (-12%)	-10,681,880 (-8%)

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The budget impact captures the potential for net budgetary savings associated with drug acquisition, reduced INR monitoring, transport, self-administration of subcutaneous injections and the need for home visits from community nurses.

As with the cost-effectiveness evaluation, no difference in standard disease monitoring and follow-up associated with rivaroxaban. This simplifying modelling assumption is a particularly conservative assumption 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 to make them more efficient, bringing additional treatment satisfaction
- A significant reduction in hospital length of stay observed in rivaroxaban patients vs dual LMWH/VKA patients in EINSTEIN-DVT. [redacted]

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