Rivaroxaban for the treatment of deep vein thrombosis and secondary prevention of venous thromboembolism.

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Date completed 18th January 2012

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 108501.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Harnan, S, Rafia, R, Poku, E, Stevens, J W, Stevenson, M, Wong, R. Rivaroxaban for the treatment of deep vein thrombosis and secondary prevention of venous thromboembolism: A Single Technology Appraisal. ScHARR, The University of Sheffield, 2012.

Contributions of authors

The review of the clinical evidence was undertaken by Sue Harnan and Edith Poku. The review of the cost-effectiveness evidence was undertaken by Rachid Rafia and Matt Stevenson. John Stevens undertook the review of the mixed treatment comparison meta-analysis. Ruth Wong re-ran the searches included in the manufacturer's submission. Matt Stevenson advised the project.

Acknowledgements

Dr Raj Patel (Consultant Haematologist, Kings Thrombosis Centre) and Dr Eddie Hampton (Senior Lecturer in Haematology, University of Sheffield) provided advice during the project. Matt Stevenson (Technical Director, ScHARR Technology Assessment Group) and Kumar Perampaladas (Technical Lead, NICE) commented on a draft version of the report. The authors wish to thank all of the above. We would also like to thank Gill Rooney, Project Administrator, ScHARR, for her help in preparing and formatting the report.

Declared competing interests of the authors:

Dr Raj Patel declared no competing interests.

Dr Eddie Hampton declared no competing interests.

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List of 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
AF	Atrial fibrilation
BCSH	British Committee for Standards in Haematology
BNF	British National Forumlary
CAMPHOR	Cambridge PH Outcome Review
CEAC	Cost effectiveness acceptability curve
CG	Clinical Guideline
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPMP	European Committee for Medical Products for Human Use
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
EPAR	European public assessment report.
EC	ExtraCranial
EED	Economic Evaluation Database
EMA	European Medicines Agency (formerly the European Agency for the Evaluation of Medicinal Products)
EOSM	End Of Study Medication
ERG	Evidence review group
FDA	US Food and Drug Administration
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
MTC	Muliple/Mixed treatment analysis

MS	Manufacturer's submission
NE SHA	North East Strategic Health Authority
NETAG	North East Treatment Advisory Group
NHS	National Health Service
NICE	National Institute for health and Clinical Excellence
NMB	Net monetary benefit
ODIXa-DVT	Oral Direct Factor Xa Inhibitor BAY-59-7939 in Patients with Acute Symptomatic Deep-Vein Thrombosis (ODIXa-DVT) study
OR	Odds Ratio
PCT	Primary Care Trust
PE	Pulmonary Embolism
PEA	Pulmonary Endodardectomy
PH	Pulmonary hypertension
PCO	Primary care organistions
PP	Per Protocol
PSA	Probabilistic Sensitivity Analysis
PSSRU	Personal Social Services Research Unit
PTS	Post Thrombotic Syndrome
QALY	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RR	Risk ratio
SA	Sensitivity analyses
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
ULN	Upper limit of normal
USA	Univariate Sensitivity Analysis
VKA	Vitamin K Antagonist
VPLS	Ventilation/Perfusion Lung Scan
VTE	Venous Thromboembolism
WTP	Willingness to pay

SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The ERG noted the following about the manufacturer's definition of the decision problem.

Population: the population selected was not fully representative of the deep vein thrombosis (DVT) population. Patients excluded from EINSTEIN-DVT include:

- Most patients with high risk of bleeding
- Patients with creatinine clearance <30mL/min, patients with liver diseases and patients with high blood pressure (systolic >180 mmHG or diastolic >110 mmHg).
- Patients with distal DVT

In addition to the above, the EINSTEIN-Ext trial:

- Only included patients in an inadequately defined group of patients "in clinical equipoise".
- Included patients with both DVT and pulmonary embolism (PE) index events. The ERG requested data from DVT patients only, which was provided by the manufacturer.

Intervention: the intervention matches the intervention described in the final scope except in that:

- Patients with creatinine clearance <50mL/min were not given the lower dose recommended in the Summary of Product Characteristics (SmPC). It is unclear in what direction this would alter the results.
- The manufacturer treatment periods were 3, 6 and 12 months. However, the clinical advisors to the ERG and a number of current clinical guidelines suggest that ongoing treatment is a valid treatment option in some patients with DVT. The manufacturer quote draft NICE guidelines on the management of venous thromboembolic diseases, which are more cautious about the risk:benefit of ongoing treatment, but do not rule it out. The ERG concludes that an assumption about treatment duration based on current clinical practice would have been appropriate.

Comparator: the comparator is Enoxaparin and vitamin K antagonist (VKA) treatment. This is mostly appropriate, and the ERG feels it is a reasonable choice of low molecular weight heparin (LMWH). However:

- The dose of LMWH used reflects American practice (1mg/kg bid), whereas the UK dose is 1.5mg/kg od. Evidence suggests these doses are largely equivalent, though a Cochrane review does not rule out the possibility that the once daily dose may be less effective for VTE recurrence. Using the twice daily dose may have been unfavourable to rivaroxaban.

- Cancer patients should have been treated with LMWH throughout according to international guidelines. Inclusion of these patients in the trial with the wrong (less effective/safe) treatment could have been favourable to rivaroxaban.

- No preventative therapy, as defined by NICE in the scope, was only included as a comparator in the EINSTEIN-Ext trial, which had an appropriately limited patient population.

- Patients indicated for treatment with unfractionated heparin are not represented in the trial, and no data for these patients and this comparator are available.

- Patients for whom VKA is not considered appropriate are only represented by cancer patients in the trial, as other groups of patients for whom VKA is not considered appropriate were not included. No data for these patients with an appropriate comparator is available.

- Time in treatment range for VKA was poor, but not outside UK norms.

Outcomes: Most of the outcomes listed in the NICE scope were included in the submission. Points noted by the ERG include:

- Health related quality of life was not measured using a validated or preference based measure.

- VTE is a composite primary endpoint. The constituent parts, DVT and PE, have very different impacts on mortality, quality of life and costs. Composite outcomes are valid where the constituent events are not thought to differ in their response to treatment.

Other relevant factors:

- Rivaroxaban could potentially increase access to anticoagulation for those of some religious denominations, as warfarin is made of porcine heparin

- Rivaroxaban could potentially increase access for patients who have problems injecting for dexterity or phobia reasons.

- Reversal of rivaroxaban anticoagulation (for example where an emergency surgical intervention is required) is a potential issue as this has not yet been standardised.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

Whilst much of the systematic review was conducted well, and the report itself was well presented, there were minor issues with the conduct and reporting of the systematic review, including:

- Poorly defined inclusion and exclusion criteria
- Study selection process lacked transparency
- Data extraction strategy was not well documented
- Quality assessment scoring was queried in three cases by the ERG, and some doubt around the answers and potential for bias remains.

However, the review was thought to be largely reliable by the ERG, and the included trials were of good quality, regardless of these issues.

Data from two trials were presented. Data from the EINSTEIN-DVT trial was considered the most relevant to this appraisal. It was a multi-centre, phase III, non-inferiority randomised controlled trial (RCT), rivaroxaban appeared non-inferior to treatment with enoxaparin/VKA for safety and efficacy outcomes. The overall hazard ratio (HR) was [redacted] for the primary efficacy outcome VTE recurrence, and for the primary safety outcome of clinically relevant bleeding, the HR is 0.97, (95% CI 0.76 - 1.22). All cause mortality HR was 0.67 (0.44 to 1.02). Rivaroxaban also appeared non-inferior in terms of adverse events and mortality.

[redacted]. The interaction test was significant when interpreted at the [redacted] and the treatment would appear to not have been proven to be equivalent in the 3 month intended treatment duration group. Bleeding events across these groups, however, looked largely similar.

Data from the EINSTEIN-Ext trial was also presented. This multi-centre, phase III RCT compared rivaroxaban to placebo in a group of patients with an index event of DVT or PE who had completed 6 or 12 months of treatment, and where it was unclear whether ongoing treatment would be advantageous or not (i.e. patients were in "clinical equipoise). Rivaroxaban was shown to be statistically superior to placebo for prevention of VTE recurrence, with an [redacted] though its safety profile was statistically significantly worse, with an HR of 5.19 (95% CI, 2.3 to 11.7) for the outcome of clinically relevant bleeding. [redacted]

[redacted]

A mixed treatment comparison (MTC) was performed to compare the efficacy of rivaroxaban in patients with cancer to the efficacy of LMWH. The MTC showed rivaroxaban to be less effective (median HR 0.98 (95% CI 0.05 to 11.0)) in the manufacturer's primary analysis and apparently less safe (major bleeding events median HR 0.68 (95% CI 0.02 to 25.8), clinically relevant non-major bleeding events median HR 1.07 (95% CI 0.09 to 12.1) than LMWH, but with large uncertainty.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

In addition to the criticisms of the decision problem as outlined in section 1.1, the ERG had a number of other criticisms regarding the evidence submitted. Most of these were, after consideration, not considered to have a large impact:

- Several groups of patients are not represented in the trial (see section 1.1 above), and therefore there is no data to inform decisions about patients at high risk of bleeding (with the exception of cancer patients), creatinine clearance <30mL/min, patients with liver diseases, patients with high blood pressure (systolic >180 mmHG or diastolic >110 mmHg) and patients with distal DVT.

- Comparisons to unfractionated heparin were not possible as patients indicated for this treatment were not included

- Some patients (15 patients with creatinine clearance <30mL/min and 23 patients with a PE index event) were included who should have been excluded according to the inclusion/exclusion criteria. It is unclear why these patients were not excluded in the per protocol analysis. As event numbers are small, inclusion of these patients has the potential to alter the estimates of efficacy.

- The MTC was based on heterogeneous evidence and the ERG has concerns about the way the analysis was conducted. The ERG concludes that the use of the results from the (network) meta-analyses would lead to inaccurate estimates of mean ICERs because they will be based on inflated expected values.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

- The manufacturer submitted a decision-analytic model constructed in Microsoft Excel(R). The economic evaluation uses a Markov approach using eleven possible health states, including venous thromboembolism recurrences, bleeding events and death.
- The manufacturer presented two analyses. The primary analysis compared the use of rivaroxaban against dual therapy LMWH/VKA delivered over three, six or twelve months in patients with acute DVT. Following a request from the ERG during the clarification process, the manufacturer submitted an exploratory cost-effectiveness analysis in a subgroup of cancer patients having adapting the existing model framework.
- For the primary analysis, the rates of bleeding events and VTE recurrences after treatment of the index DVT (at which point patients were assumed to enter the model) were taken directly from the EINSTEIN-DVT trial. The manufacturer used data from dual therapy LMWH/VKA to represent the baseline risk of events, and applied a hazard ratio to estimate the risk of events for patients treated with rivaroxaban. A systematic review of the literature was carried out to identify effectiveness data to inform the long term rates of recurrence and mortality once treatment has ceased.
- The baseline risk of events for patients with cancer was derived from the economic model for the whole population treated with rivaroxaban, adjusted for the increased risk of events in cancer patients versus non cancer patients. The treatment effect estimated from the MTC (median HR/OR) was then applied to estimate the risk of events in cancer patients treated with LMWH only. The manufacturer also assumed a shorter life expectancy, to reflect the poorer prognosis of cancer patients.
- Costs relating to the treatment and management of VTEs and adverse events such as bleedings were included in the economic model and were taken from official sources (such as British National Formulary (BNF) or National Health Service (NHS) reference costs), with reference to clinical expert opinion where appropriate. The utility values for the different health states were identified through a systematic search of the literature and was taken from different studies.
- Costs and benefits were discounted at 3.5% per annum and the uncertainty was captured in both univariate sensitivity analysis (SA) and probabilistic sensitivity analysis (PSA).
- The manufacturer reported that rivaroxaban was dominant in patients treated for 3, 6 or 12 months, i.e. provide more quality adjusted life years (QALYs) at a lower cost.
- The manufacturer reported that rivaroxaban had a 58.4% chance of being cost-effective at a willingness to pay (WTP) of £20,000 per QALY gained in patients treated for 3 months. The probabilities for patients treated for 6 and 12 months was 85.0% and 95.4% respectively.

- The exploratory analysis in cancer patients indicated that rivaroxaban was dominant compared with LMWH only.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The manufacturer reported that rivaroxaban was dominant in patients treated for 3, 6 or 12 months. However, in the PSA undertaken using the manufacturer's assumptions, the ERG found that rivaroxaban was not dominant in patients with an intended treatment duration of 3 months; these had an incremental cost effectiveness ratio (ICER) of £11,792 per QALY yielded (after model correction). Rivaroxaban remained dominant (providing more QALYs at a lower cost) compared with LMWH/VKA in the PSA in patients treated for 6 and 12 months.

The ERG believes that assumptions made by the manufacturer to be plausible, however, other plausible assumptions exist, given the uncertainties within the decision problem which may impact on the ICER and that were explored in analyses undertaken by the ERG.

It is noted that the manufacturer did not present an analysis for patients treated beyond 12 months, and only considered the use of rivaroxaban for the treatment of the index event; it is unclear why rivaroxaban was not considered for the treatment of the subsequent recurrences.

The ERG does not believe the results from the exploratory analysis in cancer patients to be robust due to limitations within the model and the uncertainties associated with the mixed treatment comparison. There were too much uncertainties in the data and assumptions made by the manufacturer. There were numerous issues in the PSA and inconsistencies were found.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

- The EINSTEIN-DVT trial was well designed in that patients were allocated to an intended treatment duration group prior to randomisation, which mirrors real-world practice.

- Most of the required outcomes were reported.

- The modelling assumptions were generally plausible and relatively few errors were found, and those that were found had very little impact on the results.

- The manufacturer responded positively to requests from the ERG for subgroup analyses according to intended treatment duration, and including only DVT patients from the EINSTEIN-Ext trial.

The report was well written.

1.6.2 Weaknesses and areas of uncertainty

- The trial was not powered to detect outcomes stratified by intended treatment duration.
- A number of patient groups were missing from the trial, and no data relating to unfractionated heparin as a comparator is available.
- Cancer patients received a treatment that is not recommended in international guidelines.
- Health related quality of life was not measured using a preference based measure.
- The primary outcome defined by NICE and commonly used in this field of research was a composite outcome, which may obscure important treatment differences.
- The MTC relied on very heterogeneous data and did not use an informative prior.
- Other modelling assumptions were plausible which could significantly impact on the results. Whilst the ERG concentrated on two (international normalised range (INR) monitoring, and relaxing the assumption of a constant ratio of DVT and PE independent of treatment), there were a number that could not be investigated due to an absence of data and time constraints. The main weakness is that the manufacturer is likely to have underestimated the uncertainty in the decision problem.
- It is noted that the manufacturer did not present an analysis for patients treated beyond 12 months, and only considered the use of rivaroxaban for the treatment of the index event; it is unclear why rivaroxaban was not considered for the treatment of the subsequent recurrences.
- The analyses undertaking for the cancer subgroup are not robust

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG explored other plausible scenarios amending the assumptions on INR monitoring and allowed the proportion of VTEs that are PEs to differ between the treatment arms. For patients with an intended treatment duration of 3 months, the ICER for rivaroxaban was always below £12,000 per QALY yielded. For patients with an intended treatment duration of 6 months, the ICER for rivaroxaban was labile, and could conceivable by either dominant or dominated. For patients with an

intended treatment duration of 12 months, the ICER for rivaroxaban was always below £15,000 per QALY gained. However, the ERG acknowledges that further sources of uncertainty have not been evaluated.

A simplistic cost minimisation analysis was undertaken to inform the appraisal committee of the cheapest intervention. This was dual LMWH/VKA treatment for those with an intended treatment duration 12 months, but was inconclusive at 3 and 6 months treatment duration as the results were dependent on the assumed INR monitoring costs.

The ERG also examined the impact of using the mean treatment effect from the MTC using different between study variability. Exploratory results indicate that at a threshold of £20,000 per QALY gained that rivaroxaban was more cost-effective than LMWH. However, there are considerable uncertainties in both the data and the assumptions used within this analysis.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem.

The evidence review group (ERG) and clinical advisors to the ERG believe that the manufacturer's description of the underlying health problem is appropriate and relevant to the decision problem. The relevant sections from the manufacturer's submission (MS)[1] are as follows.

'Venous thromboembolism (VTE) is a common disorder, with about 1 per 1,000 people per year in the general population presenting with clinical symptoms.[2-4] 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.[2,4]

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[5] 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).[6]

NICE clinical guideline 92 (Reducing the risk of venous thromboembolism in patients admitted to hospital)[7] 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.[7] Other risk factors include recent surgery, trauma and immobilisation.

Treatment for venous thromboembolism is usually initiated with anticoagulant drugs (...). 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;[8] a cumulative incidence of 24.6% at two years and 31.8% after ten years has been reported in a large cohort from Vienna.[9]

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.

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.[10] 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."[2]

2.2 Critique of manufacturer's overview of current service provision

Does the ERG believe that the manufacturer's overview of current service provision is appropriate and relevant to the decision problem under consideration?

The ERG and clinical advisors to the ERG believe that the manufacturer's overview of current service provision is mostly appropriate. The main point of difference between the MS and the opinion of the clinical advisors to the ERG relates to the current treatment pathway, specifically regarding the intended duration of treatment.

On page 20 of the MS[1] the manufacturer states

"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".

The clinical advisors to the ERG believe that, owing to changes in usual practice over recent years, it is now common for treatment to extend beyond 12 months, and possibly indefinitely depending on patient characteristics and risk factors, e.g. those who have experienced a recurrence of a VTE or have ongoing risk factors such as active cancer. This view is supported by the guidelines quoted in the MS (Table 1),[1] particularly the following statements:

- Idiopathic VTE or permanent risk factors: at least six months (British Committee for Standards in Haematology)[11,12]
- Long term VKA, depending on cause, risks, elapsed time between episodes of VTE[13]
- Long term VKA, especially if second episode of unprovoked VTE[14]
- VKA >12 months (American College of Physicians (ACP)/ American Academy of Family Physicians (AAFP))[15]
- Idiopathic VTE: consider indefinite treatment (International Consensus Statement)[16]

Table 1: Summary of international guidelines and recommendations (reproduction of Table 3, page 19 of MS)[1]

Organisation	Acute treatment		Longer term
	Heparins	VKA	
British Committee for Standards in Haematology[11,12]	✓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[13]	✓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[14]	✓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[15]	✓LMWH in preference to UH	✓3-6 months Idiopathic VTE: consider extended treatment	VKA >12 months
International Consensus Statement[16]	✓LMWH	✓ First episode of VTE and no continuing risk factor: 3-6 months. Idiopathic VTE: consider	Long term VKA – depending on cause, risks, elapsed time between episodes

		indefinite treatment.	VTE
LMWH, low molecular weight heparin; VKA, vitamin K antagonist; DVT, deep vein thrombosis; SIGN, Scottish Intercollegiate Guidelines Network; ACCP, American College of Chest Physicians; UH, unfractionated heparin; ACP, American College of Physicians; AACP, American Academy of Family Physicians.			

This point was raised with the manufacturer in the clarification letter.[17] The manufacturer states

"It is not our understanding that the treatment of DVT patients upwards of 12 months is common." (page 3)

The manufacturer goes on to cite NICE's draft guidance on `Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing'.[18] These guidelines note that: the evidence for risk of recurrence between patients assigned to longer or shorter duration of treatment is "very uncertain"; is based on "low quality evidence"; and that there is "an increase which may be of clinical importance in the longer duration group compared to the shorter duration group for major bleeding (moderate quality evidence)". The manufacturer quoted the following guidelines from this report:

> "1.2.2 Offer low molecular weight heparin (LMWH) to patients with active cancer and confirmed proximal DVT or PE, and continue the LMWH for at least 6 months.
>
> 1.2.3 Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for at least 3 months.
>
> 1.2.4 Offer a VKA beyond 3 months to patients with an unprovoked PE unless they are at increased risk of bleeding, taking into account the patient's risk of VTE recurrence and of bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment."
>
> 1.2.5 Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding. Discuss with the patient the benefits and risks of extending their VKA treatment."

The ERG notes that whilst these guidelines point to uncertainty about the benefits of long term treatment, they do not recommend that treatment should cease at 12 months, or give any other suggestions for a maximum treatment duration. In the absence of guidelines recommending against ongoing treatment, and with clinical advice to the ERG indicating that treatment is long term in patients with certain risk factors, amounting to approximately 20% of the DVT population (Personal Communication from Dr Patel and Dr Hampton, December 2011), the ERG remains of the opinion that treatment beyond 12 months in some patients is current practice in England and Wales. Whether this will change in light of the new guidelines is unclear, as the guidelines are not specific on this point. Furthermore, whether clinicians would use rivaroxaban in the same way as current anticoagulant treatment is also unclear, given the lack of evidence beyond 12 months, as stated in the Summary of Product Characteristics (SmPCs)[19,20] which recommend

"The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with Xarelto in this indication for more than 12 months is limited."

Additionally, the EINSTEIN-Ext trial includes patients who are being treated for between 12 months and 2 years. This trial design would appear to contradict the manufacturer's statements about treatment durations, and could be seen to lend weight to the view that ongoing treatment does occur in a proportion of patients.

Given that there is considerable uncertainty on this point, it would have been prudent for analyses assuming treatment >12 months to have been undertaken by the manufacturer.

A further unrelated point is that, on Page 21 of the MS, the manufacturer states "rivaroxaban will be initiated during a secondary care outpatient consultation". The ERG feel that there will be some variation in this and that in some cases, rivaroxaban would be initiated during inpatient care.

3 Critique of manufacturer's definition of decision problem

The MS contains a summary of the decision problem defined by NICE in the final scope, compared to the decision problem as addressed in the MS (reproduced here as Table 2). A rationale is provided where the MS decision problem differs from the NICE final scope. The main areas of disparity highlighted in the MS are to do with the comparator used and the subgroups considered. The ERG has additional comments to make relating to the PICO definition of the decision problem and the evidence submitted in the MS. These are outlined in sections 3.1 to 3.5.

3.1 Population

As shown in Table 2, the terminology used by the manufacturer to define the patient population differs slightly from the definition provided in the NICE scope. The clinical advisors to the ERG are happy with the differences in terminology, and do not feel that this represents a significant difference in patient populations.

The clinical evidence submitted by the manufacturer consists of two main trials both reported in one journal publication,[21]and within the MS.[1] One (EINSTEIN-DVT) is a pivotal, phase III equivalence (non-inferiority) clinical trial, whilst the other (EINSTEIN-Ext) is a phase III extension trial. Both trials have safety and efficacy outcomes. The patient population recruited into each trial differs, and neither completely covers the whole of the confirmed symptomatic DVT population defined in the NICE scope.

Table 2: Statement of the decision problem, reproduced from the MS, page 27.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale provided by the manufacturer, 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
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should	As final scope. A lifetime horizon will	NA

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale provided by the manufacturer, if different from the scope
	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.	be used.	
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

3.1.1 EINSTEIN-DVT Population

Whilst the main inclusion criteria match the population as defined by NICE, the exclusion criteria mean that a number of small subgroups of patients are excluded from the evidence base.

3.1.1.1 Excluded on basis of comorbidities or patient characteristics

These include (taken from Table 10, page 40 of the MS)[1]:

- 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
- Contraindication to anticoagulation
- Bacterial endocarditis
- Active bleeding or a high risk of bleeding
- Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg
- Childbearing potential without proper contraceptive measures
- Pregnancy or breastfeeding
- Concomitant use of strong cytochrome P-450 3A4 inhibitors (e.g. human immunodeficiency virus, protease inhibitors or systemic ketoconazole) or inducers (e.g. rifampicin, carbamazepine or phenytoin)
- Participation in another clinical trial within 30 days prior to screening
- Life expectancy of less than 3 months
- Pre-randomisation therapeutic doses of LMWH, fondaparinux or UH for more than 36 hours
- >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

Some of these exclusions are in line with the licensing of the drug (i.e. creatinine clearance <15mL/min, liver disease, active bleeding, pregnancy and breast feeding, concomitant use of some medications, contraindications to drug treatment), and some are excluded as their inclusion may have confounded outcomes or put patients at unnecessary risk (e.g. life expectancy less than 3 months, participation in another trial within 30 days, childbearing age without contraception, pre-randomisation treatments). However, a number of groups of patients who are not mentioned in the

contraindications for the drug (as listed in the SmPC)[19,20], and would therefore appear eligible for treatment, are not included in the trial evidence. These include:

- Additional indications for a vitamin K antagonist
- Creatinine clearance <30 mL/min (but not less <15mL/min)
- Clinically significant liver disease (e.g. acute hepatitis, chronic active hepatitis or cirrhosis) or alanine aminotransferase >3x upper limit of normal (ULN)
- Bacterial endocarditis
- high risk of bleeding
- Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg

Of particular note is the exclusion of patients with high risk of bleeding. This group is specifically mentioned in the NICE scope as a potential subgroup analysis. Whilst it could be argued that these groups required additional resources to treat as different treatment regimes and would therefore have presented practical challenges within the trial, this does not alter the fact that there is no evidence about the action of rivaroxaban in these groups. The manufacturer does not report having sought clinical opinion to explore this.

3.1.1.2 Excluded on basis of index event

It would also appear that only patients with proximal DVT were included in the trial. This is not apparent from the MS,[1] but is stated in the EINSTEIN-DVT study protocol[22] on page 6. The ERG attempted to clarify this point in with the manufacturer by asking for the proportion of patients with distal, provoked and spontaneous DVTs, but the question was not interpreted by the manufacturer as the ERG had intended (the question was intended to related to baseline proportions, but was answered with outcome proportions).[17] This focus on patients with proximal DVTs would appear to be in line with the expectations of the clinical advisors to the ERG, who felt that this appraisal should focus on proximal DVT patients. However, this distinction is not stated in the NICE scope,[3] nor in the SmPC,[19,20] and the ERG remains unclear on this point.

As evidence is not available for the subgroup discussed above, it is unclear whether the available evidence from different populations is applicable to these subgroups.

[redacted]

3.1.2 EINSTEIN-Ext Population

3.1.2.1 Inclusion on basis of index event

The EINSTEIN-Ext trial recruited patients with either a DVT or a PE. Whilst these events are thought to be manifestations of the same underlying condition, the inclusion of patients with PE is outside the scope produced by NICE[3] and is also outside the indication described in the (proposed) marketing authorisation.[1] The ERG requested an analysis of the study results including only DVT patients. This has been fulfilled in part by the manufacturer, though they have decided not to provide analyses of subgroups within the DVT population as the study was not designed with that level of interrogation in mind.[17]

3.1.2.2 Inclusion of those in clinical equipoise

An additional limitation of this study in the context of this assessment is that it only included patients who were in clinical equipoise (in other words patients for whom it was unclear whether continued treatment would be of benefit) and compared treatment with rivaroxaban in this group to treatment with placebo treatment. This choice of comparator is appropriate where it is unclear whether ongoing treatment is beneficial or not. The clinical advisors to the ERG estimate approximately 20% of patients require ongoing anticoagulation (Personal Communication from Dr Patel and Dr Hampton, December 2011). However, the manufacturer's understanding is that this group do not exist in any great numbers.[1,17] It therefore seems unclear how the 20% identified by our clinicians as being in need of ongoing treatment would have been classified for the purpose of this study, and whether they are included or not. It would appear from the protocol (page 5)[22] and the MS (page 40)[1] that this group were identified and excluded, though no definition of how these patients were classified is given.[22] In addition, the manufacturer states that patients who either did or did not require ongoing treatment were excluded (page 37),[1] though the protocol does not mention the exclusion of patients who do not need treatment explicitly. The ERG feels, therefore, that the population in the EINSTEIN-Ext trial is not adequately defined.

3.1.2.3 Exclusion on basis of comorbidities or patient characteristics

EINSTEIN-Ext also had very similar exclusion criteria to EINSTEIN-DVT and is therefore subject to the same criticisms as outlined in section 3.1.1.1

3.1.3 MTC populations

The populations in the studies selected for the MTC were also not solely DVT patients, with most studies recruiting both DVT and PE patients (Table 3). As such, the evidence does not directly relate to the decision problem population, but appears to be the best available evidence, according to the MS.[1] The clinical advisors to the ERG feel that given the lack of data in DVT only patients, and whilst this population is different, the results are still of use within the context of the decision problem. This is supported by the understanding that DVT and PE are manifestations of the same underlying condition.[23]

Table 3: Summary of patient population of studies included in mixed treatment comparison of LMWH treatment versus VKA treatment in DVT patients with cancer.

Study	Patient population
Deitcher et al 2006[60]	Active cancer patients with DVT and/or PE.
Hull et al 2006[61]	200 patients with cancer (solid or haematological) and proximal DVT with or without PE.
Lee et al 2003[62]	979 patients with cancer and either DVT or PE or both.
Meyer et al 2002[63]	146 patients with cancer (solid or haematological) with DVT and/or PE.
Romera-Villegas et al 2010[64]	Symptomatic proximal DVT in which a subgroup of 69 patients additionally had cancer.

3.2 Intervention

The intervention described in the MS matches the intervention described in the final scope. The technology is outlined by the manufacturer as shown in Table 4. There are two limitations

3.2.1 Patients with creatinine clearance <50mL/min

The ERG note that patients with creatinine clearance <50mL/min were not given the lower dose recommended in the SmPC.[19,20]

Table 4: Rivaroxaban characteristics. Compiled by the ERG using information given on pages 11 to 13, and in Table 2, page 15 of MS.[1]

Brand name	**Xarelto**
Approved name	**Rivaroxaban**
Therapeutic class	**Oral anticoagulant**
Anticipated indication (confirmed in December 2011)[19,20]	Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.
Mode of action	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. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.
Pharmaceutical formulation	15 mg and 20 mg film-coated tablets are relevant to this appraisal
Acquisition cost (excluding VAT)	[redacted]
Method of administration	Oral
Doses	15 mg and 20 mg
Dosing frequency	15 mg twice daily for 21 days, then 20 mg once daily[19,20]
Average length of a course of treatment	3-12 months according to assessment of individual risk-benefits, according to the MS[1].*
Average cost of a course of treatment	[redacted]
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	The SmPC advises a reduced dose in patients with moderate or severe renal impairment (i.e. creatinine clearance < 50 ml/min). The reduced dose would be 15 mg twice daily for 21 days, then 15 mg once daily.[19,20]
* The ERG disagrees with the manufacturer's understanding of length of treatment, and do not know how the assumptions made by the manufacturer on this point will affect average length of a course of treatment.	

Marketing authorisation was gained for rivaroxaban during the course of this assessment and the SmPCs have been published.[19,20]

3.2.2 Length of treatment

As discussed in section 2.2, the clinical advisors to the ERG do not recognise 12 months as a clinical cut off point for anticoagulation treatment, but agree that 3 months and 6 months treatment periods are often used. The clinical advisors to the ERG estimate approximately 20% of DVT patients would currently proceed to long term (ongoing) treatment, mainly because recurrence of VTE would indicate ongoing risk. As already outlined in section 2.2, this point was raised with the manufacturer, and a number of pieces of evidence were presented by the manufacturer.[17] However, the manufacturer was unable to provide any direct or robust evidence that contradicted the ERG's view that ongoing treatment is a current treatment option, and it does not appear that they have obtained guidance from clinical experts on this point.

Given that there is considerable uncertainty on this point, The ERG feels that it would have been prudent for analyses assuming treatment >12 months to have been undertaken by the manufacturer.

3.3 Comparators

The comparator in the pivotal EINSTEIN-DVT trial is a combination of Enoxaparin, a LMWH in common use in the UK, followed by ongoing treatment with a VKA (warfarin or acenocoumarol).

3.3.1 Enoxaparin vs. other LMWHs – EINSTEIN-DVT

Enoxaparin is not the only LMWH used in the UK for this indication. The manufacturer has not addressed the representativeness of enoxaparin in terms of clinical effectiveness (though some discussion is made in relation to cost effectiveness), nor have they declared that they have sought advice from a clinical panel regarding this. The ERG have found that current UK guidelines[25] state that there is still debate about whether LMWH drugs should be treated as a generic class of drug, or whether each drug should be regarded as a separate entity. The guidelines conclude that whilst there is little head to head evidence, the published data indicated that any differences in efficacy or safety were likely to be very small for those LMWHs that have similar action and physiochemical structures. In addition, the clinical advisors to the ERG agree that enoxaparin is an acceptable comparator, with high relevance to UK practice. As such, it is the opinion of the ERG that enoxaparin is an acceptable comparator for the purpose of this assessment.

3.3.2 Enoxaparin dose– EINSTEIN-DVT

The dose of Enoxaparin used in the trial reflected American practice (1mg/kg bid) rather than UK practice (1.5mg/kg od). Again, the ERG clinical advisors do not feel that this would have a big impact on VTE recurrence; this is supported by clinical guidelines review evidence[14] and a Cochrane review[26], though the Cochrane review does not rule out the possibility that once daily LMWH may be less effective. This could potentially disadvantage rivaroxaban.

3.3.3 Treatment of patients with cancer – EINSTEIN-DVT

UK guidelines recommend use of LMWH for patients with cancer.[11] Such a treatment regime was not incorporated into the EINSTEIN-DVT trial. Patients with cancer are likely to fare worse under LMWH/VKA treatment than under LMWH treatment, and their inclusion in the trial may disadvantage results for the whole comparator group, in comparison to normal practice in England and Wales. [redacted]

To address the issue of the comparative efficacy of rivaroxaban to LMWH in this group, an MTC has been attempted and is discussed elsewhere (sections 4.3 and 4.4).

3.3.4 "No preventative therapy" option listed in NICE scope.

The scope produced by NICE lists "no preventative therapy" as a comparator. The MS rejects this as a comparator on page 22, stating

"...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."

Communication between the ERG and NICE confirmed that this comparator was considered appropriate at the scoping workshop, though it is not clear whether this comparator was intended during the "initial treatment of DVT" stage as interpreted by the manufacturer. Indeed, to test rivaroxaban against "no preventative therapy" in patients who are clearly indicated for anticoagulation would be unethical. The ERG feels it is more likely that this was intended as a long-term treatment comparator, where the risk of bleeding may outweigh the benefits of anticoagulation (reduced VTEs). The ERG has therefore considered whether comparison to "no preventative therapy" could have been better addressed in the MS, given the available trial evidence:

- "No preventative therapy" is the treatment option once initial treatment has ceased, whether that be at 3 or 6 months, or some other time point. Patients were not followed up beyond treatment in the EINSTEIN-DVT trial, and a comparison of those who had ceased treatment with those still undergoing treatment would likely have been confounded by patient characteristics being worse in the 6 and 12 month treatment arms.

- In the EINSTEIN-Ext trial, the manufacturer has defined a group in "clinical equipoise", where it is unclear whether the balance between risk of bleeding and benefit of prevented VTEs conferred by the treatment is favourable. The MS states that patients who either did or did not require further treatment were not included in the trial (page 37) (though as already discussed in section 3.1.2, it appears from the study protocol[22] and MS[1] that in fact only patients who did require further treatment were excluded). The comparator was placebo, which the ERG feels can be equated to "no preventative therapy" as the trial end points are largely objective and unlikely to be subject to a significant placebo effect. This comparator is relevant in this group, and is possibly the only patient group for which comparison to placebo would be ethical. This trial, therefore, provides comparison to "no preventative therapy", but only in the poorly defined clinical equipoise subgroup of the whole DVT population. However, whilst data from this trial may indicate whether ongoing treatment with rivaroxaban is favourable in this group, it will not indicate whether it is better or worse than other treatments, only whether it is better or worse than no treatment.

As such, the ERG feels that the comparator "no preventative therapy" has been addressed as completely as possible by the manufacturer, but does not provide an answer as to whether rivaroxaban is the optimal treatment choice for ongoing treatment.

3.3.5 Unfractionated Heparin and LMWH in those for whom a VKA is not appropriate– EINSTEIN-DVT

Unfractionated Heparin (UH) is not used in the EINSTEIN-DVT trial as no patients for whom this is a recommended treatment option (creatinine clearance <30mL/min) were included, as stated in the MS (page 27). No clinical evidence is provided in comparison to UH in the relevant patient group.

The manufacturer has interpreted "those for whom VKA is not considered appropriate" to refer to those with cancer. The clinical advisors to the ERG believe that patients at a high risk of bleeding are also not considered to be suitable for treatment with VKA. Patient characteristics include:

- Liver impairment

- Renal failure

- Haemophilia and other severe bleeding disorders
- Previous heparin induced thrombocytopenia
- Low platelet count for any reason
- Active bleeding
- Recent peptic ulcer
- Recent intracerebral bleeding
- Severe uncontrolled hypertension
- Major trauma or recent major surgery to eye or central nervous system
- Bacterial endocarditis
- Spinal or epidural catheter

The EINSTEIN-DVT exclusion criteria exclude patients at high risk of bleeding, and it is therefore likely that all of the above were excluded from the trial. The ERG does not feel that the cancer group would necessarily serve as a proxy for other patients in this group, as rivaroxaban may act differently in some of these patient groups, e.g. renal failure. Therefore, no evidence for the use of rivaroxaban versus LMWH is available.

3.3.6 Comparator time in treatment range and compliance– EINSTEIN-DVT

Levels of compliance and time in treatment range for VKA treatment are thought to affect levels of effectiveness. The levels achieved in the comparator arm in the study are fairly representative of UK practice; time in target range (TTR) was 57.7% across all centres and 59.7% in Western European centres (page 88). This compares well with a reported UK TTR of 53% during the first 12 weeks of treatment and 59% thereafter.[27] However, the clinical advisors to the ERG feel that whilst this is representative, it is also a worryingly low figure, and there is general concern about the levels of anticoagulation achieved within the UK. It is thought that there is room for improving these figures, and were resources used to this end, better levels of anticoagulation may be possible, and better efficacy may be achieved for LMWH/VKA treatment.

It could be argued that poor TTR may make rivaroxaban look better in comparison, due to a failing of the comparator rather than improved benefits offered by rivaroxaban. The ERG is satisfied that whilst low, the TTR reported in the trial reflects real life practice. The removal of the need to maintain doses in a therapeutic range is one of the advantages of rivaroxaban, and is correctly represented in the assessment in this way.

[redacted] However, the calculations for this are not presented, and it is unclear if the trial would have been adequately powered to detect an effect.

3.4 Outcomes

Do the outcomes in the MS match the outcomes described in the final scope? If not, provide further details. Consider clinical effectiveness, adverse events, quality of life and health economic outcomes and a discussion of appropriate mechanisms for measuring these outcomes. Is the focus of the submission on appropriate outcomes or has it been limited to non-ideal outcomes?

Nearly all outcomes listed in the NICE scope were included in the submission (Table 5). There are a few points for discussion.

3.4.1 Health related quality of life

The only significant omission is that the health related quality of life (HRQoL) data reported was not in accordance with the NICE reference case. The HRQoL questionnaires that have been used are not validated or mapped to a preference based measure of quality of life, though such validation work appears to be underway.[28] Had such a measure been used, or a mapping exercise performed, some of the advantages which the manufacturer feels are not reflected in the QALYs (section 2.11, (pg 25)) could have been captured i.e. ease of treatment administration, reduced fear and reduced safety risk. However, the sensitivity of the EQ-5D to capture such benefits is also unknown. No quality of life data was collected in EINSTEIN-Ext.

Table 5: Summary of outcomes as defined in the NICE scope,[3] as recommended by the EMA Research Guidelines,[23] and as outlined in Table 14 and 15 of the MS.[1]

	NICE scope[3]	**EMA guidelines[23]**	**EINSTEIN-DVT[1]**	**EINSTEIN-Ext[1]**
Efficacy outcomes	Recurrent VTE	Recurrent, symptomatic VTE non-fatal DVT and/or nonfatal PE. Non-inferiority trials: The combined incidence of recurrent DVT/PE and VTE-related deaths, with secondary analyses for each individual component separately. Superiority trials: The combined incidence of recurrent DVT/PE and all deaths, with secondary analyses for each individual component separately.	Symptomatic, recurrent VTE	Symptomatic, recurrent VTE Secondary outcome 1: composite of DVT, non-fatal PE and all-cause mortality
	Mortality	Mortality	All cause mortality	Not listed in Table 14, but reported
	PTS and CTEPH	NR	Not listed in Table 14, but reported	Not listed in Table 14, but reported
Safety outcomes	Adverse events including bleeding events	Bleeding episodes*	Clinically relevant bleeding Vascular events	Major bleeding
Additional outcomes	HRQoL	NR	Anti-clot treatment scale Treatment Satisfaction Questionnaire Discontinuation rates ands reasons Time in Target range	Discontinuation rates and reasons
Secondary outcomes not required by EMA or NICE	NA	NA	Net clinical benefit; a composite of recurrent VTE and major bleeding	Secondary outcome 2: composite of DVT, non-fatal PE, fatal PE, all-cause mortality and vascular events Secondary outcome 3: net clinical benefit; a composite of recurrent VTE and major bleeding Post hoc: risk-benefit

NICE, National Institute for Health and Clinical Excellence; EMA, European Medicines Agency; DVT, Deep vein thrombosis; VTE, Venous thromboembolism; PE, pulmonary embolism; HRQoL, health related quality of life; PTS, post thrombotic syndrome; CTEPH, Chronic Thromboembolic Pulmonary Hypertension.
* Bleeding episodes are defined as major or minor. Major bleeding is defined as: fatal bleeding; clinically overt bleeding causing a fall in Hb level of 20g/L or more, or leading to transfusion of two or more units of whole blood or red cells; bleeding in areas of special concern, such as retroperitoneal, intracranial, intraspinal or intraocular bleeding; bleeding causing permanent treatment cessation.

3.4.2 Outcomes recommended by EMA research guidelines[23]

Whilst all the outcomes specified by NICE were reported (with the exception of HRQoL), some of the outcomes specified in the EMA document were not reported. The EMA guidelines recommend composite primary outcomes:

- Non-inferiority trials: The combined incidence of recurrent DVT/PE and VTE-related deaths, with secondary analyses for each individual component separately.

- Superiority trials: The combined incidence of recurrent DVT/PE and all deaths, with secondary analyses for each individual component separately.

The EMA primary outcomes were not reported in the corresponding EINSTEIN trials. However, all the individual of these composite primary outcomes were reported. In addition, the composite primary outcomes specified by the EMA were not specified in the NICE scope, and the ERG does not feel that their omission is problematic; composite outcomes are generally not used in economic analyses as there are differential impacts on both costs and utility for the constituent events, and whilst composite outcomes may seem to have simplicity on their side, they can be criticised for obscuring important differences in outcomes.[29]

3.4.3 Composite primary endpoint

This last point is of further interest as the primary outcome defined by NICE is itself a composite outcome. VTE recurrence includes both DVT and PE. PEs are generally caused by parts of a DVT clot breaking off and getting lodged in the arteries of the lungs. Whilst these two events are manifestations of the same underlying condition, the clinical implications of each are different, with PE being more associated with death and CTEPH. There are also different costs associated with each. The use of a composite outcome might be argued to be valid if the constituent events are not thought to differ in their response to treatment, i.e. they have similar reductions in relative risk.[29] If there is reason to believe that the two events may behave differently, then the composite outcome may not be appropriate.

3.4.4 The diagnosis of primary outcomes

The diagnosis of DVT and PE, for both index events and recurrence, described in the MS are largely consistent with those recommended by the European Medicines Agency (EMA) Committee for Proprietary Medical Products (CPMP)[23] guidelines for the evaluation of new technologies for managing VTE. Exceptions are discussed later in the report in section 4.2.1.3, "*difference between expected and confirmed events*".

3.5 Other relevant factors

3.5.1 Equity

The MS includes a section on equity issues, where no issues are reported (Page 26). The clinical advisors t the ERG and the ERG are satisfied that there do not appear to be any major issues to consider, and note that there are two advantages to rivaroxaban that could be considered as improvements in equity. These are

- The comparators in the UK are made of pig heparin, which may present access issues for people of some religious denominations. (Personal Communication with Dr Hampton, November 2011)

- In comparison to LMWH, rivaroxaban would increase access for those for whom dexterity or needle phobia is an issue.

3.5.2 Patient Access Scheme

There is no ongoing Patient Access Scheme, and no other relevant factors of which the ERG is aware.

3.5.3 Reversal of anticoagulation

The ERG is aware that reversal of anticoagulation by rivaroxaban has not been standardised, though there are promising therapies under investigation.[30] As such, there is a potential for rivaroxaban to have an adverse effect on patients through the delay of emergency surgery. The ERG assumes that these types of events would have been recorded as adverse events, and will therefore have been captured in the study outcomes, though may have been too rare to be observed in this size of patient population.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

Two systematic reviews relating to clinical effectiveness were included in the MS, one for direct evidence of efficacy for rivaroxaban versus any competitor, and a second review of indirect evidence to inform a MTC. The first of these reviews was performed systematically. The second review was not a full systematic review, as a relatively recent high quality systematic review was identified at the scoping search stage, and no further searches were conducted.

4.1.1 Searches

4.1.1.1 Direct evidence review

The manufacturer searched four databases: Medline, Medline in Process, Embase and Cochrane Central for the identification of direct evidence. Further searching through other means by the sponsor was reported including reference follow-up of included studies and guidelines reference searching. Since the searches were restricted by randomised controlled trial (RCT) study design, the ERG suggests that further sources could be searched such as the multidisciplinary Science Citation Index database and the Web of Science Conference Proceedings Index. Terms within the concept rivaroxaban were combined with the disease condition thromboembolism and a published RCT filter to identify relevant titles. The ERG repeated these searches and found that the record numbers were similar and can confirm that the included studies were retrieved by these searches. The ERG does not consider that any studies are missing.

4.1.1.2 Indirect evidence review

The indirect evidence review started with a scoping search of the Cochrane library using a simple free text search for "anticoagulation and cancer". As a recent review was identified, no further searches were performed. However, the review used (Akl et al. 2011)[31] included searches which were completed in February 2010. It is the opinion of the ERG that update searches for this review should have been performed to see if any additional relevant literature has been published since then.

The search strategy within the Akl 2011 review comprised searches for evidence in Medline, Cochrane Central, Embase and Web of Science. The ERG have repeated these searches and even though the record numbers retrieved from these databases were not given, the included studies were indeed retrieved by these searches.

4.1.1.3 Adverse events

No search strategies were given for adverse events. It is unlikely that the sponsor has missed any RCT studies reporting the safety of rivaroxaban. However, searches for non-RCT evidence for clinical parameters and variables for the model were reported in the sponsor's submission i.e. evidence on rates of recurrent VTE in patient populations with index DVTs, PEs or VTEs page 114 (16,795 records); systematic search for rates of incidence of complications of VTEs, including CTEPH and PTS in patient populations with index DVTs, PEs or VTEs page 115 (3853 records); risks of mortality in respect of the specific adverse events (2755 records) according to page 117 of the submission. Absence of these search strategies meant that they were not repeated by the ERG.

4.1.2 Inclusion criteria – direct evidence review

Guidance on undertaking systematic reviews issued by the Centre for Reviews and Dissemination (CRD)[32] and the Cochrane Collaboration Handbook[33] proposes that the decisions on study eligibility be explicit and also minimize the risk of bias and error. The MS stated that study selection was undertaken by one reviewer and checked by another, which is good practice for reducing risk of bias and error. However, the process of decision-making during different stages of the study selection process between the two reviewers was not described in the MS, and more detail about this would have been desirable.

Study selection was guided by a documented inclusion and exclusion criteria in the MS. Table 4 in the MS (page 30),[1] reproduced here as Table 6, shows inclusion and exclusion criteria for the systematic search for relevant studies. The ERG feels that some of the PICO items seem poorly defined:

The inclusion and exclusion criteria relating to the population are unspecific about the eligibility of studies which include patients with PE, either with or without DVT; the inclusion criteria state those with DVT, but the exclusion criteria state exclusion of "non-VTE" patients, which would allow for the inclusion of studies which included patients with PE. This would seem at odds with the decision problem, which specifies that only patients with symptomatic DVT should be included. It is thought possible by the ERG that these criteria were designed with the inclusion of the EINSTEIN-Ext trial in mind, which includes patients with DVT and PE as an index event. The ERG has addressed the relevance of this study population in section 3.1.2, and additional analyses have been presented by the manufacturer for this data (section 4.2.2.3), for patients within the population of the scope upon request from the ERG.

The comparator was defined as any competitor. The ERG requested clarification of this point, as a placebo controlled trial (EINSTEIN-Ext) was included, which did not seem to represent a competitor. The manufacturer confirmed that the definition was intended to represent an indication that no

competitor products were excluded from the review, rather than that placebo trials were not eligible for inclusion.

Table 6: Eligibility criteria used in search strategy (reproduction of Table 4, page 30, in MS)[1]

Criteria	Inclusion	Exclusion
Population	**Patients with acute symptomatic DVT**	**VTE prophylaxis, non-VTE indications**
Interventions:	Xarelto (rivaroxaban)	Not described
Comparator:	Any competitor	Not described
Outcomes:	Efficacy and safety outcomes	Not described
Study design:	RCTs	Not described

The ERG also notes that outcomes are defined only as efficacy and safety outcomes, without specifying what type of outcomes are of interest. The ERG assumes that only studies with outcomes of commonly acknowledged safety and efficacy relevance in the defined population, and hence of probable relevance to the NICE scope, were included. From section 5.2.2. (page 30) of the MS, it seems the manufacturer excluded studies in which patients received the intervention for the prevention of atrial fibrillation.

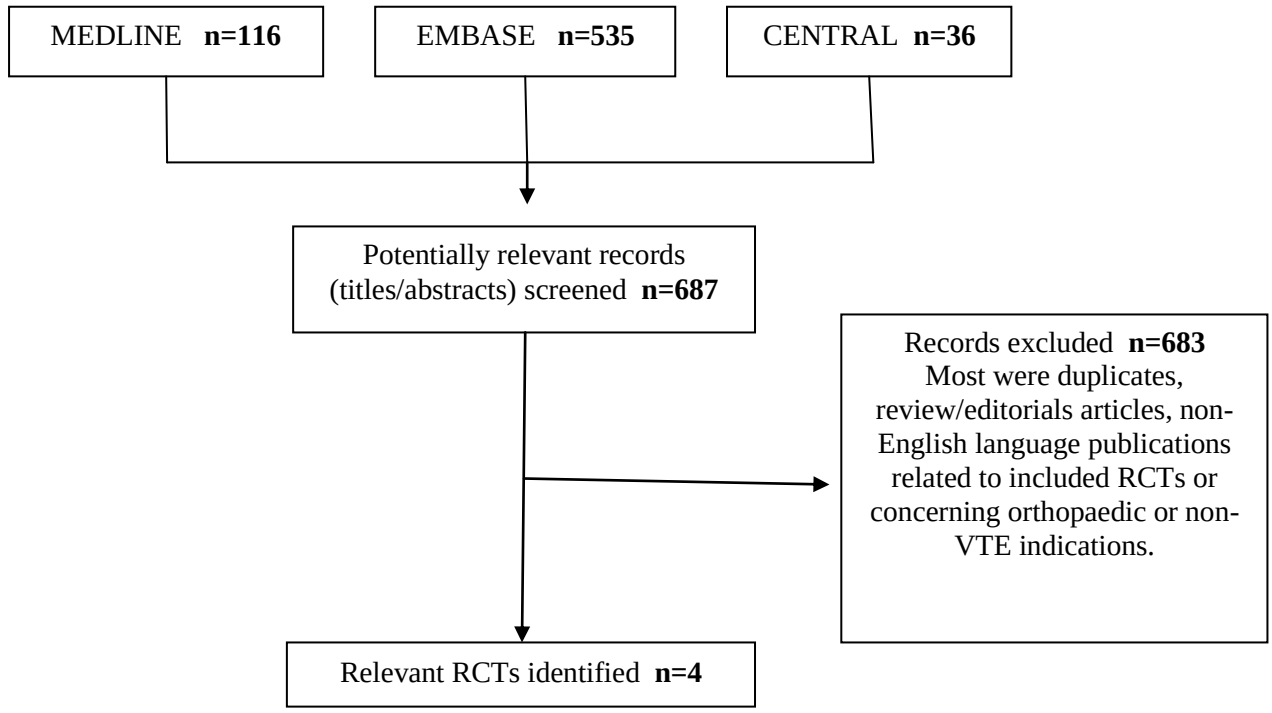
For the reasons discussed above, the ERG feels that some aspects of the study selection process were imprecise and unclear and that there is the potential for some degree of bias in this stage of the review. However, in the absence of any additional relevant literature being found by the ERG, the potential for bias does not appear to have resulted in relevant trials being missed, but may have led to the inclusion of the EINSTEIN-Ext trial, for which only a proportion of the patients were of direct relevance to the decision problem.[3] This has been addressed by the ERG in section 4.2.2.3.

4.1.3 Study selection– direct evidence review

The manufacturer included a flow diagram (Figure 2 in the MS, page 31)[1] to outline the number of studies included and excluded at each stage of the review. The flow diagram (reproduced in Figure 1) did not conform to the PRISMA statement recommendations.[34] The diagram provided sufficient information regarding the overall number of references and studies identified, and the number of

RCTs selected. However, there are some minor points to note where accuracy, transparency and reproducibility are lacking:

Figure 1 Flow diagram for identifying RCTs (reproduced from Figure 2 'Study flow diagram for the identification of references relating to RCTs' in the MS, page 31)[1]



- The MS stated that 687 records were identified from the conducted searches; of these, one record was obtained from 'non-literature database sources'. It is unclear what this source was, as this does not appear to have been defined in the MS, and is also not reflected in the flow diagram.
- Although, the MS explained that 687 of the records retrieved were excluded, the ERG assumed that this was minor typo error as the flow diagram indicated that the number of records excluded was 683. This was confirmed by the manufacturer.[17]
- The study selection process lacked transparency. Details on number of duplicates, number of studies excluded at title and abstract stage and number of full text papers screened for possible inclusion were missing. Though the manufacturer stated that, 'Where studies were published as abstracts then subsequently as full papers, the abstracts were excluded', it is unclear at what stage this decision was made. Lack of clarity in this case introduces the potential for bias in the review; linking the two publications and documenting that decision would have been a more acceptable approach. However, the ERG does not feel this is likely to have introduced bias to the review in this case.

- Records excluded were described in the flow diagram. This stated '*Most were duplicates, review articles, editorials, non-English language publications related to included RCTs or concerning orthopaedic or non-VTE indications*.' This reporting lacks clarity, in that the numbers of articles excluded for each category are not given. For most categories, this is not of great importance. However, where English language is used as a selection criterion, it is usual to list how many potentially includable studies with potentially relevant data were excluded on this basis, to give some indication of the risk of language bias affecting the results.

Overall, the above points are thought unlikely by the ERG to introduce any significant bias to the review.

In relation to study selection, the presentation of two unpublished studies in the "Overview of rivaroxaban trials" (presented in Table 5, section 5.2.3 of the MS),[1] namely the CYP cohort and EINSTEIN-PE study, was not necessary, as these studies do not fall within the NICE scope or the inclusion/exclusion criteria. However, the manufacturer's provision of information related to them is appreciated by the ERG, by way of explanation of their exclusion.

The MS presented a list of four RCTs comprising two Phase II studies and two Phase III studies[21,35,36] (Table 6 in MS, page 32, reproduced here as Table 7) comparing the intervention with other therapies in the population group as defined by the selection criteria, which is reproduced in Table 6.

Of the listed RCTs, the MS highlighted two Phase III randomised controlled trials as the main sources of clinical evidence for rivaroxaban treatment in patients with DVT and the prophylaxis of recurrent DVT and PE. The studies were the EINSTEIN-DVT study[21] and the EINSTEIN-Ext study[21]. The Phase II studies, the Oral Direct Factor Xa Inhibitor BAY-59-7939 in Patients with Acute Symptomatic Deep-Vein Thrombosis (ODIXa-DVT) study[35] and EINSTEIN dose-ranging Phase II[36] study did not directly contribute data for the review of clinical effectiveness. However, the manufacturer stated that these were included as they informed the selection of rivaroxaban doses and also served as supportive evidence on the efficacy and safety of rivaroxaban. These studies are summarised in Appendix 1.

Table 7: Table showing list of relevant RCTs (reproduced from Table 6 in MS, page 32)[1]

Study reference	Trial name/Study	Population	Intervention	Comparator
Agnelli et al 2007[35]	OXIDa-DVT Phase II study	Symptomatic proximal DVT without PE	Rivaroxaban 10mg, 20mg, or 30mg twice daily or 40mg once daily	Enoxaparin (1mg/kg) twice daily overlapping with and followed by VKA
Buller et al 2008[36]	EINSTEIN dose-ranging Phase II study	Acute symptomatic DVT without PE	Rivaroxaban 20, 30 or 40mg once daily	Enoxaparin, tinzaparin or UH overlapping with and followed by VKA
Bauersachs et al 2010[21]	EINSTEIN DVT Phase III study	Acute symptomatic DVT without any symptoms of PE	Rivaroxaban 15mg twice daily for 3 weeks then 20mg once daily for 3,6 or 12 months	Enoxaparin (body weight adjusted) followed by VKA*, for 3, 6 or 12 months
Bauersachs et al 2010[21]	EINSTEIN-Extension Phase III study	Objectively confirmed symptomatic DVT or PE that had been treated for 6 to 12 months with warfarin, acenocoumarol or rivaroxaban in patients with clinical equipoise for continued anticoagulation	Rivaroxaban 20mg once daily	Placebo

DVT, Deep vein thrombosis; EINSTEIN- OXIDa, Oral Direct Factor Xa Inhibitor; PE, pulmonary embolism; UH, unfractionated heparin; VKA, vitamin K antagonist.

*The dose of VKA was adjusted to maintain a therapeutic INR of 2.5 (range 2.0-3.0).

4.1.3 Critique of data extraction – direct evidence review

The ERG considers that the data extraction strategy outlined in Appendix 9.2.7 (page 233, in the MS) appears mostly adequate and comprehensible. The manufacturer states that data extraction was performed independently by two reviewers, although it was not stated exactly how disagreements between the two were addressed, e.g. through discussion, or involvement of a third party. In addition, there are some discrepancies between the methods stated, and the data presented, which may be a series of omissions in writing up, or may indicate a more general failure to follow the review protocol in a systematic way. According to the MS, items for which data were retrieved included the following (page 233 to 234, in the MS):

- Study characteristics: Author, title, year, country, study design, duration.
- Details of participants: number of patients in each treatment arm, age, gender, initial diagnosis, time from onset of symptoms, cause of DVT or PE, known thrombophilic condition, previous VTE.
- Details of intervention and comparators: drugs used, duration and intensity.
- Details of primary and secondary outcomes: recurrent VTE, bleeding (severity & location), all-cause mortality, treatment satisfaction (EINSTEIN-DVT only), pulmonary hypertension (to include CTEPH), PTS and other adverse events.

Data extracted was used to populate Tables 9 to 16 (page 39 to 48, in the MS).[1] From the data presented, it is evident that some fields were populated, but not listed in appendix 9.2.7 in the MS as data extraction fields. These include:

- information relating to quality assessment (Table 9, page 39)
- inclusion criteria, exclusion criteria (Table 10, page 40)
- body mass, creatinine clearance (Table 11, page 41)
- risk factors, previous use of rivaroxaban (Tables 12 & 13, page 43)
- and information on statistic analysis methods used (Table 16, page 47).

Of note also is a lack of formal data extraction, tabulation and presentation of compliance rates, though these are available elsewhere in the report (page 96 of the MS),[1] and also of time in target range (presented on page 88 of the MS).[1]

For all these data, it is unclear if the data extraction methods of double data extraction and checking were applied. There is a risk that these data are more prone to error and potentially bias. However, the ERG does not feel that the risk is significant in this report, or that these omissions should detract from the data presented as the report appears generally of high quality.

4.1.4 Quality assessment

The approach taken to quality assessment by the MS conforms to the requirements of NICE. The summary table of quality assessment provided in the MS is reproduced in Table 8. However, the ERG has two concerns.

4.1.4.1 Concealment of treatment allocation

The question "was the concealment of treatment allocation adequate?" was answered as "N/A" by the manufacturer. This may be because the trial is open label. However, this question relates to the concealment of allocation up to the point of randomisation, where the important factor is whether study personnel can predict which group a patient will be allocated to before allocation takes place. This can result in selection bias. It is the opinion of the ERG that this should have been attempted, and that a NA answer is not appropriate. However, the trial arms [redacted] so it is unlikely that selection bias has affected the results.

[redacted]

The ERG agrees, given the manufacturer's response, that the scoring is acceptable.

4.1.4.3 Blinding of outcome assessors

In addition, in light of responses received by the ERG,[17] the ERG have some concerns relating to the blinding of outcome assessors. This is discussed elsewhere in the report (section 4.2.1.3, "Difference between suspected and confirmed events").

Table 8: Quality assessment of EINSTEIN-DVT and EINSTEIN-Ext as reported in MS (Table 17, page 53).

	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

4.1.5 Evidence synthesis

No evidence synthesis was performed for the direct evidence review, due to incompatibility of the study evidence in terms of comparators and study populations. This was considered appropriate by the ERG.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The MS clinical effectiveness review identified 6 rivaroxaban studies, only four of which are published.[21,35,36] All six are listed in Table 9. Only four studies [21,35,36]met all of the inclusion criteria, as the CYP cohort study (Page 31, MS) was a single arm study, and the EINSTEIN PE (Page 31, MS) study did not select a population with symptomatic DVT. Of the four studies that met the inclusion criteria, two[35,36] were described in detail, but essentially excluded from further analysis because they were phase II, proof of concept, dose-ranging studies. The ERG agrees that it is appropriate not to focus on these studies for the previously mentioned reasons, and because:

- Neither study used the licensed doses across the whole treatment period;
    - ODIXa-DVT[35] used 10mg bid or 20 mg bid, but not 15mg bid, and

- EINSTEIN-DVT dose-ranging study[36] did not use 15mg bid for the first 21 days as indicated by the license, but rather used 20mg throughout the study.

- Outcomes reported are not defined in a way comparable to the outcomes reported in the pivotal EINSTEIN-DVT trial.[21]

Both of these studies are described and discussed in detail in Appendix 1.

Two studies, both reported in the same journal article,[21] were included in the analysis and interpretation of the MS. Of these, the ERG consider the most important and relevant information to come from the EINSTEIN-DVT[21] study. The EINSTEIN-Ext[21] has some limitations, outlined in section 3.1, mainly to do with study population and comparator, but does provided some data of relevance. Data relating to the population of interest (DVT patients) within EINSTEIN-Ext have been made available to the ERG after a request to the manufacturer and are presented in section 4.2.2.3. However, the analyses provided were limited.[17] As both trials have some relevance, data from both is presented here, including the data for the whole EINSTEIN-Ext trial, as well as the DVT subgroup of interest.

It should be noted that the ERG have not had access to the European public assessment report (EPAR) (these are expected to be made available in early February 2012). Nor have the ERG had access to correspondence between the European Medicines Agency (EMA) and the manufacturer in relation to the licensing of the product. The manufacturer state that discussions with the EMA centred on the design and conduct of the phase III trials. It is unclear if/when these documents will be made available.

Table 9: Summary of key characteristics of the clinical effectiveness studies identified in the MS. Data drawn from tables 5, 6, 10, 11 and 14 of the MS.

	Trial name	References, study type	Population			Intervention	Comparator	Outcomes
			Inclusion criteria	Exclusion criteria: both trials	Exclusion criteria specific to trial			
Excluded	**CYP cohort**	Not published Single arm trial	NR	NA	NR	NR	NR	NR
	EINSTEIN PE	In progress Phase III RCT	• Patients with symptomatic PE with or without DVT	NA	NR	NR	NR	NR
Included in review but not in analysis	**ODIXa-DVT**	Agnelli 2007[35] Manufacturer's submission [1] Phase II RCT	• Symptomatic proximal DVT without PE	NA	NR	Rivaroxaban 10, 20 or 30mg twice daily or 40mg once daily	Enoxaparin (1mg / kg) twice daily overlapping with and followed by VKA	• improvement in thrombotic burden at mean day 21 (4-point reduction in the thrombus score) w/o symptomatic recurrent VTE or VTE-related death • major bleeding
	EINSTEIN DVT dose ranging study	Buller 2008[36] Manufacturer's submission[1] Phase II RCT, dose ranging study	• Acute symptomatic DVT without PE	NA	NR	Rivaroxaban 20, 30 or 40mg once daily	Enoxaparin, tinzaparin or UH overlapping with and followed by VKA	• composite of symptomatic recurrent DVT, symptomatic fatal or non-fatal PE and asymptomatic deterioration in thrombotic burden • major and clinically relevant non-major bleeding
Include	**EINSTEIN-DVT**	Bauersachs et al 2010[21] Manufacturer's	• Acute symptomatic DVT without symptoms of PE	• Creatinine clearance <30ml/min • Clinically	• Pre-randomisat AC treatment >36 hours • >1 single dose	Rivaroxaban 15mg twice daily for 3 weeks then	Enoxaparin (body weight adjusted) followed by	• Symptomatic, recurrent VTE • Clinically relevant bleeding

	Trial name	References, study type	Population			Intervention	Comparator	Outcomes
		submission[1] Phase III RCT	• 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.	significant liver disease • Additional indications for VKA • Active or high risk of bleeding • Contraindication to AC • High blood pressure • Pregnancy, breastfeeding, childbearing potential without contraception • Concomitant use of cytochrom P-450 3A4 inhibitors • Life expectancy <3 months • Participation in other clinical trial	VKA pre-randomisation • Thrombectomy, insertion of a vena cava filter or fibrinolytic agent for current episode of thrombosis • Contraindication to enoxaparin, warfarin or acenocoumarol	20mg once daily for 3,6 or 12 months	VKA, dose-adjusted to maintain a therapeutic INR (target 2.5, range 2.0-3.0) for 3, 6 or 12 months	• Net clinical benefit (composite outcome)* • Vascular events • All cause mortality • Adverse events • ACTS • TSQM • Compliance • Time in Target Range
	EINSTEIN-Ext	Bauersachs et al 2010[21] Manufacturer's submission[1] Phase III RCT	• Objectively confirmed symptomatic DVT or PE that had been treated for 6 to 12 months with warfarin, acenocoumarol or Rivaroxaban • Clinical equipoise with respect to the need for continued anticoagulation		• Patients in whom anticoagulation treatment for their index DVT or PE should continue	Rivaroxaban 20mg once daily	Placebo	• Symptomatic, recurrent VTE • Clinically relevant bleeding • 3 composite outcomes* • Adverse events • Post hoc: risk-benefit (composite outcome).* • Compliance • Time in Target Range
		Manufacturer's clarifications[17]	• Objectively confirmed symptomatic DVT (subgroup provided by manufacturer on request of ERG)		• As above	• As above	• As above	• As above

	Trial name	References, study type	Population	Intervention	Comparator	Outcomes
VKA, vitamin K antagonist; AC, anticoagulation; DVT, Deep vein thrombosis; PE, pulmonary embolism; N, number of patients; ACTS, anti-clot treatment scale; TSQM, treatment satisfaction questionnaire; NA, not applicable; NR, not reported. * the ERG do not consider the use of composite outcomes to be relevant to a cost-effectiveness analysis as the components are not weighted, and these outcomes will not be included in the ERG report.						

4.2.1 Critique of pivotal EINSTEIN-DVT study

4.2.1.2 Trial design – EINSTEIN-DVT

The EINSTEIN-DVT study was a non-inferiority, phase III RCT, using as its primary outcome "time to event" data. The study seems well conducted, however as mentioned above, the ERG are aware that some discussions have taken place between the manufacturer and the EMA regarding the design of the trial.[17] It is unclear what these discussions entailed.

A number of aspects which relate to trial design have already been discussed in section 3, and are summarised here.

- The whole population of interest were not included (see section 3.1.1.1). Principle omissions include:
    - Patients with additional indications for a vitamin K antagonist
    - Patients with creatinine clearance <30mL/min (but not less than <15mL/min
    - Patients at high risk of bleeding, other than cancer patients
    - Patients with significant liver disease
    - Patients with high blood pressure
    - Patients with life expectancy less than 3 months
    - Only patients with proximal DVTs were included in the trial (see section 3.1.1.2). The NICE scope did not exclude this group, and it appears that this group is covered by the product SmPC.[19,20]
- The intervention was problematic in the following ways:
    - Patients with creatinine clearance <50mL/min were not given the lower dose recommended in the SmPC[19,20] (see section 3.2.1).
    - The length of treatment was 12 months, though longer term treatment is common (see section 3.2.2).
- The comparator was problematic in that:
    - The dose of LMWH used was different to UK doses (see section 3.3.2) and may overestimate efficacy in the comparator arm compared to standard practice in England and Wales, thus disadvantaging rivaroxaban
    - Patients with cancer received the wrong treatment according to international guidelines (see section 3.3.3). This may advantage rivaroxaban as patients with the wrong treatment will fare less well in the comparator arm compared to standard practice, reducing the apparent efficacy of the comparator.
    - No comparison to "no preventative therapy" was made. However, the ERG are unsure of the relevance of this outcome in the context of this trial (see section 3.3.4)

    - There is no direct evidence relating to the use of unfractionated heparin or LMWH as patients requiring these treatments were largely excluded (see section 3.3.5)
    - The time in treatment range was poor, but not outside of normal UK values (see section 3.3.6)

- The outcomes were limited in that:
    - Health related quality of life was not recorded in line with the NICE reference case (see section 3.4.1)
    - The ERG note that the use of a composite outcome depends on an assumption that the constituent events do not differ in their response to treatment. The ERG are not clear whether this is the case (see section 3.4.3).

In addition, the ERG has the following comments to make.

- Some aspects of this study were very well designed. Importantly, participants were assigned to one of three intended treatment durations (3, 6 or 12 months) based on clinical presentation, taking into account risk factors. This reflects clinical practice and ensured, through stratification at randomisation, an equal distribution of these groups across the two arms.

- However, it is possible that some patients will have been under or over diagnosed by clinicians into the treatment duration groups. As follow up ceased with treatment, it is unclear in what way, if any, under or over diagnosis would have impacted on the estimates of efficacy within the treatment duration groups and across the study as a whole. It is possible; however, that under-diagnosis of patients would have resulted in events being systematically missed. This is only likely to present a problem if levels of mis-diagnosis differed between arms of the trial, or the implications of mis-diagnosis differed according to treatment arm. The ERG does not feel that either of these is likely to be a problem in this case, but this remains unknown. Proportions of patients in each intended treatment duration group match the expectations of the clinical advisors to the ERG, and this also suggests that this potential issue is not likely to be a problem.

- A proportion of patients within the trial were treated before randomisation, so as not to delay anticoagulation. The clinical advisors to the ERG agree that this is a good trial design. (MS, page87) [1]

- However, the study design did not include a power calculation for each of the intended treatment duration groups. As a result, it is unclear whether the subgroups are powered to detect an effect, and the ability to draw conclusions as to the relative efficacy in each treatment duration subgroup is limited.

- The primary study outcomes were defined in line with the NICE scope,[3] and were similar to the outcomes recommended by the EMA.[23] However, neither of these documents specified whether data should be collected as time to event data, or simply as frequency data. Time to event data really only provides information about whether the time to the first event is lengthened. However, as DVTs can recur multiple times in an individual patient within the timeframe of these trials, and each recurrence carries with it its own costs and QALY implications, it is unclear if the time to the first event is reliably linked to overall frequency, and whether this type of data is adequate to populate a long term model where multiple recurrences can occur. As patients were censored once they had had a VTE event, frequency data was not reported for this trial.

- The EINSTEIN-DVT trial is a non-inferiority trial. This is appropriate as it would have been unethical to conduct a superiority trial, given that there are treatments already available that are potentially life-saving and preventative of irreversible damage.[3] However, draft US Food and Drug Administration (FDA) guidelines recommend that where non-inferiority trials are conducted and a placebo arm cannot be included due to ethical considerations, some other evidence should be submitted to show that the effects seen in the non-inferiority trial are equivalent to previous measures of efficacy for the comparator drug. This is known as showing that the trial has assay sensitivity:

  > "If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug." (Page 3)

  No evidence of assay sensitivity was provided, so it is unclear whether the effects seen in EINSTEIN-DVT were representative of other estimates of the efficacy of Enoxaparin/VKA treatment. This could work in favour of or against rivaroxaban, as the estimate of efficacy for Enoxaparin/VKA in EINSTEIN-DVT could theoretically be either an overestimate or an underestimate.

4.2.1.3 Results and interpretation – EINSTEIN-DVT

Table 10 summarises the key outcome data reported in the MS for EINSTEIN-DVT.

Efficacy outcomes – EINSTEIN-DVT

In the EINSTEIN-DVT trial, the manufacturer states that

"rivaroxaban would be considered statistically significantly non-inferior to comparator therapy if the upper limit of the two sided 95% confidence interval (CI) for the (HR) ratio was below the pre-defined non-inferiority margin of 2.0. This margin corresponds to maintenance of at least 50% of the proven efficacy of standard therapy and was derived based on a comprehensive meta-analysis of historical trials in this indication" (MS, page 47 to 48).

EINSTEIN-DVT reports an overall hazard ratio of [redacted] for the primary efficacy outcome, VTE recurrence, when compared to Enoxaparin/VKA, which suggests rivaroxaban is non-inferior to the comparator ($p<0.001$). A test for superiority did not prove significant ($p=0.0764$). The components (PE and DVT) of this composite outcome are listed in Table 10. DVT events appear to have occurred less often in the rivaroxaban arm, whilst PE events appear to have occurred approximately equally in each arm. For the primary safety outcome of clinically relevant bleeding, the HR is 0.97, (95% CI 0.76-1.22, $p=0.77$), which suggests rivaroxaban is non-inferior to the comparator. All cause mortality was 0.67 (95% CI 0.44 to 1.02, $p=0.06$), again indicating non-inferiority. The ERG note that this outcome approaches significance. [redacted]

Table 10: Summary of outcomes for EINSTEIN-DVT, taken from table 18 and 29, data on page 56, 58, 65, 96 of MS[1] and Bauersachs et al. 2011[21]

Trial name	**Einstein-DVT**		
References	Bauersachs et al 2010 [21] Manufacturer's submission		
Group	**Rivaroxaban N, (%)**	**LMWH/Enoxaparin N, (%)**	**Hazard ratio (95% CI, p value)**
ITT population: Safety population: PP population:	1731 1778 1525	1718 1711 1571	NA
Primary outcome VTE recurrence			
ITT population: PP population:	36 (2.1) NR	51 (3.0) NR	[redacted]
Secondary outcomes (ITT population)			
Fatal PE	1 (0.1)	0 (0)	NR
PE cannot be ruled out	3 (0.2)	6 (0.3)	NR
Nonfatal PE	20 (1.2)	18 (1.0)	NR
Recurrent DVT plus PE	1 (0.1)	0 (0)	NR
Recurrent DVT	14 (0.8)	28 (1.6)	NR
(safety population)			
Clinically relevant bleeding	139 (8.1)	138 (8.1)	0.97 (0.76 to 1.22, p=0.77)
Major bleeding	14 (0.8)	20 (1.2)	0.65 (0.33 to 1.30, p=0.21)
Clinically relevant non-major bleeding	126 (7.3)	119 (7.0)	NR
Vascular events On treatment Off treatment (30 day follow-up)	 12 (0.7) 1 (<0.01)	 14 (0.8) 4 (0.2)	 0.79 (0.36 to 1.71, p=0.55)
All cause mortality	38 (2.2)	49 (2.9)	0.67 (0.44 to 1.02, p=0.06)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Any treatment emergent AE	1078 (62.7)	1080 (63.1)	NR
[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	201 (12.0)	233 (13.6)	NR
Serious, drug related AE	[redacted]	[redacted]	NR
Cause of Death			
PE or PE not ruled out	4 (0.2)	6 (0.3)	NR
Bleeding	2 (0.1)	5 (0.3)	NR
Cancer	25 (1.4)	20 (1.2)	NR
Cardiovascular disease	2 (0.1)	4 (0.2)	NR

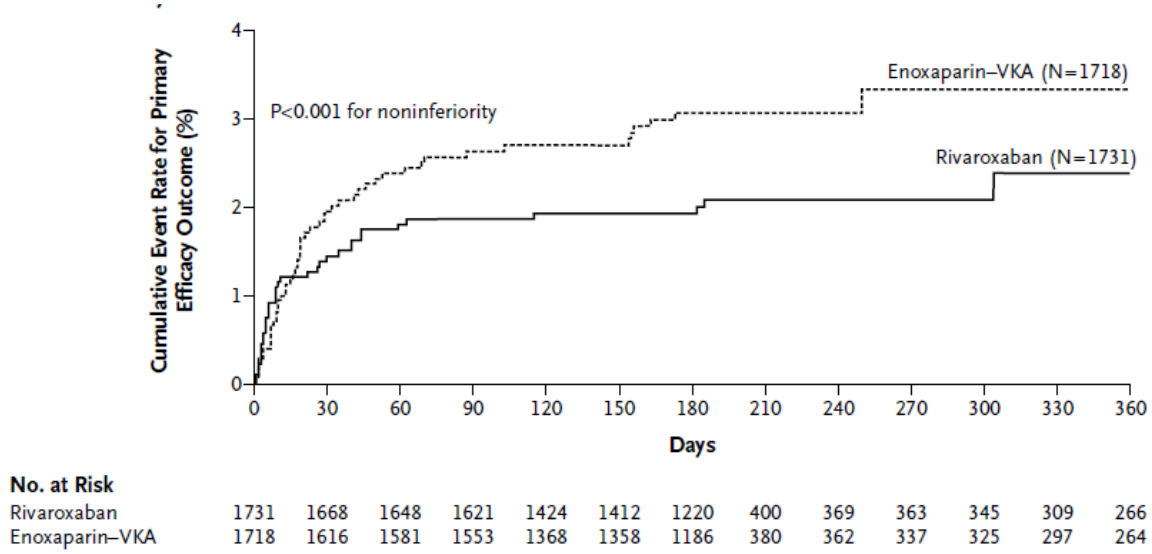
Trial name	Einstein-DVT		
other	6 (0.3)	14 (0.8)	NR
Quality of life/patient satisfaction			
ACTS burden (mean) ACTS benefits (mean)	55.2 11.7	52.6 (p<0.0001) 11.5 (p=0.006)	NR
TSQM	NR, states "consistently higher"	NR	NR
Other outcomes			
[redacted]	[redacted]	[redacted]	NR
Compliance [redacted]	[redacted]	[redacted]	NR
Time in target range	NA	57.7%	NA
ITT, intention to treat population; PP, per protocol population; NR, not reported; NA, Not applicable; 95% CI, 95% confidence interval; N, number of patients; ACTS, anti-clot treatment scale; TSQM, treatment satisfaction questionnaire; VTE, venous thromboembolism; AE, Adverse event.			

In the Kaplan Meier plot of VTE recurrence (Figure 7, page 55),[1] reproduced here as Figure 2, it is interesting to note that rivaroxaban appears to perform less well than Enoxaparin/VKA in the very early stages of anticoagulation. Similarly, rivaroxaban appears to be associated with more bleeding events early on (Figure 11, page 60).[1] From the results, however, it is not possible to determine whether either of these observations is of statistical or clinical significance.

The ERG considered whether it were possible that rivaroxaban and dual LMWH/VKA treatment could have differential effects on PEs and DVTs given the observed data. The ERG considered the evidence from the two phase II trials excluded form the review, but felt that the number of events did not provide robust evidence (Appendix 1). The ERG sought clinical advice on this matter, and no plausible biological mechanism for a differential effect on DVTs and PEs was offered. However, it is noted that in the initial period of the trial, rivaroxaban and dual LMWH/VKA reported similar levels of VTE, and that if the majority of PEs occurred in this period, the similar rates of PE events in the two arms, as observed, would be expected.

Chi-square analyses were undertaken by the ERG which reported a p-value of 0.14, indicating no significant difference, but the number of events may be too small to highlight an actual difference. Whilst it is likely to be the case that the disparity in results were caused by chance alone, the clinical impacts of a PE are more serious than that of a DVT, and it was thought prudent to highlight the potential impact of any assumption that the ratio of PE to DVT was independent of treatment. This is the subject of exploratory economic analysis later in the report.

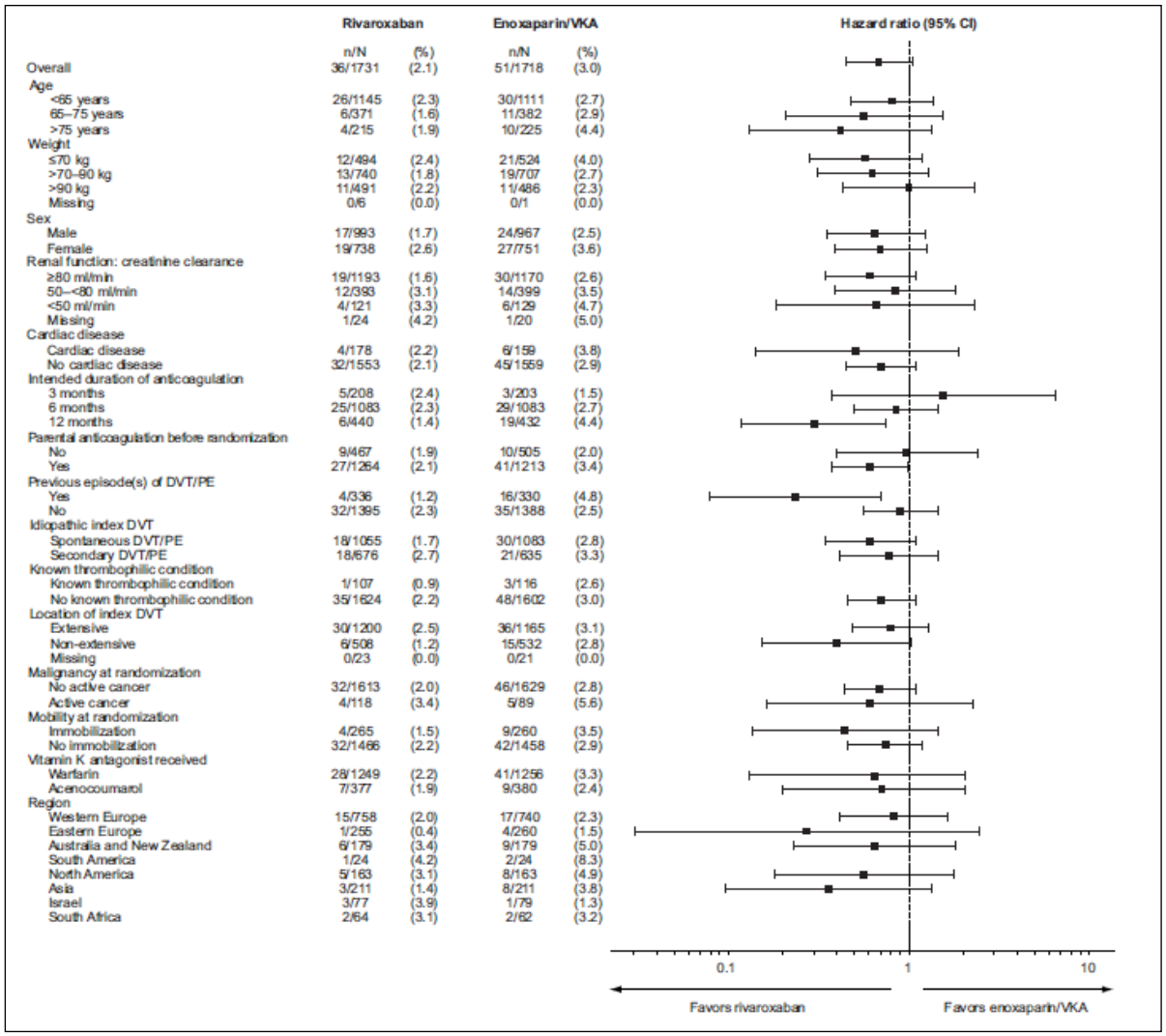
Figure 2: Kaplan-Meier plot for VTE recurrence (primary efficacy outcome) in EINSTEIN-DVT (reproduction of Figure 7, Page 55 of MS)[1]



Subgroup analyses for DVT recurrence – EINSTEIN-DVT

A large number of subgroup analyses were presented in the report (Page 56, Figure 8, reproduced here as Figure 3). Interestingly, whilst the MS suggests these were defined a priori, the ERG have not been able to locate a description of these analyses in the protocol provided by the Manufacturer.[39] These may be contained in the Statistical Analysis Plans, which were not included with the protocol. As such, it is unclear whether the subgroup analyses were planned a priori.

Figure 3: Analysis of VTE recurrence (primary efficacy outcome) across the pre-specified subgroups in EINSTEIN-DVT (reproduction of Figure 8, Page 56 in MS)[1]



As would be expected, generally the subgroup analyses shows that smaller patient numbers increased the uncertainty around point estimates, although there was generally a lack of power to make definitive conclusions. In addition, the following observations were made;

Age: there is a point estimate trend towards increasing efficacy with increasing age.

Weight: there is a point estimate trend towards decreasing efficacy with increasing weight.

Intended duration of anticoagulation. There is a numerical trend towards greater efficacy with increasing intended treatment duration. VTE recurrence HR point estimate is >1 (i.e. favours enoxaparin) in the 3 month intended treatment duration group, but with large uncertainty. The 12 month intended treatment duration group appears to experience greater efficacy in terms of VTE recurrence, with rivaroxaban being favoured in this group. In response to the ERG's request for

clarification on this matter, the manufacturer argues that the number of events are small and statistical power is lacking[17] for the subgroup analyses, and whilst the ERG agree that powering may be a problem and the difference seen may be due to chance alone, it would still seem that a conclusion of inferiority cannot be rejected in the 3 months subgroup for the outcome VTE recurrence as the upper limit of the 95% CI for the Hazard Ratio exceeds the predefined non-inferiority limit of 2.0, and the point estimate is >1. To investigate this apparent difference in efficacy according to intended treatment duration, the ERG requested an interaction test on this subgroup analysis, which was provided and is presented in Table 11. Because interaction tests in subgroup analyses are often underpowered, it is usual to interpret these at the p=0.1 significance level, rather than the more usual p=0.05. [redacted]

Parenteral anticoagulation before randomisation. The point estimate for those who did not receive parenteral anticoagulation before randomisation is lower than for those who did. This may indicate an advantage to parenteral anticoagulation, or may indicate bias introduced by confounding factors, for example, later administration of treatment (post randomisation), or selection of more severe patients for immediate treatment, or may be due to chance alone.

Previous episodes of DVT/PE. The point estimates suggest patients who have already had a VTE obtain greater relative benefit from rivaroxaban in comparison to Enoxaparin/VKA treatment than those who have not. Those who have already had a VTE are more likely to be on 12 month treatment, so these two factors are likely to be confounded [redacted]

Location of index DVT. Patients with non-extensive DVT have a trend towards gaining more benefit than extensive patients, based on the point estimate.

Malignancy at randomisation. Active cancer does not appear to affect the point estimate, but there is increased uncertainty in the active cancer group, likely due to the small number in this group.

[redacted]

Table 11: Additional interaction test statistics for the primary analysis of time to VTE recurrence. Reproduction of Table 1, page 8, manufacturer's clarifications. [17]

	Hazard ratio (95% CI)	Tests for interaction	
		Wald	Gail-Simon[147]
Previous episode of DVT/PE Yes No	[redacted]	[redacted]	[redacted]
Intended duration of anticoagulation 3 months 6 months 12 months	[redacted]	[redacted]	[redacted]
Age group <65 years 65-75 years >75 years	[redacted]	[redacted]	[redacted]
Renal function: creatinine clearance >= 80 mL/min 50 - <80 mL/min <50 mL/min Missing	[redacted]	[redacted]	[redacted]

Bleeding events – EINSTEIN-DVT

An interpretation of non-inferiority for clinically relevant bleeding is supported by the results. Clinically relevant bleeding is a composite of major bleeding and clinically relevant non-major bleeding. There was a small decrease in Major bleeding events (14/1718 (0.8%), versus 20/1711 (1.2%) for rivaroxaban and enoxaparin/VKA respectively), but a small increase in clinically relevant bleeding events (126/1718 (7.3%), versus 119/1711 (7.0%) for rivaroxaban and enoxaparin/VKA respectively).

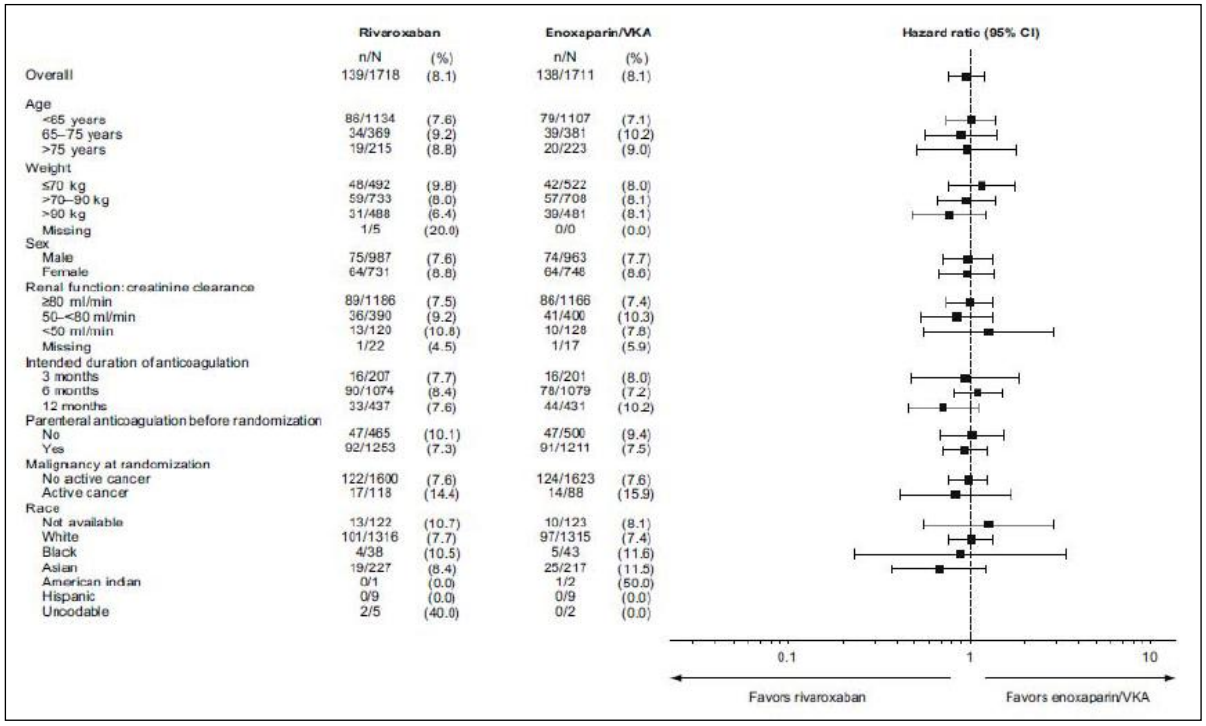
Subgroup analyses were also presented. Differences between subgroups appear less pronounced for the outcome clinically relevant bleeding than for the outcome DVT recurrence, with most close to a HR of 1 (MS Figure 12, page 61,[1] reproduced here as Figure 4). Of note amongst these are:

Weight. Numerical trend towards more bleeding in lighter patients in the rivaroxaban arm, whilst in the enoxaparin/VKA arm bleeding rates seem stable across the weight categories. The HR point estimate is <1 for patients ≤70kg.

Renal function. Point estimate HR is <1, but the confidence interval is very wide for those with creatinine clearance <50ml/min. Creatinine clearance is a measure of renal function.

Both of these factors are likely to increase the plasma levels of rivaroxaban, which may account for the increase in bleeding events. The dose ranging studies[35,36] indicate that bleeding is much more sensitive to dose than VTE recurrence. The SmPC advises a lower dose of rivaroxaban for patients with renal impairment, which is discussed elsewhere in this report. No advice to tailor doses according to weight is made, and the fixed dose nature of rivaroxaban is cited as one of its advantages. (MS, page 15, section 1.13)

Figure 4: Analysis of clinically relevant bleeding (primary safety outcome) across the pre-specified subgroups in EINSTEIN-DVT. Reproduction of Figure 12, page 61 of MS.[1]



Adverse events and mortality data – EINSTEIN-DVT

An interpretation of non-inferiority of rivaroxaban for adverse events and mortality is supported by the results and analyses of this study. Upon request from the ERG, the manufacturer provided a clarification of Tables 29 and 30 of the MS,[1] where a transposition error had occurred. These are provided in Appendix 2. The events entitled "specific adverse events" in the tables were not thought by the clinical advisors to the ERG to have a significant impact on HRQoL, and were mostly well balanced across treatment arms.

Health related quality of life – EINSTEIN-DVT

The HRQoL measures used in the study were the Anit-Clot Treatment Scale (ACTS) and Treatment satisfaction questionnaire (TSQM). As already discussed in section 3.4, neither of these measures has been mapped to the EQ-5D or other preference based measures. (MS, page 64).[1] In addition, the

ACTS does not appear to have been validated and is therefore difficult to interpret. An evaluation, however, does appear to be ongoing.[28]

Whilst improvements in HRQoL were shown using this tool, without direct valuation or a validated mapping exercise, it is not possible to interpret the size of these improvements in relation to overall health.

Additional comments and clarifications relating to the results and interpretation of EINSTEIN-DVT

In addition to the comments made above, there were a number of other points for clarification of minor to moderate importance made in relation to the results and interpretation of the results.

Patients who did not fulfil the inclusion/exclusion criteria. There were 23 patients with PE as the index event and 15 patients with creatinine clearance <30mL/min who were included in the trial, but who should have been excluded according to the selection criteria. It is unclear why these were included. The ERG requested clarification on these points, and of how they were dealt with in the analysis of the results.

- **Creatinine clearance.** 15 were included in the intention to treat (ITT) population, and 13 of these remained in the per protocol (PP) population (manufacturer's clarifications, page 19) .[17]The ERG asked for clarification on the effect of the inclusion of these patients in the trial data. As the number of events in the trial was small, even a small number of inclusions from outside the inclusion/exclusion criteria has the potential to alter estimates of efficacy, especially if there was a difference in distribution of events between the two arms in these patients. The manufacturer was unable to provide analyses excluding these patients. There are two relevant pieces of information related to this point within the MS:
    - Figure 8, page 56 of the MS,[1] reproduced in this report as Figure 3, shows a subgroup analysis for patients with creatinine clearance <50mL/min, which will include the patients with creatinine clearance <30mL/min. 4/121 and 6/129 in the rivaroxaban and enoxaparin/VKA arms respectively had DVT events. It is not clear how many of these events occurred in patients with <30mL/min.
    - [redacted] Again, this dealt with all patients with clearance levels below 50mL/min together, and it is not clear how including those with levels <30mL/min has affected results.

It remains unclear why these patients were included, and whether their inclusion affects the results. In addition, these patients were not routinely excluded from the PP analysis, (though two were excluded, presumably for other reasons, according to the Manufacturer's clarifications (Personal Communication from Bayer plc, December 2011)), even though their clearance levels could be interpreted as a major deviation from the study protocol, and should therefore have been excluded.

- **Patient with PE index event.** These patients were excluded in the PP analysis. A comparison of the ITT analysis with the PP analysis indicates that the estimate of efficacy is not altered, although this analysis involved the exclusion of patients additional to those with index PE. The ERG feels it is unlikely that the inclusion of patients with PE has introduced bias.

[redacted]

Analysis by compliance level. The ERG asked the manufacturer to offer potential explanations for the apparent differences in efficacy in the treatment duration subgroups. Based on clinical advice, the ERG was especially interested in exploring the possibility that compliance in the comparator arm or the rivaroxaban arm may have driven the apparent difference in efficacy. The manufacturer provided the following explanation, which goes some way to exploring the relationship between time in target range and efficacy, which could be considered a product of compliance (at least in part), but does not address issues of compliance directly:

[redacted]

In addition, compliance data is provided elsewhere in the manufacturer's response to the ERG request for clarifications[17] (reproduced here as Figure 5), and whilst no formal analysis has been completed

and the [redacted] (see section *"sufficient compliance"* below[redacted]

Compliance would therefore not appear to be likely to provide an explanation for the apparent differences in efficacy, where rivaroxaban appears to have superior efficacy in comparison to enoxaparin/VKA in these subgroups.

[redacted]

Subgroup analyses suggested in NICE scope. Nice requested subgroup analyses 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)

Only one of the subgroup analyses suggested by NICE were provided, that for the cancer subgroup, via an MTC. The ERG asked for clarification on why other groups were not included in the trial, as the marketing authorisation and draft SmPC do not exclude use in some of the excluded groups (see section 3.1.1above). The manufacturer responded that as the comparator in the trial was enoxaparin with VKA, it would not have been ethical to include groups contraindicated for this treatment. Whilst this is a reasonable argument, it is not an insurmountable obstacle, and the trial could have been designed to allow for use of appropriate treatment in subgroups of patients contraindicated for enoxaparin with VKA. As it is, it is very difficult to draw conclusions as to the safety and efficacy in these patient groups.

The manufacturer also argue that risk:benefit of anticoagulation in relation to bleeding was considered when allocating patients to the intended treatment duration, "since patients at higher (lower) risk of

bleeding may be less suited to longer (shorter) duration anticoagulation." (page 9, manufacturer's clarifications),[17] and therefore the need for a subgroup analysis is negated. Whilst this may be an adequate way of dealing with those with a higher risk of bleeding who were included in the trial, it does not provide data on those subgroups who were not included, or provide any indication of how they would have benefited from rivaroxaban.

Creatinine clearance. The ERG asked for clarification on the exclusion of patients with creatinine clearance <30mL/min, and the use of a normal dose for those with clearance of 50mL/min, though the SmPC states a lower dose (15mg bid for 21 days, then 15mg od thereafter) for this group. The ERG also asked what the evidence is for the lower dose in this group. The responses (page 10, manufacturer's clarifications)[17] show that the evidence for efficacy in these groups is not based on trial data:

> "The recommended dose for patients with creatinine clearance <50mL/min is based on pharmacokinetic modelling of plasma levels of rivaroxaban, as a modest increase was noted in this group. Previous dose ranging study data was used to calculate a therapeutic dose for this group."

The ERG would have liked to see data for this dose in this group and feel that conclusions about efficacy in this group are associated with uncertainty.

Sufficient compliance. The ERG asked for clarification of what constituted "sufficient compliance" for the per protocol analysis, as defined on page 50, figure 5. This was provided by the manufacturer and is included in Appendix 3. This did not provide any information relating to the clinical grounds for [redacted] as sufficient, but explained the following:

- Compliance in the rivaroxaban arm was judged sufficient [redacted] was taken in both the twice daily period of the trial and the once daily period of the trial.

- Compliance in the enoxaparin/VKA arm was judged sufficient if the enoxaparin treatment period [redacted] or more, and [redacted] INR visits were completed during the VKA treatment period.

Parenteral anticoagulation. The ERG also asked for clarification of why some patients did not receive parenteral anticoagulation before randomisation, as implied in the subgroup analyses in Figure 8, page 56 of the MS (reproduced as Figure 3 above). The manufacturer was unable to provide data on this as the trial did not specifically record this data. However, they were able to show that the time to therapeutic INR was not different between the groups (Table 12, reproduced from manufacturer's clarifications),[17] and as such the ERG feels that this factor is unlikely to have a large effect on estimates of efficacy.

Table 12: Time to therapeutic INR (INR>=2.0) in days from randomisation among patients with/without parenteral anticoagulation prior to randomisation (safety population) (reproduction of Table 11, page 24 of manufacturer's clarifications).[17]

	Parenteral anticoagulation prior to randomisation	
	[redacted]	[redacted]
Number of patients Mean SD 25th percentile Median 75th percentile	[redacted]	[redacted]

Difference between suspected and confirmed events. DVT events were captured within the trial in a two stage process. Patients presenting with suspected VTE were subject to diagnostic tests to confirm the event, and the events were confirmed by an external, blinded committee. A higher proportion of suspected events presenting in the enoxaparin/VKA arm (52/214 (24.3%)) were confirmed to be DVT events by the committee than in the rivaroxaban arm (36/229 (15.7%) (p=0.06). The ERG requested clarification of the criteria used to define a suspected DVT event, and the criteria used to confirm the event (Table 13). These mostly matched with EMA research recommendations, but there are some exceptions, which are discussed here, along with a number of potential explanations for this apparent difference;

Explanation 1 - Suspected events relied on patients self-presenting, based on a booklet detailing symptoms (though these criteria were not included in the manufacturer's response).[17]As such, the open label nature of this trial may have lead to patients being more likely to present with suspected VTEs in the rivaroxaban arm, if for example, patients were less trusting of the newer intervention, this

may account for the apparent difference in proportions of suspected events becoming confirmed events between the two arms.

Explanation 2 - Whilst the committee were blinded, the clinicians completing the case notes do not appear to have been blinded, as this was an open label trial. This is a possible source of bias for some of the diagnostic tests used. For example, the EMA states

"Compression ultrasonography (US) has been documented to have adequate sensitivity and specificity for symptomatic, proximal DVT, but is less adequate for distal DVT. The findings can be interpreted by the observer only, who should be well trained and carefully selected by the study co-ordinator"
As such, the US tests may have been subject to the potential for bias. The likelihood of this bias affecting results is not thought by the ERG to be large because this was a multi-centre trial, and it would seem unlikely that differential interpretations due to expectation bias would have affected all operators.

Explanation 3 - The final criteria listed by the manufacturer is

[redacted]

"Diagnosis on clinical signs is discouraged. The number of such episodes, especially if leading to changed or renewed therapy, must, however, be noted and accommodated for in the analyses."

And further state

"Sensitivity analyses should be performed to assess the robustness of the conclusions of the study to the decisions of the clinical events committee regardless of unconfirmed cases of VTE."

Both of these analyses should have been performed by the manufacturer, but were not presented in the submission.[1]

Some or all of the above explanations may contribute to the apparent difference in the proportion of suspected VTEs being confirmed in the rivaroxaban arm being lower than the proportion confirmed in the enoxaparin/VKA arm. However, the ERG remains unsure on this point, and it is possible that the differences are due to chance alone.

Table 13: Criteria used to define a suspected DVT event, and the criteria used to confirm the event. Compiled from the manufacturer's clarifications,[17] and the EMA research guidelines.[23]

	EINSTEIN-DVT diagnostic criteria	EMA research guidelines diagnostic criteria
General information	[redacted]	More than half of patients presenting with clinical signs and symptoms of DVT and/or PE will not have objective proof of these disorders.
PE	[redacted]	The following diagnostic methods are considered acceptable for documentation of DVT and PE in studies of drug efficacy and safety: **PE** • Pulmonary angiography or • Spiral CT (for large segmental emboli). • Ventilation –perfusion (V/Q) lung scanning to rule out clinically important PE. High probability findings on V/Q scan to diagnose PE. Other types of findings should be considered "non-diagnostic", and be verified through pulmonary angiography. • In the presence of symptoms indicative of PE in a patient with demonstrated DVT, "non-diagnostic" findings on V/Q scan are sufficient

		for a diagnosis of PE **Recurrent PE** • Repeat pulmonary angiography with the finding of a new intraluminal filling defect or a new, sudden cut-off in an arterial branch, not present on the first examination. • Repeat sCT showing new embolism • Repeat V/Q scan with the finding of a new perfusion defect, segmental or larger, with a ventilation mismatch • Demonstration of fresh PE at autopsy
DVT	[redacted]	**DVT** • Ascending venography • Compression ultrasonography (US) for symptomatic, proximal DVT, but less adequate for distal DVT. Findings can interpreted by the observer only, who should be carefully selected by the study co-ordinator **Recurrent DVT** • New or extended intraluminal filling defect seen on at least two projections during repeat ascending venography • New thrombosis on US examination, in the case of proximal DVT

	[redacted]	
DVT and/or PE	[redacted]	Diagnosis on clinical signs is discouraged. The number of such episodes, especially if leading to changed or renewed therapy, must, however, be noted and accommodated for in the analyses.

Textual clarifications. A number of small textual clarifications were also sought and were resolved. These are included in Appendix 4. Most were corrected as anticipated by the ERG, and none were thought to have an impact on the overall assessment.

4.2.2 Critique of EINSTEIN-Ext trial

4.2.2.1 Trial design – EINSTEIN-Ext

The principle limitations of the EINSTEIN-Ext trial have already been described in section 3 and are summarised here.

Problems with the population are a potential limitation in the context of this assessment and include:

- The trial included patients with DVT or PE as the index event, rather than solely patients with DVT as the index event (see section 3.1.2.1). This has been partially addressed by the provision of further analyses by the manufacturer (presented in section 4.2.2.3). [17]
- Only patients in clinical equipoise were included, not the whole DVT population (see section 3.1.2.2).
- With similar inclusion and exclusion criteria to the EINSTEIN-DVT trial (Table 9), the whole population of interest was not covered by this trial (see section 3.1.1.1 and section 3.1.2.3)

The intervention was problematic in the following ways:

- Patients with creatinine clearance <50mL/min were not given the lower dose recommended in the SmPC[19,20] (see section 3.2.1).

The comparator is also a limitation in that:

- Placebo is not an active comparator. As such, results from this study will only provide information about whether it is better to treat patients in clinical equipoise with rivaroxaban, rather than not treat them at all; it does not provide information on whether rivaroxaban is the best choice for ongoing treatment in comparison to other active treatments. A trial with an additional active comparator arm could have provided comparative data for the efficacy of rivaroxaban versus, for example, usual care with LMWH/VKA (see section 3.3.4).

The outcomes were largely acceptable, except that:

- HRQoL data was not recorded (see section 3.4)

- There is some doubt about the appropriateness of the use of a composite outcome (see section 3.4).

The ERG has an additional comment:

- From the analyses provided in the trial it is not possible to tell which patients had 12 months treatment in total, and which had more than 12 months in total. Some may have received up to 2 years treatment. Whilst the manufacturer states that the proportional hazard assumption held [redacted] these results were not presented as subgroup analyses.

4.2.2.3 Results and interpretation – EINSTEIN-Ext

Efficacy outcomes – *EINSTEIN-Ext*

The results from the EINSTEIN-Ext trial are presented in Table 14. These show that rivaroxaban significantly reduces the rate of recurrent DVTs [redacted] Table 14 shows the constituents (PE and DVT) of the composite outcome (VTE). Both PE and DVT events occur less often in the rivaroxaban arm. The number of clinically relevant non-major bleeding events was increased in the rivaroxaban arm (32 (5.4%)) compared to the placebo arm (7 (1.2%), p<0.001), with a non-significant trend towards an increase in major bleeding events in the rivaroxaban arm, (4 (0.7%)) compared to the placebo arm, (0 (0%), p=0.11). The safety outcome "clinically relevant bleeds" was significantly higher in the rivaroxaban arm, with an HR of 5.19 (95% CI, 2.3 to 11.7, p=0.001), however this outcome is a composite that does not weight the health impact of each event.

[redacted]

Specific adverse events are worse in the rivaroxaban arm (Appendix 2, Table 2), but all cause mortality similar in both arms (Table 13) for both the analyses with DVT and PE patients, and the analyses with the DVT only patients. [redacted]

Table 14: Summary of outcomes for EINSTEIN-Ext, taken from Tables 18 and 29, data on page 59 of MS[1] and data from the Manufacturer's clarification document.[17]

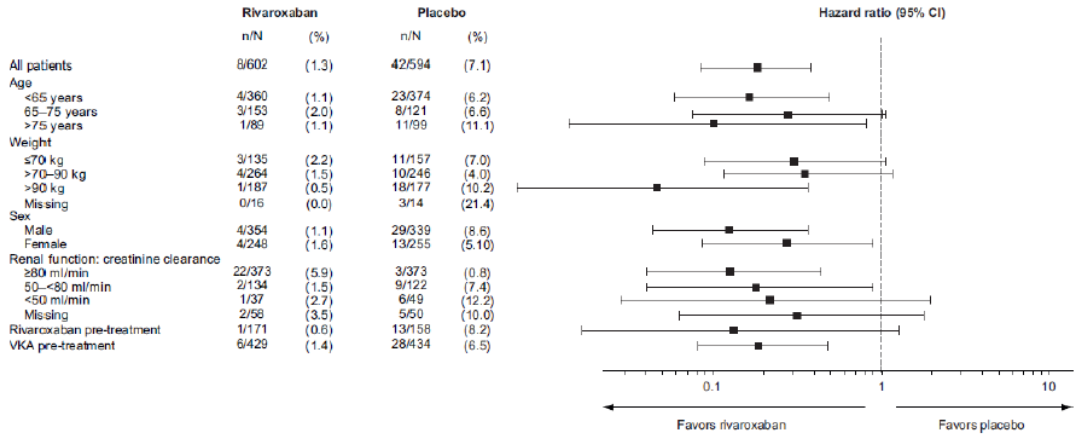
Trial name	**Einstein-Ext**			**Einstein-Ext; DVT patients only**		
References	Bauersachs et al 2010[21] Manufacturer's submission[40]			Manufacturer's clarifications[17]		
Group	**Rivaroxaban N, (%)**	**Placebo N, (%)**	**Hazard ratio (95% CI, p value)**	**Rivaroxaban N, (%)**	**Placebo N, (%)**	**Hazard ratio (95% CI, p value)**
ITT population: Safety population: PP population:	602 598 550	594 590 534	NA	[redacted]	[redacted]	[redacted]
Primary outcome: VTE recurrence ITT population: PP population:	 8 (1.3) NR	 42 (7.1) NR	[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcome						
Fatal PE	0	1	NR	[redacted]	[redacted]	[redacted]
PE cannot be ruled out	1	0	NR	[redacted]	[redacted]	[redacted]
Nonfatal PE	2	13	NR	[redacted]	[redacted]	[redacted]
Recurrent DVT	5	31	NR	[redacted]	[redacted]	[redacted]
Adverse events (safety population)						
Clinically relevant bleeding (major or clinically relevant non-major bleeding)	NA	NA	5.19 (2.3 to 11.7, p=0.001)	[redacted]	[redacted]	[redacted]
Major bleeding	4 (0.7)	0 (0)	p=0.11	[redacted]	[redacted]	[redacted]
Clinically relevant non-major bleeding	32 (5.4)	7 (1.2)	p<0.001	[redacted]	[redacted]	
Vascular events On treatment Off treatment (30 day follow-up)	 3 (0.5) 2 (0.3)	 4 (0.7) 0 (0.0)	 0.74 (0.17 to 3.3, p=0.69)	[redacted]	[redacted]	
All cause mortality	1 (0.2)	2 (0.3)	NR	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious, drug related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Quality of life/patient satisfaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N, number; CI, confidence interval; ITT, intention to treat; PP, per protocol; PTS, post thrombotic syndrome; AE, adverse event.

Subgroup analyses – EINSTEIN-Ext

Subgroup analyses of these studies are subject to the same cautions as outlined for the EINSTEIN-DVT analyses, for example, in terms of powering. Only two subgroup analyses stand out (Figure 10, page 58,[1] reproduced here as Figure 6): a seemingly increased advantage for those who are over 75 years of age, and those who are over 90kg in weight and were treated with rivaroxaban. In part this appears to contradict the results of the EINSTEIN-DVT trial, where increased weight leads to an apparent reduction in efficacy. On the other hand, EINSTEIN-DVT subgroup analyses also revealed a similar trend towards increasing benefit with increasing age.

Figure 6: Analysis of VTE recurrence (primary efficacy outcome) across the pre-specified subgroups in EINSTEIN-Ext (reproduction of Figure 10, page 58 of MS)[1]



No further studies were identified by the ERG.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The multiple treatment comparison (MTC) included the five trials listed in Table 15. Its aim was to allow a comparison of rivaroxaban to LMWH in the cancer subgroup of patients. The included studies were taken from a recent Cochrane review completed by Akl et al.[31]

Table 15: Summary of characteristics of trials included in the MTC.

Study	Patient population	Trial length	LMWH	Other treatment
Deitcher et al 2006[41]	Active cancer patients with DVT and/or PE.	175 days (6 months)	Enoxaparin (i) 1 mg/kg bid for five days followed by 1-1.5 mg/kg daily for 175 days (ii) 1.5 mg/kg od for 175 days	1 mg/kg enoxaparin for five days followed by warfarin targeting an INR of 2-3 for 175 days.
Hull et al 2006[42]	200 patients with cancer (solid or haematological) and proximal DVT with or without PE.	12 weeks	Tinzaparin (175 antiXa/kg daily is reported in MS, though original study reports 3 months)	UH for five days (5000 units or 80 units/kg) followed by VKA targeting an INR of 2-3.
Lee et al 2003[43]	979 patients with cancer and either DVT or PE or both.	6 months	Dalteparin (200 IU/kg daily in month 1 and 150 IU/kg in months 2-6) or	Dalteparin for 5-7 days (200 IU/kg daily) followed by VKA targeting INR 2-3.
Meyer et al 2002[44]	146 patients with cancer (solid or haematological) with DVT and/or PE.	3 months	Enoxaparin (1.5 mg/kg daily)	4 days of enoxaparin (1.5 mg/kg daily) followed by 3 months of warfarin targeting an INR of 2-3.
Romera-Villegas et al 2010[45]	Symptomatic proximal DVT in which a subgroup of 69 patients additionally had cancer.	6 months	Tinzaparin 175 IU anti-xa / kg od.	3 mg acenocoumarol od targeting an INR of 2-3.
DVT, deep vein thrombosis; PE, pulmonary embolism; IU, international units; INR, international normalised range; VKA, vitamin K antagonist.				

Heterogeneity

As can be seen from Table 15, the studies appear heterogeneous in terms of:

- The length of follow up. The data used in the primary analysis (one of three MTC analyses presented by the manufacturer) comes from three of the five studies, all with data measured at different time points.
    - Data in Table 21 of the MS for Hull et al 2006[46] appears to relate to data at 12 months even though study medication ceased at 3 months and despite the availability of data at 3 months. Other values come from measurements taken at the end of treatment, one at 3 months[44] and one at 6 months[43]. Interestingly, however, the use of this data will have advantaged LMWH efficacy, and therefore disadvantaged the relative efficacy of rivaroxaban in comparison.

- It is clear that bleed events were taken from the 3 month measure for Hull et al 2006[42] as this data is not available at 12 months.

- It is unclear whether the Hazard Ratios (Table 20 in the MS)[1] used in the MTC Primary analysis came from the same time points, or different time points, as the ERG were unable to identify these in the relevant publications.

- The specific LMWH used and dose used. As discussed previously in section 3.3.1, there is debate about whether to assess efficacy of LMWHs as a class of drugs or to treat each separately. The ERG was previously satisfied that enoxaparin was a reasonable proxy for LMWH use in England and Wales, in the absence of other direct comparison data. This meta analysis pools data from trials using three different LMWHs. The doses used appear to be roughly equivalent to UK doses and it could therefore be argued that they should be of a largely comparable therapeutic nature. However, the discussion of possible heterogeneity between these drugs is partial and clinical opinion has not been sought by the manufacturer on this matter. The MS provides a comparison of Lee 2003,[43] which focussed on dalteparin, with the results of the Akl et al[31] meta analysis, to show that there is little heterogeneity between results on the basis of the LMWH used. This analysis is provided in Table 16 (reproduced from MS), and shows very similar results between the Cochrane review and the Lee 2003[43] study on its own for VTE recurrence. The lack of heterogeneity is not entirely surprising, as Lee 2003[43] data contributes 672/1018 (66%) of the patient data, and will therefore have strongly influenced the analysis. In addition, the difference between minor and major bleeding, which are important factors in this assessment, do look different. The ERG is not entirely convinced by this test for heterogeneity, and would have liked to see a discussion of the results of formal heterogeneity tests.

Table 16: Relative effectiveness of long-term LMWH vs LMWH/VKA dual therapy in VTE patients with cancer. Reproduction of Table 24, page 74 of MS.[1]

	Cochrane meta-analysis[31]		**Lee 2003[43]**	
	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.

HR = hazard ratio, RR = risk ratio.

- The Heparin/VKA combination used and dosing schedule used. A mixture of anticoagulants, in combination or on their own, are included in this set of studies, and it is unclear to what extent they are comparable. The manufacturer did not discuss this point, nor did they report seeking clinical opinion on the matter.

- Populations included. As discussed in section 3, the MTC trials included patients with PE or DVT, and one study included patients of DVT alone. The proportion of DVT and PE patients in each study are not reported in the MS, thought the clinical advisors to the ERG do not feel that the ratio of PE:DVT patients is likely to have vastly affected outcomes. However, the manufacturer did not discuss this point, nor did they report seeking clinical opinion on the matter.

Quality assessment of MTC studies

The MS submission reproduced the quality assessment provided in the Cochrane review. However, this included studies not relevant to this appraisal, and no discussion of the quality of the evidence relating only to the data that was used was provided. The ERG has reproduced the quality assessment selecting only the studies of relevance in Table 17.

Table 17: Reproduction of quality assessment reported in Akl 2011,[31] selecting only trials of relevance to this assessment.

	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of providers	Blinding of data collectors	Blinding of data analysts	Blinding of outcome adjudicators	Incomplete data outcome reported	Free of selective reporting	Free of other bias	ITT analysis
Hull 2006[42]	Y	U	N	N	N	Y	N	Y	Y	Y	Y
Lee 2003[43]	Y	Y	N	N	U	Y	Y	Y	Y	Y	Y
Meyer 2002[44]	Y	Y	N	N	N	N	Y	Y	Y	Y	Y
Deitcher 2006[41]	Y	U	N	N	N	N	N	Y	Y	Y	N
Romera 2009[45]	Y	N	N	N	Y	N	Y	Y	Y	Y	Y

Y, yes; N, no; U, unclear; ITT, intention to treat.

Studies involved in the primary analysis of VTE recurrence were Hull 2006[42] Lee 2003,[43] and Meyer 2002.[44] Blinding of participants and providers appears to be poor. The impact of this in terms of bias

is likely to be small as the outcomes are objectively determined, except in the case of the Hull[42] study, where the outcome adjudicators were not blinded.

All of the studies except Romera[45] were involved in the analyses of bleeding rates. Deitcher 2006[41] has similar limitations as the study by Hull et al[42] and in addition does not provide an ITT analysis.

Otherwise, the studies generally appear well conducted.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

In general, the ERG has concerns with the way the (network) meta-analysis has been implemented and the impact that the prior information has had on the results. The ERG has outlined a number of problems with the conduct of the MTC above, and would like to highlight the following points of interest:

- Overall, there is a lack of clarity about where data has come from, and a lack of depth in the analysis of study characteristics in relation to one another.
- Additional searches were not conducted to update the Akl et al[31]. The ERG has conducted update searches following the Akl et al. search strategy. The results were sifted, but no further eligible RCT studies were identified.
- The MS states the study by Romera Villegas et al[45] is an RCT, however it appears from the online abstract to be a systematic review. This is also reported as an RCT in the citing Cochrane review, Akl et al.[31]
- On Pg 71 of the MS[1] it is stated that

  "the treatment interaction term for presence of active cancer was [redacted]

  [redacted]. Indeed the use of data that does not come from the cancer group in this MTC seems to negate the point of the comparison, which is to study the effects in cancer patients. Therefore, the ERG feels the "secondary analysis 2" presented by the MS is more

relevant, as this uses only the data from the cancer subgroup. However, the ERG additionally believes that because of the way the (network) meta-analysis has been implemented, the results of this analysis may not provide a good estimate of the uncertainty associated with the true treatment effect, although the point estimate may be reasonable. See below for more discussion on this point. The point estimate shows rivaroxaban to be less effective than LMWH for VTE (HR 1.32 (95% Critical Interval (CrI), 0.06 to 32.3), whilst major bleeding is better (OR 0.24 (95% CrI, 0.00 to 9.44) and non-major bleeding is worse (OR 1.61 (95% CrI, 0.11 to 26.5). Considering the results across the three analyses, it would appear however, that a choice of the primary analysis would have disadvantaged rivaroxaban. The ERG remains unconvinced about the appropriateness of the analyses as they have been implemented.

- Tau values – in meta-analyses the parameter Tau is commonly used to describe the between-study standard deviation. The MS presents tables of results including estimates of precision (i.e. the inverse of the variance), which are labelled as tau. The ERG believes that estimates of the between-study standard deviation would be more informative.
- It is argued that only dalteparin is licensed specifically in people with cancer in the UK. However, enoxaparin and tinzaparin do not appear to be contraindicated in those with cancer, so the rationale for only looking at data from Lee 2003[43] seems weak (page 73, 78).

In addition, the ERG has a number of technical issues with the conduct of the MTC, as outlined here.

4.4.1 MTC methods in relation to NICE DSU TSD2

Section 5.7.5 of the submission presents the results of random effects (network) meta-analyses of hazard ratios for VTE recurrence, and of binary data for VTE recurrence, clinically relevant non-major bleeding and major bleeding.

The analysis was conducted following the general guidance outlined in NICE DSU TSD2.[47] Treatment effects are estimated using Markov chain Monte Carlo methods. These combine sample data with external information which is characterised using prior distributions for the parameters in the model. Ideally the analysis would incorporate genuine prior information, although when there is sufficient sample data this tends to dominate any prior information that may be available so that eliciting it from experts is often not efficient. In most practical examples, such as this STA, it is common to incorporate prior information using reference prior distributions. Such prior distributions are often thought of as being non-informative, although whether they are truly non-informative

depends on the specific parameterisation. In addition, when there is relatively little sample data being analysed, the prior information can dominate and should be described with care.

NICE DSU TSD2 states that it has become standard practice to use a uniform prior distribution on the range (0, 2) for the between-study standard deviation for log-odds ratios and log hazard ratios. However, the document also notes that there are major disadvantages in routinely using vague prior distributions because, in the absence of a reasonable number of large trials, the posterior distribution of the between-study standard deviation will be poorly identified and likely to include values that are implausibly high or possibly implausibly low and will not represent reasonable beliefs.

In this STA, the analyses were conducted using a uniform prior distribution on the range (0, 5) for the between-study standard deviation when analysing hazard ratios and odds ratios. Although this was taken from the WinBUGS code included in NICE DSU TSD2, it is even more extreme than that described with caution in Section 6.2. Half of the analyses included four or less data points and there are not many more data points available in the primary analyses. Consequently, the prior distribution for the between-study standard deviation will have a large impact on the results. In fact, as a consequence of the prior distribution not representing genuine prior beliefs then, without much Bayesian updating of the prior distribution for the between-study standard deviation to its posterior distribution, the posterior distributions for the treatment effects will not represent meaningful beliefs.

In the clarification letter, the ERG attempted to encourage the manufacturer to consider using a more informative prior distribution for the between-study standard deviation so as to avoid implausible estimates of treatment effect. Unfortunately, this question was not interpreted as the ERG had intended. NICE DSU TSD2 discusses the use of alternative prior distributions for the between-study standard deviation when there are a limited number of studies. The ERG believes that a uniform prior distribution on the range (0, 0.6) would have provided a more reasonable choice for the between-study standard deviation in the absence of a reasonable number of studies; this prior distribution is still reasonably uncertain and it acknowledges the possibility of moderate heterogeneity between studies.

The ERG re-analysed the primary data using a uniform prior distribution for the between-study standard deviation on the range (0, 5) as used in the MS, a uniform prior distribution on the range (0, 2), as recommended in NICE DSU TSD2, and a uniform prior distribution on the range (0, 0.6) as a sensitivity analysis. These analyses are presented in section 4.5.

When using a uniform prior distribution for the between-study standard deviation on the range (0, 5) the means of the posterior distributions are greater than the 97.5%-iles, suggesting that the distributions for the treatment effects are highly skew and essentially unstable.

When using a uniform prior distribution for the between-study standard deviation on the range (0, 2) the means and standard deviations of the posterior distributions are considerably reduced, as are the ranges of the 95% credible intervals. The ERG believes that these results are more likely to represent genuine belief about the true treatment effects than those presented in the MS.

However, there was still evidence of very little Bayesian updating of the between-study standard deviation so that unless it is believed that there is extreme heterogeneity in treatment effects the ERG believes that results based on even a uniform prior distribution on the range (0, 2) may be generating results with too wide posterior distributions.

The medians of the posterior distributions are less affected because medians tend not to be influenced by extreme values. However, the ERG points out that a purpose of the evidence synthesis is to characterise the uncertainty associated with input parameters in economic models. Such uncertainty can be represented by drawing samples from the joint posterior distribution for treatment effects for each outcome, thereby preserving the underlying probability distribution and the correlation between treatment effects.

The ERG point out that if samples were taken from the joint posterior distribution proposed by the sponsor for use in a probabilistic sensitivity analysis, then this would produce a biased estimate of the ICER. Although this was not done in the MS, the ERG is concerned that the MS used independent lognormal distributions to represent uncertainty, thereby approximating without justification the true uncertainty.

4.4.2 Predictive distribution of a new study

In a random effects meta-analysis with extreme heterogeneity, as suggested by the results of the (network) meta-analyses presented by the manufacturer, the mean of the random effects distribution is a measure of the average treatment effect across studies but it does not apply to any specific study. The fact that there is heterogeneity between studies means that there are some treatment effects in the population in which the "new treatment" has large effects and other treatment effects in the population in which the "comparator treatment" has large effects depending on patient-level characteristics. The ERG asked the manufacturer to provide the (posterior) predictive distribution of a randomly selected new study in the population in order to quantify the range of treatment effects consistent with the heterogeneity between studies that was being assumed. However, the manufacturer provided estimates of the study-specific treatment effects, which does not address the question asked.

4.4.3 Between study standard deviations

The ERG requested that the between study standard deviation (and 95% credible interval) should be provided. The ERG was attempting to encourage the manufacturer to give some thought to the results that were being generated. The 95% credible intervals for the between-study standard deviation provided by the manufacturer in response to the question all had upper limits exceeding one, which is indicative of extreme heterogeneity. In addition, at least one 95% credible interval for the between-study standard deviation had a value as large as 4.88, which is indicative of very little updating of the prior distribution, which had an upper limit of 5.

Again, the ERG believes that the manufacturer should have considered using a more plausible prior distribution for the between-study standard deviation unless the manufacturer genuinely believes that treatment effects are expected to be as heterogeneous across studies as the results suggest.

In conclusion, the ERG notes that as a consequence of the general use of an extremely uncertain prior distribution for the between-study standard deviation with very few data points:

1) irrespective of any differences in the within study precision, the weights associated with individual treatment effects are likely to be more equal than might be reasonably expected with a less diffuse estimate of the between-study standard deviation

2) the (posterior) distributions for the treatment effects are often implausibly wide and highly skew

3) estimates of mean hazard ratios and odds ratios may be implausibly large and possibly unstable to such an extent that the mean may be estimated to be greater than the upper limit of the 95% credible interval

4) (posterior) predictive distributions for treatment effects in the population are likely to be implausibly large and implausibly small

As such, any use of the results from the (network) meta-analyses to characterise uncertainty about parameters in the economic model will lead to inaccurate estimates of mean ICERs because they will be based on inflated expected values.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Two further pieces of work were undertaken by the ERG.

4.5.1 Reanalysis of the MTC data

The ERG undertook a reanalysis of the MTC data, using a uniform prior distribution for the between-study standard deviation. The results of these analyses are presented in Tables 18 to 21.

Table 18.1: VTE recurrence (time to event, hazard ratio) - U(0,5)

Node	mean	SD	2.5%	Median	97.5%
hr[1,2]	4257.0	913800.0	0.05213	1.413	36.73
hr[1,3]	204.5	36370.0	0.04103	0.6809	11.65
hr[2,3]	1.05	24.82	0.09175	0.481	2.665
SD	0.8579	0.9667	0.02001	0.5008	3.818

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; HR, hazard ratio.

Table 18.2: VTE recurrence (time to event, hazard ratio) - U(0,2)

Node	mean	SD	2.5%	Median	97.5%
hr[1,2]	2.579	13.32	0.1825	1.397	10.1
hr[1,3]	1.028	3.577	0.1262	0.6744	3.641
hr[2,3]	0.5614	0.4551	0.1694	0.4834	1.465
SD	0.5654	0.4812	0.0197	0.4226	1.781

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; HR, hazard ratio.

Table 18.3: VTE recurrence (time to event, hazard ratio) - U(0, 0.6)

Node	mean	SD	2.5%	Median	97.5%
hr[1,2]	1.6	0.8766	0.5388	1.425	3.761
hr[1,3]	0.7305	0.3047	0.3136	0.679	1.481
hr[2,3]	0.4988	0.1546	0.2634	0.4771	0.8666
SD	0.2575	0.1673	0.01116	0.2379	0.5753

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; HR, hazard ratio.

Table 19.1: VTE recurrence (dichotomous, odds ratio) - U(0,5)

Node	mean	sd	2.5%	Median	97.5%
OR[1,2]	19.26	2634.0	0.3259	1.581	8.435
OR[1,3]	4.246	702.8	0.1686	0.6932	2.893
OR[2,3]	0.4745	0.4347	0.1954	0.4371	0.9269
SD	0.4643	0.5073	0.0126	0.3127	1.851

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

Table 19.2: VTE recurrence (dichotomous, odds ratio) - U(0,2)

Node	mean	sd	2.5%	median	97.5%
OR[1,2]	2.252	9.066	0.3722	1.584	7.045
OR[1,3]	0.8805	2.129	0.1894	0.6921	2.487
OR[2,3]	0.4623	0.1921	0.208	0.4359	0.8791
SD	0.4209	0.3839	0.0123	0.3094	1.49

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

Table 19.3: VTE recurrence (dichotomous, odds ratio) - U(0,0.6)

node	mean	sd	2.5%	median	97.5%
OR[1,2]	1.761	0.9156	0.6393	1.574	4.018
OR[1,3]	0.741	0.2956	0.3236	0.6925	1.453
OR[2,3]	0.4529	0.123	0.2543	0.4391	0.734
SD	0.2451	0.1634	0.01065	0.2216	0.5708

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

Table 20.1: Major bleeding - U(0,5)

Node	mean	SD	2.5%	median	97.5%
OR[1,2]	928.1	133100.0	0.01326	0.6181	23.07
OR[1,3]	210.4	45210.0	0.02496	0.6895	18.93
OR[2,3]	2.034	18.77	0.2127	1.112	6.936
SD	1.179	0.9652	0.05568	0.9129	3.872

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

Table 20.2: Major bleeding - U(0,2)

Node	mean	SD	2.5%	median	97.5%
OR[1,2]	1.486	8.315	0.05049	0.6249	7.029
OR[1,3]	1.32	4.627	0.0781	0.6875	6.001
OR[2,3]	1.323	1.04	0.3503	1.1	3.748
SD	0.8268	0.505	0.04997	0.7602	1.877

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

Table 20.3: Major bleeding - U(0,0.6)

Node	mean	SD	2.5%	median	97.5%
OR[1,2]	0.7642	0.5353	0.188	0.6373	2.114
OR[1,3]	0.7856	0.4423	0.2464	0.6899	1.904
OR[2,3]	1.145	0.3875	0.5686	1.087	2.069
SD	0.3279	0.1693	0.02132	0.342	0.5874

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

Table 21.1: Non-major bleeding - U(0,5)

node	mean	sd	2.5%	median	97.5%
OR[1,2]	463.7	76420.0	0.09107	1.327	18.21
OR[1,3]	29.5	2465.0	0.1009	1.058	11.65
OR[2,3]	1.139	12.79	0.2463	0.8023	2.813
SD	0.8535	0.7552	0.0646	0.6345	3.09

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

Table 21.2: Non-major bleeding - U(0,2)

node	mean	sd	2.5%	median	97.5%
OR[1,2]	2.468	29.52	0.1769	1.331	9.499
OR[1,3]	1.67	8.863	0.1844	1.06	6.119
OR[2,3]	0.9006	0.5284	0.3215	0.8019	2.086
SD	0.6817	0.441	0.05926	0.5892	1.765

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

Table 21.3: Non-major bleeding - U(0,0.6)

Node	mean	sd	2.5%	median	97.5%
OR[1,2]	1.497	0.8066	0.4813	1.346	3.525
OR[1,3]	1.149	0.5095	0.457	1.06	2.438
OR[2,3]	0.826	0.2335	0.471	0.7913	1.389
SD	0.3425	0.1591	0.02811	0.3566	0.5869

1, rivaroxaban; 2, long term LMWH; 3, dual heparin/VKA; SD, standard deviation; OR, odds ratio.

4.5.2 Update of Akl et al.[31]

The ERG undertook additional searches to update the Akl et al.[31] systematic review. The searches followed the same search strategy as reported in Akl et al.,[31] covering the years 2010 and 2011. The searches were sifted by title, abstract and full text. No further relevant RCT studies were found.

4.6 Conclusions of the clinical effectiveness section

Table 22 summarises remaining uncertainties for the clinical data.

The methods of the review of direct evidence were sometime unclear, though the ERG does not suspect that any studies have been missed, and rate the systematic review as reliable.

The evidence from EINSTEIN-DVT, a non-inferiority, open label, randomised trial upon which the MS focuses, is generally a well conducted study which is highly relevant to the decision problem.

However, the study fails to provide information on some important subgroups of patients, such as those with high risk of bleeding, and creatinine clearance <30mL/min, as these groups were excluded

Table 22 Uncertainties in clinical data and direction of effect.

Issue	**Is the current assumption favourable or unfavourable to rivaroxaban?**
Ongoing treatment option not represented	Unknown
Use of Enoxaparin to represent LMWHs	Probably no effect
Enoxaparin dose	Possibly unfavourable to rivaroxaban
Wrong comparator (cancer)	Favourable to rivaroxaban (in whole cohort)
HRQoL measurements	Unknown
Potentially rare adverse events which occur as a consequence of not being able to reverse rivaroxaban anticoagulation, being missed in this trial	Potentially favourable to rivaroxaban
All cause mortality HR is shown to be significant	Unfavourable to rivaroxaban, but may be dependent on intended treatment duration
Lack of allocation concealment	Unknown
Under or over-diagnosis of patients into the wrong treatment duration group	Unknown
Subgroup by those with and without a previous VTE	Favourable to rivaroxaban for those without previous VTE Unfavourable to rivaroxaban for those with previous VTE
Inclusion of patients who did not fulfil the selection criteria	Unknown

from the study. Patients with distal DVT appear also to have been excluded, even though the SmPC[19,20] does not exclude them from treatment. A small number of patients (with PE and/or creatinine clearance <30mL/min) who should have been excluded were included, and it is unclear why this occurred, why all these patients were not excluded in the per protocol analysis, or what effect their inclusion/exclusion would have on the results.

The intervention was appropriate, though the dose was not reduced in patients with creatinine clearance <50mL/min as recommended in the SmPC. [19,20]

The comparator was, for the most part, appropriate. However, the enoxaparin component of the comparator was delivered at a dose which differs from the standard dose used in England and Wales,[48] though clinical opinion suggests that this would not advantage estimates of efficacy for rivaroxaban, and indeed may disadvantage estimates of the effect of rivaroxaban for VTE recurrence. Patients with cancer were treated with standard therapy, despite UK and international clinical guidelines recommending the use of LMWH in this patient group. An MTC was presented to address estimates of efficacy comparing rivaroxaban to LMWH in this group. Unfractionated heparin was not used, and no conclusions relating to this can be drawn. The time in treatment range and compliance levels seen for VKA treatment seemed comparable with values reported for England and Wales.

All outcomes identified by NICE were reported, with the exception of health related quality of life data. Whilst a measure of quality of life was used, this was not in line with the NICE reference case, and was not a preference-based measure or a validated tool. The validity of the use of the composite outcome (VTE) depends on the assumption that similar reductions in hazard ratios will occur for all components of the outcome, i.e. PE and DVT, in response to treatment.

The study appears relatively free of bias in its conduct. The results indicate that rivaroxaban is non-inferior to enoxaparin/VKA treatment for VTE recurrence and rates of clinically significant bleeding, on average, when considering the selected group of patients all together.

However, subgroup analyses indicate that rivaroxaban may be less effective in certain groups of patients, including those who are clinically indicated to receive 3 months of treatment. The ERG feels that the data relating to VTE recurrences in this group does not definitively prove non-inferiority. Patients whose index event was a recurrence of a previous DVT or PE appear to obtain more relative benefit from rivaroxaban than those whose index event was their first DVT. [redacted]

However, it should be noted that major bleeding events in the intended treatment groups do not appear different, and as such the balance between risk and benefit is unknown. No subgroup analysis was provided for bleeding events in the subgroups "previous episode of DVT/PE".

Bleeding events, adverse events and mortality results support the non-inferiority of rivaroxaban to enoxaparin/VKA treatment. Subgroup analyses indicate there may be increased bleeding rates for those who are ≤70kg and those with poor renal function in those taking rivaroxaban. Rivaroxaban patients scored more favourably on the quality of life measure used than those in the comparator group.

Only one subgroup analysis included in the NICE scope was provided, mainly because there were no data available from the trial for patients in the other subgroups mentioned by NICE as these patients were excluded. The subgroup analysis provided was for patients with cancer, and involved an MTC to allow a comparison between rivaroxaban and LMWH, which is standard anticoagulant treatment for patients with cancer. The ERG felt that the results generated by the MTC were limited by the available evidence and also by the way the analysis was conducted. The results of the MTC using a uniform prior distribution on the range (0,0.6) shows that rivaroxaban is less effective than LMWH at preventing VTE recurrence, but induces fewer major bleeding events. The credible intervals are wide, and the ERG has concerns about the accuracy of the point estimates and credible intervals.

The ERG are of the understanding that antiocoagulation is used long term in approximately 20% of patients with a DVT. The EINSTEIN-DVT trial provided no data on longer term treatment with rivaroxaban, and data from the EINSTEIN-Ext provided data versus placebo, rather than an active treatment in a poorly defined population of patients. This trial showed that rivaroxaban is effective at decreasing recurrence of VTE in patients with an index DVT, but with some increase in clinically relevant non-major bleeding rates, and a non-significant increase in major bleeding. The effects of long term treatment with rivaroxaban in comparison with long term treatment with LMWH/VKA, whether this be in patients indicated for long term treatment or those in an equivocal state, is unknown.

In conclusion, the decision problem has been fairly well addressed by the evidence provided. Gaps in the population include those at high risk of bleeding, those with a non-proximal DVT and those with renal impairment. There is no information relating to how rivaroxaban compares to treatment with unfractionated heparin and LMWH in patients who would normally be treated with these. The data relating to the cancer subgroup of patients is not considered robust by the ERG. The ERG also has concerns about the efficacy of rivaroxaban in patients who fall into the 3 month intended treatment duration, and there is no evidence relating to long term treatment with rivaroxaban compared to other active treatments. However, for patients in a poorly defined class of “clinical equipoise”, ongoing treatment appears better than no preventative therapy, and in the majority of patients treated for one year or less for proximal DVT in England and Wales, rivaroxaban appears to be non-inferior to treatment with Enoxaparin/VKA.

5 COST EFFECTIVENESS

5.1 Review of the cost-effectiveness evidence

The manufacturer's submission included a review of the cost-effectiveness evidence.[1] Four databases were searched; Medline, Embase, EconLit and NHS EED. The manufacturer used search terms that covered deep vein thrombosis, treatment and cost-effectiveness.

The searches identified 1,479 publications, of which 15 publications were reviewed at full-text level and four studies were included and data extracted. Extraction tables are available in the MS in Table 33 (p. 100 – p. 103)

The manufacturer stated that none of the studies identified were directly relevant to the decision problem.[1] The ERG agrees with this statement based on the studies included in the review, and therefore, no further description or critique was carried out by the ERG.

5.2 Summary and critique of the manufacturer's submitted economic evaluation

5.2.1 Economic evaluation

5.2.1.1 Overview of the manufacturer's economic evaluation

The manufacturer submitted a decision-analytic model constructed in Microsoft Excel software.[1,49] The economic evaluation uses a Markov approach using eleven possible health states, including venous thromboembolism recurrences, bleeding events and death. A description of the different health states and transitions between these states is given in section 5.2.1.6 of the ERG report.

The manufacturer presented two analyses. The primary analysis (or main analysis) compared the use of rivaroxaban against dual therapy with low molecular weight heparins and vitamin K antagonists (VKA) (termed dual therapy LMWH/VKA hereafter) delivered over three, six or twelve months in patients with acute DVT. In its original submission to NICE, the manufacturer also presented a cost-minimisation analysis in a subgroup of cancer patients and compared the use of rivaroxaban with LMWH only (using dalteparin).[1] Following a request from the ERG during the clarification process, the manufacturer submitted an exploratory cost-effectiveness analysis in a subgroup of cancer patients adapting the existing model framework.[17]

For the primary analysis, the rates of bleeding events and VTE recurrences after treatment of the index DVT (at which point patients were assumed to enter the model) were taken directly from the EINSTEIN-DVT trial.[50] The manufacturer used data from dual therapy LMWH/VKA to represent the baseline risk of events, and applied a hazard ratio to estimate the risk of events for patients treated with rivaroxaban. In its original submission to NICE, the manufacturer used effectiveness data (for the baseline risk of events and treatment effect) from the whole trial population, instead of using data specific by intended treatment duration.[1] The economic model was updated following a request from the ERG using effectiveness data specific by intended treatment duration.[17] The ERG believes this analysis to be more appropriate. A systematic review of the literature was carried out to identify effectiveness data to inform the long term rates of recurrence and mortality once treatment has ceased.[40]

The baseline risk of events for patients with cancer was derived from the economic model for the whole population treated with rivaroxaban, adjusted for the increased risk of events in cancer patients versus non cancer patients. The treatment effect estimated from the MTC (median Hazard Ratio or odds ratio (where appropriate)) was then applied to estimate the risk of events in cancer patients treated with LMWH only. The manufacturer also assumed a shorter life expectancy, to reflect the poorer prognosis of cancer patients. Further details are available in section 5.2.1.10 of the ERG report.

Costs relating to the treatment and management of VTEs and adverse events (AEs) such as bleedings were included in the economic model and were taken from official sources (such as British National Formulary (BNF)[48] or NHS reference costs[51]), with reference to clinical expert opinion where appropriate. The utility values for the different health states were identified through a systematic search of the literature[40] and were taken from different studies.

Costs and benefits were discounted at 3.5% per annum and the uncertainty was captured in both univariate sensitivity analysis (SA) and probabilistic sensitivity analysis (PSA).

5.2.1.2 Decision problem

The MS partially addressed the scope issued by NICE.[3] The patient population modelled reflected the patient population included in the EINSTEIN-DVT trial and matched broadly the patient population defined by NICE in the scope,[3], but there is some changes in wording to reflect the licensed indication given by the EMA.[23] The clinical advisors to the ERG believed this to be appropriate.

The MS main analysis compared the use of rivaroxaban with dual therapy LMWH/VKA delivered over three, six or twelve months in patients with acute DVT using effectiveness data taken from the EINSTEIN-DVT trial.[50] No analysis was provided for patients initially treated with Unfractionated Heparin as defined by NICE in the scope.[3] However, experts believed that UH is seldom used in patients with VTE (mainly for those with renal failure and those having thrombolysis for massive PE).

Furthermore, continued therapy with LMWH or UH was considered as a comparator in the NICE scope for people for whom a VKA is not considered an appropriate comparator. This issue was partially addressed in the original MS using a cost-minimisation approach in a subgroup of patients with cancer, but no formal cost-effectiveness analysis was originally conducted, and patients with cancer are not the only patients for whom this treatment is appropriate. A formal cost-effectiveness analysis in cancer patients was requested by the ERG in the clarification letter sent to the manufacturer.[17] The ERG suggested that an exploratory analysis could be undertaken using the existing framework, but populating the model with the relative efficacies, costs and bleed rates for rivaroxaban and LMWH (and possibly a lower life expectancy to reflect the poorer prognoses for this subgroup of patients), to allow a comparison that does not rest on the assumption of cost-minimisation. The manufacturer responded positively to this request, and presented an exploratory cost-effectiveness analysis in a subgroup of patients with cancer.[17]

The scope issued by NICE[3] considered two subgroups of patient:

- patients with an underlying risk of recurrent VTE including the presence of active cancer,
- patients with an underlying risk of bleeding (for example people over 60 years of age)

The MS partially addressed the subgroup consideration for patients with an underlying risk of recurrent VTE providing an analysis in patients with cancer only.[1] The manufacturer did not present an analysis in patients with an underlying risk of bleeding, such as patients aged over 60 years of age. The ERG did not request an analysis by age to be undertaken due to equity and accessibility issues. Furthermore the ERG believed that there were no data to base this on as most patients with an underlying risk of bleeding were excluded from the trial (see section 3.1)

Finally, the manufacturer provided subgroup analyses for patients treated over three, six or twelve months.[1,17]

5.2.1.3 Population

The MS main analysis[1] evaluated patients with acute DVT treated over three, six or twelve months with rivaroxaban or dual therapy LMWH/VKA according to the intended treatment duration determined pre-randomisation in the EINSTEIN-DVT trial.[50]

As discussed in the clinical effectiveness section (section 2.2), clinical opinion was sought and indicated that in practice, the intended treatment duration is based on clinical factors at presentation including the location of DVT and other risk factors.

In the economic model, the manufacturer assumed patients to be treated for three, six or twelve months according to the intended treatment duration observed in the EINSTEIN-DVT clinical trial.[50] The ERG sought clinical opinion on the validity of the intended treatment duration used in the trial and how this reflects UK clinical practice. Clinicians agreed that in clinical practice, patients would be treated for three, six months or for a longer treatment period. However, our experts did not share the view that cessation of treatment at 12 months is common in the UK, and suggested that clinical practice has changed in recent years and that there is a group of patients which are more likely to be treated on an ongoing basis if clinical characteristics and risk factors indicate that this is appropriate. Our experts also believed that those who were assigned to the 12 months treatment group in the EINSTEIN-DVT trial[50] could be considered a surrogate for patients who may receive treatment on an ongoing basis in clinical practice.

The manufacturer was contacted and clarification was requested on the reasons why no analysis was performed in patients treated on an ongoing basis.[17] The manufacturer did not provide such analysis as the manufacturer did not agree with the view expressed by our clinicians, and did not consider treatment longer than 12 months to be common. The manufacturer's argument, however, centres around patients experiencing their first DVT, and in this context, the view that few go on to long term treatment may be more accurate. However, the population of interest to this assessment is symptomatic DVT, whether it is a recurrence or a first event. The ERG clinicians are of the opinion that up to 20% of VTE patients experiencing their first DVT or a recurrence of a DVT would go on to receive ongoing treatment.

The ERG acknowledges the responses from the manufacturer and the absence of data for patients treated on an ongoing basis, but disagrees with the statement from the manufacturer that this group does not exist. The ERG would have liked to see an exploratory analysis examining the effect of ongoing treatment on the ICER, acknowledging that such analysis would rely on further assumptions.

5.2.1.4 Intervention

The economic model considered the use of rivaroxaban (Xarelto®) according to its license indication, i.e. 15 mg twice a day for 21 days, followed by 20 mg once a day for the remaining duration of anticoagulation treatment.[52,53]

5.2.1.5 Comparators

The comparator for the main analysis is dual therapy LMWH/VKA as defined by NICE in the scope.[3] The manufacturer[1] stated that there are four LMWH treatments licensed for the treatment of DVTs or PEs; Fragmin® (dalteparin sodium), Clexane® (enoxaparin sodium), Innohep® (tinzaparin sodium) and Zibor® (bemiparin sodium).

In the economic model, for the main analysis, the daily cost of Clexane® (enoxaparin) was used by the manufacturer for LMWH, assuming a dose of 1.5 mg/kg once daily. This was supported by a survey conducted by IMS health data, showing that Clexane® accounted for a [redacted] share of the LMWH usage in England and Wales for the treatment of VTEs, compared with Fragmin® and Innohep®, which represent a [redacted] and a [redacted] share of the usage respectively.[40] Clexane® was the LMWH used in the EINSTEIN-DVT trial[50] and can either be self administered or given by a nurse.

Clinical opinion was sought and the clinical advisors to the ERG agreed that the use of Clexane® in the economic model to reflect clinical practice in England and Wales is a reasonable assumption. Furthermore, the manufacturer compared the daily drug acquisition costs (excluding administration and/or monitoring) for the different LMWH and showed that the daily cost of Clexane® (£9.77) was less expensive than Innohep® (£11.85) but more expensive than Fragmin® (£8.471)[a]). The ERG is satisfied with the assumption made by the manufacturer and calculated that the daily drug acquisition costs for Clexane® (£9.77) was close to the weighted average daily drug acquisition costs (£10.03[b]) of LMWH treatments (Table 23) using data from IMS health.

Table 23: Weighted average daily drug acquisition cost of LMWH treatments

	Share of usage	**Daily drug acquisition cost**
Clexane®	[redacted]	£9.77
Innohep®	[redacted]	£11.85
Fragmin®	[redacted]	£8.47
Weighted average		£10.03

The manufacturer's economic model also used the recommended dose in the UK i.e. 1.5 mg/kg once daily[52]but used effectiveness data from the EINSTEIN-DVT trial which used 1mg/kg twice daily.[50] Clinical opinion was sought with the clinical advisors to the ERG believing that the difference in efficacy between the two regimens is likely to be minimal. However, the experts also believed that patients receiving 1.5mg/kg are theoretically more likely to develop adverse events such as bleedings because the higher dose could lead to larger peaks in plasma levels of the drug than two lower doses (with lower peaks) spread out over time. Therefore, using 1.5 mg/kg once daily in the economic model for the cost but using the effectiveness for 1mg/kg twice daily from the EINSTEIN-DVT trial may be a conservative assumption in favour of the LMWH arm.

For patients treated with a VKA, the manufacturer assumed that patients received warfarin at a daily dose of 6mg. The BNF recommends a daily dose between three to nine mg.[48] Expert opinion was sought which found the assumptions used by the manufacturer to be satisfactory.

[a] A lower cost is available for oncology patients.
[b] Calculated by the ERG

Finally, in cancer patients, the manufacturer assumed that patients were treated with LMWH only, and used Fragmin® (dalteparin sodium) as it is commonly delivered in the oncology setting. The ERG's clinicians agree with this assumption.

5.2.1.6 Model structure

The manufacturer's model structure uses a Markov approach where individuals were able to move between eleven possible health states; on treatment ("On Tx"), recurrent DVT ("rVTE – DVT"), recurrent PE ("rVTE – PE"), intracranial bleeding event ("Major bleed – IC"), extra cranial bleeding event ("Major bleed – EC"), Clinically Relevant Non-Major (CRNM) bleeding event ("CRNM bleed"), "Post IC bleed" in patients who previously experienced an intracranial (IC) bleeding event, "Post-thrombotic syndrome" (PTS), "chronic thromboembolic pulmonary hypertension" (CTEPH), "long-term CTEPH" and "death".[1] A simplified schematic of the model structure and transitions between health states is presented in Figure 7. The economic model uses a 3 month cycle length, with a lifetime horizon in the basecase.

Patients enter the model following an index DVT event and receive treatment in the "On Tx" health state. Patients are then at risk of a bleeding event, or a recurrent VTE.

Patients with an EC major bleeding event or CRNM bleeding event were assumed to stop treatment for a month (and have a reduction in QoL for a month) and could then either go back on to treatment or stay off treatment. Patients with an IC event were assumed to stop treatment after the event, and then move to the "off treatment" or enter the "Post IC bleed" health state. Patients in the EC and IC bleed health states also had an additional risk of mortality.

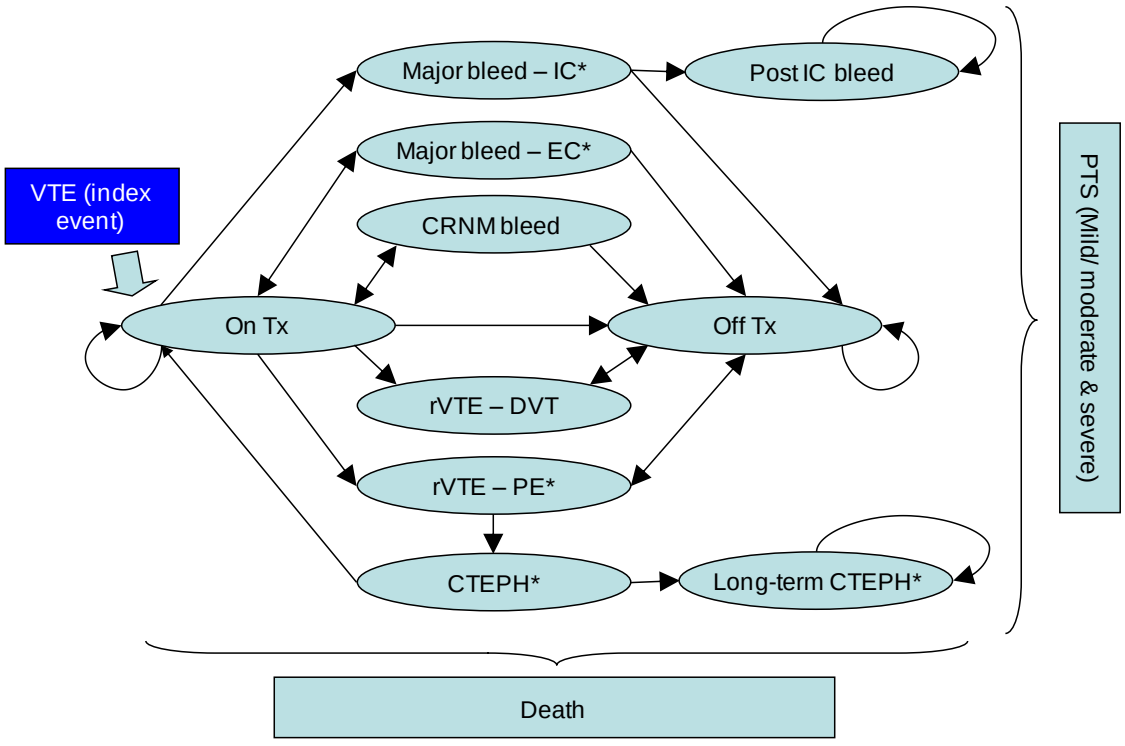
Recurrent VTEs can be either a DVT or a PE. Patients were assumed to be treated for six months with dual therapy LMWH/VKA (and have a reduction in QoL for a month) and then cease treatment, with a long-term probability of re-occurrence of VTE (DVT or PE). Patients that develop a PE were at risk of CTEPH. Additionally, patients were at risk of PTS in the economic model. Patients with a PE had an increase risk of mortality, but not patients with a DVT.

The ERG finds the manufacturer's model structure generally satisfactory. Discussion with clinical experts indicated that the structure chosen by the manufacturer captures the main health states for patients treated for their index DVT (VTE recurrences and bleeding events). The manufacturer's economic model only included bleeding as an adverse reaction following rivaroxaban or dual therapy with LMWH/VKA despite other adverse events reported in the trial (Table 10). Expert opinion was sought and the clinical advisors to the ERG believed this to be appropriate as bleeds are associated with large impacts on QoL and resource use, whilst the other adverse events reported in the EINSTEIN-DVT trial[22] have negligible impacts on QoL and costs.

The manufacturer's economic evaluation made the assumption that patients were treated for six months after a recurrent VTE with dual therapy LMWH/VKA, and ceased treatment thereafter.[1] Clinical opinion was sought and indicated that patients are more likely to be treated on an ongoing basis after a recurrent VTE. Furthermore, the manufacturer's economic model did not incorporate the costs and decreases in QoL due to adverse events for the treatment of the recurrent VTE. The manufacturer's economic evaluation only considered the use of dual therapy LMWH/VKA after a recurrent VTE.

The ERG asked the manufacturer to clarify why patients were assumed to be treated for six months after a recurrent VTE instead of an ongoing basis as suggested by our clinical experts.[17] In response to the ERG comment, the manufacturer stated that six months of treatment is a fairly typical length of treatment in the UK and represent a conservative approach. Constraints were also imposed due to the model structure and the absence of tunnel states. The manufacturer believed that assuming longer treatment duration would lead the economic model to suggest greater cost savings.[17]

Figure 7: Structure of the manufacturers' economic model (reproduction of Figure 16, p. 106, MS,[1] November 2011)



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

Our experts believed that patients are treated on an ongoing basis after a recurrent VTE. Furthermore, the ERG does not agree with the manufacturer's statement that assuming longer treatment duration would lead to greater cost-savings. Whilst this may be true in the current economic model for the subgroups of patients for whom rivaroxaban reduces the number of recurrent VTEs, such as patients treated for six or 12 months for their index DVT event (see Figure 3), rivaroxaban appears to be associated with more VTE recurrences in patients treated for three months (compared with patients treated with dual therapy LMWH/VKA for 3 months) and therefore higher costs are likely to be accrued in the rivaroxaban arm. Of note, if bleedings were included, this might not be the case anymore.

The ERG also has concerns about the assumptions made by the manufacturer that patients with a recurrent VTE can only receive dual therapy LMWH/VKA. Indeed, according to the indication in its proposed licence[19,20], rivaroxaban can also be used for the treatment of a recurrent VTE. In the current economic model, the use of rivaroxaban will reduce the cost for patients experiencing a recurrent VTE (as this is cheaper than dual therapy LMWH/VKA assuming the monitoring used in the manufacturer's economic model).

Due to the constraints imposed by the current model structure, it was not possible for the ERG to adapt the economic model to assume longer treatment durations and estimate the impact of this on the ICER.

An exploratory analysis was however conducted by the ERG assuming a less intensive monitoring in patients treated with a VKA, therefore reducing the treatment costs of LMWH/VKA for the treatment of the index event and for patients experiencing a recurrence. We did not change the efficacy for patients treated for a recurrence. Results of this analysis are presented in section 6 of the ERG report.

5.2.1.7 Effectiveness data

- *Probabilities of bleeding events and recurrent VTEs whilst on treatment*

The probabilities of recurrent VTEs, CRNM bleeds and major bleeds for patients treated with dual therapy LMWH/VKA were taken directly from the EINSTEIN-DVT trial[50] and are presented in Table 24 with the values used in sensitivity analysis and the PSA. The probabilities were assessed for three time periods; 0-3 months, 3 – 6 months and 6 – 12 months. Note that the values used in the PSA (alpha, beta) are incorrect where no events were observed, and the ERG would recommend an uninformative prior to be used (for example adding 0.5 to both the alpha and beta value).

Table 24: Probabilities of VTEs and bleeding events for patients treated with dual therapy LMWH/VKA (reproduction of Table 36, p. 112, MS,[1] November 2011)

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

The probabilities of recurrent VTEs, and major bleeds for patients treated with rivaroxaban were derived applying a hazard ratio (assuming proportional hazards) calculated from the EINSTEIN-DVT trial[50] to the baseline risk of events from the dual therapy LMWH/VKA arm (table 24).

The manufacturer reported that the use of rivaroxaban reduces the risk of VTE by 38% (HR 0.68, CI: 0.44 – 1.04) and the risk of major bleeding by 35% (HR: 0.65, CI: 0.33 – 1.28).[1]

The probability of CRNM bleeding for patients treated with rivaroxaban was derived applying a risk ratio calculated from the EINSTEIN-DVT trial to the baseline risk of events from the dual therapy LMWH/VKA arm (Table 24). The manufacturer calculated a risk ratio of 1.05 (95% CI 0.83 to 1.34). The risk ratio was incorrectly used as a hazard ratio in the economic model, but this had almost no impact on the ICER after correction by the ERG.

In addition to the above, the manufacturer[1] assumed that the probability that a recurrent VTE is a DVT (conditional on one occurring) was [redacted] both treatment arms based on the number of events from the EINSTEIN-DVT trial.[50] The remaining VTEs are PEs. The MS[1] also assumed that the probability that a major bleeding event was intracranial (conditional on one occurring) was 12.5% in both arms based on the number of events from the EINSTEIN-DVT trial.[50]

The ERG has concerns with the approach used by the manufacturer. First, the manufacturer used data from the whole trial population to estimate the probabilities for patients treated with dual therapy LMWH/VKA, instead of using data stratified by intended treatment duration. Biases could have been introduced by pooling data from the different subgroups because of potential differences in the risk of VTE recurrences or bleeding events between the different intended treatment duration subgroups.

Similarly, the manufacturer used data from the whole trial population to calculate the treatment effect of rivaroxaban vs. dual therapy LMWH/VKA instead of using the data specific to the intended treatment duration group (three, six or twelve months). Clinical data (see section 4.2.1.3) suggested that rivaroxaban might be less effective compared with LMWH/VKA for VTE recurrences in patients treated for three and six months compared with patients treated for 12 months (Figure 3). No formal test of interaction was provided by the manufacturer to reject this hypothesis in its original submission, however tests were provided upon request by the ERG in the clarification letter.[17] [redacted]

The manufacturer also applied the treatment effect using a hazard ratio, assuming proportional hazard. No statistical test was provided by the manufacturer to support this assumption in its original submission.

Clarifications were sought from the manufacturer by the ERG requesting analyses using effectiveness data by intended treatment duration group, separately.[17] The manufacturer responded positively to the ERG request and provided analyses using data specific by intended treatment duration.[17] Table 25 lists VTE and bleeding probabilities for patients treated with dual therapy LMWH/VKA, whilst Table 26 lists the hazard ratios for rivaroxaban vs. dual therapy by intended treatment duration. As before, the values used in the PSA (alpha, beta) are incorrect where no events were observed.

[redacted]

The ERG believes the analysis using data specific by intended treatment duration to be more appropriate.

The ERG also requested clarification from the manufacturer on the use of a hazard or risk ratio (and the assumption of proportional hazards) to represent the treatment effect in preference to using separate probabilities for the rivaroxaban and the comparator arm.[17] In response, the manufacturer performed a statistical test and described [redacted]

The model was updated by the manufacturer to use data specific by intended treatment duration. The ICERs for these new analyses are presented in section 5.

[redacted] The split DVT/PE by treatment arms and intended treatment duration is presented in Table 27. This has been calculated by the ERG based on the information provided in the clarification letter.[17]

Table 25: baseline risk of events for patients treated with dual therapy LMWH/VKA, by intended treatment duration (reproduction of Table 12, p. 29, Clarification letter,[17] December 2011)

	Point estimate	Lower	Upper	Alpha	Beta
3 month population					
0-3 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 month population					
0-3 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-6 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 month population					
0-3 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-6 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-12 months					
Major bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRNM bleed probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of VTE probability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26: Treatment effect (rivaroxaban vs. dual therapy LMWH/VKA), by treatment duration (reproduction of Table 13, p. 30, Clarification letter,[17] December 2011)

Outcome and patient group	Point estimate	Lower	Upper
Incidence of recurrent VTE (hazard ratio)			
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
Incidence of major bleed (hazard ratio)			
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
Incidence of CRNM bleeds (risk ratio)			
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]

Table 27: Proportion of VTEs that are DVTs – proportion (number of DVTs / number of VTEs)

	Rivaroxaban	Dual therapy LMWH/VKA	All
3 months	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
All	[redacted]	[redacted]	[redacted]

The data suggests that using data by the initial treatment received [redacted] of VTEs were PEs in the rivaroxaban arm versus [redacted] in the dual therapy arm. The ERG also undertaken a chi-square test, and found that the differences [redacted]

Because PEs are associated with greater cost implications and reduction in QoL compared with DVTs, the ERG explored a scenario using specific data by treatment arms. Results of this analysis are presented in section 5.2.1 of the ERG report. Note that we did not examine the impact of using data

by intended treatment duration given the small sample size when splitting patients by treatment arms and intended treatment duration.

The manufacturer assumed that the probability that a major bleeding event is an IC bleeding event (conditional on one occurring) was the same between the two treatment arms in the economic model (12.5%). It is unclear why the manufacturer assumed this to be the same irrespective of the treatment arm (and intended treatment duration). No data was presented to support or reject this assumption. The split between intracranial/extracranial (IC/EC) bleeds is likely to affect the ICER as IC bleeds are associated with greater cost implication and reduction in QoL compared with EC bleeds. The impact of this assumption in the model has not been formally examined in the economic model by the ERG in the absence of data by treatment arm. This remains an area of uncertainty in the model. If the proportion of major bleeding events that are IC bleeds is higher in the rivaroxaban arm, this assumption will favour rivaroxaban. If the proportion is higher in the dual therapy LMWH/VKA arm, this assumption will favour the dual therapy arm.

- *Discontinuation rate*

The discontinuation rate whilst on treatment was taken from the EINSTEIN-DVT trial,[50] and was assumed to be the same irrespective of the initial treatment received and intended treatment duration.[1] The manufacturer included the following reasons for discontinuation: non compliant with study medication, protocol violation, patient convenience, switch to commercial drug, insufficient therapeutic effect and bleeding adverse events. The manufacturer reported the total discontinuation for those reasons: [redacted] This equated to an overall 3 month probability of [redacted]

The model additionally assumes that all patients with IC bleeds, [redacted] of patients with major EC bleeds and [redacted] of patients with CRNM bleeds discontinue treatment, based on [redacted]

The MS stated that assuming the same discontinuation rate irrespective of the initial treatment was a conservative assumption;[1] however the ERG disagrees with this [redacted]

There is also double counting as the manufacturer included bleeding events to calculate the discontinuation rate whilst this was already included in the economic model. The discontinuation rate was calculated from the whole trial population, rather than specifically by intended treatment duration. There was also a mismatch between the economic model and the report, as the manufacturer

stated that [redacted] of patients discontinued treatment after an EC bleed, but used [redacted] in the economic model.

Despite these limitations, sensitivity analyses conducted by the manufacturer showed that a variation in the discontinuation rate had a limited impact on the results.[1]

- *Probability of VTE recurrences after treatment cessation (at the end of the intended treatment duration)*

The manufacturer carried out a systematic review of the literature to identify trial-based and observational literature providing evidence on rates of recurrent VTE in patient populations with index DVTs, PEs or VTEs.[40] 16,795 potentially relevant studies were identified in Medline, Embase and Cochrane Library literature databases, and 129 studies were included. Of those, the manufacturer reported that 16 publications had a long follow-up period, and 13 were believed to be relevant by the manufacturer;

- "the Prandoni cohort" (terminology used by the manufacturer) has been described in three publications, with data from the most recent publication used.[8] This comprised a cohort of 1,626 patients with clinically symptomatic proximal DVT and/or PE from centres based at the University of Padua, Italy, who were initially treated with anticoagulation.
- "the Vienna cohort" (terminology used by the manufacturer) (Eichinger 2010[9]) has been described in ten publications, with data from the most recent publication used.[9] This comprised a cohort of 929 patients with a first VTE from four thrombosis centres in Vienna and Austria, who had completed at least 3 months of anticoagulation treatment.

The manufacturer's economic model used data from the Prandoni cohort[8] in the basecase analysis as this included more patients and estimated the three month probability of VTE recurrence to be 1.26% (95% CI 1.09% to 1.46%) using data at 10 years only. The manufacturer also assumed that 19.2% of VTEs were PEs after cessation of treatment using data from Prandoni et al (1996).[6] Sensitivity analyses were conducted by the manufacturer varying the rates within the 95% CI and showed a minimal impact on the results.

The ERG finds the approach used by the manufacturer to identify evidence on the rate of long term VTE recurrences generally satisfactory and transparent. Note that the ERG did not attempt to reproduce the systematic review presented by the manufacturer due to time and resource constraints. The manufacturer used data from the Prandoni cohort,[8] however, this is an old cohort, and might not

reflect the current long term risk of VTE recurrences with current treatment. The manufacturer also assumed that the risk of recurrent VTEs was the same after end of treatment for each intended treatment duration group and initial treatment received. Notably, patients in the Prandoni cohort received different anticoagulant treatments. Despite this, the sensitivity analysis conducted by the manufacturer showed that a variation in this parameter within the 95% CI had a minimal impact on the results.

The manufacturer further assumed that 19.2% of VTEs were PEs. Note that this is very different to the proportion estimated in the EINSTEIN-DVT trial for the treatment of the index event ([redacted]). The ERG cannot explain the reason of this difference. An error was also identified by the ERG, in that the probability of PE recurrences after the first year was incorrectly divided by 4 ([redacted] This had been corrected by the ERG (section 6) and showed to have a very small impact on results.

- *Probabilities of CTEPH and PTS*

The manufacturer carried out a systematic review of the literature to identify trial-based and observational literature providing evidence on rates of incidence of complications of VTEs, including CTEPH and PTS, in patient populations with index DVTs, PEs or VTEs. [40] 3,853 potentially relevant studies were identified, and 42 studies were included. Of those, 3 publications considered the incidence of CTEPH. In the base case, the manufacturer used data from Miniati et al.(2006)[54] as this study was used in the recent NICE VTE guideline development[18]2) and was in line with the other two identified sources. The manufacturer's economic model assumed that 1.25% (95% CI 0.03% to 2.46%) of incident PEs would progress to CTEPH in the base case.

Furthermore, of the 42 studies included in that review, the manufacturer stated that 39 studies provided data on the incidence of PTS, with the longest and most robust prospective cohort studies described in two papers authored by Prandoni et al[6,55]. Only severe PTS were included in the economic model as the review of utility studies [1] suggested that mild PTS was of little detrimental effect on quality of life. The manufacturer's economic model used data from more recent publication from Prandoni et al (1997)[55] estimated in 528 patients in the base case and assumed a cumulative incidence of severe PTS of 2.7 at one year and 8.1% after five years. This equated to a 3 months probability of 0.68% the first year and 0.36% thereafter.

The ERG finds the approach used by the manufacturer to identify evidence on the rate of CTEPH and PTS generally satisfactory and transparent. Note that the ERG did not attempt to reproduce the systematic review presented by the manufacturer due to time and resource constraints. However, the ERG is concerned that the manufacturer assumed that the risk of CTEPH and PTS was the same

irrespective of the intended treatment duration or initial treatment received, but also acknowledges the lack of evidence which contributes to this assumption. These rates were varied in SA in the MS and did not change the conclusions.

- *Risks of mortality*

In addition to the general risk of mortality associated with age, the manufacturer included the additional risk of mortality associated with PEs, major bleedings and CTEPH. The manufacturer carried out a systematic review of the literature 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.[40] Searches were conducted in Medline, Embase, Econ Lit and Cochrane Library literature databases and identified 2,755 potentially relevant studies, of which 17 studies were included.

Data from the EINSTEIN-DVT trial[50] was used to estimate the mortality rate during the acute phase of treatment (whilst treated with rivaroxaban or dual therapy LMWH/VKA for the index event). The manufacturer assumed that 20.4% of PEs occurring in the acute phase would lead to death, based on 10 deaths occurring across both treatment arms in the EINSTEIN-DVT trial either attributed to PEs or for which PEs could not be ruled-out as an underlying cause, in comparison with 49 PEs.

The incidence of mortality among patients with recurrent PEs (after the acute phase of treatment) was taken from Prandoni et al. (2007) and assumed to be 33.1% (95% CI 25.0% - 41.2%) based on 43 deaths among 130 patients with an index VTE who had then experienced a recurrent PE.[8]

The risk of death after a bleed was taken from a review by Linkins et al.(2010)[56] which included 23,518 patients and 39 randomised controlled trials involving VKA treatment for at least 6 months and including 11 trials of VTE patients specifically. The authors found that the proportion of bleeds that were fatal did not differ significantly by indication (p=0.32). Based on data from this study, the manufacturer assumed that 43.6% (CI: 36.5% to 50.7%) of IC bleeds and 3.9% (CI: 2.5% to 5.4%) of EC bleeds were fatal respectively.

Finally, the mortality rate for patients with CTEPH was taken from an analysis of registry data from a UK specialist centre for pulmonary hypertension (PH) treatment.[57] The study prospectively included all patients diagnosed with CTEPH between January 2001 to June 2006 and reported a three year

survival of 70% in the 148 non-surgical patients, 76% in the 321 surgical patients, and 74% in the 469 patients overall (i.e. 26% mortality). The manufacturer's economic model assumed a 3 months mortality risk of 2.48% (95% CI 2.05% to 2.93%) using data for the whole population.

The ERG finds the approach used by the manufacturer to identify evidence generally satisfactory and transparent. Note that the ERG did not attempt to reproduce the systematic review presented by the manufacturer due to time and resource constraints. It is unclear why the mortality rates after a PE were different between the EINSTEIN-DVT trial[50] and Prandoni cohort (20.4% vs. 33.1%),[8] although this might be due to the small size. The ERG cannot explain the reason of this difference. Of note, the manufacturer showed that the mortality rates from PE was amongst the 15 most sensitive parameters in univariate SA.[1]

5.2.1.8 Resource use and costs

- *Drug acquisition costs*

In the economic model, the manufacturer assumed that patients in cycle 0 are treated for 21 days in the rivaroxaban arm, and 9.6 days in the dual therapy LMWH/VKA arm based on the mean duration of treatment with LMWH observed in the EINSTEIN-DVT trial.[50] In the rivaroxaban arm, the remainder of the 3 month cycle comprises 70.3 days treatment with rivaroxaban, whilst in the dual therapy LMWH/VKA arm, the remainder of the 3 months cycle comprises 81.7 days treatment with VKA only. Subsequent cycles assume 3-months of treatment with rivaroxaban or a VKA dependent on the treatment arm.

The manufacturer[1] used the recommended dose for LMWH (clexane®) and rivaroxaban in the economic model, instead of the actual dose received in the trial. The ERG sought clarification from the manufacturer.[17] The manufacturer stated that the mean administered drug dose was not recorded in the Clinical Study Report (CSR) and that the dose in the trial for LMWH (1 mg/kg twice daily) was different from the one used in current clinical practice (1.5mg/kg once daily).[17] To explore the impact of this assumption, the manufacturer conducted a sensitivity analysis varying the weight of patients (in kg) within the range observed in the trial to calculate the cost for LMWH. The manufacturer showed that the conclusions remained unchanged within this analysis.

The unit cost of rivaroxaban was set out by the manufacturer at £2.10 per tablet of 15 or 20mg. This price has been agreed with the Department of Health and was confirmed by the manufacturer during

the clarification process. Therefore, the daily acquisition cost for patients treated with rivaroxaban was estimated to be £4.20 the first 21 days (15 mg twice a day), and £2.10 thereafter (20mg once a day).

The drug acquisition cost for patients treated with LMWH and VKA was taken from the BNF.[48] The daily cost for patients treated with enoxaparin (Clexane® used in the economic model) was calculated to be £9.77 daily, assuming a 1.5 mg/kg daily dose and a mean weight of 80kg. The daily cost of warfarin was calculated to be £0.07 once a day, assuming a daily maintenance dose of 6mg (the BNF indicate a daily dose between 3-9 mg daily).[48]

The ERG finds the approach used by the manufacturer to be satisfactory. As previously detailed (section #), the manufacturer used exonaparin in the economic model as this is the most used LMWH in England and Wales, was used in the EINSTEIN-DVT trial and can be self-administered. Furthermore, the ERG calculated that the daily drug acquisition cost of Clexane® (£9.77) was similar to the weighted average drug acquisition cost across LMWH used (£10.03[c]). The manufacturer conducted sensitivity analyses where the price ranged within ±30% (encompassing the daily cost for other LMWH) and showed that the conclusions remained unchanged. Finally, the manufacturer assumed a mean weight of 80kg, instead of the 82kg observed in the trial, which has an impact only for the cost of LMWH.[1,50] The clinical advisors to the ERG agreed that the assumption used by the manufacturer were appropriate.

- *Administration*

The manufacturer assumed in the economic model that rivaroxaban was self-administered.

The manufacturer further assumed that patient education would be successfully delivered to 92% of patients taking Clexane® (enoxaparin) and these patients would be self-administered based on the assumption used in NICE CG92[18] and therefore no costs was assumed for these patients. The manufacturer did not include the costs of patient education.

Of the 8% of patients for whom patient education was unsuccessful, the manufacturer assumed that 80% are treated by a nurse at home using data from a survey.[58] The remaining are assumed to be treated in clinic, with 7.5% requiring transportation (£30.86 – NHS reference costs).

Clinical opinion was sought and believed these assumptions to be reasonable. Note that there was a discrepancy between the economic model and the report, as the manufacturer stated that 8.55% of patients treated in clinic required transportation, but used 7.5% in the economic mode

[c] Calculated by the ERG

- *Monitoring*

[redacted] Clarification from the manufacturer was requested as to whether patients treated with rivaroxaban would need to be monitored for liver function in clinical practice. The manufacturer confirmed that no monitoring is required, referring to the draft SmPC stating that no liver or other monitoring is necessary or appropriate.[17] Clinical opinion was also sought and believed these assumptions to be reasonable.

For patients treated with a VKA, the manufacturer assumed that patients received 9 INR visits in the first 3 months of treatment, followed by 5 visits thereafter over 3 months. Clinical opinion was sought, and different views were expressed. One of our experts found the assumptions used by the manufacturer plausible. Our second clinical expert disagreed with the assumptions made by the manufacturer, and believed that six visits in the first 3 months and 2-3 thereafter would be a more accurate estimate.

The manufacturer further assumed that 66% of INR monitoring visits happen in the primary care and 34% in the secondary care based on a national survey (semi-structure interviews) conducted in healthcare professionals leading anticoagulation care, or PCT/health board recommended knowledgeable persons.[58] This encompassed a total of 78 PCTs in England, three local health boards in Wales and one PCT from a health board in Scotland.

For visits happening in primary care, the manufacturer assumed that half of the visits were undertaken by GPs and the remaining by nurses.[1] Both our experts disagreed with this distribution, suggesting this might be plausible for the first visit, but for follow-up visits, nurses would be more involved and would be responsible for seeing the patient, taking the blood and communicating subsequent dosing and recall instructions, whereas the doctor will only be involved in the dosing on the first visit, unless complications such as bleeding or bruising occurred and GP advice was necessary. Clinical advisors to the ERG suggested that a 25/75% split would be a more accurate estimate. Furthermore, our advisors suggested that there might be costs associated with transportation or phlebotomy service for patients that cannot be transported to the clinic. Such costs would not occur in the rivaroxaban arm.

Unit costs in primary care were taken from the Personal Social Services Research Unit (PSSRU).[59] The cost per visit for patients treated in primary care was assumed to be £27 in the economic model, assuming half of the visits in the primary setting were with a GP (£36) and the remaining with nurses (£12) and that the cost of the INR blood test was assumed to be £3.[60]

The cost per visit for patients treated in secondary care was taken from the NHS reference costs[51] and was assumed to be £47.19 for the first visit (consultant and non-consultant led) and £24.69 for the following visits (consultant and non consultant led).[51] Clinical advisors to the ERG believed that for the follow-up visits, patients were much more likely to visit a nurse rather than a consultant, and therefore incur less costs.

Within the STA process, a submission was made by the Northumberland PCT.[61] This suggested an annual cost of warfarin + monitoring at about £200/year. The Northumberland PCT was contacted for additional information on their estimation of the costs, and referred to a work undertaken by North East Treatment Advisory Group (NETAG) on behalf of primary care organisations (PCOs) in the North East Strategic Health Authority (NE SHA) area for patients treated for atrial fibrillation (AF). Clinical advisors to the ERG believed that there might be small differences in monitoring for the different indications, with some patients more unstable, and therefore requiring slightly more frequent monitoring. However, the clinical advisors acknowledge that there is no evidence base to support this assumption.

The ERG sought other sources of evidence, but there is a lack of information on the monitoring for patients treated with a VKA in the UK. The recent draft NICE guidance for the management of venous thromboembolic diseases and the role of thrombophilia testing[18] suggested an annual monitoring cost alone around £147 per year based on a published study from Jowett et al (2006).[62] However, this study was not limited to patients treated for VTEs, but included 617 patients with a long term indication for oral anticoagulation with the clinical indications for warfarin in rank order being atrial fibrillation, mechanical prosthetic heart valves, recurrent pulmonary embolism or deep vein thrombosis, cardiomyopathy, and transient ischaemic attack or stroke. Clinical advisors to the ERG believed that there might be small differences in monitoring for the different indications, with some patients more unstable, and therefore requiring slightly more frequent monitoring. However, the clinical advisors acknowledge that there is no evidence base to support this assumption.

To further explore this issue, the ERG also sought clarification from the manufacturer on the levels of monitoring observed in the EINSTEIN-DVT trial.[50] The manufacturer stated that the INR monitoring was protocol driven and is therefore not necessarily generalisable to clinical practice in England and Wales. Despite this limitation, data from the trial suggested a mean number of visits of 8.1 for the first 3 months and 4.2 the subsequent quarters. The manufacturer conducted a scenario using the values from the trial and showed that the conclusion remained unchanged.[17]

The ERG acknowledges that the monitoring in the clinical trial[50] was protocol driven but highlight that monitoring in clinical trials is also usually more extensive than in clinical practice and therefore the levels recorded in the trial may suggest that less monitoring visits may occur in real life than are assumed by the manufacturer in the economic model.

Because monitoring is likely to be an important parameter within the calculation of the ICER, the ERG examined further the assumptions on monitoring in the economic model using estimates/advice made by our clinical advisors, i.e.:

- six visits the first three months and 3 visits thereafter (instead of nine visits at first, and five thereafter)
- 25% of visits in the primary care with a GP and the remaining 75% with a nurse (instead of 50/50% split)
- Cost of follow up for non-consultant led visit in secondary care (£18 instead of £24)

Results of this analysis are presented in section 6 of the ERG report. Costs associated with transportation and visit to a phlebotomy service were not included in the absence of robust data about these proportions.

Using the manufacturer's assumptions[1] on the number of visits (nine visits the first three months and five thereafter) and estimated weighted cost per visit (£33.77 for the first INR visit and £26.23 for the subsequent visits), the annual cost of monitoring alone was estimated to be around £656. Using the ERG assumptions, the annual monitoring cost was estimated to be £290 (both values exclude drug acquisition costs). Overall, our estimates of monitoring costs were higher than the figure mentioned by the Northumberland Primary Care Trust (PCT) (about £200/year) or used in the NICE CG92 (£147), but lower than the figure used by the MS (£656).

- *Costs for the different health states*

The costs applied to the different health states are summarised in Table 28.

Table 28: Management costs for the different health states (reproduction of Table 52, p. 155, MS,[1] November 2011)

Health states		Value	Source
1	DVT	£899.81	Derived from results of a survey[63], NHS reference cost[51], NICE CG92.[18] and BNF[48]
2	PE	£1,873.31	Derived from results of a survey[63], NHS reference cost[51], NICE CG92.[18] and BNF[48]
3	Minor bleed	£126.34	Derived from NHS reference cost[51]
4	Extra-cranial bleed	£942.05	Derived from NHS reference cost[51]
5	Intra-cranial bleed	£6,906.13	Derived from NHS reference cost[51] and expert opinion
6	Off-treatment	£0	
7	Off-treatment (post IC bleed)	£1,206.50	Derived from NICE CG92[18]
8	CTEPH (surgery and on-going)*	£7,901	Derived from [57] , NICE CG92,[18] PSSRU[59]
9	CTEPH (on-going)*	£3,719	Derived from NICE CG92[18] PSSRU[59]
12	PTS severe	£96.01	Derived from Goodacre,[64] NICE CG92[18] NHS Reference Costs 2009-10[51]

* ongoing costs

- *Management cost for recurrent DVTs and PEs.*

The manufacturer assumed that patients with a recurrent DVT or PE can be managed either in an inpatient or outpatient setting. The proportion of patients managed in the outpatient setting was taken from a survey[63] and showed that 69% of DVTs and 17% of PEs are managed in the outpatient setting. These proportions were varied in SA by the manufacturer.

For patients managed in the outpatient setting, the manufacturer assumed that patients with DVTs would require one emergency admission, one Doppler ultrasound, and one D-dimer. Patients with PEs were assumed to require one emergency admission, one CT angiography, one chest x-ray, one electrocardiogram and one D-dimer.

The management cost in the outpatient setting was calculated to be £194.84 for DVTs and £271.29 for PEs. Most of the unit costs for the resource use in the outpatient setting were taken from NHS reference costs,[51] with the exception of the cost of a chest x-ray and the cost of a D-Dimer. These costs were taken from a recent diagnostics technology report for NICE[65] and from NICE CG92[18] respectively.

For patients managed in the inpatient setting, the unit cost for the management of a recurrent DVT was taken from the NHS Reference Costs (Healthcare Research Group (HRG) code QZ20Z: Deep Vein Thrombosis –£814.39)[51] The unit cost for the management of PEs was also taken from the NHS Reference Costs but calculated as an average cost across three HRG codes relating to PEs, weighted by activity (DZ09A, DZ09B and DZ09C – £1,584.68).

Based on the proportion of patients treated in the outpatient and inpatient setting, the weighted average cost for the management of a DVT and a PE was calculated to be £386.90 and £1,361.40 respectively.

In addition to the management costs associated with a DVT and a PE, the manufacturer included the cost of 6 months treatment with dual therapy LMWH/VKA (£512) in order to account for the treatment of recurrent VTE assumed within the model. This equated to a cost of £899.81 and £1,873.31 for the DVT and PE health state.

Clinical advisors to the ERG believe the assumptions made by the manufacturer to be reasonable.

- *Management costs associated with bleeding events*

The cost associated with the management of a major EC bleeding event was taken from the NHS reference costs and was assumed to be £942.05 as an average of the costs across 10 HRGs relating to gastrointestinal bleeds with intermediate or major complications (FZ16Z, FZ25A, FZ29Z, FZ30Z, FZ38D, FZ38E, FZ38F, FZ43A, FZ43B, FZ43C).[51] Similarly, the cost associated with the management of a minor EC bleeding event was taken from the NHS reference cost (HRG code: VB07Z: Accident and Emergency Services: Minor Injury Service: Not Leading to Admitted - £126.34).

The cost associated with the management of an IC bleeding event was assumed to be £6,906.13 by the manufacturer and was taken from the NHS reference cost[51] supplemented by expert opinions. The cost was based on the HRG AA23Z (Haemorrhagic Cerebrovascular Disorders – £2.580.99) and the assumption that patients stay 14 days in rehabilitation (HRG VC04Z: Rehabilitation for stroke - £308.94 per day).

Finally, the management cost of follow-on care after an IC bleed was assumed to be identical to the follow-on care for a major ischaemic stroke, and was assumed to be £1,206.50 per quarter derived from the value used in NICE CG92[18], which accounted for the mix of patient dependency that results after a major stroke (38% dependent, 62% independent).[18]

Clinical advisors to the ERG believe the assumptions made by the manufacturer to be reasonable.

- *Severe PTS*

The manufacturer assumed that patients with a severe PTS require 3 vascular outpatient appointments (£161.98 for the first appointment, and £111.03 thereafter) in the first year and two GP visits (£36.00 per visit) every year thereafter, using a similar approach as used in a previous HTA report.[64] Based on these assumptions, the management costs for the first year were estimated to be £384.04 (£96.01 each 3 months) and £72.00 for each subsequent year (or £18.00 every 3 months).

- *CTEPH*

Finally, the manufacturer assumed that 68.4% of patients with CTEPH require a pulmonary endodartectomy (PEA) [57] in the basecase. The unit cost of a PEA was taken from NHS reference costs using the weighted average across two HRGs (AA23Z, VC04Z - £6,109.86).[51]

The ongoing cost for the management of patients with CTEPH was assumed to be £3,719.17 per quarter based on the estimate made for NICE CG92 and inflated to 2010.[18]

Based on these assumptions the management cost for CTEPH was calculated to be £7,901 the first 3 months and £3,719 thereafter.

Note that there was a discrepancy for the management cost of CTEPH between the economic model and the report.

5.2.1.9 Health Related Quality of Life

A systematic review of the literature was carried out by the manufacturer to identify evidence on Health Related Quality of Life (HRQol) associated with DVTs, PEs, bleedings, CTEPH and PTS in patients with an index VTE (DVT or PE or both).[40] Searches were performed on the Medline, EMBASE and Cochrane Library and Econ Lit literature databases.

The searches identified 2,811 potentially relevant studies and six studies were considered relevant by the manufacturer after review of the titles, abstracts and full papers. Two further studies were included by the manufacturer for the population baseline[66] and the post IC bleed health state.[67]

The manufacturer's economic model assumed a baseline utility value of 0.825 based on the landmark national EQ-5D survey conducted by Kind et al (1998) measured using the visual analogue scale (VAS).[66] The study included members of the public aged 18 and over.

The utility value for the DVT, PE, EC bleed, IC bleed, CRNM bleed and PTS, was calculated applying a disutility (or decrement in utility) to the baseline utility value (0.825). The relative decrement in utility was taken from an evaluation of patient preferences in VTE conducted by Locadia et al.[68] The manufacturer acknowledged the limitations within the study in that preferences were elicited by patients rather than the general public. However, the manufacturer stated that this study provided time trade off utilities for the different health states. The manufacturer also assumed that the relative decrement in utility for major EC bleed was similar to GI bleed and that the relative decrement in utility for major IC bleed was similar to haemorrhagic stroke. The relative decrement in utility for severe PTS was taken from Lenert et al.[69]

In addition to the above, the manufacturer assumed a utility value of 0.56 for patients with CTEPH based on Meads et al.[70] using the Cambridge PH Outcome Review (CAMPHOR) instrument calculated in a sample of 308 patients. The manufacturer used this data stating that the estimates from this instrument were comparable to estimates using the EQ-5D.

The manufacturer did not find a utility value following an IC bleed. Therefore (for the post IC bleed health state), the manufacturer assumed that the utility would be similar to patients with a stroke and assumed a utility of 0.713 taken from Rivero-Arias et al.(2008)[67] because of the similarities in functional outcomes after a stroke or IC bleed.[71] The utility value was estimated using the EQ-5D in a sample of 1,283 people who had experienced stroke or transient ischemic attacks measured over two years.[67]

In addition, the manufacturer also identified a study reporting a decrease in utility for patients attending an anticoagulation clinic treated with warfarin or LMWH. [72] However, no reduction in QoL was assumed in the basecase economic model.

The manufacturer did not assume a reduction in QoL for patients experiencing a minor bleed event.

Health state utility values and the duration used in the economic model are summarised in Table 29.

Table 29: Health state utility values used in the cost-effectiveness evaluation (Adaptation from Table 46, p. 134, MS,[1] November 2011)

Model state	Point estimate	Adjustments to utility norm due to modelled events	Source	Duration
Population norm	0.825	NA	Kind 1998[66]	NA
Post IC bleed	0.71	NA	Rivero-Arias 2010[67]	Chronic
CTEPH	0.56	NA	Meads 2008[70]	Chronic
DVT	0.729	0.884[d]	Derived from Locadia et al. (2004)[68] and Kind et al.(1998)[66]	1 month
PE	0.547	0.663		1 month
EC bleed	0.287	0.684		1 month
IC bleed	0.564	0.347		3 months
PTS	0.767	0.930	Derived from Lenert et al.(1997)[69] and Kind et al.(1998)[66]	Chronic

The utility decrements for patients experiencing a DVT, PE or a major EC bleed event was assumed to last a month in line with the assumption used in NICE CG92.[18] The utility decrement for patients with an IC bleed event was assumed to last three months. Other events were assumed to be chronic. Finally, health state utility values were assumed to be constant over time, i.e. no variation by age.

The ERG is generally satisfied with the assumptions made by the manufacturer to value the different health states. A systematic review of the literature was conducted to identify potential sources of evidence and this appears to be of reasonable quality; however, the ERG did not replicate the systematic review due to time and resource constraints. The manufacturer assumed that the utilities for the IC and EC bleed health states were identical to GI bleeds and haemorrhagic stroke respectively. The manufacturer also used data from different studies that used different methods to value the different health states. Whilst this is not very robust, the ERG acknowledges that all the evidence was not available from one study, conforming to the NICE reference case (using EQ-5D and time trade off estimated from the general population).

[d] Locadia quoted a population norm (own health) as 0.95 (95% CI 0.81-1.00) and therefore further adjustment was applied to the values reported in the study, multiplying by 0.825/0.95

The health state utility value for patients experiencing an IC bleed was derived from Locadia et al. (2004)[68] whilst the utility value for the post IC bleed health state was taken from Rivero-Arias et al. (2010)[67] Clarification was requested from the manufacturer on the choice of these studies, and a justification why other sources were not considered, such as data from O'Meara et al.[73] (0.29) or Meenan et al.[74] (0.62).

In response to the ERG comments, the manufacturer stated that the O'Meara et al.(1994)[73] and Meenan et al.[74] studies had limitations and that the utility values used in the economic model for the IC bleed health state derived from Locadia et al.(2004)[68] were more robust. The main criticism of these studies were that the O'Meara study[73] included only 36 patients and that the utility values were elicited using the standard gamble and did not differentiate utility by severity of IC bleeds. Likewise, the manufacturer rejected the Meenan et al.[74] study as it was unclear which elicitation technique was used. Utility values were also elicited from US patients, and there were uncertainties whether differentiation of minor and severe IC bleed was undertaken according to mRS. The manufacturer examined the impact on the ICER using different utility values (0.299 – 0.82) and reported that the conclusions remained unchanged.

Furthermore, the ERG requested that the manufacturer clarify its choice of using a utility value of 0.71 for the post IC bleed health state. In response to the ERG, the manufacturer commented that 65% of survivors were found to be functionally independent (mRS 0-2) one year post-ischaemic stroke, compared with 68% of intra-cerebral bleed survivors, and that there were no significant difference in functional status between ischaemic stroke and all intracranial haemorrhage (odds ratio 0.74, 0.37-1.48).[71] Therefore, data from Rivero-Arias et al.(2010)[67] was used to represent the post IC bleed health state. In this study, 74% of patients were considered to be independent 2 years post event, and 26% were dependent. The manufacturer explains the possible differences in functional status by the longer follow-up period. The manufacturer also state that the same utility as the IC bleed health state (0.33) was not used to be conservative.

The ERG is satisfied with the responses from the manufacturer. However, the ERG disagrees with the statement that a higher utility for the post IC bleed state is necessarily a conservative approach as this will be dependent on whether rivaroxaban is more efficacious at preventing major IC bleeding events or not.

5.2.1.10 Cancer subgroup analysis

In its original submission to NICE[1] the manufacturer did not provide a formal cost-effectiveness analysis for the subgroup of patients with cancer, but presented a cost-minimisation analysis on the basis that there were an absence of significant differences and because of statistical and clinical heterogeneity in the study populations and designs.

The ERG requested the manufacturer to conduct an exploratory analysis and to provide an indicative ICER for rivaroxaban compared with LMWH in the cancer subgroup population, if possible, using the existing model framework. The manufacturer responded positively to the ERG request and provided an exploratory analysis in cancer patients using outputs from the MTC described above (Section 4.4). Patients with cancer were assumed to be treated for 6 months only. However, note that some patients were treated for a shorter duration in the included studies for the MTC.

In order to estimate the cost-effectiveness of rivaroxaban against LMWH in cancer patients, the manufacturer amended the economic model and made the following assumptions:

- The manufacturer re-used the risk of events from the rivaroxaban arm calculated from the primary analysis in the whole population treated for six months (this included both patients with and without cancer) and assumed this to be the baseline risk of events before adjustment for the increase risk of events in the cancer vs. non cancer patients.
- The baseline risk of events from the rivaroxaban arm is then adjusted to reflect the increased risk of events among cancer patients vs. non cancer patients, adjusted for the prevalence of cancer in the baseline data (assumed to be 6%) as cancer patients were included in the EINSTEIN-DVT trial. The manufacturer calculated the HR/RR for the risk of events between the whole population (including cancer and non cancer patients) and patients with cancer.
    - The estimated the HR/RR for the risk of events for the whole trial population vs. cancer patients to be:

    - Because the HR/RR calculated above included cancer patients, the manufacturer adjusted the HR/RR used in the economic model for the prevalence of cancer patients in the baseline data. The adjusted HR/RR are presented below:

- Once the manufacturer calculated the baseline risk of events for patients treated with rivaroxaban, the next step was to estimate the risk of events for patients treated with LMWH. This was done by applying a HR/RR to the baseline risk of events. The manufacturer conducted an MTC in the absence of direct evidence and applied the reciprocated HR/RR for rivaroxaban vs. LMWH in the economic model to estimate the risk of events in LMWH patients. The HR/RR were calculated from the median and assuming a between study variability of U(0,5).
- Before inversion, the HR/RRs for rivaroxaban against LMWH were:
    - VTE recurrence: HR of 1.440 (95% CI 0.070 to 31.400)
    - Major bleeding: HR of 0.640 (95% CI 0.010 to 30.100)
    - CRNM bleeding: RR of 1.320 (95% CI 0.090 to 18.700)
- The manufacturer assumed that cancer patients are treated with LMWH only (dalteparin) and did not include monitoring costs.
- The manufacturer also included some costs associated with transportation and administration by district nurses for patients treated with LMWH.
- Finally, the manufacturer assumed a median survival of 5 years for cancer patients based on data from Rachet et al (2010)[75] to reflect the poorer prognosis (lower life expectancy) of patients with cancer.

The ERG acknowledges the positive response from the manufacturer and the efforts made to provide an exploratory analysis in the subgroup of patients with cancer. Nevertheless, the ERG has some concerns with the approach used by the manufacturer and the robustness of the analysis.

1) The ERG has some concerns on the robustness of the estimated treatment effect (taken from the MTC conducted by the manufacturer). As previously described (Section 4.4), the manufacturer used a uniform prior distribution for the between-study standard deviation of U(0,5) when synthesising hazard ratios and odds ratios in the MTC. The ERG believes that a smaller between-study standard deviation is more appropriate, such as U(0,2) or U(0,0.6).
2) In addition, the manufacturer used the treatment effect calculated from the median instead of the mean, which is believed to be more appropriate by the ERG in an economic evaluation.

The medians of the posterior distributions are less affected because medians tend not to be influenced by extreme values. This was examined by the ERG in a scenario analysis presented in Section 6. The ERG showed using the mean, rivaroxaban was no longer associated with a gain in QALYs.

3) There are also concerns with the approach used by the manufacturer to characterise the uncertainty in the economic model for patients with cancer. Indeed, the manufacturer sampled the treatment effect (HR/RR) using an arbitrary lognormal distribution, assuming no correlation with the baseline risk of events, instead of using the correlated samples from the joint posterior distribution. For information, the ERG compared the mean treatment effect taken from the MTC (calculated by the ERG) with the mean treatment effect calculated in the economic model (over 5,000 iterations in the PSA). The analysis showed that there were some inconsistencies. The mean OR for major bleedings was estimated to be 928.1 using results from the MTC assuming a between study variability of U(0,5) as used by the manufacturer. The mean OR calculated in the economic model over 5,000 iterations was 5.2.

4) The manufacturer used rivaroxaban for the baseline risk of events and applied a HR/OR to estimate the risk of events in cancer patients treated with LMWH. Whilst this may be reasonable approach, the ERG has some concerns that results are biased toward the rivaroxaban arm given the concerns regarding the outputs of the MTC, and the approach used by the manufacturer to sample the treatment effect (use of arbitrary lognormal) described above. In the economic model, the HR/ORs were sampled within extreme values (for example between 0.01 and 378.85 for VTEs and between 0.0004 and 406.08 for major bleedings, calculated over 5,000 iterations). However, because rivaroxaban was used for the baseline risk of events, large gains in QALYs (rivaroxaban vs. LMWH) can be expected when the treatment effect is varied at the lower 95% CI (i.e. increase in risk of events for patients treated with LMWH). On the contrary, only small gains are possible for LMWH when the treatment effect is varied at the upper 95% CI (i.e. reduction in the risk of events in patients treated with LMWH). For illustration, let's assume that the baseline risk of events in the rivaroxaban arm is 5%. Using a HR of 0.1 (rivaroxaban vs. LMWH), the risk of events for patients treated with LMWH will be about 40.13% (i.e. an absolute increase of 35.13% compared with rivaroxaban). If the HR for rivaroxaban against LMWH is 10 (i.e. rivaroxaban is associated with poorer outcomes compared with LMWH), the risk of events for the LMWH arm will be about 0.51% (i.e. an absolute reduction of 4.49% compared with rivaroxaban).

5) There were also inconsistencies in the economic model, with the sum of the transition probabilities over 1 possible in the PSA. This is due to the absence of correlation in the model, issues with the MTC, the arbitrary lognormal distribution and the absence of constraints in the current model structure. This led to negative values in the LMWH arm in

few occasions for both VTEs and bleedings (For example 2.4% over 5,000 iterations for VTEs).

6) There was also an error in Sheet "[redacted] The cell was linked to the wrong cell. This was not in favour of rivaroxaban, as part of the administration costs for LMWH were missed.

7) The analysis in the subgroup of cancer patients relies on several assumptions. Data not specific to cancer patients were used for the risk of events once treatment cease; it is unclear if this is appropriate. The ERG did not conduct a systematic review of the literature, but found a study showing that the probability of readmission for VTEs within 6 months was almost four times higher among Medicare patients with cancer than among Medicare patients without malignancy.[76]

8) The manufacturer assumed a median life expectancy of 5 years; however it is unclear if this reflects the life expectancy of patients with a DVT.

9) It is also unclear what the risk of events in cancer patients is. The manufacturer re-used results from the main analysis and adjusted the risk for the increased risk in cancer vs. non cancer patients. It is unclear whether the estimate from the manufacturer reflect the baseline risk of events.

10) The manufacturer also assumed the same baseline utility value and impact on Qol in the general population and patients with cancer. It is likely that the baseline utility value is different between cancer vs. non cancer patients. VTEs might also affect differently cancer patients.

Overall, the ERG has some concerns with the accuracy of the exploratory analysis conducted by the manufacturer in cancer patients. Whilst the ERG acknowledges that this is an exploratory analysis, the ERG does not believe results of this analysis to be robust.

5.2.1.11. Sensitivity analysis

The manufacturer conducted a series of one-way deterministic sensitivity analyses. The probabilities of clinical events on dual LMWH/VKA therapy and treatment effects in relation to efficacy and safety variables for rivaroxaban vs. dual LMWH/VKA therapy were varied by using the upper and lower 95% CI values. Utility values were set at upper and lower 95% CI values or, where these were not available, the interquartile (IQR). Resource usages were also varied in SA. Unit costs were varied by ±30% and discounting ranged between 0% to 6%. The time horizon was also varied from lifetime to 5 years. Assumptions about the monitoring were also explored varying the setting of care (primary/secondary/hybrid). The MS also varied the mean baseline age from 46 years to 66 years.

In addition to the above, the manufacturer also conducted a series of multivariate, deterministic sensitivity analyses, varying several parameters at the same time. Analyses conducted are presented in Table 30.

Table 30: Multivariate SA conducted by the manufacturer (reproduction of Table 53, p. 158, MS,[1] November 2011)

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 for the probability of death with event
State-related utility weightings (all parameters)	All utility parameters
VKA OAC monitoring	Parameters for VKA drug monitoring

5.2.1.12. Probabilistic Sensitivity analysis

The manufacturer conducted PSA over 1,000 iterations. The manufacturer varied the probabilities for dual LMWH/VKA therapy of recurrent VTEs, major bleeds, CRNM bleeds and all other clinical events, according to Beta distributions. The treatment effects in relation to efficacy and safety variables for rivaroxaban vs. dual LMWH/VKA therapy were sampled from a lognormal distribution. Utilities were sampled according to Beta distributions using the 95% CI or IQR where available. Unit costs were sampled according to Gamma distributions with means equal to the point estimates and standard errors assumed to be equal to 30% of those means.

The ERG has some serious concerns with the PSA conducted by the manufacturer, notably in cancer patients;

1) The manufacturer sampled the unit costs assuming an arbitrary 30% standard error around the mean. It is unclear why the unit costs from the NHS reference costs were not sampled with the standard error calculated from the IQR for example.

2) the values used in the PSA for the Beta distribution (alpha, beta) are incorrect where no events were observed, and the ERG would recommend an uninformative prior to be used (for example adding 0.5 to both the alpha and beta value).

3) In its original submission to NICE, the manufacturer sampled all clinical parameters independently. Clarification was requested from the manufacturer as to why correlation was not included and whether an analysis of correlation was undertaken. In response, the manufacturer has undertaken two exploratory PSAs to assess the potential impact of assuming differing degrees of correlation between the risks of VTEs and bleedings by using identical random draws used to sample from the same tails of correlated distributions (positive correlation) or by using identical random draws used to sample from opposite tails of correlated distributions (negative correlation). Whilst the ERG acknowledges the response from the manufacturer, some issues remains.

11) There are also some concerns with the approach used by the manufacturer to characterise the uncertainty in the economic model. Indeed, the manufacturer sampled the treatment effect (HR/RR) using an arbitrary lognormal distribution, assuming no correlation with the baseline risk of events, instead of using the samples from the joint posterior distribution. For information, the ERG compared the mean treatment effect taken from the MTC (calculated by the ERG) with the mean treatment effect calculated in the economic model over 5,000 iterations in the PSA. The analysis showed that there were some inconsistencies. The mean OR for major bleedings was estimated to be 928.1 using results from the MTC assuming a between study variability of U(0,5) as used by the manufacturer. The mean OR calculated in the economic model over 5,000 iterations was 5.2.

12) In addition, the manufacturer used a between study variability of U(0,5) increasing the uncertainty in the data. The ERG believes that a smaller between study variability such as U(0,2) or U(0,0.6) is more appropriate.

13) There were also inconsistencies in the economic model, with the sum of the transition probabilities over 1 possible in the PSA. This is due to the absence of correlation in the model, issues with the MTC, the arbitrary lognormal distribution and the absence of constraints in the current model structure. This led to negative values in the LMWH arm in few occasions for both VTEs and bleedings (For example 2.4% over 5,000 iterations for VTEs).

Overall, the ERG has some concerns with the PSA undertaken by the manufacturer, notably for the cancer subgroup analysis. Due to time and resource constraints, the PSAs were not amended.

5.2.1.13. Model validation

The manufacturer stated that the economic model has been assured through internal and external validation.

The manufacturer stated that the internal validity was ensured by quality control of the model by the model developers, as well as a model audit performed by an external health economist.

The MS also reported that an extensive external validation was undertaken in consultation with experts in DVT treatment, and comparing outputs of the model with the EINSTEIN-DVT trial and other sources.

Despite the validation and model checking conducted by the manufacturer, the ERG identified some errors/inconsistencies in the economic model. These are described below:

- In the reporting of outputs, the number of bleeding events was inverted between the two arms (error in [redacted] This had no impact on the results.
- The risk ratio for CRNM bleeding events was used as a hazard ratio in the economic model [redacted] but this had almost no impact on the ICER after correction by the ERG.
- There was a discrepancy between the economic model and the report, as the manufacturer stated that [redacted] of patients discontinued treatment after an EC bleed, but used [redacted] in the economic model.
- There was a discrepancy between the economic model and the report, as the manufacturer stated that 8.55% of patients treated in clinic required transportation, but used 7.5% in the economic model.
- There was a discrepancy for the cost of CTEPH between the economic model and the report.
- There was an error in Sheet "[redacted]. The cell was linked to the wrong cell.
- An error was also identified by the ERG, in that the probability of PE recurrences after the first year was incorrectly divided by 4 ([redacted]
- there were also inconsistencies in the economic model, with the sum of the transition probabilities over 1 over few iterations in the PSA, due to the absence of constraints and correlation. This lead to negative values for the LMWH arm in 2.4% of iteration in the subgroup analysis.

None of the errors identified had a significant impact on the results.

5.2.1 Results included in the manufacturer's submission

The MS included two analyses:

- the primary analysis conducted in the whole trial population, by intended treatment duration,
- a cost-minimisation analysis and an exploratory cost-effectiveness analysis in a subgroup of patients with cancer.

This section of the report summarise the results presented by the manufacturer. Limitations of these analyses are discussed in Section 5.2. The additional analyses undertaken by the ERG is described in Section 6.

5.2.2.1 Primary analysis – whole trial population

In its original submission to NICE, the manufacturer provided separate cost-effectiveness analyses for patients treated with rivaroxaban against dual therapy LMWH/VKA for the three intended treatment duration (3, 6 or 12 months) using effectiveness data from the whole trial population, irrespective of the intended treatment duration (Section 5.1).[1] In addition to those, the ERG requested analyses to be conducted using data specific to the intended treatment duration and using different time horizons.

5.2.2.1.1. Results for patients for whom three months of anticoagulation treatment is appropriate

Using a lifetime horizon, the manufacturer reported that rivaroxaban was dominant (i.e. provided more QALYs at a lower cost) compared with dual therapy LMWH/VKA in patients treated for three months, using data by intended treatment duration, or estimated from the whole trial population (Table 31).

Using data by intended treatment duration, the rivaroxaban strategy was less costly (savings of £218.05) but also provided more QALYs (0.0015) compared with dual therapy LMWH/VKA. [redacted]

Table 31: Cost-effectiveness results for patients for whom three months of anticoagulation is appropriate (reproduction of Table 14, p. 30, Clarification letter[17] December 2011)

Time horizon	Treatment	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£)
Duration specific						
3 months						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
1 year						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
Lifetime						
	RIV	1,138.08	13.3373	-	-	-
	LMWH/VKA	1,356.13	13.3358	-218.05	0.0015	Dominated*

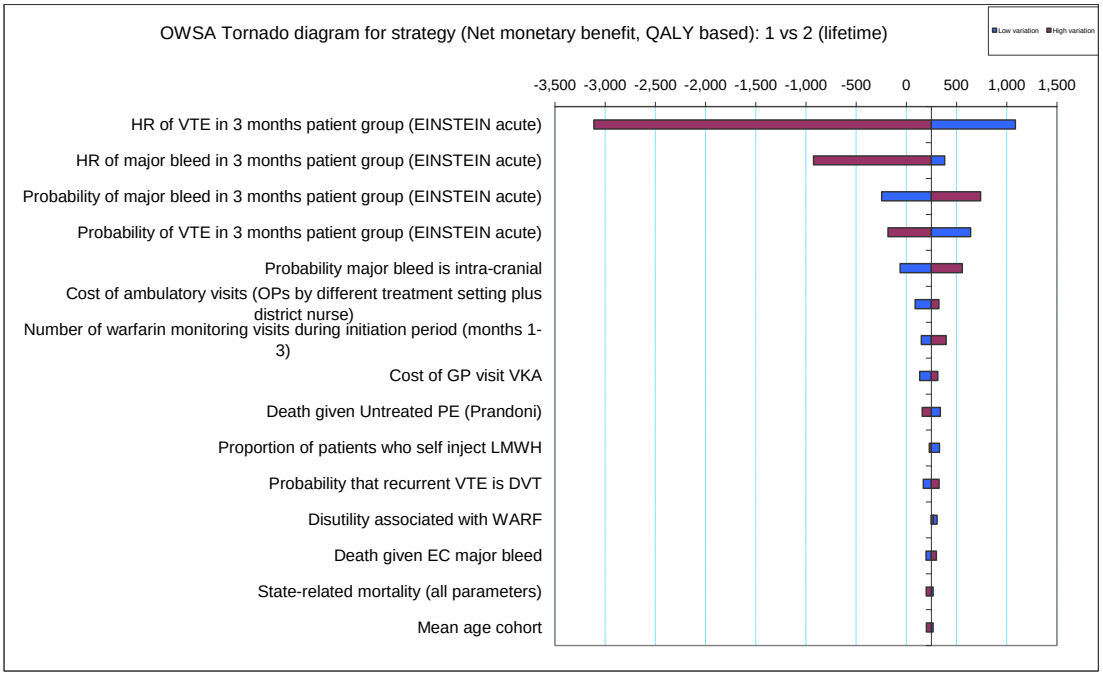
Whole study						
3 months						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
1 year						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
Lifetime						
	RIV	1,135.24	13.3481	-	-	-
	LMWH/VKA	1,298.09	13.3251	-162.85	0.0230	Dominated*

* dual therapy LMWH/VKA is dominated compared with rivaroxaban.

Figure 8 shows the 15 most sensitive parameters using the net monetary benefit (NMB) measure at a willingness to pay (WTP) of £20,000 per QALY gained using data specific to patients treated for 3 months and assuming a lifetime horizon. The analysis showed that rivaroxaban is no longer cost-effective at a WTP threshold of £20,000 per QALY gained when setting:

- the treatment effect (HR) of rivaroxaban for VTE recurrences at the upper 95% CI
- the probability of VTE recurrences (baseline risk of events) at the upper 95% CI
- the treatment effect (HR) of rivaroxaban for major bleedings at the upper 95% CI
- the probability of major bleed (baseline risk of events) at the lower 95% CI
- the probability of a major bleed being intra-cranial (baseline risk of events) at the lower 95% CI.

Figure 8: Tornado plot - Net Monetary Benefit of rivaroxaban vs. LMWH/VKA, 3 months of treatment, lifetime horizon, duration specific inputs (reproduction of Figure 3, p. 31, Clarification letter[17] December 2011)



Results for the PSA were run over 1,000 iterations, using effectiveness data specific to patients treated for 3 months under a lifetime horizon are presented in Figure 9 for the cost-effectiveness plane and Figure 10 for the cost effectiveness acceptability curve (CEAC).

The manufacturer reported that rivaroxaban had a 58.4% chance of being cost-effective at a WTP of £20,000 per QALY gained. Rivaroxaban was dominant (provided more QALYs at a lower cost) in 48.5% of cases and was dominated (provided less QALYs at a higher cost) in 6.4% of iterations.

Figure 9: Cost-effectiveness plane, rivaroxaban vs. LMWH/VKA, 3 months of anticoagulation treatment, lifetime horizon, duration specific inputs (reproduction of Figure 4, p. 32, Clarification letter[17] December 2011)

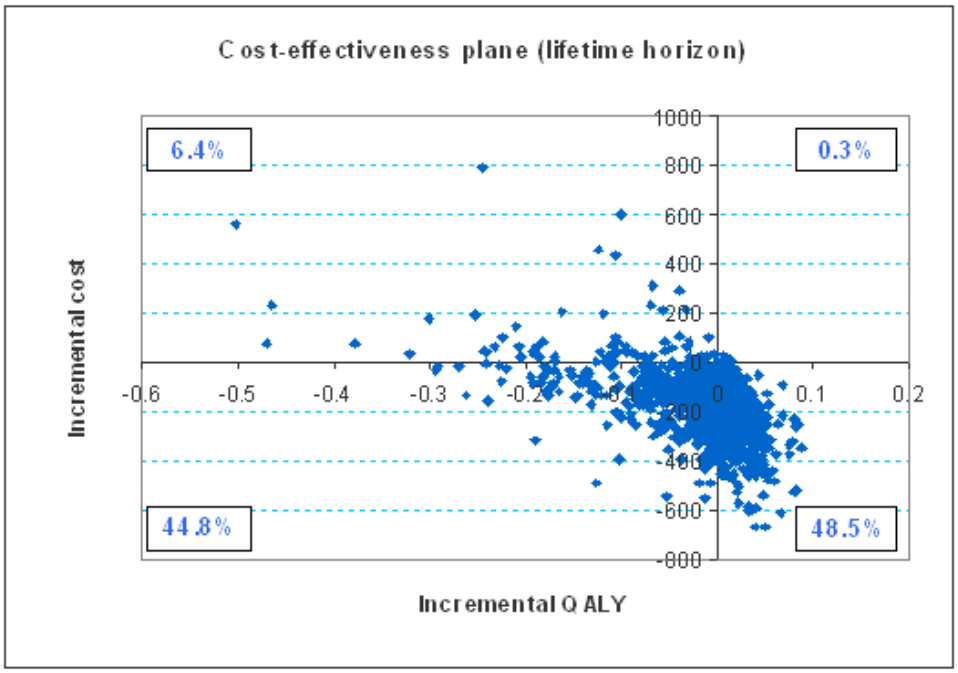
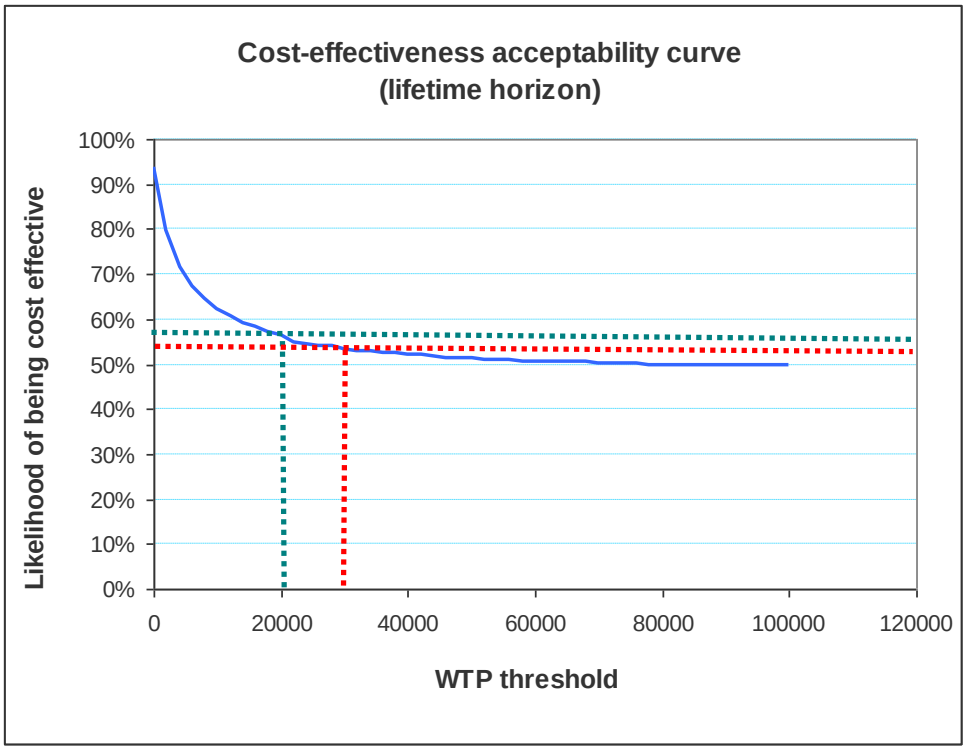


Figure 10: CEAC, rivaroxaban vs. LMWH/VKA, 3 months of anticoagulation treatment, lifetime horizon, duration specific inputs (reproduction of Figure 5, p. 32, Clarification letter[17] December 2011)



5.2.2.1.2. Results for patients for whom six months of anticoagulation treatment is appropriate

Using a lifetime horizon, the manufacturer reported that rivaroxaban was dominant (i.e. provided more QALYs at a lower cost) compared with dual therapy LMWH/VKA in patients treated for six months, using data by intended treatment duration, or estimated from the whole trial population (Table 32).

Using data by intended treatment duration, the rivaroxaban strategy was less costly (savings of £110.10) but also provided more QALYs (0.0108) compared with dual therapy LMWH/VKA. [redacted]

Table 32: Cost-effectiveness results for patients for whom six months of anticoagulation is appropriate (reproduction of Table 15, p. 33, Clarification letter[17] December 2011)

Time horizon	Treatment	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£)
Duration specific						
6 months						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
1 year						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
Lifetime						
	RIV	1,339.55	13.3581	-	-	-
	LMWH/VKA	1,449.66	13.3473	-110.10	0.0108	Dominated*
Whole study						
6 months						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
1 year						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
Lifetime						
	RIV	1,318.20	13.3647	-	-	-
	LMWH/VKA	1,442.42	13.3446	-124.22	0.0201	Dominated*

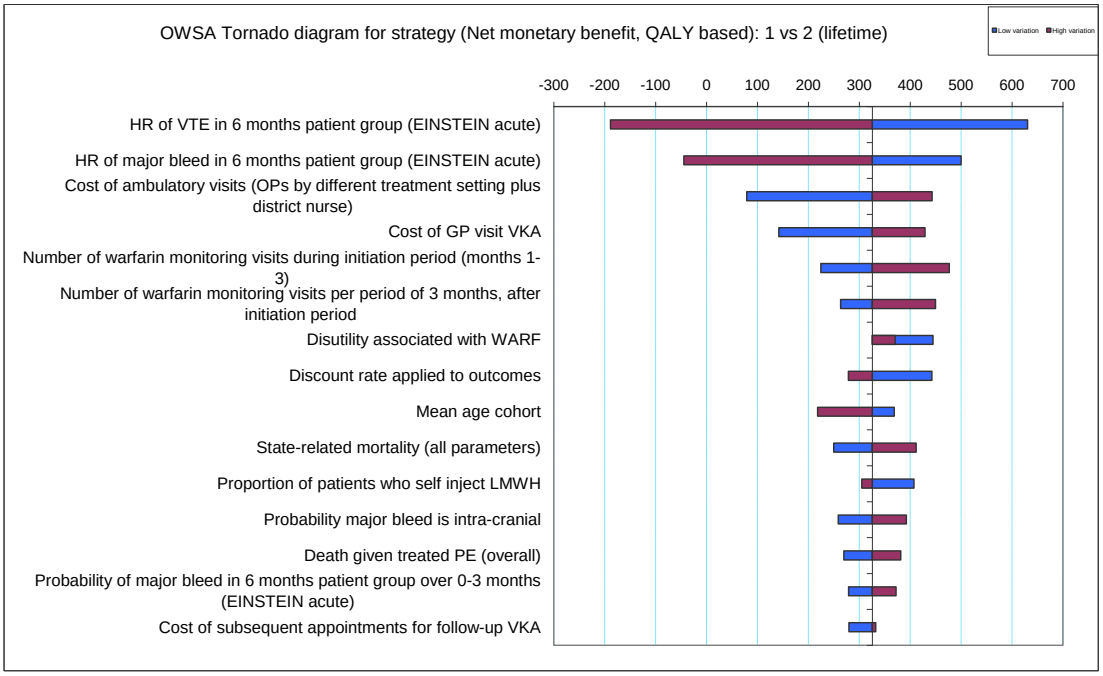
* dual therapy LMWH/VKA is dominated compared with rivaroxaban.

Figure 11 shows the 15 most sensitive parameters using the NMB measure at a WTP of £20,000 per QALY gained using data specific to patients treated for six months and assuming a lifetime horizon. The analysis showed that rivaroxaban is no longer cost-effective at a WTP threshold of £20,000 per QALY gained when setting:

- the treatment effect (HR) of rivaroxaban for VTE recurrences at the upper 95% CI

- the treatment effect (HR) of rivaroxaban for major bleedings at the upper 95% CI

Figure 11: Tornado plot - Net Monetary Benefit of rivaroxaban vs. LMWH/VKA, 6 months of treatment, lifetime horizon, duration specific inputs (reproduction of Figure 6, p. 34, Clarification letter[17] December 2011)



Results for the PSA were run over 1,000 iterations, using effectiveness data specific to patients treated for 6 months under a lifetime horizon are presented in Figure 12 for the cost-effectiveness plane and Figure 13 for the CEAC.

The manufacturer reported that rivaroxaban had a 85.0% chance of being cost-effective at a WTP of £20,000 per QALY gained. Rivaroxaban was dominant (provided more QALYs at a lower cost) in 68.7% of cases and was dominated (provided less QALYs at a higher cost) in 6.4% of iterations.

Figure 12: Cost-effectiveness plane, rivaroxaban vs. LMWH/VKA, 6 months of anticoagulation treatment, lifetime horizon, duration specific inputs (reproduction of Figure 7, p. 35, Clarification letter[17] December 2011)

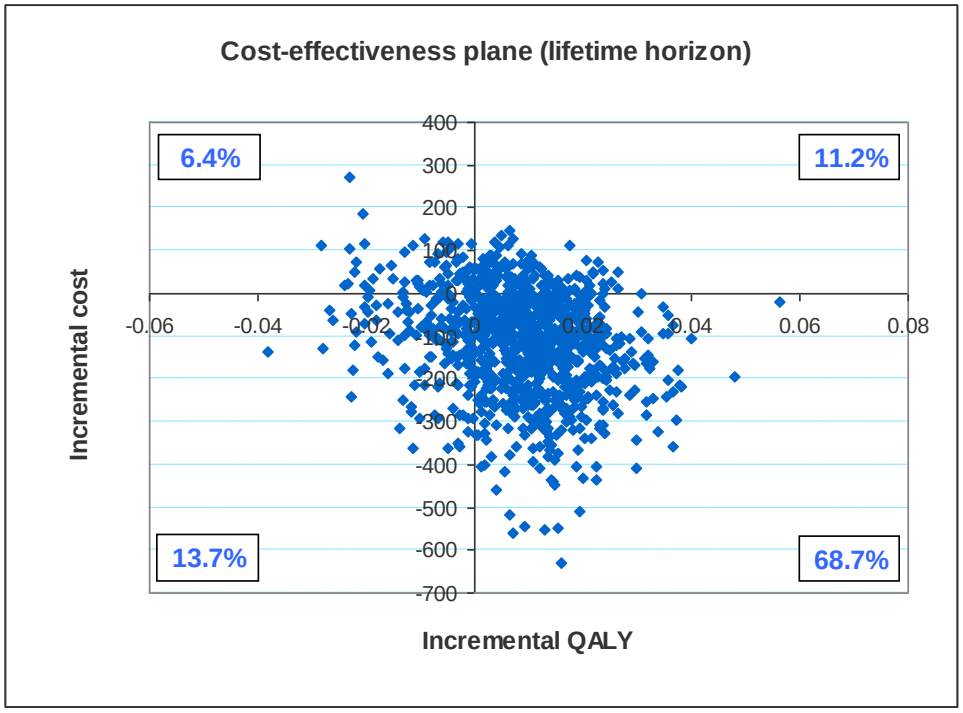
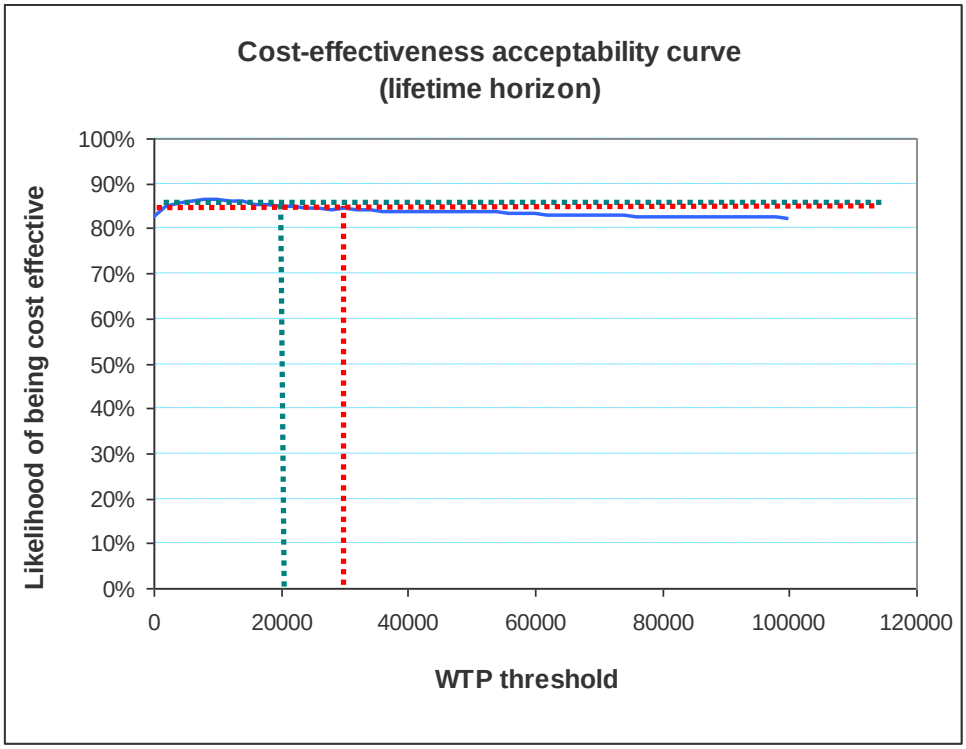


Figure 13: CEAC, rivaroxaban vs. LMWH/VKA, 6 months of anticoagulation treatment, lifetime horizon, duration specific inputs (reproduction of Figure 8, p. 35, Clarification letter[17] December 2011)



5.2.2.1.2. Results for patients for whom twelve months of anticoagulation is appropriate

Using a lifetime horizon, the manufacturer reported that rivaroxaban was dominant (i.e. provided more QALYs at a lower cost) compared with dual therapy LMWH/VKA in patients treated for 12 months, using data by intended treatment duration, or estimated from the whole trial population (Table 33).

Using data by intended treatment duration, the rivaroxaban strategy was less costly (savings of £37.39) but also provided more QALYs (0.0458) compared with dual therapy LMWH/VKA [redacted]

Table 33: Cost-effectiveness results for patients for whom 12 months of anticoagulation treatment is appropriate (reproduction of Table 16, p. 36, Clarification letter[17] December 2011)

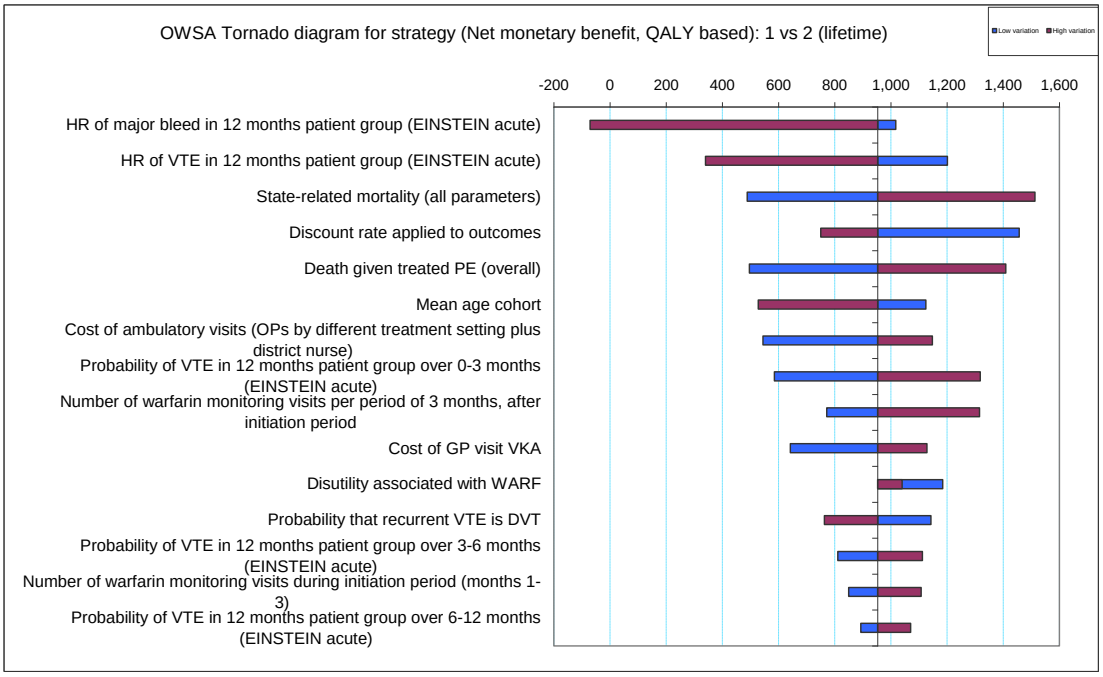
Time horizon	Treatment	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£)
Duration specific						
1 year						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
Lifetime						
	RIV	1,595.22	13.3969	-	-	-
	LMWH/VKA	1,632.61	13.3511	-37.39	0.0458	Dominated*
Whole study						
1 year						
	RIV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH/VKA					
Lifetime						
	RIV	1,643.08	13.3769	-	-	-
	LMWH/VKA	1,675.88	13.3565	-32.80	0.0205	Dominated*

* dual therapy LMWH/VKA is dominated compared with rivaroxaban.

Figure 14 shows the 15 most sensitive parameters using the NMB measure at a WTP of £20,000 per QALY gained using data specific to patients treated for 12 months and assuming a lifetime horizon. The analysis showed that rivaroxaban was no longer cost-effective at a WTP threshold of £20,000 per QALY gained when setting:

- the treatment effect (HR) of rivaroxaban for major bleedings at the upper 95% CI

Figure 14: Tornado plot - Net Monetary Benefit of rivaroxaban vs. LMWH/VKA, 12 months of treatment, lifetime horizon, duration specific inputs (reproduction of Figure 9, p. 36, Clarification letter[17] December 2011)



Results for the PSA were run over 1,000 iterations, using effectiveness data specific to patients treated for 12 months under a lifetime horizon are presented in Figure 15 for the cost-effectiveness plane and Figure 16 for the CEAC.

The manufacturer reported that rivaroxaban had a 95.4% chance of being cost-effective at a WTP of £20,000 per QALY gained. Rivaroxaban was dominant (provided more QALYs at a lower cost) in 48.8% of cases and was dominated (provided less QALYs at a higher cost) in 2.7% of iterations.

Figure 15: Cost-effectiveness plane, rivaroxaban vs. LMWH/VKA, 12 months of anticoagulation treatment, lifetime horizon, duration specific inputs (reproduction of Figure 10, p. 37, Clarification letter[17] December 2011)

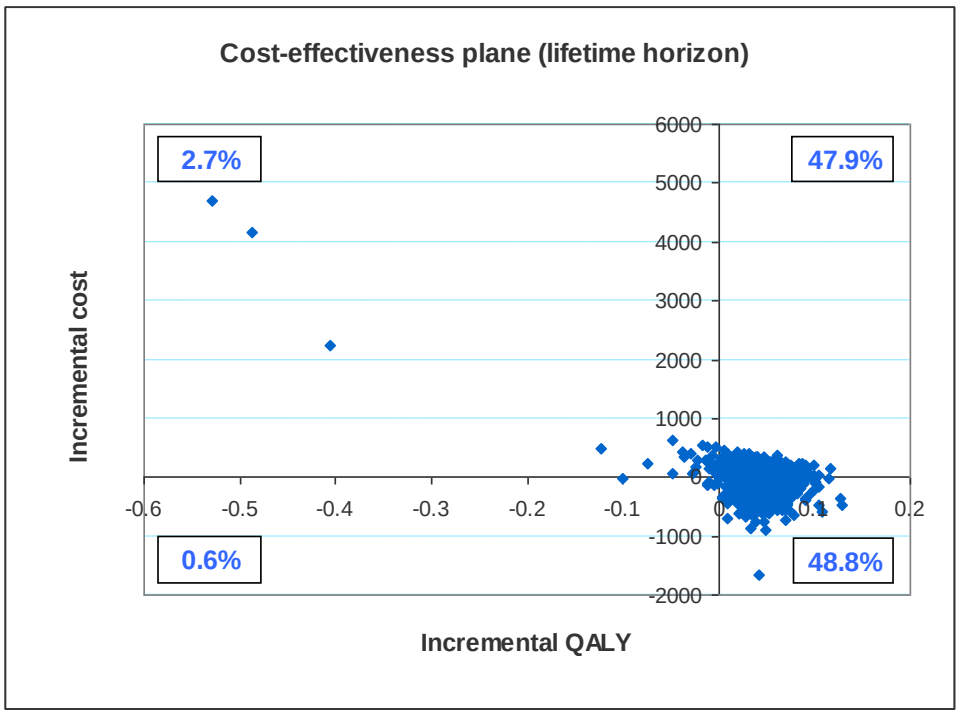
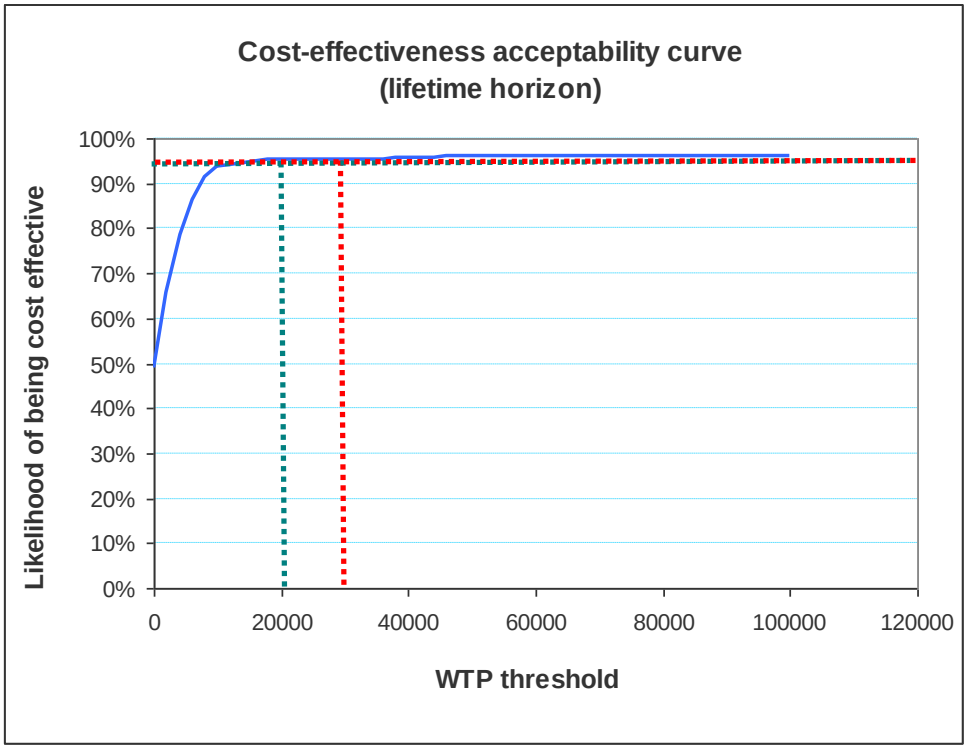


Figure 16: CEAC, rivaroxaban vs. LMWH/VKA, 12 months of anticoagulation treatment, lifetime horizon, duration specific inputs (reproduction of Figure 11, p. 38, Clarification letter[17] December 2011)



5.2.2.2 Subgroup analysis – cancer patients

In its original submission to NICE,[1] the manufacturer submitted a cost-minimisation analysis in a subgroup of patients with cancer treated for 6 months comparing rivaroxaban against LMWH only (dalteparin). In addition to this analysis, an exploratory cost-effectiveness analysis was requested by ERG.

5.2.2.2.1. Results for the cost-minimisation analysis in cancer patients treated for 6 months

The manufacturer presented a cost-minimisation analysis comparing patients treated over 6 months with rivaroxaban against dalteparin in the oncology setting. The manufacturer only included drug acquisition costs as cancer patients are assumed to be already frequently monitored and that the administration of dalteparin would not impose substantial additional burden outside of drug costs.

The manufacturer estimated that the use of rivaroxaban was associated with a savings of £904 compared with patients treated with LMWH (dalteparin).

Table 34: Cost minimisation of rivaroxaban vs. LMWH in the cancer subgroup (reproduction of Table 79, p. 209, MS[1] November 2011)

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

5.2.2.1.2. Results for patients for whom six months of anticoagulation treatment is appropriate

In the exploratory analysis conducted by the manufacturer, using a lifetime horizon, the manufacturer reported that rivaroxaban may be dominant compared with LMWH (dalteparin) in cancer patients treated for six months (Table 35). The manufacturer reported that rivaroxaban was less costly (savings of £1,085.38) but also provided more QALYs (0.0013) compared with LMWH (dalteparin). [redacted]

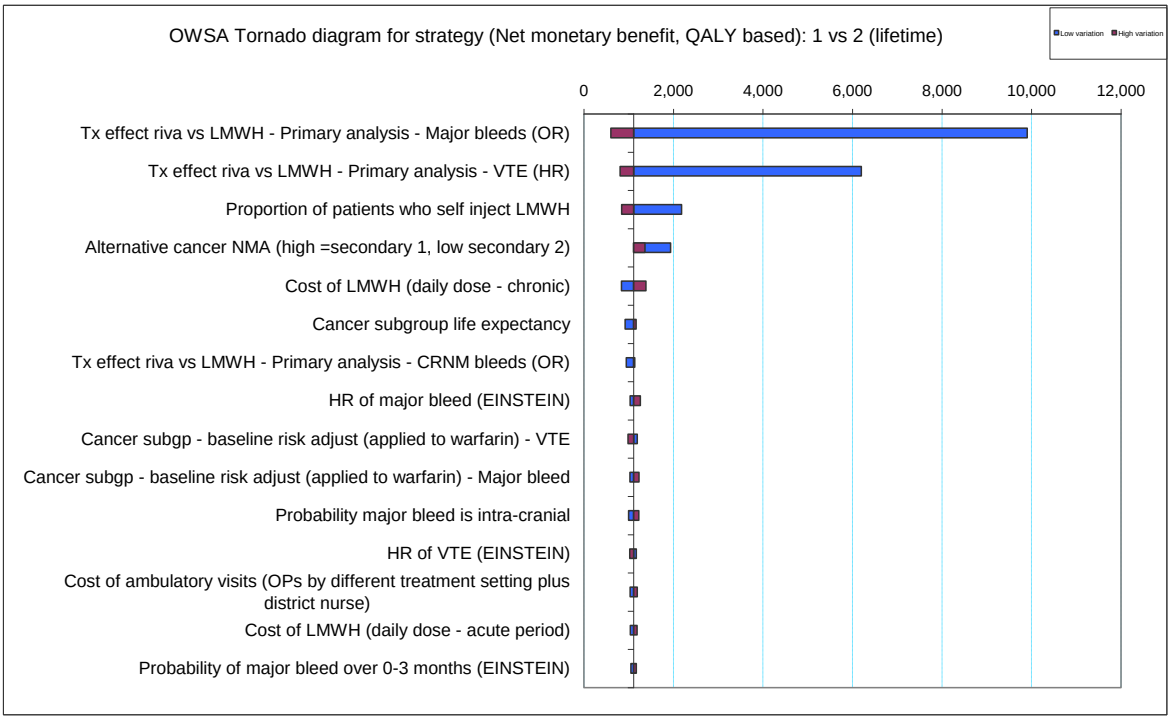
Table 35: indicative cost-effectiveness results for cancer patients for whom six months of anticoagulation treatment is appropriate (reproduction of Table 21, p. 42, Clarification letter[17] December 2011)

Time horizon and treatment	Total costs (£)	Total QALYs	Inc costs (£)	Inc QALYs	ICER (£)
6 months					
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year					
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lifetime					
Rivaroxaban	1,117.13	4.6799	-	-	-
LMWH	2,202.52	4.6786	-1,085.38	0.0013	Dominated*

* LMWH is dominated compared with rivaroxaban.

Figure 17 shows the 15 most sensitive parameters using the NMB measure at a WTP of £20,000 per QALY gained assuming a lifetime horizon. The analysis showed that rivaroxaban is cost-effective at a £20,000 per QALY gained threshold under all the scenarios examined (Figure 17).

Figure 17: Tornado plot - Net Monetary Benefit of rivaroxaban vs. LMWH/VKA, 6 months of treatment in cancer patients, lifetime horizon (reproduction of Figure 13, p. 43, Clarification letter[17] December 2011)



Results for the PSA were run over 1,000 iterations under a lifetime horizon are presented in Figure 18 for the cost-effectiveness plane and Figure 19 for the CEAC.

The manufacturer reported that rivaroxaban had a 95.0% chance of being cost-effective at a WTP of £20,000 per QALY gained. Rivaroxaban was dominant (provided more QALYs at a lower cost) in 61.5% of cases.

Figure 18: Cost-effectiveness plane, rivaroxaban vs. LMWH/VKA, 6 months of anticoagulation treatment in cancer patients, lifetime horizon, duration specific inputs (reproduction of Figure 14, p. 44, Clarification letter[17] December 2011)

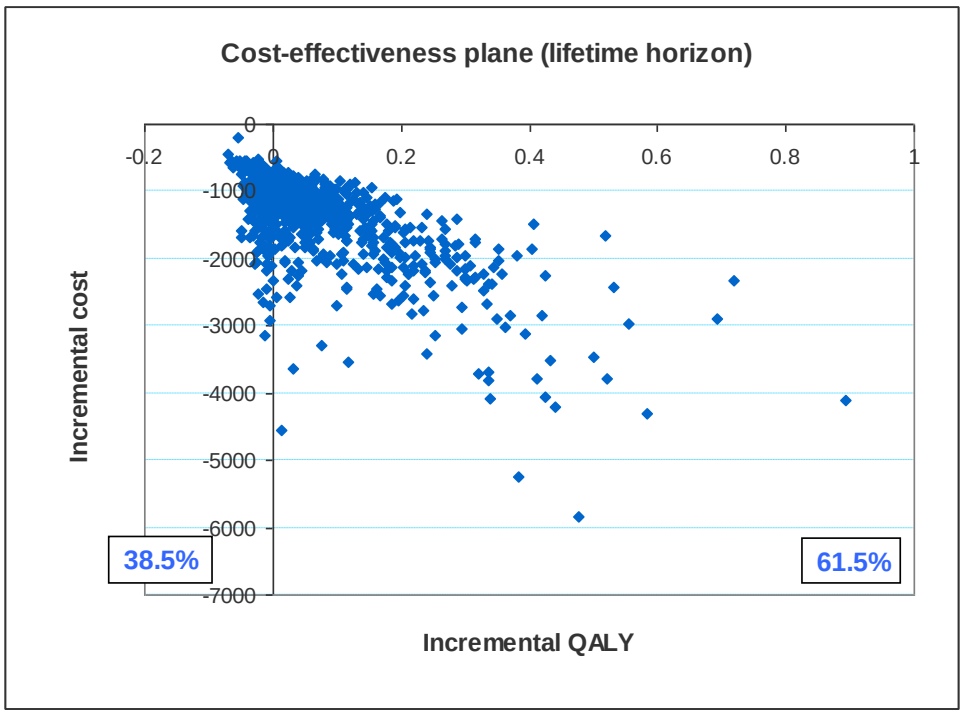
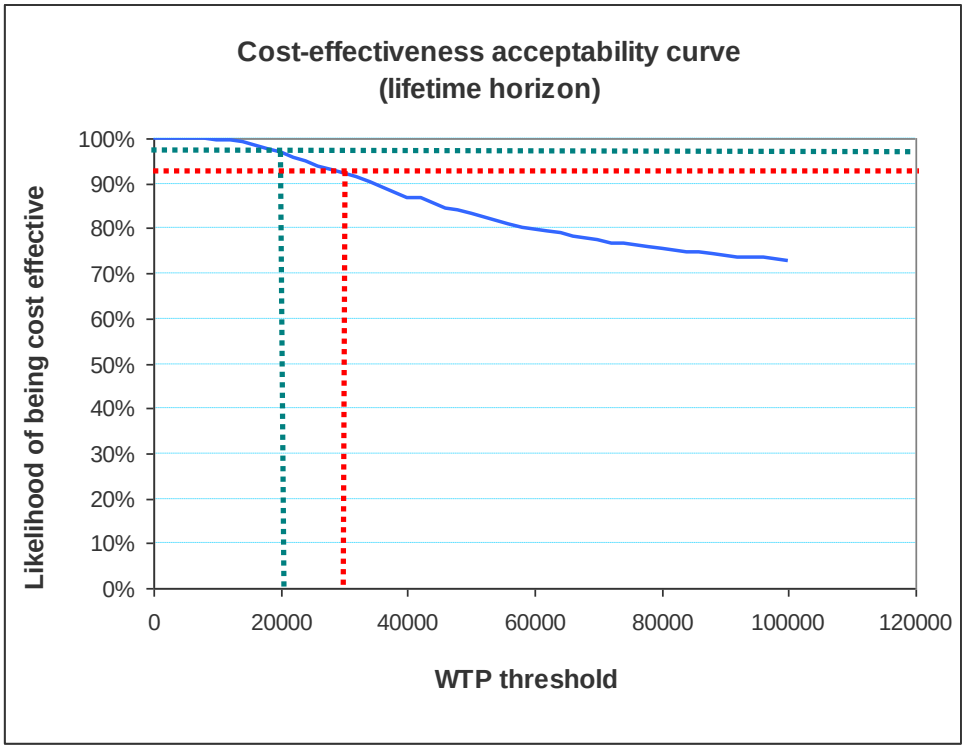


Figure 19: CEAC, rivaroxaban vs. LMWH/VKA, 6 months of anticoagulation treatment in cancer patients, lifetime horizon, duration specific inputs (reproduction of Figure 15, p. 44, Clarification letter[17] December 2011)



5.2.3 Comment on validity of results presented with reference to methodology used

In all the analyses conducted by the manufacturer, rivaroxaban was reported to be dominant i.e. led to a saving in costs, but also a gain in QALYs. Savings in costs were however small ranging from £38 to £218 (for the analyses using data by intended treatment duration). The gains in QALYs were similarly small, ranging from 0.0015 to 0.0458 compared with LMWH/VKA.

The ERG noted that the model is non-linear, and that rivaroxaban was no dominant in the PSA in patients treated for 3 months, but provided less QALYs at lower cost. The ICER of rivaroxaban compared with LMWH was £11,792 per QALY yielded in patients treated for 3 months. This has not been reported by the manufacturer. Rivaroxaban remained dominant (providing more QALYs at a lower cost) compared with LMWH/VKA in the PSA in patients treated for 6 and 12 months.

The ERG also noted that the model is based on a series of assumptions, but that there are uncertainties around some of the assumptions made which may impact the ICER due to the very small estimated gain in QALYs and saving in costs with the use of rivaroxaban compared with LMWH/VKA.

The ERG believes that results presented by the manufacturer may be plausible, but there are large uncertainties in the data and the assumptions that were made. The manufacturer estimated the INR monitoring cost to be around £656 annually for patients treated with a VKA. The ERG estimate was around £290 using inputs from our clinical advisors. Similarly, in their submission to this appraisal, the Northumberland PCT reported a value of £200 based on work done in AF. It is unclear what the "true" INR monitoring costs are for patients treated for VTE with a VKA.

There were disagreements within the ERG about the plausibility of assuming that the ratio of DVTs to PEs was independent of treatment received. The ERG sought clinical advice on this matter, and no plausible biological mechanism for a differential effect on DVTs and PEs was offered. [redacted]

The ERG also noted that other assumptions may impact the ICER such as whether the proportion of major bleeds that are IC bleeds are the same between treatment arms, or the assumptions made that the effectiveness is the same by treatment arm once treatment cease.

Finally, the manufacturer did not present an analysis for patients treated beyond 12 months, and only considered the use of rivaroxaban for the treatment of the index event; it is unclear why rivaroxaban was not considered for the treatment of the subsequent recurrences

The manufacturer presented an exploratory analysis in the cancer subgroup of patients following a request from the ERG. The ERG has concerns with this analysis and the validity of results presented by the manufacturer. The ERG did not find the analysis robust.

5.2.4 Summary of uncertainty and issues

Uncertainties and potential impact on results are summarised in Table 36.

Table 36: Summary of uncertainties

Summary of uncertainties	Has the impact on the ICER been examined?	If so, what are the results? If not, is it possible to give any indication of the direction of the results?
The original MS used data estimated from the whole trial population. Additional analyses were provided by the manufacturer following a request from the ERG using data on the baseline risk of events, and treatment effect by intended treatment duration. Is using data by intended treatment duration for the acute phase of treatment appropriate? Is it likely to change the ICER?	This has been formally examined by the manufacturer following a request from the ERG	Rivaroxaban remained dominant compared with LMWH/VKA in all the analyses provided by the manufacturer (primary analyses). The impact in terms of QALYs and Costs are described below; **3 months group** Using data by intended treatment duration, rivaroxaban was associated with a smaller gain in QALYs but a greater saving in costs compared with using data for the whole population. **6 months group** Using data by intended treatment duration, rivaroxaban was associated with a smaller gain in QALYs and a lower saving in costs compared with using data for the whole population. **12 months group** Using data by intended treatment duration, rivaroxaban was associated with a greater gain in QALYs and a greater saving in costs compared with using data for the whole population.
The manufacturer assumed that the proportions of VTEs that are PEs are the	This has been formally examined by the ERG, using data by initial treatment received	Results of these analyses are presented in section 6 of the ERG report.

Summary of uncertainties	Has the impact on the ICER been examined?	If so, what are the results? If not, is it possible to give any indication of the direction of the results?
same irrespective of the initial treatment received. [redacted] Is using data by initial treatment received (and possibly by intended treatment duration) more appropriate? Is it likely to change the conclusion?	only (not by intended treatment duration)	Assuming a different split DVTs/PEs by initial treatment received in the acute phase of treatment, rivaroxaban was no longer associated with a gain in QALYs in patients treated for 3 and 6 months. The ICER was above £20,000 per QALY gain in patients treated for 3 months when assuming a different split and rivaroxaban. The ICER was below £20,000 per QALY gain in patients treated for 6 months when assuming a different split for DVTs/PEs, although rivaroxaban was dominated when this assumption (different split) was combined with a different set of assumptions on INR monitoring costs. Rivaroxaban remains dominant compared with LMWH/VKA in patients treated for 12 months assuming a different split for DVTs/PEs. The ICER remains below £20,000 per QALY gained when this assumption (different split) was combined with a different set of assumptions on INR monitoring costs.

Summary of uncertainties	Has the impact on the ICER been examined?	If so, what are the results? If not, is it possible to give any indication of the direction of the results?
Similarly, the manufacturer assumed that the proportion of major bleeds that are IC bleeds are the same irrespective of the initial treatment received, but no data have been presented to support or reject this assumption. Is using data by initial treatment received (and possibly by intended treatment duration) more appropriate? Is it likely to change the conclusion?	This has not been formally examined by the ERG due to the absence of data.	The ICERs are likely to change, but no analyses were conducted due to the absence of data. **Indicative impact on the ICER:** Results will be biased in favour of the treatment that is associated with more IC bleeds (if any).
There are uncertainties about the INR monitoring for patients with VTE treated with a VKA in England and Wales. The manufacturer assumed 9 visits the first 3 months, and 5 visits thereafter. Clinical advisors to the ERG suggested a less intensive monitoring. What is the INR monitoring for VTE patients treated with a VKA in England and Wales? Is it likely to change the conclusion?	This has been formally examined by the ERG assuming 6 visits the first 3 months, and 3 visits thereafter.	Results of these analyses are presented in section 6. In patients treated for 3 months, rivaroxaban remained dominant amending the assumptions about monitoring only. The ICER was above £20,000 per QALY gained when this assumptions was amended (monitoring) in combination with assuming a different split DVTs/PEs. In patients treated for 6 months, rivaroxaban was no longer dominant amending the assumptions about monitoring only,

Summary of uncertainties	Has the impact on the ICER been examined?	If so, what are the results? If not, is it possible to give any indication of the direction of the results?
		but the ICER for rivaroxaban was below £20,000 per QALY gained compared with LMWH/VKA. Rivaroxaban was dominated when we amended this assumption (monitoring costs) in combination with the assumption of different split between DVTs/PEs. In patients treated for 12 months, the ICER for rivaroxaban was below £20,000 per QALY gained amending the assumption about monitoring.
Are the costs and utility used in the economic model appropriate? Several assumptions have been made by the manufacturer. Is it likely to change the conclusion?	This has been formally examined by the manufacturer in SA	Results were not sensitive to a change in costs and utilities in univariate sensitivity analysis. It is unclear whether the conclusions will change if parameters were varied simultaneously.
The manufacturer did not present an analysis in patients treated longer than 12 months.	This has not been formally examined due to the absence of data	**indicative impact on the ICER:** It is unclear whether the treatment effects of both rivaroxaban and LMWH/VKA will be sustained after 12 months. It is unclear on the effect on the ICER of modelling continued treatment.
The manufacturer assumed that patients were	This has not been formally examined.	**indicative impact on the ICER:**

Summary of uncertainties	Has the impact on the ICER been examined?	If so, what are the results? If not, is it possible to give any indication of the direction of the results?
treated for 6 months after a VTE recurrence. Clinical advisors to the ERG suggested that patients would be treated on an ongoing basis. Furthermore, the manufacturer assumed patients to receive 6 months of dual therapy LMWH/VKA after a recurrence. However, patients may be entitled to receive rivaroxaban.		It is unclear how this would affect the ICER. If treatment with rivaroxaban after a recurrence is cheaper and more effective, results will be favourable to the treatment that is associated with less recurrence.
Effectiveness data was assumed to be same by intended treatment duration and initial treatment received, after the acute phase of treatment	This has not been formally assessed in the absence of data	It is unclear how this will affect the results
The manufacturer assumed different split for DVTs/PEs and mortality rate from PEs in the acute phase of treatment and once treatment cease. It is unclear if this represents clinical practice?	This has not been formally examined, but the manufacturer varied the mortality rates from PEs in SA.	The manufacturer indicated that results were sensitive to these assumptions. Increasing the mortality rate from PEs will be against the treatment that is associated with more PEs.
The manufacturer presented an exploratory analysis in cancer patients. The manufacturer	This has not been formally examined	**indicative impact on the ICER:** If a higher risk of events is assumed, this will be against

Summary of uncertainties	Has the impact on the ICER been examined?	If so, what are the results? If not, is it possible to give any indication of the direction of the results?
used results from the rivaroxaban arm (from the main analysis) and adjusted the risk of events to reflect the increase in risk in cancer patients vs. non cancer patients using data from the EINSTEIN-DVT trial. It is unclear if this is representative of the risk of events in the cancer population?		rivaroxaban as outputs from the MTC indicated that rivaroxaban had poorer outcomes compared with LMWH.
In cancer patients, the treatment effects were taken from the MTC. The manufacturer used the median. The ERG believes that the mean HR/OR would be more appropriate. The manufacturer also used a between study variability of U (0,5). The ERG believes this to be high and believes that a between study variability of U(0,2) or U(0,0.6) is more appropriate. Furthermore, is the analysis robust? Is it likely to change the conclusions?	This has been partially examined by the ERG in an exploratory analysis using the mean treatment effect assuming a between study variability of U(0,5), U(0,2), U(0,0.6) The model relies on a series of assumptions and data not specific to cancer patients were used. It is unclear if these are appropriate.	Exploratory analyses was undertaken by the ERG using the mean treatment effect assuming a between study variability of U(0,5), U(0,2), U(0,0.6). Results are presented in section 6. It is unclear how a change in other assumptions would affect the ICER due to the absence of data.
Are results from the PSA robust?	This has not been formally examined due to time and resource constraints. Several issues	

Summary of uncertainties	Has the impact on the ICER been examined?	If so, what are the results? If not, is it possible to give any indication of the direction of the results?
	were identified (Section 5.2.1.12), notably for the subgroup of cancer patients.	

5.2.5 Conclusion of the economic section

The manufacturer reported that rivaroxaban was dominant in patients treated for 3, 6 or 12 months. However, in the PSA undertaken using the manufacturer's assumptions, the ERG found that rivaroxaban was not dominant in patients with an intended treatment duration of 3 months; these had an ICER of £11,792 per QALY yielded (after model correction). Rivaroxaban remained dominant (providing more QALYs at a lower cost) compared with LMWH/VKA in the PSA in patients treated for 6 and 12 months.

The ERG believes that assumptions made by the manufacturer to be plausible, however, other plausible assumptions exist, given the uncertainties within the decision problem which may impact the ICER.

The ERG explored other plausible scenarios amending the assumptions on INR monitoring and allowed the proportion of VTEs that are PEs to differ between the treatment arms. For patients with an intended treatment duration of 3 months, the ICER for rivaroxaban was always below £12,000 per QALY yielded. For patients with an intended treatment duration of 6 months, the ICER for rivaroxaban was labile, and could conceivable by either dominant or dominated. For patients with an intended treatment duration of 12 months, the ICER for rivaroxaban was always below £15,000 per QALY gained.

A simplistic cost minimisation analysis was undertaken to inform the appraisal committee of the cheapest intervention. This was dual LMWH/VKA treatment for those with an intended treatment duration 12 months, but was inconclusive at 3 and 6 months treatment duration as the results were dependent on the assumed INR monitoring costs

The ERG note that other assumptions may impact the ICER such as assuming the proportion of major bleeds that are IC bleeds are independent of treatment, and assuming that the risks of events after treatment cessation is independent of treatment. The impact of these assumptions has not been explored due to the absence of robust data.

It is noted that the manufacturer did not present an analysis for patients treated beyond 12 months, and only considered the use of rivaroxaban for the treatment of the index event; it is unclear why rivaroxaban was not considered for the treatment of the subsequent recurrences.

The manufacturer presented an exploratory analysis in the cancer subgroup of patients following a request from the ERG. The ERG has concerns with this analysis and the validity of results presented by the manufacturer. The ERG did not find the analysis robust.

6. ADDITIONAL WORK UNDERTAKEN BY THE ERG

The ERG identified and corrected the following errors identified during the review:

- In the reporting of outputs, the number of bleeding events was inverted between the two arms (error [redacted]).
- The lack of uninformative priors being incorporated for the parameters for the Beta distribution in those variables where no events were observed.
- Finally, an error is corrected for the probability of PE recurrences ([redacted]) after the first year (which had been incorrectly divided by 4).

The ERG comment that these amendments made no material difference to the ICER.

Additional work was undertaken by the ERG to explore other plausible scenarios on INR monitoring costs, and assuming that the proportion of VTEs that are PEs might be different between the two arms. It was not possible for the ERG to explore the impact of amending assumptions for other issues identified during the review due to time and resource constraints, and data limitation.

The ERG explored a scenario analysis assuming less intensive INR monitoring for patients treated with a VKA compared with the assumptions used by the manufacturer. After consultation with the clinical advisors to the ERG, the following assumptions have been made;

a. 6 INR monitoring visits the first 3 months and 3 INR visits thereafter (instead of 9 at first and 5 thereafter assumed by the manufacturer)

b. 75% of visits in the primary care are done by nurses (instead of a split 50/50 assumed by the manufacturer)

c. Follow-up visits in secondary care are done by non-consultants led only (instead of assuming a mix of consultants and non-consultants led)

The impact of these assumptions were to result in the cost of INR monitoring of £290 for patients treated with warfarin for 12 months. A lower figure (£241) for this value was used in a recent single technology appraisal of dabigatran,[77] however this was for patients with atrial fibrillation, which is believed by the clinical experts to the ERG to require less intensive monitoring.

A scenario analysis was also conducted to examine the impact on results assuming that the proportion of VTEs that are PEs is treatment-specific, using data from the EINSTEIN-DVT trial. Whilst the

difference did not reach statistical significance (p=0.14) this could be due to a small number of events. Given the marked differences in the health and financial consequences following PE or DVT conducting an exploratory analysis was deemed prudent. The analysis assumes that;

a. [redacted] VTEs are DVTs in patients treated with dual therapy LMWH/VKA

b. [redacted] VTEs are DVTs in patients treated with rivaroxaban

Finally, a cost-minimisation was undertaken assuming the treatment effect to be the same between rivaroxaban and LMWH/VKA. This scenario assumes that the two drugs provide the same clinical benefits, but are associated with different costs in terms of drug acquisition, administration and monitoring.

Results are presented using a lifetime horizon for the PSA results only (1,000 iterations) as the model showed non-linearity when comparing the results from the deterministic and probabilistic analysis. In addition to the ICER, the net monetary benefit (NMB) at a WTP of £20,000 or £30,000 per QALY gained was also reported. A positive NMB indicates that rivaroxaban is cost-effective at the examined WTP. Finally, the analyses use data by intended treatment duration.

6.1. Probabilistic cost-effectiveness results in patients for whom 3 months of anticoagulation treatment is appropriate – exploratory analyses conducted by the ERG.

A summary of the analyses undertaken by the ERG are provided in Table 37; care must be taken in interpreting the cost-effectiveness of interventions which are cost saving but provide a reduction in overall QALYs.

Table 37 Summation of ERG exploratory analyses in patients for whom 3 months of anticoagulation treatment is appropriate.

		Incremental Cost (£)	Incremental QALY	Cost Per QALY lost (£) *
1	Manufacturer Basecase	-180	-0.02	11,787
2	As 1, but errors corrected	-182	-0.02	11,792
3	As 2 with INR monitoring costs altered	-66	-0.02	4,144
4	As 2 with differential PE:DVT ratio assumed	-170	-0.03	5,031
5	As 2 with INR monitoring costs altered and with differential PE:DVT ratio assumed	-51	-0.04	1,203
* When evaluating cost per QALY lost, values greater than the assumed threshold are deemed cost-effective, with values under the threshold indicating that a treatment would not be cost-effective				

More detailed results for the different analyses are presented in Table 38 to Table 42 with the mean incremental cost and QALY values plotted in Figure 20.

Figure 20: additional work undertaken by the ERG - cost effectiveness plane in patients for whom 3 months of anticoagulation treatment using other plausible assumptions

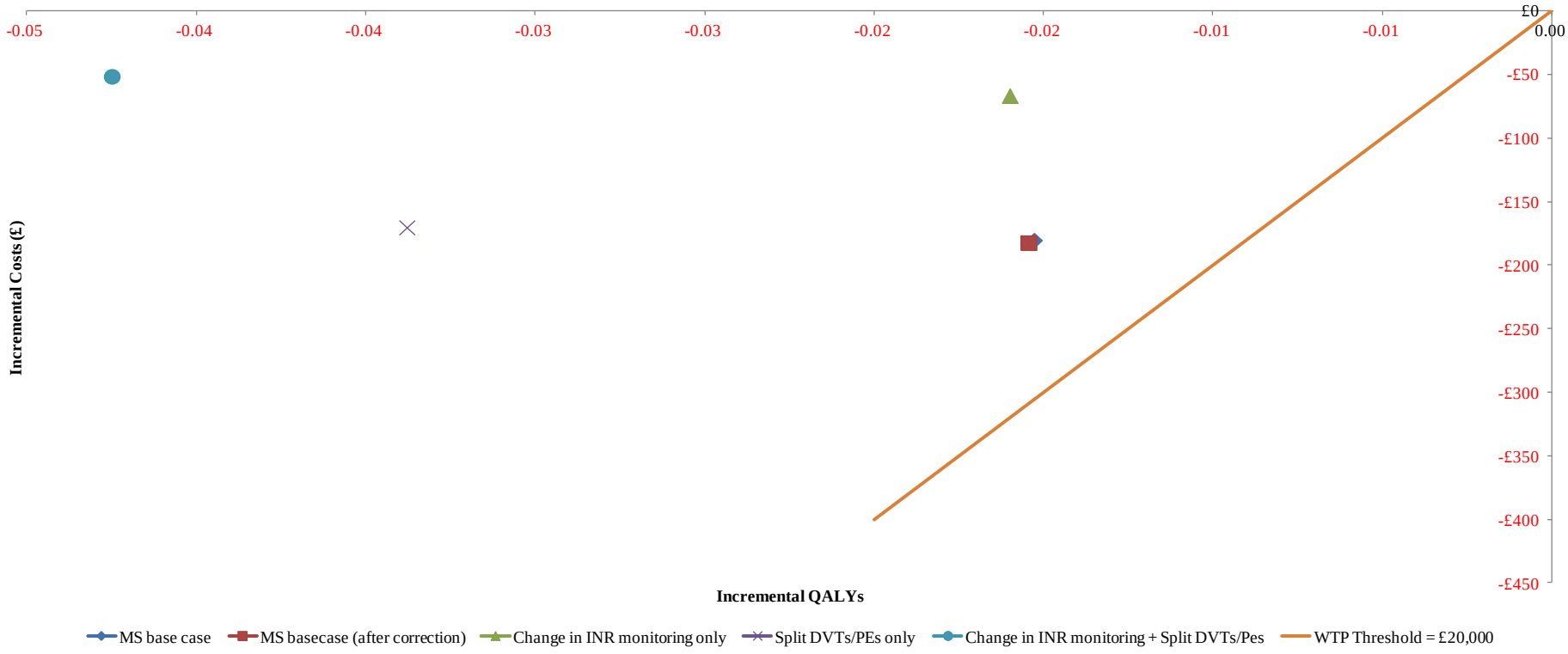


Table 38: Probabilistic base case analysis (in patients treated for 3 months) using the manufacturer's assumptions (before amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	£11,787 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£245	-£245
Event costs	£706	£689	£18
Bleed cost	£81	£160	-£79
PTS/CTEPH	£184	£175	£9
Total Cost	£1,187	£1,367	-£180
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.10	1.08	0.01
No of maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	13.32	13.33	-0.02
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£125.41**	**-£278.12**	

Table 39: Probabilistic base case analysis (in patients treated for 3 months) using the manufacturer's assumptions (after amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	£11,792 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£241	-£241
Event costs	£892	£874	£18
Bleed cost	£80	£165	-£84
PTS/CTEPH	£298	£289	£9
Total Cost	£1,486	£1,668	-£182
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.23	1.22	0.01
No of maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	12.98	13.00	-0.02
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£126.66**	**-£280.97**	

Table 40: Probabilistic base case analysis (in patients treated for 3 months) after amendment of errors identified in the model, assuming less intensive INR monitoring (same split DVTs/PEs between arms).

LIFETIME (40 years)	**ICER estimate:**	£4,144 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£128	-£128
Event costs	£726	£711	£16
Bleed cost	£78	£159	-£81
PTS/CTEPH	£304	£295	£10
Total Cost	£1,324	£1,391	-£66
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.23	1.22	0.01
No of maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	12.97	12.99	-0.02
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£253.44**	**-£413.28**	

Table 41: Probabilistic base case analysis (in patients treated for 3 months) using the manufacturer's assumptions on INR monitoring (after amendment of errors identified in the model) and assuming a different split DVTs/PEs between treatment arms.

LIFETIME (40 years)	**ICER estimate:**	£5,031 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£216	£99	£117
Monitor cost	£0	£240	-£240
Event costs	£891	£870	£21
Bleed cost	£79	£161	-£81
PTS/CTEPH	£296	£282	£13
Total Cost	£1,482	£1,651	-£170
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.22	1.21	0.01
No of maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	12.96	12.99	-0.03
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£505.59**	**-£843.35**	

Table 42: Probabilistic base case analysis (in patients treated for 3 months) after amendment of errors identified in the model assuming less intensive INR monitoring and assuming a different split DVTs/PEs between treatment arms.

LIFETIME (40 years) **ICER estimate:** £1,203 **per QALY yielded**

Costs

	Rivaroxaban	LMWH/VKA	Increment
Drug cost	£215	£99	£117
Monitor cost	£0	£128	-£128
Event costs	£726	£703	£23
Bleed cost	£74	£155	-£80
PTS/CTEPH	£299	£282	£17
Total Cost	£1,315	£1,366	-£51

Outcomes

No of deaths	0.94	0.94	0.00
No of VTEs	1.22	1.21	0.01
No of maj Bleeds	0.01	0.02	-0.01
QALYs (discounted)	12.97	13.01	-0.04

	WTP = £20,000	WTP = £30,000
NMB	**-£798.56**	**-£1,223.39**

6.2. Probabilistic cost-effectiveness results in patients for whom 6 months of anticoagulation treatment is appropriate – exploratory analyses conducted by the ERG.

A summary of the analyses undertaken by the ERG are provided in Table 43; care must be taken in interpreting the cost-effectiveness of interventions which are cost saving but provide a reduction in overall QALYs.

Table 43. Summation of ERG exploratory analyses in patients for whom 6 months of anticoagulation treatment is appropriate.

		Incremental Cost (£)	**Incremental QALY**	**Cost Per QALY gained or *lost* (£) ***
1	Manufacturer Basecase	-101	0.01	Dominant
2	As 1, but errors corrected	-104	0.01	Dominant
3	As 2 with INR monitoring costs altered	89	0.01	11,323
4	As 2 with differential PE:DVT ratio assumed	-91	-0.00	*26,343*
5	As 2 with INR monitoring costs altered and with differential PE:DVT ratio assumed	99	-0.00	Dominated
* When evaluating cost per QALY lost, values greater than the assumed threshold are deemed cost-effective, with values under the threshold indicating that a treatment would not be cost-effective				

More detailed results for the different analyses are presented in Table 44 to Table 48 with the mean incremental cost and QALY values plotted in Figure 21.

Figure 21: additional work undertaken by the ERG - cost effectiveness plane in patients for whom 6 months of anticoagulation treatment using other plausible assumptions

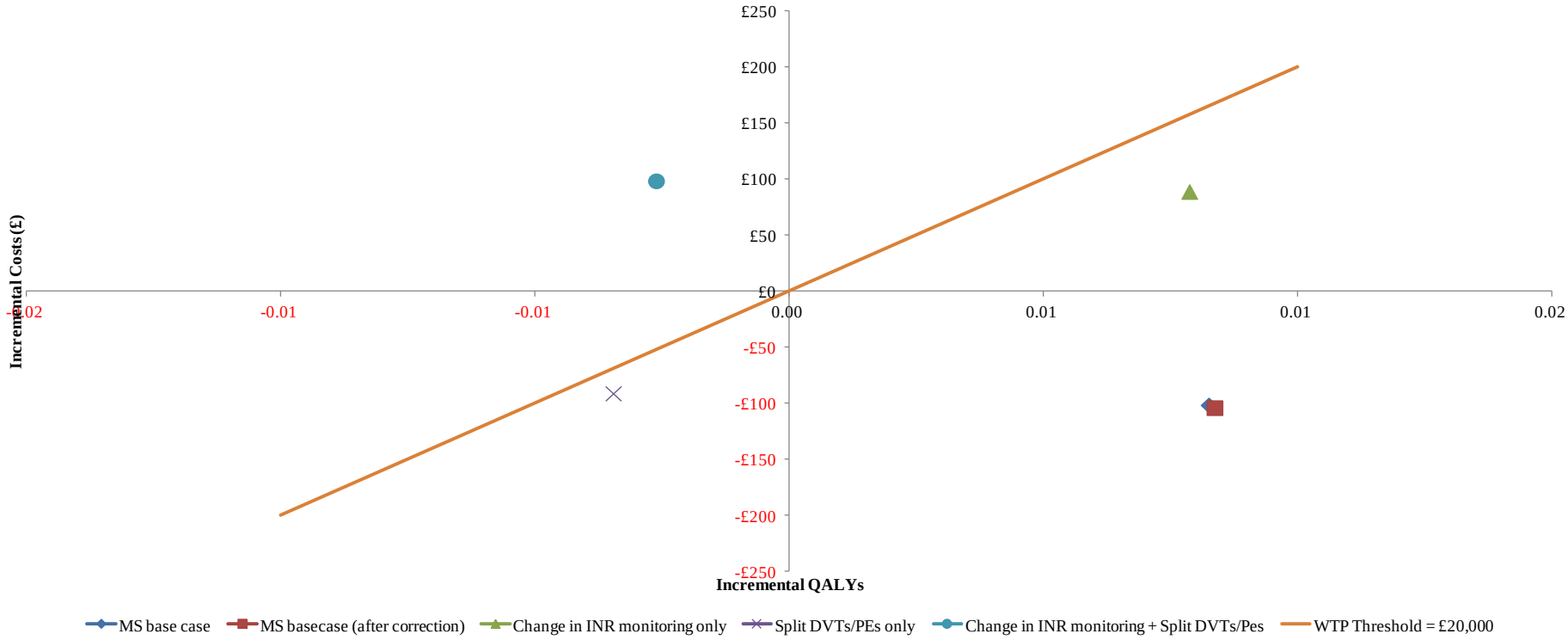


Table 44: Probabilistic base case analysis (in patients treated for 6 months) using the manufacturer's assumptions (before amendment of errors identified in the model).

LIFETIME (40 years) **ICER estimate:** dominant

Costs

	Rivaroxaban	LMWH/VKA	Increment
Drug cost	£394	£105	£289
Monitor cost	£0	£366	-£366
Event costs	£685	£689	-£4
Bleed cost	£92	£111	-£19
PTS/CTEPH	£174	£176	-£2
Total Cost	£1,345	£1,447	-£101

Outcomes

No of deaths	0.94	0.94	-0.00
No of VTEs	1.08	1.08	-0.00
No of maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.36	13.35	0.01

	WTP = £20,000	WTP = £30,000
NMB	**£266.58**	**£349.14**

Table 45: Probabilistic base case analysis (in patients treated for 6 months) using the manufacturer's assumptions (after amendment of errors identified in the model).

LIFETIME (40 years) **ICER estimate:** dominant

Costs

	Rivaroxaban	LMWH/VKA	Increment
Drug cost	£394	£105	£289
Monitor cost	£0	£370	-£370
Event costs	£865	£869	-£4
Bleed cost	£91	£108	-£17
PTS/CTEPH	£290	£292	-£2
Total Cost	£1,640	£1,744	-£104

Outcomes

No of deaths	0.94	0.94	-0.00
No of VTEs	1.21	1.21	-0.00
No of maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.02	13.01	0.01

	WTP = £20,000	WTP = £30,000
NMB	**£271.29**	**£355.00**

Table 46: Probabilistic base case analysis (in patients treated for 6 months) after amendment of errors identified in the model, assuming a less intensive INR monitoring (same split DVTs/PEs between arms).

LIFETIME (40 years)	**ICER estimate:**	£11,323 per QALY gained	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£394	£105	£289
Monitor cost	£0	£182	-£182
Event costs	£701	£704	-£3
Bleed cost	£95	£108	-£13
PTS/CTEPH	£290	£292	-£2
Total Cost	£1,481	£1,392	£89
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.21	1.22	-0.00
No of maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.01	13.00	0.01
	WTP = £20,000	**WTP = £30,000**	
NMB	**£68.33**	**£147.08**	

Table 47: Probabilistic base case analysis (in patients treated for 6 months) using the manufacturer assumptions about INR monitoring (after amendment of errors identified in the model) and assuming a different DVT/PE split between treatment arms.

LIFETIME (40 years)	**ICER estimate:**	£26,343 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£394	£105	£289
Monitor cost	£0	£365	-£365
Event costs	£867	£868	-£1
Bleed cost	£96	£113	-£17
PTS/CTEPH	£305	£302	£3
Total Cost	£1,662	£1,753	-£91
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.21	1.22	-0.00
No of maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.01	13.01	-0.00
	WTP = £20,000	**WTP = £30,000**	
NMB	**£21.93**	**-£12.65**	

Table 48: Probabilistic base case analysis (in patients treated for 6 months) after amendment of errors identified in the model, assuming less intensive INR monitoring and assuming a different DVT/PE split between treatment arms.

LIFETIME (40 years)	**ICER estimate:**	dominated	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£394	£105	£289
Monitor cost	£0	£181	-£181
Event costs	£708	£709	-£1
Bleed cost	£91	£103	-£12
PTS/CTEPH	£294	£291	£3
Total Cost	£1,487	£1,388	£99
Outcomes			
No of deaths	0.94	0.94	0.00
No of VTEs	1.22	1.22	-0.00
No of maj Bleeds	0.01	0.01	-0.00
QALYs (discounted)	13.01	13.01	-0.00
	WTP = £20,000	**WTP = £30,000**	
NMB	**-£151.00**	**-£177.14**	

6.3. Probabilistic cost-effectiveness results in patients for whom 12 months of anticoagulation treatment is appropriate – exploratory analyses conducted by the ERG.

A summary of the analyses undertaken by the ERG are provided in Table 49.

Table 49: Summation of ERG exploratory analyses in patients for whom 12 months of anticoagulation treatment is appropriate.

		Incremental Cost (£)	**Incremental QALY**	**Cost Per QALY gained (£)**
1	Manufacturer Basecase	-13	0.04	Dominant
2	As 1, but errors corrected	-10	0.04	Dominant
3	As 2 with INR monitoring costs altered	323	0.04	8,397
4	As 2 with differential PE:DVT ratio assumed	-3	0.03	Dominant
5	As 2 with INR monitoring costs altered and with differential PE:DVT ratio assumed	332	0.03	12,263

More detailed results for the different analyses are presented in Table 50 to Table 54 with the mean incremental cost and QALY values plotted in Figure 22.

Figure 22: additional work undertaken by the ERG - cost effectiveness plane in patients for whom 12 months of anticoagulation treatment using other plausible assumptions

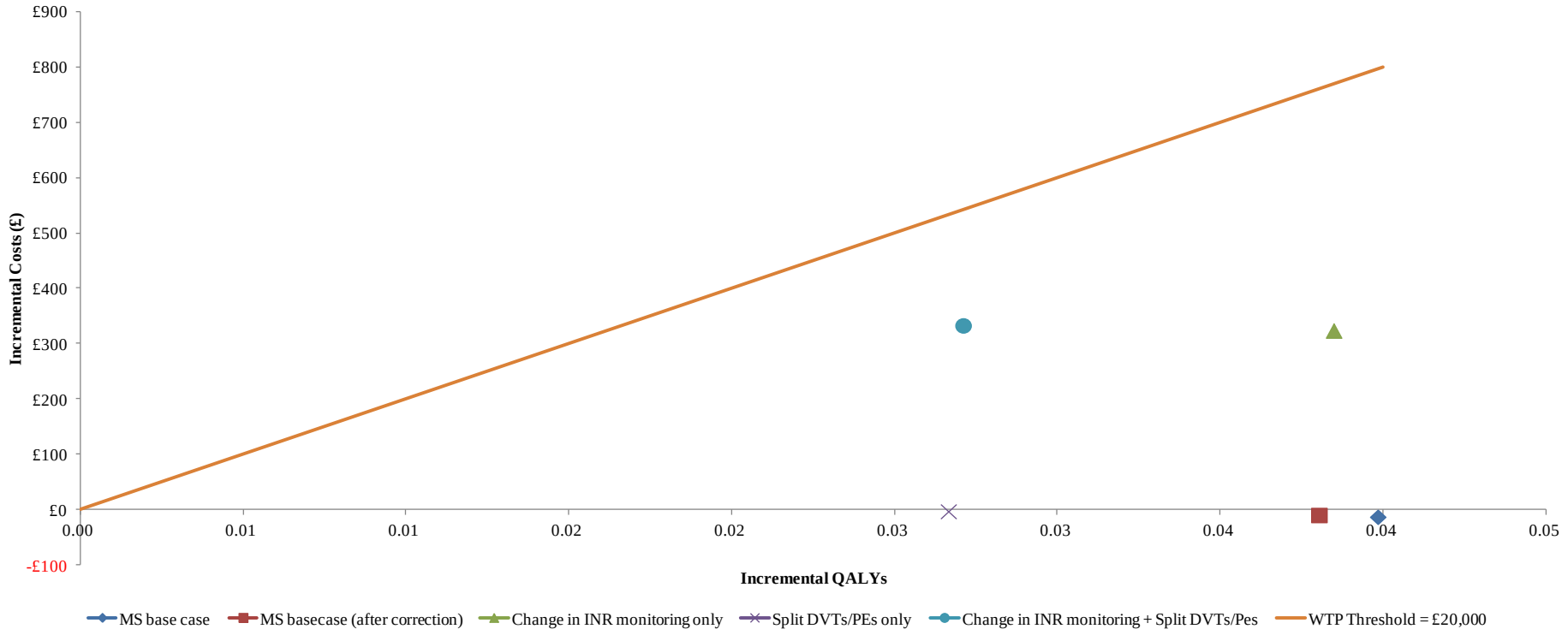


Table 50: Probabilistic base case analysis (in patients treated for 12 months) using the manufacturer's assumptions (before amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£746	£116	£630
Monitor cost	£0	£595	-£595
Event costs	£645	£685	-£39
Bleed cost	£54	£44	£10
PTS/CTEPH	£163	£183	-£19
Total Cost	£1,608	£1,621	-£13
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.05	1.08	-0.03
No of maj Bleeds	0.00	0.00	0.00
QALYs (discounted)	13.39	13.35	0.04
	WTP = £20,000	**WTP = £30,000**	
NMB	**£810.27**	**£1,208.75**	

Table 51: Probabilistic base case analysis (in patients treated for 12 months) using the manufacturer's assumptions (after amendment of errors identified in the model).

LIFETIME (40 years)	**ICER estimate:**	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£745	£116	£629
Monitor cost	£0	£593	-£593
Event costs	£832	£871	-£39
Bleed cost	£56	£44	£12
PTS/CTEPH	£283	£303	-£20
Total Cost	£1,916	£1,926	-£10
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.18	1.21	-0.03
No of maj Bleeds	0.01	0.00	0.00
QALYs (discounted)	13.06	13.02	0.04
	WTP = £20,000	**WTP = £30,000**	
NMB	**£770.85**	**£1,151.27**	

Table 52: Probabilistic base case analysis (in patients treated for 12 months) after amendment of errors identified in the model, assuming less intensive INR monitoring (same split DVTs/PEs between arms).

LIFETIME (40 years)	**ICER estimate:**	£8,397 per QALY gained	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£745	£116	£629
Monitor cost	£0	£273	-£273
Event costs	£679	£712	-£33
Bleed cost	£55	£36	£20
PTS/CTEPH	£280	£299	-£19
Total Cost	£1,759	£1,436	£323
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.19	1.21	-0.03
No of maj Bleeds	0.01	0.00	0.00
QALYs (discounted)	13.06	13.02	0.04
	WTP = £20,000	**WTP = £30,000**	
NMB	**£446.67**	**£831.61**	

Table 53: Probabilistic base case analysis (in patients treated for 12 months) using the manufacturer's assumptions about INR monitoring (after amendment of errors identified in the model) and assuming a different DVT/PE split between treatment arms.

LIFETIME (40 years)	**ICER estimate:**	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£745	£116	£629
Monitor cost	£0	£594	-£594
Event costs	£836	£871	-£35
Bleed cost	£53	£43	£10
PTS/CTEPH	£282	£296	-£14
Total Cost	£1,916	£1,920	-£3
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.18	1.21	-0.03
No of maj Bleeds	0.00	0.00	0.00
QALYs (discounted)	13.05	13.03	0.03
	WTP = £20,000	**WTP = £30,000**	
NMB	**£536.49**	**£803.10**	

Table 54: Probabilistic base case analysis (in patients treated for 12 months) after amendment of errors identified in the model assuming less intensive INR monitoring and assuming a different DVT/PE split between treatment arms.

LIFETIME (40 years)	**ICER estimate:**	£12,263 per QALY gained	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£745	£116	£629
Monitor cost	£0	£274	-£274
Event costs	£676	£706	-£30
Bleed cost	£57	£37	£21
PTS/CTEPH	£280	£293	-£14
Total Cost	£1,758	£1,426	£332
Outcomes			
No of deaths	0.94	0.94	-0.00
No of VTEs	1.18	1.21	-0.03
No of maj Bleeds	0.01	0.00	0.00
QALYs (discounted)	13.06	13.03	0.03
	WTP = £20,000	**WTP = £30,000**	
NMB	**£209.79**	**£480.93**	

6.4 Cost-minimisation analysis, assuming the same treatment effect between rivaroxaban and LMWH/VKA

Finally, an analysis was conducted which assumed the same efficacy between the two drugs. This analysis, therefore, only compares the drug and monitoring costs.

Using the manufacturer assumption on INR monitoring, rivaroxaban was cost-saving in patients treated for 3 months (£114) and 6 months (£64), but not in patients treated for 12 months (£36).

Table 55: Drug and monitoring costs by intended treatment duration and treatment arm (using MS assumption's on monitoring)

	Rivaroxaban	**LMWH/VKA**	**Incremental**
3 months	£236	£350	-£114
6 months	£427	£491	-£64
12 months	£811	£774	£36

Amending the assumption on INR monitoring, rivaroxaban was associated with an increase in cost in all intended treatment duration subgroups (£14, £144 and £402 respectively).

Table 56: Drug and monitoring costs by intended treatment duration and treatment arm (using a less intensive monitoring than assumed by the manufacturer)

	Rivaroxaban	LMWH/VKA	Incremental
3 months	£236	£221	£14
6 months	£427	£284	£144
12 months	£811	£408	£402

6.5. Exploratory analysis in cancer patients – examining different HR

The ERG explored 3 scenarios, using the mean HR/OR assuming a between study variability of U(0,5), U(0,2) and U(U,0.6).

In addition to the above, the ERG corrected the following errors:

- [redacted] the cell was linked to the wrong cell [redacted]
- Finally, an error is corrected for the probability of PE recurrences ([redacted] after the first year (which had been incorrectly divided by 4).

Results are presented for the deterministic sensitivity analysis as there were issues with the PSA. A summary of the analyses undertaken by the ERG are provided in Table 57.

The ERG believes these results to be exploratory rather than definitive due to the caveats listed below.

The main uncertainties within the analyses relate to:

- The baseline risk of events – it was necessary for the manufacturer to make a series of assumptions to represent the risk of events, and it is unclear to what extent this reflect the risk of events in the cancer population,
- The treatment effect was taken from the MTC, however there were considerable uncertainty in the relative treatment effects,
- Data not specific to cancer patients were used for the risk of events once treatment cease; it is unclear if this is appropriate. The ERG did not conduct a systematic review of the literature, but found a study showing that the probability of readmission for VTEs within 6 months was almost four times higher among Medicare patients with cancer than among Medicare patients without malignancy.
- The manufacturer assumed a median life expectancy of 5 years, however it is unclear if this reflect the life expectancy of patients with a DVT.
- The manufacturer also assumed the same baseline utility value and impact on Qol in the general population and patients with cancer. It is likely that the baseline utility value is different between cancer vs. non cancer patients. The impact of VTEs in cancer patients may also be different.

Table 57. Summation of ERG exploratory analyses in cancer patients

		Incremental Cost (£)	Incremental QALY	Cost per QALY gained (£)	Cost Per QALY lost (£) *
1	Manufacturer Basecase	-£1,085	0.00135	Dominant	
2	As 1, but errors corrected	-£1,272	0.00129	Dominant	
3	As 2 using mean HR assuming U(0,5)	-£1,141	-0.03272		34,865
4	As 2 using mean HR assuming U(0,2)	-£1,202	-0.01594		75,408
5	As 2 using mean HR assuming U(0,0.6)	-£1,253	-0.00319		392,242
* When evaluating cost per QALY lost, values greater than the assumed threshold are deemed cost-effective, with values under the threshold indicating that a treatment would not be cost-effective					

More detailed results for the different analyses are presented in Table 58 to Table 62 with the mean incremental cost and QALY values plotted in Figure 23.

Figure 23: Exploratory analysis in cancer patients using the mean treatment effect and using different between study variability.

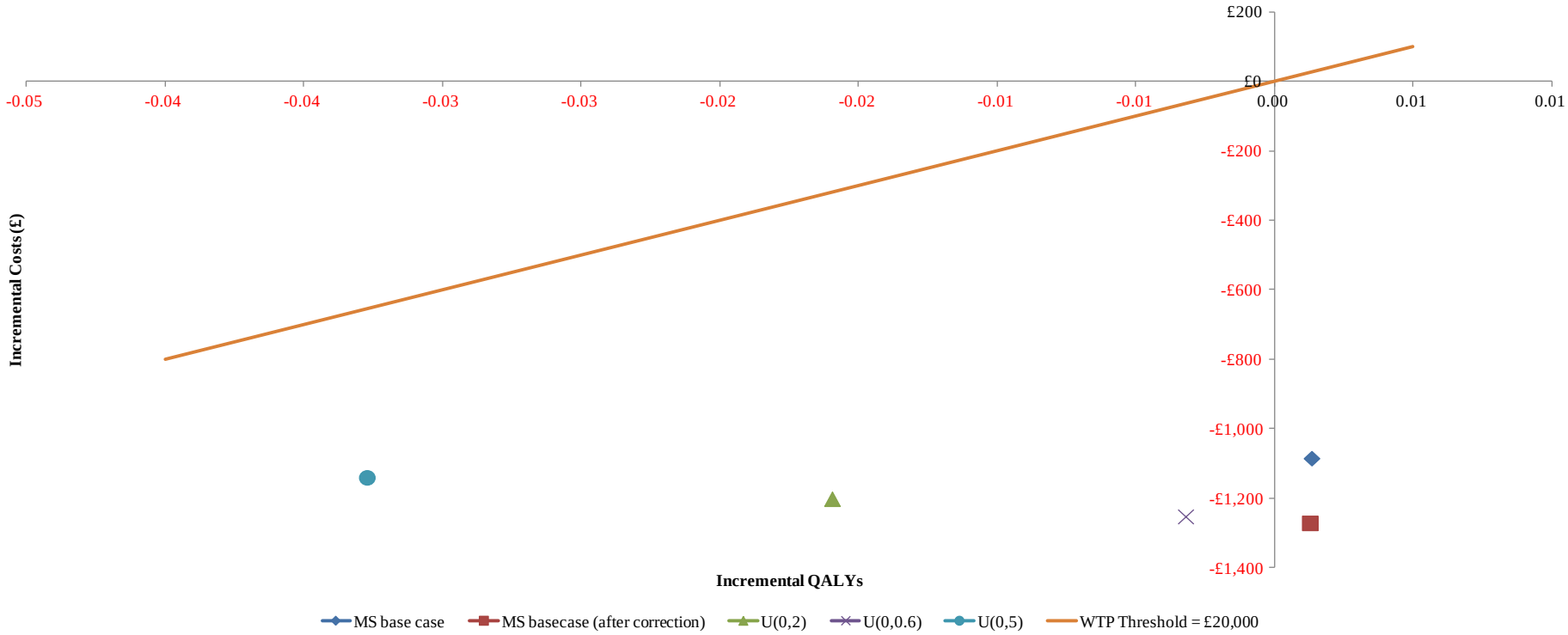


Table 58: Deterministic base case analysis (in cancer patients) using the manufacturer's assumptions (before amendment of errors identified in the model).

LIFETIME (40 years)	ICER estimate:	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£365	£1,146	-£781
Monitor cost	£0	£262	-£262
Event costs	£563	£535	£28
Bleed cost	£122	£196	-£74
PTS/CTEPH	£67	£63	£4
Total Cost	£1,117	£2,203	-£1,085
Outcomes			
No of deaths	1.00	1.00	-0.00
No VTEs	0.32	0.31	0.01
No maj Bleeds	0.03	0.04	-0.01
QALYs (discounted)	4.68	4.68	0.00135
	WTP = £20,000	**WTP = £30,000**	
NMB	**£1,112.35**	**£1,125.83**	

Table 59: Deterministic base case analysis (in cancer patients) using the manufacturer's assumptions after amendment of errors identified in the model.

LIFETIME (40 years)	ICER estimate:	dominant	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£365	£1,146	-£781
Monitor cost	£0	£449	-£449
Event costs	£725	£694	£30
Bleed cost	£122	£199	-£77
PTS/CTEPH	£91	£87	£4
Total Cost	£1,303	£2,574	-£1,272
Outcomes			
No of deaths	1.00	1.00	0.00
No VTEs	0.35	0.34	0.01
No maj Bleeds	0.03	0.04	-0.01
QALYs (discounted)	4.63	4.63	0.00129
	WTP = £20,000	**WTP = £30,000**	
NMB	**£1,297.41**	**£1,310.27**	

Table 60: Deterministic base case analysis (in cancer patients) using the manufacturer's assumptions after amendment of errors identified in the model, using the mean HR assuming U(0,5)

LIFETIME (40 years)	**ICER estimate:**	£34,865 **per QALY sold**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£365	£1,242	-£876
Monitor cost	£0	£490	-£490
Event costs	£725	£633	£91
Bleed cost	£122	£0	£122
PTS/CTEPH	£91	£78	£13
Total Cost	£1,303	£2,443	-£1,141
Outcomes			
No of deaths	1.00	1.00	0.00
No VTEs	0.35	0.32	0.03
No maj Bleeds	0.03	0.00	0.03
QALYs (discounted)	4.63	4.66	-0.03272
	WTP = £20,000	**WTP = £30,000**	
NMB	**£486.33**	**£159.16**	

Table 61: Deterministic base case analysis (in cancer patients) using the manufacturer's assumptions after amendment of errors identified in the model, using the mean HR assuming U(0,2)

LIFETIME (40 years)	**ICER estimate:**	£75,408 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£365	£1,192	-£826
Monitor cost	£0	£468	-£468
Event costs	£725	£668	£56
Bleed cost	£122	£94	£28
PTS/CTEPH	£91	£83	£8
Total Cost	£1,303	£2,505	-£1,202
Outcomes			
No of deaths	1.00	1.00	0.00
No VTEs	0.35	0.33	0.02
No maj Bleeds	0.03	0.02	0.01
QALYs (discounted)	4.63	4.64	-0.01594
	WTP = £20,000	**WTP = £30,000**	
NMB	**£883.34**	**£723.91**	

Table 62: Deterministic base case analysis (in cancer patients) using the manufacturer's assumptions after amendment of errors identified in the model, using the mean HR assuming U(0,0.6)

LIFETIME (40 years)	**ICER estimate:**	£392,242 **per QALY yielded**	
Costs			
	Rivaroxaban	**LMWH/VKA**	**Increment**
Drug cost	£365	£1,158	-£792
Monitor cost	£0	£454	-£454
Event costs	£725	£689	£36
Bleed cost	£122	£170	-£48
PTS/CTEPH	£91	£86	£5
Total Cost	£1,303	£2,556	-£1,253
Outcomes			
No of deaths	1.00	1.00	0.00
No VTEs	0.35	0.34	0.01
No maj Bleeds	0.03	0.04	-0.01
QALYs (discounted)	4.63	4.63	-0.00319
	WTP = £20,000	**WTP = £30,000**	
NMB	**£1,189.14**	**£1,157.19**	

7 Overall conclusions

The ERG believes that assumptions made by the manufacturer to be plausible, however, other plausible assumptions exist, given the uncertainties within the decision problem which may impact the ICER. The ERG explored other plausible scenarios amending the assumptions on INR monitoring and allowed the proportion of VTEs that are PEs to differ between the treatment arms. For patients with an intended treatment duration of 3 months, the ICER for rivaroxaban was always below £12,000 per QALY yielded. For patients with an intended treatment duration of 6 months, the ICER for rivaroxaban was labile, and could conceivable by either dominant or dominated. For patients with an intended treatment duration of 12 months, the ICER for rivaroxaban was always below £15,000 per QALY gained. However, the ERG acknowledge that further sources of uncertainty have not been evaluated.

A simplistic cost minimisation analysis was undertaken to inform the appraisal committee of the cheapest intervention. This was dual LMWH/VKA treatment for those with an intended treatment duration 12 months, but was inconclusive at 3 and 6 months treatment duration as the results were dependent on the assumed INR monitoring costs.

The ERG also examined the impact of using the mean treatment effect from the MTC using different between study variability. Exploratory results indicate that at a threshold of £20,000 per QALY gained that rivaroxaban was more cost-effective than LMWH. However, there are considerable uncertainties in both the data and the assumptions used within this analysis.

7.1 Implications for research

The ERG identified the following areas of uncertainty that could be considered for future research:

- The null hypothesis could not be rejected in the subgroup of patients who were in the 3 months intended treatment duration group. A trial powered to investigate efficacy and safety in this group would be beneficial.
- Data on long term use of rivaroxaban beyond 12 months, in comparison to an active comparator would be of value. There are clearly difficulties in terms of long term follow up with this type of trial, but the data would be very useful to inform decisions about long term use.
- Rivaroxaban has not been trialled in a number of subgroups, namely patients at high risk of bleeding (with the exception of cancer patients), creatinine clearance <30mL/min, patients with liver diseases, patients with high blood pressure (systolic >180 mmHG or diastolic >110 mmHg) and patients with distal DVT. Trials carefully conducted in these groups with appropriate comparators would also provide the data to inform decisions about the use of rivaroxaban.
- More accurate reporting of INR monitoring costs by patient aetiology would be beneficial.
- An investigation into whether the ratio of PEs to DVTs are independent of treatment may also be worth additional research, as would investigating whether there is an overall mortality benefit associated with rivaroxaban.

8 Appendices

Appendix 1 Summary of the two trials that were excluded from further analysis

The primary efficacy outcome in the OXIDa-DVT study (n=613)[35] was thrombotic burden at day 21 (assessed by quantitative complete compression ultrasonograpy (CCUS); ≥4point improvement in thrombus score) without recurrent, symptomatic VTE or VTE-related death. The analysis of the primary efficacy outcome was performed in the per-protocol (PP) population. This was defined as patients without major protocol deviations (that is treatment compliance > 80%, not receiving prohibited medication) who had CCUS assessment between days 18 and 26 or who experienced symptomatic or objectively confirmed extension of DVT or recurrence, PE or VTE-related death up to day 26.[35]. Outcomes occurring within 3 calendar days of treatment cessation were included in the analysis. According to the report.[35] a supportive analysis was performed in the intention-to-treat population. The primary efficacy outcome occurred in 53.0%, 59.2%, 56.9% and 43.8% of patients on rivaroxaban 10mg, 20mg, 30mg twice daily and 40mg once daily respectively compared to 45.9% in patients who received anticoagulation with LMWH/VKA. According to the MS, no significant trend in dose-response relationship was demonstrated between the primary efficacy outcome and twice daily dosing of rivaroxaban (p=0.67). Safety analyses performed included patients who had received at least one dose of the study treatment and had relevant safety assessments up to within 2 calendar days of stopping medication.[35] Examination of safety outcomes revealed that there was no major bleeding in patients who were treated with LMWH/VKA, on the other hand this occurred in 1.7%, 1.7%, 3.3% and 1.7% of patients on rivaroxaban 10mg, 20mg, 30mg twice daily and 40mg once daily respectively.

In the EINSTEIN-DVT dose-ranging study,[36] patients with acute symptomatic proximal DVT (n=543) were randomised to receive 20mg (n=136), 30mg (n=134), or 40mg (n=136) once a day in the intervention arm of the study. Patients in the comparator arm received a LMWH with a VKA. The primary efficacy outcome was a composite endpoint of symptomatic recurrent DVT, symptomatic fatal or non-fatal PE, and asymptomatic deterioration in thrombotic burden. Individual components of primary efficacy outcome were considered as secondary efficacy outcomes. The authors stated that all efficacy outcomes were performed in the per-protocol (PP) population and in the modified intention-to-treat (ITT) population. The PP population (n=449) was defined as all patients suitable for ITT analyses without any pre-specified major protocol deviations including rivaroxaban intake less than 80% verified by tablet count, LMWH treatment less than 4 days, no INR measurement within the first week or interval between INR measurements > 28days, ultrasonography or perfusion lung scan > 10

days after stopping treatment.(Buller 2008) The modified ITT population included all randomised patients who had rivaroxaban treatment, had confirmed DVT and in whom the primary outcome was evaluable.[36] The evaluation of safety of treatment was based on the combination of a major and clinical relevant non-major bleeding occurring up to 48 hours after study treatment cessation. Safety analyses performed on the all patients who received at least one dose of the study treatment following randomisation. This population was referred to as the safety population (n= 542).[36] For patients in the intervention arm, the primary efficacy outcome was achieved in 6.1%, 5.4% and 6.6% of patients on 20mg, 30mg, and 40mg once daily doses of rivaroxaban respectively. On the other hand, 9.9% of patients in the comparator experienced the composite endpoint. According to the MS, the frequency of a major bleed was 1, 2, and 0 in the 20mg, 30mg and 40mg groups respectively compared to 2 events in the comparator group. The main findings of the Phase II trials are shown in Table 1.

Table 1 Main findings in the OXIDa-DVT study and the EINSTEIN-DVT dose-ranging study. Compiled by the ERG using information from Table 6 in MS,[1] page 32, information in section 5.2.6 (page 33 to 35) and the published journal articles.[35,36]

OXIDa-DVT study		**Rivaroxaban**				**Enoxaparin/VKA**
		10mg bd	**20mg bd**	**30mg bd**	**40mg od**	
Primary efficacy outcome (thrombotic burden)	At 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)
	At 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) (1.0
*Minor bleeding		3.4	7.7	9.1	9.9	6.3
EINSTEIN-DVT dose-ranging study		**Rivaroxaban**				**LMWH/VKA**
		20mg od	**30mg od**	**40mg od**		
Primary efficacy outcome (composite endpoint)		6.1 (2.5 –	5.4 (2.0-	6.6 (2.9 –		9.9 (4.9 -17.5)

		12.1)	11.3)	12.6)	
Secondary efficacy outcomes	Symptomatic recurrent VTE	2.6	3.6	1.7	6.9
	Symptomatic recurrent VTE or deterioration of thrombotic burden	6.1	5.4	6.6	9.9
Major bleeding 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)
Major bleeding		0.7	1.5	0.0	1.5
*Clinically relevant non-major bleeds		5.2	4.5	2.2	7.3
*Premature discontinuation of treatment		13.0	14.0	9.0	11.0
*Adverse events		7.0	5.0	4.0	4.0
*Death (any cause)		3.0	6.0	1.5	3.6
*Death (due to bleeding)		0.0	0.0	0.0	0.7

Abbreviation: bd-twice daily; od-once daily: LMWH-low molecular weight heparin; VKA-vitamin K antagonist

Values shown are proportion of patients experiencing the specified outcome with the stated 95% confidence interval.

*These outcomes were not reported in the MS but were obtained by the ERG from the published reports of the studies. (Agnelli, 2007 and Buller, 2008)

Both Phase II studies performed analyses if the primary efficacy outcome in the per-protocol (PP) population, that is patients who complied with the trial protocol. PP analysis is a method of demonstrating the best potential of the treatment under investigation, provided the rate of non-compliance and other protocol deviations are minimal. The introduction of bias in this type of analysis may be investigated by a supporting ITT analysis. It was reported in the EINSTEIN-DVT dose-ranging study [36], that observed estimates of efficacy were similar in the PP and modified ITT analyses, though the exact composition of the modified ITT population remains unclear. Comparing the two Phase II studies, the manufacturer concluded that both studies showed similar efficacy for the twice-daily and once-daily rivaroxaban dosing regimens although the studies were concerned with different primary efficacy outcomes. The ERG notes that this type of comparison may lead to misinterpretation of some of the efficacy-related findings in the described studies.

The MS further asserts that with regards to safety, '*all rivaroxaban regimens were numerically better than heparin/VKA'*(page 35, in the MS) with once-daily schedules being better than twice-daily dosing. Whilst the ERG assumes that this statement is with reference to the primary safety outcomes of the two studies, available evidence (not included in the MS) from the published reports showed that minor bleeding occurred in 3.4 – 9.9% of patients on twice daily rivaroxaban regimens compared to 6.3% of patients in the Enoxaparin/VKA arm. Furthermore, frequency of events such as premature discontinuation of medication, adverse events and death differed between patients on once daily dosing of rivaroxaban and patients on LMWH/VKA with some patients in the intervention group having more episodes of some of these outcomes. (See Table 1 of this Appendix).

To investigate the apparent differential effect of rivaroxaban on PEs compared to DVTs seen in the EINSTEIN-DVT trial, the ERG considered the PE and DVT events in these two trials as reported in the journal articles.[35,36] The results are presented in Tables 2 and 3 of this Appendix.

Table 2 Incidence of Recurrent DVT, PE, or VTE-Related Death up to Day 84 (+14): Intention-to-Treat Population (n=543). Reproduced from Agnelli et al. 2007[35]

	Rivaroxaban				Enoxaparin/VKA (n=112)
	10 mg BID (n=106)	20 mg BID (n=100)	30 mg BID (n=111)	40 mg OD (n=114)	
OD indicates once daily.					
Values are n (%).					
Any event	2 (1.9)	2 (2.0)	2 (1.8)	3 (2.6)	1 (0.9)
Death (VTE-related)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
PE, nonfatal	0 (0.0)	1 (1.0)	1 (0.9)	1 (0.9)	0 (0.0)
Recurrent DVT	1 (0.9)	1 (1.0)	1 (0.9)	1 (0.9)	1 (0.9)

Table 3 Efficacy outcomes in the per protocol population (n = 449). Reproduced from Buller et al. 2008.[36]

	Rivaroxaban			LMWH/VKA n = 101
	20 mg, n = 115	30 mg, n = 112	40 mg, n = 121	
Primary efficacy outcome				
n (%)	7 (6.1)	6 (5.4)	8 (6.6)	10 (9.9)
95% CI[*]	2.5%-12.1%	2.0%-11.3%	2.9%-12.6%	4.9-17.5%
Symptomatic events, n (%)	3 (2.6)	4 (3.6)	2 (1.7)	7 (6.9)
Death (VTE-related)	0 (0.0)	2 (1.8)	1 (0.8)	0 (0.0)
PE, nonfatal	1 (0.9)	1 (0.9)	0 (0.0)	1 (1.0)
Recurrent DVT	2 (1.7)	1 (0.9)	1 (0.8)	7 (6.9)[†]
Asymptomatic deterioration on ultrasound and/or perfusion lung scanning, n (%)	4 (3.5)	2 (1.8)	6 (5.0)	3 (3.0)

Agnelli et al.[35] report 1 PE or VTE related death in the 10mg bid rivaroxaban arm, versus 0 in the comparator arm. DVT rates are the same in both; 1 event.

Buller et al[36] report 1 PE or VTE related death in the rivaroxaban arm versus 1 in the comparator arm. However, DVTs follow a similar pattern to that seen in the EINSTEIN-DVT trial, with 2 events in the rivaroxaban arm, and 7 in the comparator arm. In other words, rivaroxaban appears to reduce the number of DVTs, but not the number of PEs.

However, the ERG felt that this evidence was too weak to be presented, given the above criticisms and the small number of events observed.

Appendix 2 Correction of Tables 29 and 30 from the MS.

Table 1. Most common adverse events in EINSTEIN-DVT and EINSTEIN-Ext (to replace Table 29 of the MS, page 81, provided in the manufacturer's clarification letter as Table 33, page 63)

	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	[redacted]	[redacted]	[redacted]	[redacted]
Serious	201 (12.0)	233 (13.6)	[redacted]	[redacted]
Drug-related and serious	[redacted]	[redacted]	[redacted]	[redacted]
Any	1078 (62.7)	1080 (63.1)	[redacted]	[redacted]
Specific adverse events				
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Epistaxis	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 2. Relative and absolute risk differences (%) for the most common adverse events in EINSTEIN-DVT and EINSTEIN-Ext (to replace Table 30 of the MS, [1] page 82, provided in the manufacturer's clarification letter, as Table 34, page 64)

	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 (see MS for reference). CIs for the ARDs were calculated using a Normal approximation to the Binomial.

ARD: absolute risk difference.

Appendix 3 Definition of `sufficient compliance'

A subject on rivaroxaban was to be considered valid for per protocol analysis if

[redacted]

Appendix 4 Reproduction of Section D of the manufacturer's clarifications – textual and additional clarifications.

D1. Please clarify whether the references to sections 2.9 and 2.10 in section 2.12 are correct, as these sections do not seem to reference appropriate sources of data to answer the question posed by section 2.12 (page 25).

Section 2.12 asks for references to support the advantages for rivaroxaban described in previous sections.

The draft SmPCs for rivaroxaban (references 2-3) are key references, which describe the circumstances in which rivaroxaban should be delivered to patients to whom it is prescribed.

Also relevant are the SmPCs for the LMWHs (37, 39, 40, 41), warfarin (87) and fondaparinux (89), and the PILs (88, 90, 91), which describe the administration requirements and extensive contraindications associated with the current standard of care.

Safety issues in relation to LMWH and warfarin have been discussed in references 7, 10 and 13.

Increased treatment satisfaction with rivaroxaban in comparison to LMWH/VKA is supported by an analysis described in reference 18.

D2. Please confirm that the sentence 'from these 687 were excluded...' should read 'from these, 683 were excluded..' to match Figure 2 (page 30, section 5.2.2)

We confirm that the sentence should read `from these, 683 were excluded'.

D3. Please clarify the asterisk attached to the statement 'treatment period 3, 6, or 12 months' on page 37, Figure 3.

In the internal diagram from which Figure 3 was taken, the asterisk refers to a footnote which describes the selection of treatment duration by investigators, as described elsewhere in the submission (for example in Table 9, page 39).

D4. Page 42, states that 53% of patients in EINSTEIN-EXT had participated in EINSTEIN-DVT. However, the figure on Page 38 suggests this figure is 34%. Note that the numbers quoted in Figure 6 (page 51) suggest 53% is the correct value. Please clarify.

The study identification numbers within Bayer of EINSTEIN-DVT and EINSTEIN-PE studies are both 11702, and this appears to be associated with some confusion.

Figure 4 on page 38 of the submission correctly states the source of patients in EINSTEIN-Ext. This Figure corresponds with the NEJM article,[16] which states:

From February 2007 through March 2009, a total of 1197 patients were enrolled in the Continued Treatment Study. Of these patients, 34.1% had completed the Acute DVT Study and 19.1% had completed the Acute PE (Pulmonary Embolism) Study of the EINSTEIN program; the remaining 560 patients (47.5%) were referred from outside both these studies (Fig. 1B).

A bullet on page 42 states that `53.0% had participated in EINSTEIN-DVT'. This should more accurately read `53.2% had participated in EINSTEIN-DVT/PE'.

Figure 6 (the CONSORT flow diagram for EINSTEIN-Ext) on page 51 states that 632 of the 1197 randomised patients were from study 11702 and a further 5 randomised patients had pre-treatment both in and outside study 11702. In total therefore, 637 of 1197 randomised patients, or 53.2%, had at least some pre-treatment in EINSTEIN-DVT or EINSTEIN-PE.

See also B11.

D5. Table 15 (Page 45) defines "Treatment emergent AEs", which are not referred to in table 14. Table 14 uses "other adverse events" and "adverse events". Please clarify the definitions of adverse events by defining the two categories used in table 14.

Please note that Table 14 on page 44 is a summary of the outcomes measured and their categorisation as primary, secondary etc. The `other' in `other adverse events (AEs)' in column 2 refers merely to the various adverse events monitored in this study besides the safety related endpoints listed above that bullet (vascular events, all cause mortality). We can understand why the bullet may be interpreted in another way, but the intention of this bullet was simply to highlight that there were other outcomes, relating to safety, that were measured and collected in EINSTEIN-DVT besides those already stated.

The protocols for EINSTEIN-DVT and EINSTEIN-Ext contain the following identical wording in relation to safety outcomes:

This protocol definition of treatment-emergent AEs is reflected in Table 15 of the submission. Therefore we could consider the existing format of presentation of AE data in Table 29 and 30 on pages 81-82 of the submission to be appropriate.

D6. Please confirm that the asterisk in the boxes listing 'excluded from PP' refer to footnote e and f for the treatment arm and comparator arm, respectively (page 50, Figure 5).

We confirm that this is the case. The asterisk aside `n=29 intake of strong CYP3A4 inducer' refers to footnote e. The asterisk aside `n=21 wrong intake of medication' refers to footnote f.

D7. Unexpected imbalances between drop-outs have been scored "no". Please clarify why this has been scored "no", when data in figure 5 (p50) suggest otherwise (total end of study medication (EOSM) in treatment arm = 298, total EOSM in comparator arm = 338. Specifically, withdrawal of consent is very different between groups). Have failure to comply and withdrawal of consent been combined?

It is true that fewer patients, both in absolute number and proportionally, withdrew in the rivaroxaban arm than in the comparator arm (298 vs 338, 17.2% vs 19.7%). Put another way, patients randomised to rivaroxaban appeared to have greater adherence

than patients randomised to the comparator. This observation remains the case after deducting withdrawals due to the termination of the study by the sponsor (196 vs 244, 11.3% vs 14.2%). The level of discontinuation and differences between treatment arms are nevertheless small.

The quality assessment of EINSTEIN-DVT (appendix 3 of the submission) indeed scores this trial as `no' in response to `Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?'

The favourable quality rating reflects:

The overall level of discontinuation was judged to be relatively small, as a proportion of the overall study population, particularly once withdrawals that occurred due to the sponsor's actions were taken into account.

Further consideration of discontinuation data (see the section headed discontinuation in section 6.3.1 on pages 113-114 of the submission) suggested low and similar levels of discontinuation when considering more relevant reasons for discontinuation.

The statistical methods which were employed (Cox regression, see Table 16 in section 5.3.6 on page 47 of the submission) accounts for time to event, so any imbalance may be reasonably judged to be appropriately `adjusted for'.

Treatment satisfaction with rivaroxaban has been shown to be higher than with LMWH/VKA.[18] As the question asks, this may to some extent `explain' any difference in discontinuation observed.

D8. Page 56 (mortality), please clarify if the p-value quoted as 'p=0.063' is for non-inferiority or superiority.

We assume this question relates to a statement on page 58. The direction of treatment effect for the all-cause mortality outcome was in favour of rivaroxaban rather than in favour of the comparator (HR: 0.67, 95% CI 0.44 to 1.02, p=0.063). The p-value corresponds to a null hypothesis of no difference, so the test performed is one of superiority.

D9. Please clarify that the third line on page 59 should read comparator group, and not placebo group (re EINSTEIN-DVT).

The text should indeed refer to the comparator rather than placebo group: `there were fewer deaths in the rivaroxaban group than the comparator group'. See also Table 18 on page 62.

D10. Please confirm that the title in Figure 12 (page 61) should read EINSTEIN-DVT.

We confirm that Figure 12 relates to EINSTEIN-DVT, not EINSTEIN-Ext.

Addiitionally, Figure 13 on page 64 shows an incorrect graphic. Please see instead Appendix Figure 4 from the NEJM article.[16]

D11. Page 63 paragraph 4 states 10 CRNM bleeds, table 18 states 7. Please clarify the true number of bleeds.

Both numbers refer to the placebo arm of the EINSTEIN-Ext trial, but each number is taken from a different study population and analysis. Both numbers are correct within the context in which they are provided.

The number of bleed events and the number of patients experiencing bleeds (two different quantities) will depend on the group of patients considered relevant, and the start and end point chosen in counting the events or patients. The more patients one considers and the longer one follows-up these patients, the greater the number of events, or patients experiencing events, one would expect to observe.

Page 63, paragraph 4 reports 10 patients experiencing CRNM bleeds in the context of a post hoc composite net benefit outcome. This value refers to the number of patients reporting this event between randomisation and the planned end of study treatment in the ITT population of 598 patients.

Table 18 reports 7 patients experiencing CRNM bleeds in the context of a safety analysis conducted in the trial's safety population. This value refers to the number of patients reporting this event in the safety analysis / safety population of 590 patients reported in the NEJM publication.

D12. Please clarify if the final bullet point of page 66 should read 'was numerically in favour' as the non-inferiority nature of this trial does not support claims to superiority (page 66, final bullet point).

We recognise that EINSTEIN-DVT did not demonstrate statistical superiority of rivaroxaban vs the comparator in the primary efficacy outcome ($p<0.001$ for non-inferiority, $p=0.0764$ for superiority).

Statistical superiority was however achieved in the net clinical benefit outcome. This outcome has the benefit of being a direct measurement of the risk-benefit trade-off associated with treatment (defined in Table 15 on page 45 of the submission). The HR for this outcome was 0.67, 95% CI 0.47 to 0.95, $p=0.03$.

The bullet point referred to is in a qualitative overview of the studies, and there are of course limitations in depending overly on p-values.[71-73] The direction of the treatment effect for the primary efficacy outcome (HR=0.68) was in favour of rivaroxaban rather than in favour of the comparator. The direction of the treatment effect for the primary safety outcome (HR=0.97) was also in favour in rivaroxaban, but the effect size was smaller (HR closer to one).

D13. Please clarify what data were included in the secondary analyses reported on page 75, Table 25. In Table 25, three analyses are presented. There is some description of which data was used in secondary analyses 1 and 2, but this is not clearly described. We would like to be clear what data sources were used in all three analyses, so that it is clear how they differ from each other.

Data used in the primary and two secondary analyses presented in Table 25 on page 75 were taken from Table 20 on page 71.

The primary analysis is of data from `EINSTEIN-DVT – whole population', Hull et al 2006, Lee et al 2003, and Meyer et al 2002.

Secondary analysis 1 is of data from `EINSTEIN-DVT – whole population' and Lee et al 2003.

Secondary analysis 2 is of data from `EINSTEIN-DVT – cancer subgroup', Hull et al 2006, Lee et al 2003, Meyer et al 2002.

Analyses presented in Tables 26-28 (pages 76-77) followed the same approach.

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