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Rivaroxaban for the treatment of pulmonary embolism and the prevention of recurrent venous thromboembolism

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Vicky Copley, Research Fellow, SHTAC
Karen Pickett, Research Fellow, SHTAC
Keith Cooper, Senior Research Fellow, SHTAC
Jonathan Shepherd, Principal Research Fellow, SHTAC

Correspondence to Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
First Floor, Epsilon House
Enterprise Road, Southampton Science Park
Southampton SO16 7NS
Email: jps@soton.ac.uk
www.southampton.ac.uk/shtac

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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.

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Contributions of authors

V Copley (Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; K Pickett (Research Fellow) critically appraised the clinical-effectiveness systematic review and drafted the report; K Cooper (Senior Research Fellow) critically appraised the health economic systematic review and the economic evaluation and drafted the report; J Shepherd (Principal Research Fellow) critically appraised the clinical-effectiveness systematic review, the health economic systematic review and the economic evaluation, drafted the report and project managed the review.

[redacted].

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LIST OF ABBREVIATIONS

ACTS	Anti Clot Treatment Scale
AIC	Academic in confidence
BNF	British National Formulary
CIC	Commercial in confidence
CRD	Centre for Reviews and Dissemination
CRNM	Clinically relevant non-major bleeding
CSR	Clinical study report
CTEPH	Chronic ThromboEmbolic Pulmonary Hypertension
DVT	Deep Vein Thrombosis
EC	Extracranial
ERG	Evidence Review Group
LMWH	Low Molecular Weight Heparin
HR	Hazard Ratio
HRG	Healthcare resource group
HRQoL	Health related quality of life
IC	Intracranial
ICER	Incremental cost-effectiveness ratio
INR	International Normalised Ratio
mL	millilitre
NMB	Net monetary benefit
NR	Not reported
PCC	Prothrombin Complex Concentrate (PCC)
PE	Pulmonary embolism
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTS	Post Thrombotic Syndrome
rFVIIa	activated recombinant factor VII
RCT	Randomised Controlled Trial
RR	Relative Risk
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TSQM	Treatment Satisfaction Questionnaire for Medication
UH	Unfractionated heparin
VKA	Vitamin K Antagonist
WTP	Willingness to pay

SUMMARY

Scope of the manufacturer submission

The scope of the manufacturer's submission is the clinical-effectiveness and cost-effectiveness of rivaroxaban for the treatment of pulmonary embolism (PE) and prevention of recurrent VTE. The decision problem specified in the submission generally accords with the scope of the NICE appraisal with a few exceptions. The decision problem does not include patients with severe renal disease or with an increased risk of bleeding, or patients who are haemodynamically unstable. The manufacturer states that rivaroxaban is not suitable for these groups based on the draft Summary of Product Characteristics (SmPC). Also, the submission does not compare rivaroxaban with fondaparinux, stating that this drug is rarely used in the NHS and a lack of trial evidence to support such a comparison.

Summary of submitted clinical-effectiveness evidence

The clinical-effectiveness evidence in the MS is based on a systematic review which identified one large multi-national Randomised Controlled Trial (RCT) (the EINSTEIN-PE trial), which assessed the non-inferiority of rivaroxaban to the current standard of treatment, Low Molecular Weight Heparin (LMWH) and Vitamin K antagonist (VKA). Patients in the comparator arm received the LMWH drug enoxaparin (for a minimum of five days until anticoagulation was established) overlapping with the VKA drug (either warfarin or acenocoumarol) for either 3, 6 or 12 months (intended treatment duration determined by the treating physician prior to randomisation).

The primary efficacy outcome of the trial was symptomatic recurrent VTE, defined as "the composite of recurrent DVT, non-fatal or fatal PE including unexplained death for which PE could not be ruled out". The intention-to-treat (ITT) analysis showed that symptomatic recurrent VTE events occurred in 50 (2.1%) patients in the rivaroxaban arm compared to 44 (1.8%) patients in the LMWH+VKA arm. The associated hazard ratio (HR) was 1.12, with 95% confidence intervals of 0.75 to 1.68 (P = 0.003, one-sided) confirming the non-inferiority of rivaroxaban (non-inferiority judged if the upper limit of the two sided 95% CI for the HR was below the pre-defined non-inferiority margin of 2.0). A superiority test showed that rivaroxaban was not superior to dual LMWH+VKA (P = 0.57, two-sided).

[redacted].

[redacted]
[redacted].

The primary safety outcome was clinically relevant bleeding, defined as major bleeding and other clinically relevant non-major bleeding. The primary safety outcome was observed in 249 (10.3%) of the rivaroxaban group, and 274 (11.4%) of the LMWH+VKA group, HR= 0.90 (0.76-1.07, p=0.23). There was a statistically significant difference favouring rivaroxaban in major bleeding, n=26 (1.1%) vs n=52 (2.2%) (HR 0.49, 95% CI 0.31 to 0.79, p=0.003).

There were 58 deaths among patients in the rivaroxaban arm, compared to 50 deaths in the LMWH+VKA group, HR 1.13 (95% CI 0.77 to 1.65, p=0.53). The incidence of death caused by PE or where PE could not ruled-out, or by bleeding appeared similar between treatments.

[redacted].

The incidence of adverse events and serious events was around 80% and 20%, respectively, in both trial arms (not statistically significant). Permanent discontinuation of the study drug was also similar between arms.
[redacted].

Health related quality of life (HRQoL) was not measured in the EINSTEIN-PE trial, however, the manufacturer reports patient treatment satisfaction data which they suggest is indicative of HRQoL. It is stated that patient treatment satisfaction was consistently higher in the rivaroxaban arm than in the LMWH+VKA arm over the treatment period (statistically significant), based on

Anti-Clot Treatment Scale and Treatment Satisfaction Questionnaire for Medication (TSQM) scores.

Summary of submitted cost-effectiveness evidence

The manufacturer's submission to NICE includes:

i) a review of published economic evaluations of pharmaceutical interventions for the treatment and secondary prevention of VTE.
ii) a report of an economic evaluation undertaken for the NICE Single Technology Appraisal (STA) process. The cost-effectiveness of rivaroxaban is compared to LMWH+VKA for the treatment of PE and prevention of recurrent VTE.

Depending on the assumed anticoagulation treatment duration, the cost-effectiveness analysis uses either a 13 or 14-state Markov model to estimate the cost-utility of rivaroxaban compared to LMWH+VKA in adults with an acute PE. Results are presented by duration of anticoagulation therapy (3 months/6 months/12 months/lifelong). The model has a lifetime horizon of 40 years and a cycle length of 3 months. A separate cost-minimisation analysis comparing rivaroxaban to LMWH monotherapy was undertaken to inform the appraisal of the potential value of rivaroxaban in PE patients with active cancer.

The cost-effectiveness analysis shows that at all treatment durations except lifelong rivaroxaban dominates LMWH+VKA, i.e. rivaroxaban is cheaper and more effective than LMWH+VKA. For lifelong treatment the incremental cost per Quality Adjusted Life Year (QALY) gained is £13,252.

The net monetary benefit (NMB) at a willingness-to-pay threshold (WTP) of £20,000 per QALY was reported as an outcome from deterministic sensitivity analyses for 3, 6, and 12 months' treatment durations. The NMB was positive in all analyses. Overall the NMB was sensitive to parameters including the treatment effect for recurrent VTE, major bleeds, and warfarin (International normalised ratio, INR) monitoring visits (the latter becoming increasingly prominent with increased treatment duration). The incremental cost-effectiveness ratio (ICER) was reported as the outcome from deterministic sensitivity analysis for lifelong treatment duration and was most sensitive to changes in the assumed frequency of INR monitoring visits.

Results of the probabilistic sensitivity analysis (PSA) indicate that at a threshold willingness to pay of £20,000 per QALY the probability that rivaroxaban is cost-effective compared to

LMWH+VKA is 99.9%, 95.9%, 93.7% and 59.1% for 3 months, 6 months, 12 months and lifelong treatment respectively.
The cost-minimisation analysis indicates that over a six month period rivaroxaban is associated with a cost saving of £903.39 compared to dalteparin for treatment of PE in active cancer patients.

Commentary on the robustness of submitted evidence

Strengths

- The decision problem generally accords with the scope of the appraisal, with a few exceptions.
- The MS conducted a systematic search for clinical and cost-effectiveness studies of rivaroxaban. One large multi-national open-label RCT was included. It appears unlikely that the searches missed any additional clinical-effectiveness or cost-effectiveness studies that would have met the inclusion criteria.
- The included RCT is of reasonable quality and low risk of bias (though due to the nature of the comparator drug administration methods it was not patient or clinician-blinded).
- The MS appears to present unbiased estimates of the primary outcome for rivaroxaban versus LMWH+VKA.
- The economic model presented in the model used an appropriate approach for the disease area, and generally plausible assumptions.
- The cost-effectiveness analysis generally meets the requirements of the NICE reference case, with the exception of the active cancer subgroup in which a cost-minimisation analysis was performed.

Weaknesses and Areas of uncertainty

- The patient population in the trial may not be fully representative of the treatment population in general. In particular, patients with severe renal failure were excluded from the RCT.
- The clinical-effectiveness of rivaroxaban is supported by just one trial (though, as stated, of reasonable quality) which assessed outcomes over a 12 month period. No other trials, including those assessing the effectiveness and safety of long-term treatment beyond 12 months, are known to be in progress.

- There is little evidence to inform the treatment effect of rivaroxaban relative to LMWH+VKA beyond 12 months. Rivaroxaban becomes much less cost-effective for lifelong treatment if higher hazard ratios are assumed for the treatment effect after 12 months.
- The EINSTEIN-PE trial included a subgroup of patients with active cancer, but the number of patients is small and there were wide confidence intervals. Furthermore, treatment with a VKA is not recommended in such patients. The manufacturer did not consider it appropriate to conduct an indirect comparison of rivaroxaban with long-term LMWH monotherapy and therefore the MS presents a cost-minimisation analysis rather than a cost-effectiveness analysis, based on the assumption of equivalent efficacy and safety. The ERG considers this analysis to be speculative.

Summary of additional work undertaken by the ERG

The ERG amended the base case for lifelong treatment in order to correct an apparent model wiring error. This reduced the ICER calculated by the manufacturer. The PSA for the amended lifelong base case was re-run.

The ERG also explored plausible scenarios including amendments to the assumptions on location and frequency of INR monitoring, and variation to the efficacy and safety effects of rivaroxaban. In these scenarios rivaroxaban always dominated LMWH+VKA at treatment durations up to 6 months and was generally cost-effective at a WTP threshold of £20,000 per QALY in the 12 month treatment case, one scenario excepted. In two scenarios in the lifelong treatment case rivaroxaban was not cost-effective at a WTP threshold of £30,000 per QALY.

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Bayer plc on the clinical-effectiveness and cost-effectiveness of rivaroxaban for the treatment of pulmonary embolism (PE) and prevention of recurrent venous thromboembolism (VTE). It identifies the strengths and weakness of the MS. A clinical expert was consulted to advise the Evidence Review Group (ERG) and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 17th December 2012. A response from the manufacturer via NICE was received by the ERG on 7th January 2013 and this can be seen in the NICE evaluation report for this appraisal.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The overview of the disease is clear, detailed and appears to be accurate.

2.2 Critique of manufacturer's overview of current service provision

The overview of current service provision is clear and appears to be accurate. Extensive reference is made to the recent NICE clinical guideline on the management of Venous Thromboembolism (VTE) (CG 144)[1].

2.3 Critique of manufacturer's definition of decision problem

Population

The population described in the decision problem is 'people with pulmonary embolism', in accordance with the population specified on page 2 of NICE's scope. (NB. The scope also more specifically mentions 'acute symptomatic pulmonary embolism' in the remit/appraisal objective on page 1). This is not mentioned in the decision problem, however, the manufacturer does mention 'patients with symptomatic PE' in their systematic review inclusion criteria- Section 3.1.2 of the ERG report below.) The licence indication for rivaroxaban for the treatment of DVT and PE is restricted to adults. The scope and decision problem do not make a distinction between children and adults.

The decision problem includes the three subgroups specified in the NICE scope: underlying risk of bleeding; provoked or unprovoked VTE; presence of active cancer. These would appear to be clinically relevant subgroups: active cancer is a risk factor for PE; and whether or not the PE is provoked or unprovoked is a prognostic factor (i.e. likelihood of VTE recurrence is greater if index event is unprovoked). Intended duration of treatment is used as a proxy by the manufacturer for underlying risk of bleeding (because the assigned treatment duration was influenced by initial clinician assessment of the risk-benefit of anticoagulation for each patient in the key licensing trial - EINSTEIN-PE).[2]

Intervention

The decision problem does not specify the recommended rivaroxaban dose, though this is given later on in the MS. The dose used in the MS economic evaluation reflects the draft Summary of Product Characteristics (SmPC) ('Treatment of DVT and prevention of recurrent DVT and PE' - recommended dose for the initial treatment of acute DVT is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE). (NB. The draft SmPC, dated October 2012, appears to have been superseded by a newer document reflecting the new licenced indication for rivaroxaban for the treatment of acute PE http://www.xarelto.com/html/downloads/Xarelto-Prescribing_Information-Nov-2012.pdf. Doses appear the same.) The MS notes that a reduced dose should be given to patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min), and risk of bleeding (see MS Table 2 page 19).

Comparators

The comparators in the decision problem match the NICE scope with the exception of fondaparinux which was not included in the decision problem. The stated comparators (Low Molecular Weight Heparin (LMWH) and vitamin K antagonist (VKA)) are the current standard of treatment for PE in the NHS. The manufacturer suggests that there is a lack of evidence specific to fondaparinux, and that it appears to be seldom used.

[redacted] The ERG is not aware of any comparative trials of rivaroxaban and fondaparinux. Furthermore, the ERG's clinical advisor agreed that fondaparinux is rarely used in practice.

Unfractionated heparin (UH) is specified as a comparator in the scope, in subgroups of patients with very severe renal failure, increased risk of bleeding, PE and haemodynamic instability. However, the decision problem does not include these subgroups of patients as the draft SmPC states that rivaroxaban is not suitable for these subgroups of patients.

The ERG is not aware of any other relevant licensed comparators not included (based on treatment recommendations in NICE CG 144).

The scope requires consideration of continued therapy with LMWH for people in whom a VKA is not considered appropriate. The manufacturer interprets this to mean patients with active cancer. It is not stated whether there are any other subgroups of patients in whom VKA would not be indicated. The British National Formulary (BNF)[3] states contra-indications to warfarin include pregnancy and breastfeeding, severe hepatic and severe renal impairment (the SmPC states rivaroxaban is not recommended in these patients either). The submission made to NICE for this appraisal on behalf of the British Society of Haemostasis and Thrombosis suggests that intravenous drug users with a VTE would receive LMWH rather than a VKA due to issues around being able to satisfactorily monitor coumarin therapy in these patients. Patients who are "technically difficult" (patients with poor venous access for blood sampling) would also not receive VKA.

Outcomes

The outcomes specified in the decision problem generally match the NICE scope and there do not appear to be any clinically relevant outcomes omitted. Health-related quality of life (HRQoL) is specified in the scope, and the manufacturer notes that this was not measured in the EINSTEIN-PE trial, though the trial did measure treatment satisfaction which they suggest can be considered indicative of HRQoL. Additional outcomes are reported in the submission (though not specified in the decision problem) and include: net clinical benefit; time in target in the International Normalised Ratio (INR) range with LMWH+VKA; and healthcare resource utilisation (duration of hospital).

Economic analysis

The economic evaluation proposed in the decision problem is appropriate to the NICE scope (with the exception that a cost-minimisation analysis rather than a cost-utility analysis was conducted for the cancer subgroup – see MS Section 7.9).

Other relevant factors

The MS states that there are no known equity or equality issues.

3 CLINICAL-EFFECTIVENESS

3.1 Critique of manufacturer's approach to systematic review

3.1.1 Description of manufacturer's search strategy

The manufacturer conducted separate literature searches for: clinical-effectiveness studies (MS Section 6.1); studies to be considered for an indirect comparison / mixed treatment comparison (MS Section 6.7.1); cost-effectiveness studies (MS Section 7.1); HRQoL (MS Section 7.4.5); and costs and resources (MS Section 7.5.3). The ERG considers these literature searches fit for purpose. Search methodology was documented transparently by the manufacturer, with satisfactory database selection (see below, though for the sake of completeness perhaps ISI Web of Science could have been used in all searches). All strategies comprise appropriate utilisation of free text, index terms, RCT, cost and quality of life related search filters, and were appropriately combined into sets.

For the clinical-effectiveness search the manufacturer included all of the databases required by NICE, plus CINAHL and Bayer's in-house clinical trials database (Trialfinder). The search strategy in MS Appendix 10.2 is transparent and reproducible. Reference lists of included articles, key review papers and relevant guidelines were also checked for other relevant studies. Additional searching for conference material on databases such as Web of Science or Zetoc was not undertaken in the clinical searches (though not mentioned as a pre-requisite for this section by NICE).

The indirect and mixed treatment comparisons search was based on a Cochrane systematic review of anticoagulation in patients with cancer,[4] and included the NICE required databases plus ISI Web of Science. The American Society for Clinical Oncology and the American Society of Hematology were hand searched with supplementary PubMed searches.

The manufacturer's cost-effectiveness search was an update of the search conducted by the National Clinical Guideline Centre (NCGC) (which informed NICE Clinical Guideline 144[1]). This search covered all of NICE's required databases, plus also the NICE website was searched to identify any relevant economic models.

The clinical-effectiveness searches across Medline, Embase and Medline In-Process was re-run by the ERG Information Scientist, as a benchmark, and produced a similar return of results allowing for different database start dates. The other searches documented were not re-run as they also appeared to be of good quality.

The manufacturer did not report searching on-going clinical trials databases for studies recently completed or in progress. The ERG Information Scientist searched the following clinical trials registries: UKRCN Study Portfolio and ClinicalTrials.gov. The FDA and EMA websites were also checked. The results were examined by an ERG researcher with nothing additionally relevant being identified, confirming the manufacturer's statement that no completed or ongoing studies of rivaroxaban for pulmonary embolism and venous thromboembolism are likely to be available in the next 12 months.

The manufacturer also reports systematic searches for particular economic model input parameters (e.g. complications of VTE). Brief details of these searches are given (e.g. databases) but full search strategies are not supplied. A reference is given for these searches to an unpublished systematic review conducted by IMS Health for Bayer (Reference 115 in the MS). The ERG has not appraised these searches.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection.

The inclusion and exclusion criteria for the clinical-effectiveness systematic review are clearly stated (MS Section 6.2, Table 6 page 46). The criteria generally reflect the decision problem

and, in turn, the NICE scope. The population is defined as 'patients with symptomatic PE' whereas the NICE scope specifies 'people with pulmonary embolism' (page 2), so the inclusion criteria therefore does not appear to include patients who have had a PE who may no longer be symptomatic following treatment, but could be at risk of recurrent VTE (prevention of recurrent VTE is mentioned in the remit/appraisal objective in the NICE scope) (see Section 3.1.3 below).

In terms of intervention, the criteria include "rivaroxaban vs any comparator" which is broader than the scope and the decision problem which specifies LMWH+VKA as the comparator (the NICE scope also including fondaparinux as a comparator, but the decision problem excluded it – as discussed in Section 2.3 of this report). Eligibility of specific efficacy and safety outcomes are not reported, so in theory the systematic review could have included outcomes that are outside the decision problem and scope (and does so – length of hospital stay is reported on MS page 94, and time in INR range, reported on MS page 101 – neither of these are specified in the NICE scope or decision problem).

Only RCTs were eligible for inclusion, though there was no restriction on inclusion based on any assessment of methodological quality or risk of bias. Setting was not used as an inclusion criterion.

A PRISMA flowchart is provided (MS Figure 3 page 48), and the numbers of studies included/excluded at each stage balance. Reasons for exclusion are given in the flowchart, though citations for the 27 records excluded at full-text record assessment stage are not given (this is recommended by the Cochrane Collaboration in systematic reviews).[5]

The manufacturer does not make any statement about how closely their inclusion/exclusion criteria match the decision problem or NICE scope, and any other biases in their selection of studies.

3.1.3 Identified studies

One trial was included in the MS – the EINSTEIN-PE trial. Summary details of the RCT are given in MS Tables 8, 9, 10, 11 and Figures 4 and 5. A copy of the trial report in the New England Journal of Medicine is available.[2] This was supported by Bayer HealthCare and Janssen Pharmaceuticals. The ERG requested a copy of the clinical study report (CSR),

however the manufacturer did not supply it and reported that it is not Bayer policy to supply CSRs. [redacted].

Although the PRISMA flowchart reports that one trial met the inclusion criteria (EINSTEIN-PE), the MS presents, for information, an overview of seven rivaroxaban studies (MS Table 7, Section 6.2.3 page 49). Only one of these trials meets the inclusion criteria (EINSTEIN-PE). However, a second trial included in the table (EINSTEIN-Ext)[6] is stated not to meet the inclusion criteria for the systematic review of clinical-effectiveness because "it was not a study of patients with symptomatic PE" (MS page 49). However, the scope of the appraisal and decision problem defines the population of relevance as 'people with pulmonary embolism' and therefore could be considered broader than solely people with acute symptomatic pulmonary embolism. The remit specified in the scope also includes the prevention of recurrent VTE (which was the aim of EINSTEIN-Ext)[6]. Eligibility criteria for EINSTEIN-Ext[6] were an objectively confirmed symptomatic DVT or PE and treatment for 6 to 12 months with a VKA or rivaroxaban and if there was equipoise regarding the need for continued anticoagulation. The trial therefore appears to be relevant, in part, to the scope and decision problem (though the comparator was placebo rather than LMWH+VKA, which is outside of the scope but exclusion of this study contradicts the manufacturer's inclusion criteria which states "any comparator" was eligible – MS Table 7 page 49).

[redacted]. Despite exclusion of this trial from the manufacturer's systematic review of clinical-effectiveness they briefly report results on MS page 50, and on MS page 94/95 for the whole trial population. The ERG has not included these results in this report.

The ERG is not aware of any other relevant RCTs and considers that the MS is likely to have identified all relevant RCT evidence. No non-RCTs are included. The MS has not listed any ongoing trials and states that no results from completed or on-going trials are likely to be available in the next 12 months, based on their search of their in house trials database. The ERG has searched other trials databases and has not identified anything relevant (see Section 3.1.1 of the ERG report).

3.1.4 Description and critique of the approach to validity assessment

The manufacturer has provided a tabulated quality assessment of the EINSTEIN-PE trial on MS page 67 (Table 14) and in Appendix 3 (Table 100, MS page 299). The quality assessment follows the NICE criteria and is appropriate. Table 1 shows the ERG independent assessment of study quality and the MS assessment. As this table shows, the ERG generally agrees with the manufacturer's assessment.

Table 1: Manufacturer and ERG assessment of trial quality of EINSTEIN-PE study

NICE QA Criteria for RCT	MS response	ERG response
1. Was the method used to generate random allocations adequate?	Yes	Yes
2. Was the allocation adequately concealed?	N/A	Yes. The manufacturer has probably marked this as N/A in their quality assessment as the trial was open-label. However, this QA question refers to whether or not the treatment allocation could have been foreseen by patients and investigators prior to randomisation, and the ERG notes that this was adequately concealed through the use of a central computerised allocation system.
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Stated as "Investigators and patients were not blinded to treatment. Outcome assessors were blinded to treatment allocation" on MS page 67. In Appendix 3 of MS (page 300), stated as: "No (Investigators & Patients). "Yes (Outcome assessors)."	No. This was an open-label trial. Potential bias from this was limited by a requirement that suspected cases of symptomatic recurrent VTE had to be independently assessed by a central independent adjudication committee (CIAC), who were blinded to treatment allocation, to be classed as events in the primary efficacy analysis. The MS suggests that some safety outcomes were also assessed by the CIAC, but it is not clear specifically which ones

		were. The ERG sought clarification from the manufacturer about this, and they confirmed that bleeding and vascular events were assessed by the CIAC. Additionally, death events were independently adjudicated. However, the lack of patient blinding may have affected some of the more subjective outcomes, such as patient treatment satisfaction and pain-related adverse events, but due to the method of treatment administration for the comparator in this study, patient blinding would not have been feasible. [redacted].
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No. Overall treatment discontinuation rates between arms were similar (p = 0.07). However, a higher proportion of patients in the LMWH+VKA arm (4.9%) withdrew their consent than in the rivaroxaban arm (2.7%) (the p-value for this is not provided by the manufacturer, so it is not possible to tell if this is a statistically significant difference).
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
7. 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

One concern that the ERG has identified about the EINSTEIN-PE trial is that the trial population may not be fully representative of the PE patient population. The trial excluded patients with a creatinine clearance of < 30 mL/min, clinically significant liver disease, and a high risk of bleeding. The clinical expert consulted by the ERG stated that within their local clinical practice

they treat a range of people with PE including some of those excluded from the trial, and the patient population in the trial is not wholly representative of the general treatment population. The ERG note that the trial excluded patients with severe renal failure (a creatinine clearance of 15-29 mL/min), who are a group at higher risk of bleeding according to the SmPC. However, the SmPC advises that rivaroxaban can be used with caution with these patients and recommends use of the standard dose, unless the risk of bleeding in these patients outweighs the risk for recurrent VTE, in which case a lower dosage of 15 mg once daily is recommended after the first three weeks of treatment (instead of 20 mg once daily). As these patients are at a higher risk of bleeding and were excluded from the trial, it is possible that the trial may have underestimated the rate of bleeding that may be seen in clinical practice with rivaroxaban.

Furthermore, the ERG notes that despite the screening criteria for the trial excluding patients with a creatinine clearance of < 30 mL/min, six patients with a creatinine clearance of < 30 mL/min were included in the trial in the end (as shown in Table 9, MS page 56). The ERG sought clarification from the manufacturer about the reasons for this, but the manufacturer did not provide a reason why these patients were included. In terms of the justification for excluding patients with a creatinine clearance of < 30 mL/min, in their response to the ERG's request for clarification, the manufacturer stated that the reason for this was that the trial design was "set with regard for EMA requirements and designs of other RCTs for novel treatments for the treatment of pulmonary embolism and deep vein thrombosis" (manufacturer's clarifications, page 3). The manufacturer acknowledges that there are limited clinical data available to determine the safety and efficacy of rivaroxaban with these patients, and the ERG concludes that the likely outcomes for these patients are currently unknown. The trial also excluded patients who needed thrombolysis, which means that a proportion of patients with extensive PE were not included in the trial and that the findings cannot be generalised to these patients. However, the SmPC states that rivaroxaban is not recommended for use with haemodynamically unstable PE patients or patients who require thrombolysis as its safety and efficacy in this group is unknown.

A further point noted by the ERG is that the MS states (page 62) that some of the patients allocated to the 12 month treatment duration did not necessarily complete the full 12 months of treatment when enrolment in the study was discontinued (see Section 3.1.6 of the ERG report for details of the discontinuation protocol). The MS does not state the reasons for this or provide data about the number of patients who did not complete treatment (clarification was sought from

the manufacturer), but the ERG notes that the study protocol states that treatment could be discontinued in this group when the enrolment target was met. In their response to the ERG's request for clarification, the manufacturer confirmed that this was protocol-specified. The trial journal publication[2] notes that treatment discontinuation rates between arms due to the termination of the trial were similar (5.2% [n = 125] and 5.5% [n = 132] for the rivaroxaban and LMWH+VKA arms, respectively), so this is likely to have had a similar impact on outcomes in both arms. This translates to 13.8% of patients in rivaroxaban arm and 14.6% of patients in the LMWH+VKA arm who were allocated to 12 months of treatment not completing the full treatment length [redacted]. This is worth noting, but given the low and similar rates of symptomatic VTE recurrence shown in the results for patients in each arm receiving this treatment duration (see Section 3.3.2 of this report and MS page 72), this is unlikely to have had an impact on the results.

3.1.5 Description and critique of manufacturer's outcome selection

The outcomes included in the EINSTEIN-PE trial are reported in MS Table 8 (Section 6.3.2 page 52) and further defined in MS Table 11 (Section 6.3.5 page 58). In general they match the outcomes in the NICE scope and decision problem and are appropriate. The ERG notes that symptomatic recurrent VTE events were measured up to the end of the intended treatment period (MS page 63) and possibly up to 30 days after treatment ended (Table 8 MS page 53) (the exact period of measurement is unclear in the MS). The clinical expert consulted by the ERG advised that risk of VTE recurrence is cumulative over time, and therefore rates of future symptomatic recurrent VTE events could be higher than found in the trial as it only measured these within a limited follow-up period. For example, one study[7] shows that the incidence of recurrent VTE one year following anticoagulation treatment among patients with a first episode of VTE was 11.0%, followed by 19.6% at three years, 29.1% at 5 years and 39.9% at 10 years. A shorter treatment duration of up to 6 months was associated with a higher risk of VTE recurrence.[7] The cumulative incidence was also higher in patients with unprovoked VTE,[7] and these patients made up 64.5% of the EINSTEIN-PE sample (see Table 9, MS age 57). The short follow-up period in the EINSTEIN-PE trial means that it is unknown how rivaroxaban might modify this cumulative risk of recurrence into the future once treatment is ceased.

Vascular events (ischaemic stroke, myocardial infarction, ischaemic stroke) are listed in MS Section 6.10.3 page 99 and it is implied that these are safety events. The ERG clinical advisor confirmed these would be regarded as safety outcomes.

Outcomes included in the scope/decision problem that were not originally reported by the EINSTEIN-PE trial[2] were the complications of PE and DVT (pulmonary hypertension, heart failure, and Post Thrombotic Syndrome (PTS)).
[redacted].

As mentioned above, HRQoL was not directly measured in the trial. However, the trial measured treatment satisfaction using the Anti-Clot Treatment Scale (ACTS) and the Treatment Satisfaction Questionnaire for Medication (TSQM) instruments. The manufacturer considers these to be the "closest outcomes recorded in EINSTEIN-PE to health-related quality of life" (MS page 60). ACTS is reported to be validated (no further detail is given, but a reference is provided to a 2012 journal paper). The MS does not state whether the TSQM is validated, but following request for clarification from the ERG the manufacturer provided a citation to a 2005 study testing the construct validity of the instrument (manufacturer's clarifications, page 17). These treatment satisfaction data were not used to estimate utility values in the manufacturer's economic evaluation.

Outcomes from the trial that are not explicitly included in the scope/decision problem are: net clinical benefit; time in target range with LMWH+VKA; and various healthcare resource utilisation outcomes (duration of hospital stay, visits to healthcare providers, diagnostic procedures).

3.1.6 Description and critique of the manufacturer's approach to trial statistics

Enrolment for the EINSTEIN-PE trial was discontinued when the pre-specified number of VTE events to provide a statistical power of 90% (88 events) had been reached. The MS presents the trial results for all outcome measures of relevance to the scope (including the number of patients included in each analysis), but does not report some relevant data for some of the analyses, which we have detailed below (the ERG requested these data from the manufacturer). No interim data are reported.

Data for the primary efficacy outcome, symptomatic recurrent VTE, were analysed using a Cox proportional hazard model, stratified by intended treatment duration (3, 6 and 12 months) and adjusted for the presence of malignancy at baseline. It was pre-specified that for non-inferiority to be concluded, the upper limit of the two-sided 95% CI for the hazard ratio for the symptomatic recurrent VTE outcome had to be below 2.0. The MS states that this translated to rivaroxaban needing to be at least 50% as efficacious as LMWH+VKA in preventing symptomatic recurrent VTE to be considered non-inferior. However, it should be noted that the trial protocol,[8] and manufacturer's response to clarification questions from the ERG, state that this margin actually translates to a retention of at least 66% of the effect of LMWH+VKA (a more conservative estimate). The manufacturer calculated the non-inferiority margin based on a meta-analysis of 14 historical trials of the impact of UFH/LMWH followed by VKA in comparison to placebo treatment, no treatment or a less effective treatment on VTE recurrence among patients with acute DVT and/or PE, which is detailed in the trial protocol.[8] This is an appropriate and recommended approach to calculating the margin.[9;10] The ERG notes that only two of the included studies were based on patients with PE only, so the treatment effect found in the meta-analysis is not entirely relevant to the PE patient population. The ERG also notes that the manufacturer did not report literature search dates or the databases searched, so it is uncertain whether or not the meta-analysis captured all relevant studies. However, despite these concerns, the ERG suggests that the manufacturer's non-inferiority margin calculation is on the whole appropriate (and this is supported by the results of the EINSTEIN-PE trial which show a similar rate of symptomatic VTE recurrence in the LMWH+VKA arm to that found in the in the combined UFH/LMWH and VKA group in the meta-analysis).

The manufacturer conducted an ITT analysis (rivaroxaban n= 2419; LMWH+VKA n=2413) and per-protocol analysis (rivaroxaban n=2224; LMWH+VKA n=2238) of symptomatic recurrent VTE. The safety analysis was based on the safety population, which consisted of all patients who had received at least one dose of the study drug (rivaroxaban n = 2412; LMWH+VKA n = 2405). As can be seen, the number of patients included in the safety analysis is broadly similar to the number included in the ITT analysis. The symptomatic recurrent VTE and clinically relevant bleeding (the primary safety outcome) results are presented in the MS as the number and proportion of patients who experienced an event

[redacted], along with associated

hazard ratios and 95% CIs. A Kaplan-Meier plot is used to show the proportion of symptomatic recurrent VTE and bleeding events that occurred over time in each arm. Other adverse event data are presented in terms of the number and proportion of patients who experienced an event (with p-values reported for some events), with associated relative risk ratios, absolute risk differences and 95% CIs. Additionally, a number of pre-specified subgroup analyses were conducted to test for non-inferiority in terms of the symptomatic VTE outcome according to patient baseline characteristics,

[redacted]. Pre-specified subgroup analyses based on patient baseline characteristics were also conducted for the clinically relevant bleeding outcome,

[redacted].

The ERG notes that 19 subgroup analyses of the recurrent VTE data were reported (MS Figure 7 page 73) while only 10 subgroup analyses of the clinically relevant bleeding data were reported (this was also the case in the trial journal publication),[2] which raises the possibility that primary safety data may not have been reported for some pre-specified subgroups. (The ERG sought clarification from the manufacturer. The manufacturer stated that different subgroup analyses were pre-specified for the recurrent VTE and clinically relevant bleeding analyses, based on the factors associated with the risk of occurrence of each.) These were specified in a separate statistical analysis plan rather than in the trial protocol. All three of the subgroups of interest in the NICE scope were included in the efficacy analysis, but only two of the three are in the safety analysis. (Omitted was provoked or unprovoked VTE. The manufacturer suggests that this is not a predictor of bleeding – manufacturer's clarifications, page 8-9.)

The manufacturer specified that if non-inferiority was found for the primary efficacy outcome, superiority was then to be tested for this (based on the two-sided 95% CIs for the hazard ratio) and also for the primary safety outcome (defined for the superiority analysis as bleeding that occurred while patients were receiving treatment).

Patient treatment satisfaction, a secondary outcome, was measured in only a subsample of the trial patients (n = 2283) (MS page 37) drawn from Canada, France, Germany, Italy, The

Netherlands, UK and the US, as these were the countries for which a translation of the measurement scales was available at the start of the trial. The manufacturer states in their clarifications to the ERG that the "Characteristics of patients involved in this sub-study appeared representative of the overall EINSTEIN PE population in terms of age, gender, prior history of VTE, and nature of index PE" (manufacturer's clarifications, page 15), although they have not provided data to substantiate this claim. They confirmed that 1200 patients in the rivaroxaban arm and 1197 patients in the LMWH+VKA arm took part in this sub-study. Patient treatment satisfaction data were analysed using repeated measures regression analyses. The MS states that analyses of the ACTS measure were ITT analyses, and in their clarifications to the ERG, the manufacturer indicated that the TSQM data analyses were also ITT analyses. The ERG, however, suggests that they are not ITT analyses.

[redacted]. The manufacturer has only reported minimal results for the patient treatment satisfaction analyses in the MS, in terms of mean scores for each arm and p-values for the ACTS measures (these were not reported for the TSQM measure, and the ERG requested the TSQM results from the manufacturer) and some commentary on changes over time on both the ACTS and TSQM measures.

The manufacturer's approach to data analysis is, on the whole, appropriate, but the patient treatment satisfaction data should be treated with caution, as some patients appear to be missing from these analyses and it is not clear how representative this sub-sample is of the wider PE population (though note, treatment satisfaction data were not used to estimate utility values in the manufacturer's economic evaluation).

3.1.7 Description and critique of the manufacturer's approach to the evidence synthesis

The manufacturer presents a narrative review of the EINSTEIN-PE trial, including tabulated data. As only one study was identified as relevant to the review, a meta-analysis was not conducted. The tabulated data and the data in the narrative mostly reflect the data reported in the trial paper,[2] with the exception

that [redacted]

[redacted] and one data point relating to an adverse event in Table 18 (MS page 79) differ to the data in the paper. However, the differences are minor and do not affect the interpretation of the data for either outcome. We have provided an overview of how the data presented in the MS for recurrent symptomatic VTE events differ from those presented in the paper[2] in Table 2 for information. Additionally, the number of patients stated to have discontinued the study drug due to an adverse event in Table 18 (MS page 79) differs to the number stated in Table 13 (MS page 64) and Figure 5 (MS page 65), but as the discrepancy in numbers is small this does not affect the interpretation of the data. (The ERG sought clarification from the manufacturer about why these data differed, and the manufacturer stated that this was due to the data in Table 13 and Figure 5 being drawn from a different data source to the data in Table 18; the data in Table 13 and Figure 5 related to the *primary* reason for premature termination of the study treatment as judged by the investigator.)

Some of the data reported in the MS were extracted from the CSR, so the ERG was unable to check these because, as stated earlier, the manufacturer did not supply the CSR.

Table 2 : Differences between the MS and trial publication in number of patients reported to have experienced the primary efficacy outcome, recurrent symptomatic VTE, in the ITT population

As reported in MS / paper[2]	Treatment group (n)	Primary efficacy outcome	Death (PE)	Death (PE cannot be excluded)	Symptomatic PE and DVT	Symptomatic recurrent PE only	Symptomatic recurrent DVT only
Data reported in MS	Rivaroxaban (2419)	50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	LMWH+VKA (2413)	44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Data reported in paper	Rivaroxaban (2419)	50	**2**	8	0	**22**	18
	LMWH+VKA (2413)	44	1	**5**	2	**19**	17

Note. Numbers that differ between the MS and paper[2] are highlighted in bold.

On MS page 81, the manufacturer states that they considered conducting an indirect comparison of rivaroxaban to long-term LMWH in patients with cancer, as there are no head-to-head RCTs of the clinical and cost-effectiveness of rivaroxaban in this group and this was a subgroup specified to be of interest in the scope. On reviewing this possibility, the manufacturer conducted a scoping search for relevant trials and identified a Cochrane systematic review of long-term VTE treatment in patients with cancer, which was published in 2011 and included

searches up to February 2010.[4] The manufacturer notes that their previous submission to NICE for TA 261 included an indirect comparison of the clinical-effectiveness among patients with cancer which drew on five trials (of long-term LMWH versus dual heparin VKA) included in a meta-analysis in the Cochrane review. The manufacturer acknowledges that an ERG report conducted by ScHARR[11] of the STA submission for TA 261 criticised the indirect comparison as not being robust and noted heterogeneity between the studies included in the meta-analysis in the Cochrane review. In their present submission the manufacturer states that it is unlikely that any new evidence has been published since the previous ERG report (January 2012)[11] (ScHARR updated searches and found no new evidence), and so based on this and the lack of robustness noted about the previous indirect comparison, they concluded that it was not worthwhile to conduct another indirect comparison. The ERG considers that this decision is justified given the limitations of the previous indirect comparison as discussed by ScHARR and acknowledged by the NICE Appraisal Committee. (See Section 4.1 of this report for details of the manufacturer's cost-minimisation analysis in patients with cancer.)

The manufacturer provides a summary in the MS of outcome data relating to VTE recurrence and bleeding in cancer patients from each of the five studies included in the meta-analysis in the Cochrane review,[4] along with data from the EINSTEIN-PE and EINSTEIN-DVT trials (MS Tables 20 to 23 on pages 85 to 88) relating to the impact of rivaroxaban in comparison to dual heparin/VKA on these outcomes for the cancer patients included in these trials. The manufacturer has provided tabulated data showing the results from each of these seven trials with no commentary about what the data show. As these data were not derived from an indirect comparison and are of limited usefulness (for example, the EINSTEIN-DVT trial included patients with DVT without PE, and is therefore not relevant to the decision problem)[6], the ERG has not provided any further critical appraisal of this nor summarised the results in this report.

3.2 Summary statement of manufacturer's approach

The ERG's assessment of the quality of the systematic review included in the MS, based on the CRD criteria,[12] is provided in Table 3. The systematic review is of a good quality according to the CRD criteria. Publications were screened for inclusion based on title and abstract by two reviewers independently, which is considered to be a desirable approach in conducting systematic reviews for reducing the likelihood that relevant studies will be missed.[12] It is implied that the full texts retrieved for further screening were also screened independently by two

reviewers, but this is not clear. The processes used for data extraction and quality assessment (e.g. whether or not these were performed by one or more reviewers) are also not clear.

The evidence included in the review reflects the decision problem defined in the MS, although as stated earlier in this report, some additional outcomes from the EINSTEIN-PE trial were included which were not specified in the scope (e.g. net clinical benefit and health care resource utilisation). Overall, there is a low chance of systematic error in the systematic review based on the methods used by the manufacturer.

Table 3 Quality assessment (CRD criteria) of MS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. The inclusion and exclusion criteria are stated in MS Section 6.2, Table 6 page 46, although, as detailed above, these do not fully reflect the scope.
2. Is there evidence of a substantial effort to search for all relevant research? Ie all studies identified	Yes. The manufacturer searched the databases specified by NICE, plus other databases including their database of trials. They also carried out manual searches of the reference lists of the included paper and of relevant reviews and guidelines. However, the manufacturer did not search for conference proceedings or ongoing trials (except for within their own trial database).
3. Is the validity of included studies adequately assessed?	Yes. The manufacturer has provided a tabulated quality assessment of the included EINSTEIN-PE trial on MS page 67 and page 299, which is appropriate and follows the NICE criteria. In Section 6.10.2 of the MS (page 95), the manufacturer has also considered issues of bias and study quality in their interpretation of the trial results and this is appropriate, although it may have benefited from consideration about the extent to which the trial results are generalisable to the PE patient population given that some patient groups were excluded from the study (e.g. patients with a creatinine clearance of < 30 mL/min).
4. Is sufficient detail of the individual studies presented?	Yes. Detailed information is provided about the patients included in the EINSTEIN-PE trial, as well as the methods and results of the trial.
5. Are the primary studies summarised appropriately?	Yes. The manufacturer has summarised the EINSTEIN-PE trial appropriately in a narrative review and provided supporting data for most outcomes.

3.3 Summary of submitted evidence

In this section of the report, we provide a summary of the clinical-effectiveness evidence submitted by the manufacturer (with the exception of duration of hospital stay and time in the INR range which were not in the scope/decision problem. However, we do report net clinical benefit, which was also not in the scope/decision problem, as it comprises the primary efficacy outcome and one of the safety outcomes – major bleeding). Data have been checked by the ERG against the original journal publication,[2] and we noted only a few minor discrepancies. Some of the results presented below are only available in the CSR, and the ERG could not check these data as the manufacturer did not supply a copy of the CSR to the ERG.

3.3.1 Summary of results for symptomatic venous thromboembolism recurrence (the primary efficacy outcome)

Symptomatic recurrent VTE was defined as "the composite of recurrent DVT, non-fatal or fatal PE including unexplained death for which PE could not be ruled out" (MS page 69). The manufacturer presents an ITT [redacted] analysis of symptomatic recurrent VTE. The ITT analysis was based on VTE events which occurred up to the end of the intended treatment duration. [redacted]. The ITT analysis showed that symptomatic recurrent VTE events occurred in 50 (2.1%) patients in the rivaroxaban arm compared to 44 (1.8%) patients in the dual LMWH+VKA arm. The associated hazard ratio was 1.12, with 95% CIs of 0.75 to 1.68, which confirmed non-inferiority of rivaroxaban (P = 0.003, one-sided). Superiority was then tested for, and the result of this showed that rivaroxaban was not superior to dual LMWH+VKA (P = 0.57, two-sided). As Table 4 shows, there

[redacted]

Table 4. Non-inferiority and superiority results for symptomatic recurrent VTE for each trial population

Trial population	Hazard ratio (95% CIs)	$P_{non\text{-}inf}$	P_{sup}
ITT population	1.12 (0.75 to 1.68)	0.003	0.57
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

3.3.2 Subgroup analyses results for symptomatic venous thromboembolism recurrence

In terms of subgroups of relevance to the scope, the manufacturer reports subgroup results for the intended duration of treatment (3, 6 and 12 months; which the manufacturer used as a proxy measure of patients' underlying risk of bleeding), provoked/unprovoked index event, and the presence of active cancer at baseline. The intended treatment duration [redacted] the 95% CIs around the hazard ratio for the patients with active cancer at baseline presented in Figure 7 (MS page 73) are wide, indicating much uncertainty around where the true effect for these patients lies. This is probably due to the low number of events occurring in each arm for these patients (2 of the 114 patients in the rivaroxaban arm with active cancer at baseline experienced symptomatic recurrent VTE in comparison to 3 of the 109 patients in the LMWH+VKA arm with active cancer at baseline).

3.3.3 Summary of results for net clinical benefit

The outcome of a net clinical benefit (composite of symptomatic recurrent VTE and major bleeding) was experienced in 83 patients (3.4%) in the rivaroxaban group and 96 patients (4.0%) in the dual LMWH+VKA therapy group (HR: 0.85, 95% CI, 0.63 to 1.14, P=0.28).

3.3.4 Summary of results for patient treatment satisfaction

Patient treatment satisfaction was measured by the ACTS Burdens, ACTS Benefits and TSQM scales at day 15 and months 1, 2, 3, 6 and 12 in a subgroup of 2283 patients. The findings from the analyses of the ACTS Burdens and ACTS benefits scales are presented in Table 5 (the manufacturer states that these are ITT analyses, but the ERG suggests that they are not; see our discussion of this in Section 3.1.6). The manufacturer reports mean scores on these scales

for each arm across timepoints. The manufacturer reports that patient treatment satisfaction, as measured by all three scales, was consistently higher in the rivaroxaban arm than in the LMWH+VKA arm over the treatment period. However, the ERG notes that the recently published conference abstract that presents these data[13] (this abstract was published after the MS was submitted to NICE) shows that ACTS Benefits scores were only higher in the rivaroxaban group than the LMWH+VKA group from month two onwards.

Table 5. Comparison of patient treatment satisfaction scores between the rivaroxaban arm and the LMWH+VKA arm

Treatment satisfaction measure	Rivaroxaban arm (mean)	LMWH+VKA arm (mean)	P value
ACTS Burdens	55.4	51.9	0.0001
ACTS Benefits	11.9	11.4	0.0001

Higher total scores indicate higher satisfaction

3.3.5 Summary of adverse events

The primary safety outcome was clinically relevant bleeding, defined as major bleeding and other clinically relevant non-major bleeding (see MS Table 11 page 58 for bleeding definitions. NB. The trial journal publication refers to this as 'first episode' clinically relevant bleeding). The primary safety outcome was observed in 249 (10.3%) of the rivaroxaban group, and 274 (11.4%) of the LMWH+VKA group, HR= 0.90 (0.76-1.07, p=0.23). The manufacturer suggest these results indicate a "comparable safety profile" of rivaroxaban and LMWH+VKA, though it should be pointed out that a test of superiority was used rather than a test for non-inferiority/equivalence, so comparability cannot strictly be concluded on the basis of a non-statistically significant difference.

The number and percentage of patients reporting major bleeding (and constituents thereof) and clinically relevant non-major bleeding are reported in MS Table 16 page 74 (reproduced in this report – Table 6). (NB. MS Table 16 does not report the constituents of fatal and non-fatal bleeding episodes, whereas Table 3 of the trial journal publication does[2].) The main type of bleeding observed was clinically relevant non-major bleeding (though, unlike major bleeding, no HR, 95% CI and p-value is given for this outcome). There was a statistically significant difference favouring rivaroxaban in major bleeding n=26 (1.1%) vs n=52 (2.2%) (HR 0.49, 95% CI 0.31 to 0.79, p=0.003). Kaplan–Meier curves for the cumulative rate of clinically relevant bleeding and major bleeding are provided (MS Figures 8 and 9, pages 75 and 76, respectively).

Table 6– Bleeding outcome results from the EINSTEIN-PE trial

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

The results given correspond with those given in the trial publication[2]

Adverse events in the safety population were measured up two days after the last documented study drug intake. It is presumed that this was on the assumption that, given the pharmacokinetics of the drugs, they would be out of the patient's system in 48 hours and therefore the adverse events occurring after that are unlikely to be related to them. In the trial journal publication it is stated that "Three patients in the rivaroxaban group and one patient in the standard-therapy group had a fatal bleeding episode when they were no longer taking a study medication" (footnote to Table 3, page 1293)[2], and these patients are therefore not included in the primary efficacy data related to clinically relevant bleeding/major bleeding (Table 6) (they are, however, reported in the mortality rate data, presumably because these events occurred outside the defined two days post-cessation of drug). It is not stated how close to the two day cut-off these events took place, however, the clinical advisor to the ERG commented that it remains possible that if these events took place close to the cut-off they may have been due to the drug or its cessation. If these events are included then the incidence of fatal major bleeding would be 5 (0.2%) and 4 (0.2%) for rivaroxaban and LMWH+VKA respectively.

The MS reports the incidence of mortality for the safety population (MS Table 17 page 78 – reproduced below in Table 7). There were 58 deaths among patients in the rivaroxaban arm, compared to 50 deaths in the LMWH+VKA group, HR 1.13 (95% CI 0.77 to 1.65, p=0.53). Table 7 also reports the numbers of patients whose death was caused by PE or where PE was not ruled out, and also when caused by bleeding.

[redacted]

Table 7 – Mortality and incidence of complications of DVT / PE

	Rivaroxaban	LMWH+VKA	Hazard ratio
	N (%)		(95% CI, p-value)
Safety population	2412	2405	
Deaths	58 (2.4)	50 (2.1)	1.13 (0.77 to 1.65, P=0.53)
Caused by PE or where PE not ruled-out	11 (0.5)	8 (0.3)	NR
Caused by bleeding	5 (0.2)	4 (0.2)	NR
Pulmonary hypertension	[redacted]	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]	[redacted]
Post thrombotic syndrome	[redacted]	[redacted]	[redacted]

All of the data in the table correspond with the data provided in Table 3 of the trial publication[2] with one minor exception (the trial journal publication reports that 7 deaths were due to PE/where PE cannot be ruled out in the LMWH+VKA arm, whilst the MS reports 8 deaths). Table 3 of the trial journal publication[2] also reports the number of patients whose death was caused by other factors (e.g. myocardial infarction).

MS Table 18 page 79 reports emergent adverse events (excluding clinically relevant bleeding and recurrent VTE) from EINSTEIN-PE for the safety population. These are classified in terms of: any; serious event; resulting in permanent discontinuation of study drug; and, leading to prolonged hospitalisation. The table is reproduced in Table 8 of this report.

[redacted]. Incidence of serious events was just below 20% in both arms. There were no statistically significant differences between trial arms for events.

[redacted]. All data correspond with data presented in Table 3 of the trial journal publication[2], with the exception that the p-value for 'any' adverse event is 0.29 in the MS and 0.24 in the publication.

[redacted]. Other adverse events of interest are reported in MS Table 18, including acute coronary event, cerebrovascular events etc. No statistical data

are reported (p values, HR etc, but relative risks and absolute risk differences are reported in MS Table 22, page 92) (NB. Due to a table numbering error in the MS there are two instances of Table 22 and Table 23.) These data correspond to the data reported in the trial journal publication.[2]

Table 8 – Summary of adverse events in the EINSTEIN-PE trial

	Rivaroxaban	LMWH+VKA	P-value
	N (%)		
Safety population	2412	2405	
Adverse events			
Any	1941 (80.5)	1903 (79.1)	0.29
Serious event	476 (19.7)	470 (19.5)	0.86
Resulting in permanent discontinuation of study drug	123 (5.1)	99 (4.1)	0.10
Leading to prolonged hospitalisation	475 (19.7)	430 (17.9)	0.82
Other adverse events of interest			
Acute coronary event	15 (0.6)	21 (0.9)	NR
Cerebrovascular event	12 (0.5)	13 (0.5)	NR
Systemic embolism	5 (0.2)	3 (0.1)	NR
Alanine aminotransferase level of more than three times the upper limit of the normal range and a bilirubin level of more than twice the upper limit of the normal range	5 (0.2)	4 (0.2)	NR

NR = Not reported

MS Table 22 on page 92 (which should actually be Table 24 due to a numbering mistake in the MS) provides relative risk and absolute risk differences (%, 95% CI) [redacted]. These have not been reproduced here,

MS Figure 10 page 77 reports relative safety in the pre-specified subgroups of EINSTEIN-PE. (NB. as stated earlier in Section 3.1.6 of this report, not all of the subgroups reported for the primary efficacy analysis (MS Figure 7 page 73) are shown for the safety analysis.) The manufacturer describes the results as 'consistent'. The ERG notes some wide confidence intervals for some of the subgroups, due to low numbers of recurrent VTE events.

The manufacturer reports subgroup results for two of the three subgroups in the NICE scope / decision problem: the intended duration of treatment (3, 6 and 12 months; which the manufacturer used as a proxy measure of patients' underlying risk of bleeding), and the presence of active cancer at baseline. Results for the subgroup based on provoked/unprovoked index event were not reported (the manufacturer reported, following a query from the ERG, that

evidence shows this is not a predictor of bleeding and therefore it was not included in the statistical analysis plan of the trial – manufacturer's clarifications, page 8).

- [redacted]
- [redacted]

3.4 Summary

Overall the MS provides an unbiased estimate of the treatment effect. It is based on a well conducted systematic review of clinical-effectiveness, which yielded one relevant RCT. The RCT itself is of reasonable quality with low risk of bias. The main weakness of the trial is lack of patient and investigator blinding, but most of the outcomes were independently adjudicated. The trial was designed to test the non-inferiority of rivaroxaban with LMWH+VKA, and the statistical methods used in this analysis (e.g. setting of the non-inferiority margin) appear to be appropriate.

The MS states that rivaroxaban can be considered non-inferior to the current standard of care in terms of recurrence of VTE. The MS also states that the two treatments had a similar level of clinically relevant bleeding (though not formally tested for equivalence) indicating a comparable safety profile of rivaroxaban.

The MS interpretation of the evidence is generally appropriate, but it should be acknowledged:

- The patient population in the trial may not be fully representative of the treatment population in general. In particular, as patients with severe renal failure were excluded from the trial, the rate of bleeding that may be seen in clinical practice with rivaroxaban may have been underestimated.
- The trial only assessed outcomes up to a 12 month period, so the effectiveness and safety of long-term treatment with rivaroxaban relative to LMWH+VKA beyond 12 months are unknown.
- The risk of VTE recurrence is cumulative over time and the short follow-up period used in the EINSTEIN-PE trial means that it is unknown how rivaroxaban might modify this cumulative risk into the future once treatment is ceased.

- The patient treatment satisfaction data should be interpreted with caution as they were based on a subgroup of patients and the manufacturer did not fully describe this subgroup. The manufacturer states that this subgroup was generally representative of the wider trial population, but they have not provided any data to support this.
  [redacted]
- Although bleeding adverse events, vascular events and death events were independently adjudicated,
  [redacted]

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

iii) a review of published economic evaluations of pharmaceutical interventions for the treatment and secondary prevention of VTE.

iv) a report of an economic evaluation undertaken for the NICE STA process. The cost-effectiveness of rivaroxaban is compared to LMWH+VKA for the treatment of PE and prevention of recurrent VTE.

Manufacturer's review of published economic evaluations

The MS describes a systematic search of the literature which was conducted to identify economic evaluations of rivaroxaban using several health economic databases and medical databases. See Section 3.1.1 of this report for the ERG critique of the search strategy. The review did not identify any studies that evaluated the cost-effectiveness of rivaroxaban specifically.

CEA Methods

Depending on the assumed anticoagulation treatment duration, the cost-effectiveness analysis uses either a 13 or 14-state Markov model to estimate the cost-utility of rivaroxaban compared to LMWH+VKA in adults with an acute PE. Results are presented by duration of anticoagulation therapy (3 months/6 months/12 months/lifelong).

A separate cost-minimisation analysis comparing rivaroxaban to LMWH only was undertaken to inform the appraisal of the potential value of rivaroxaban in reducing the monitoring burden for PE patients with active cancer (MS Section 7.9.3 page 269). This lies outside the NICE reference case.

The 14 Markov model states are detailed in MS Section 7.2.2 (MS page 112) and Table 26 (MS page 114). These states describe the management and complications of VTE and include an on-treatment state for the index event; two off-treatment states (off-treatment post index PE and off-treatment post DVT); three recurrent event states (DVT, PE and PE post DVT); three acute bleeding states; and two long-term complication states. Disease progression is not explicitly modelled as DVT and PE are generally acute conditions not classified by severity (MS Section 7.2.5 page 116).

The model has a lifetime horizon of 40 years and a cycle length of 3 months. Costs and outcomes are discounted at 3.5% per annum. The perspective of the model is the UK NHS/Personal Social Services (PSS) and results are presented as incremental cost per QALY gained (MS Table 27 page 117).

The principal measures of rivaroxaban clinical-effectiveness used in the model are derived from the EINSTEIN-PE trial[2]. Estimates obtained from EINSTEIN-PE inform both the model probability of a recurrent VTE whilst on rivaroxaban and the probability of an adverse event (bleed) whilst on rivaroxaban, compared to treatment with LMWH+VKA.

Quality of life in the model is determined by the disease health states. No mapping to utility was undertaken. A systematic literature review was conducted for relevant HRQoL data which yielded six studies (MS Table 42 page 152). Two further studies were used in order to fully populate the model utilities as the six studies identified by the systematic review did not provide all of the utilities required in the model (MS page 151 and Section 7.4.9 page 156).

A systematic review of the literature was undertaken to identify resource and cost data associated with the treatment of VTE (MS Section 7.5.3 page 164). Twenty publications were included after final screening (MS Table 44 page 166). The model reflects resource use related to initial treatment and ongoing treatment and monitoring costs (MS Section 7.5.5 page 173).

The model dosing data for rivaroxaban match those in the draft SmPC (MS Section 6.10.4 page 102). The dosing data for LMWH (enoxaparin) are based on the UK licensed dose although this is different to the dosing regime which was delivered in the EINSTEIN-PE trial (MS Section 7.5.5 page 174).

Unit costs in the model are taken from the BNF64[3], Personal Social Services Research Unit (PSSRU) [14], NHS reference costs 2010/11[15] and NICE Clinical Guideline 92 on reducing VTE risk in hospital patients.[16]

One-way deterministic sensitivity analyses were performed for a large number of model parameters including treatment effects and utilities (MS Section 7.6.2 page 193 and Table 52 page 194). Probabilistic sensitivity analyses (PSA) were also carried out (MS Section 7.6.3 page 195).

The MS states that two clinical experts were approached early in model development to provide validation on the initial model structure and parameter values tested in the model (MS Section 7.5.4 page 172 and Section 7.6.1 page 193). The MS notes that the expert comments were taken into account during the finalisation of the model structure, and that parameter values were refined following the literature review and results from EINSTEIN-PE. The model was also validated by comparison of its outcomes with those of EINSTEIN-PE (MS Section 7.7.1 page 196).

CEA Results

Results of the base-case economic evaluation are presented separately according to four treatment durations: 3, 6, or 12 months, or lifelong (Table 9). To be consistent with the MS, and to maintain clarity, Table 9 is presented in the non-standard results format adopted in the MS. At all treatment durations except lifelong, rivaroxaban dominates LMWH+VKA, i.e. rivaroxaban is cheaper and more effective than LMWH+VKA. For lifelong treatment the incremental cost per QALY gained is £13,252 (Table 9). The manufacturer states that there is a greater discounted

life expectancy and quality-adjusted life expectancy with rivaroxaban compared to LMWH+VKA, irrespective of treatment duration (MS page 252).

Results of the PSA indicate that at a threshold willingness to pay (WTP) of £20,000 the probability that rivaroxaban is cost-effective compared to LMWH+VKA is 99.9%, 95.9%, 93.7% and 59.1% for 3 months, 6 months, 12 months and lifelong treatment respectively (MS Table 85 page 258).

Table 9 Base case cost-effectiveness results by treatment duration. (Reproduced from MS Tables 81-84.)

Technologies	Total costs (£)	Total LY	Total QALYs	Incr. costs (£)	Incr. LY	Incr. QALYs	ICER (£) (QALYs)
3 Months of Treatment							
Rivaroxaban	4,511	14.571	11.940	-	-	-	-
LMWH+VKA	4,907	14.546	11.912	396	-0.025	-0.027	Dominated[a]
6 Months of Treatment							
Rivaroxaban	4,546	14.630	11.992	-	-	-	-
LMWH+VKA	4,759	14.622	11.979	213	-0.008	-0.013	Dominated[a]
12 Months of Treatment							
Rivaroxaban	4,881	14.683	12.035	-	-	-	-
LMWH+VKA	5,015	14.671	12.015	133	-0.011	-0.020	Dominated[a]
Lifelong Treatment							
LMWH+VKA	9,493	15.303	12.375	-	-	-	-
Rivaroxaban	10,868	15.333	12.479	1,375	0.030	0.104	13,252

[a] Dominated treatment (LMWH+VKA) is less effective and more expensive than rivaroxaban

The cost-minimisation analysis indicates that over a six month period rivaroxaban is associated with a cost saving of £903.39 compared to LMWH (dalteparin) for treatment of PE in active cancer patients (MS Table 90 page 269). However the ERG considers that this analysis is speculative because, as acknowledged in the MS (MS Section 7.9.3 page 269), there are few data and no robust analyses to support the assumed equivalence of rivaroxaban and dalteparin in treatment of PE.

4.2 Critical appraisal of the manufacturer's submitted economic evaluation

Manufacturer's review of published economic evaluations

Comprehensive searches were performed using the same search terms employed by the National Clinical Guideline Centre (NCGC) for NICE CG144[1] (MS page 106). The inclusion and exclusion criteria for the systematic review are listed in MS Table 24 (MS page 105). Inclusion criteria were: relevant economic study design (cost-utility analysis, cost-benefit analysis, cost-effectiveness analysis, cost-consequence analysis, comparative cost analysis); incremental cost and QALYs outcome or any other measure of effectiveness reported together with costs; patients with suspected or confirmed PE or DVT; any pharmaceutical for the treatment and secondary prevention of VTE; and any comparators. Non-English language articles and unpublished reports were excluded.

60 studies were identified from screening 1113 titles and abstracts. Of these 54 studies were excluded because they did not meet the review's eligibility criteria. One further study was added giving seven studies included for full review[17-23]. A tabulation of these studies' methods and results is given in MS Table 25 (MS page 108). They were quality-assessed using the NICE suggested format (MS Appendix 11 page 312).

None of the included studies evaluated the cost-effectiveness of rivaroxaban specifically. The MS concluded on the basis of this review that none of the included studies was directly relevant to the decision problem.

The ERG considers it unlikely that any cost-effectiveness studies of rivaroxaban were missed by the manufacturer as the literature search methods appear sound. The ERG consequently did not re-run the cost-effectiveness search.

Critical appraisal of manufacturer's submitted economic evaluation

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 10 below, drawn from common checklists for economic evaluation methods (e.g. Drummond and colleagues[24]). The critical appraisal checklist indicates that overall the manufacturer follows recommended methodological guidelines.

Table 10 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well-defined question?	Yes	Evaluation designed to address NICE scope, as given in statement of decision problem (MS Table 5 page 40)
Is there a clear description of alternatives?	Yes	Dual therapy of LMWH (enoxaparin, until anticoagulation is established) overlapping with a VKA, typically warfarin.
Has the correct patient group / population of interest been clearly stated?	Yes	Given in MS Section 2.2 page 24.
Is the correct comparator used?	Yes	
Is the study type reasonable?	Yes	Cost utility analysis (separate cost minimisation analysis)
Is the perspective of the analysis clearly stated?	Yes	NHS / PSS
Is the perspective employed appropriate?	Yes	According to the NICE reference case
Is effectiveness of the intervention established?	Yes	Non-inferiority versus comparator based on data from EINSTEIN-PE trial
Has a lifetime horizon been used for analysis?	Yes	A lifetime horizon of 40 years has been used.
Are the costs and consequences consistent with the perspective employed?	Yes	
Is differential timing considered?	Yes	Costs and health benefits discounted at 3.5% per year.
Is incremental analysis performed?	Yes	MS Tables 81-84, page 251-252 for the base case results
Is sensitivity analysis undertaken and presented clearly?	Yes	Results of deterministic sensitivity analysis are presented in MS Figures 15-18 (MS page 254-257). Summary of PSA given in MS Table 85 (MS page 258).

NICE reference case

The NICE reference case requirements have also been considered for critical appraisal of the submitted economic evaluation in Table 11. The submitted evaluation conforms with the NICE reference case. However it also includes a cost minimisation analysis for a subgroup of patients which lies outside the reference case.

4.2.1 Modelling approach / Model Structure

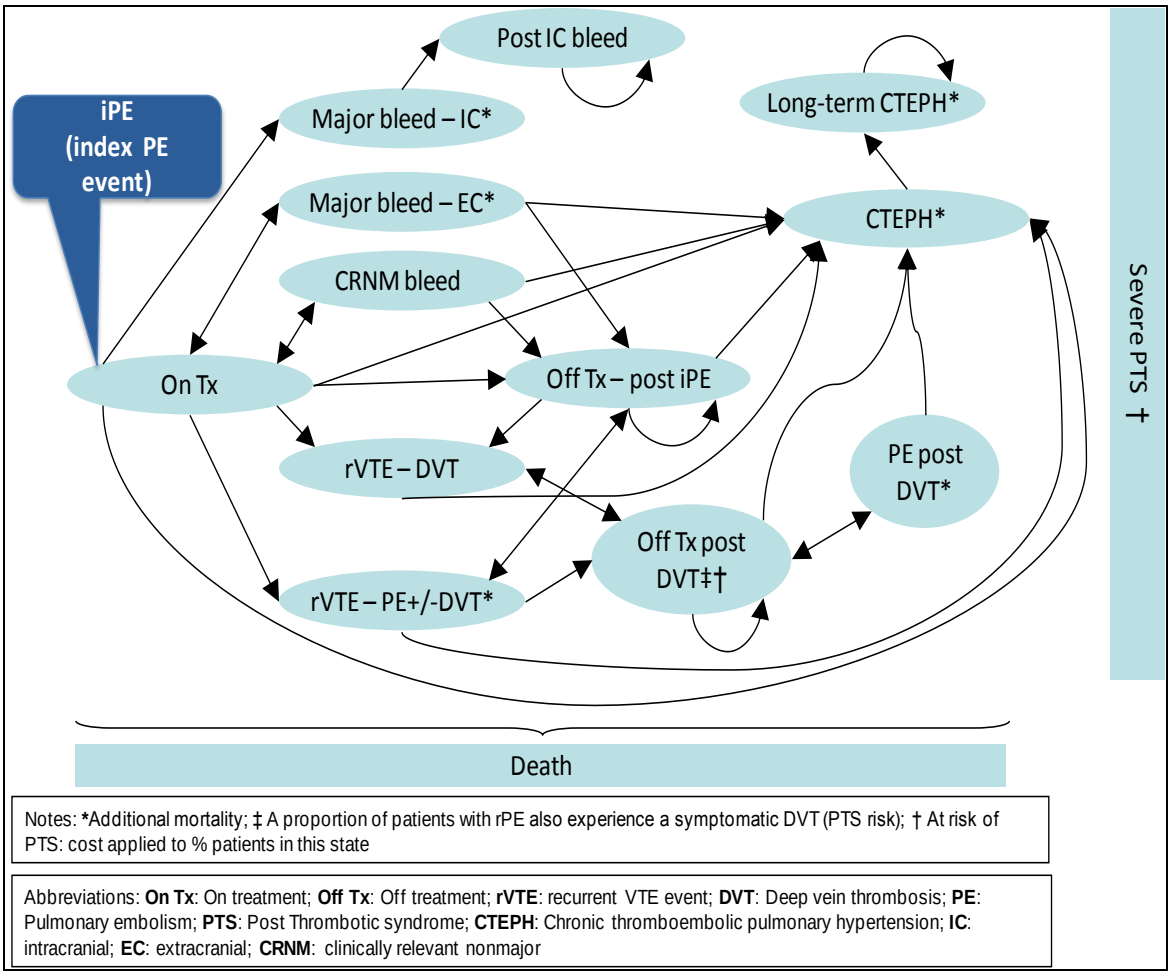
The manufacturer presents a Markov model developed in Microsoft Excel. A Markov model structure was adopted so as to allow flexibility in consideration of multiple treatment durations (MS Section 7.2.3 page 114).

Table 11 NICE reference case requirements

NICE reference case requirements:	Included in submission	Comment
Decision problem: As per the scope developed by NICE	Yes	
Comparator: Alternative therapies routinely used in the UK NHS	Yes	Fondaparinux and unfractionated heparin are not considered.
Perspective on costs: NHS and PSS	Yes	
Perspective on outcomes: All health effects on individuals	Yes	
Type of economic evaluation: Cost-effectiveness analysis	Yes	A cost minimisation analysis was also conducted for subgroup of patients with active cancer, due to lack of clinical-effectiveness data.
Synthesis of evidence on outcomes: Based on a systematic review	Yes	
Measure of health benefits: QALYs	Yes	
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	Yes	
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes	
Source of preference data: Representative sample of the public	Yes	
Discount rate: 3.5% pa for costs and health effects	Yes	
Notes: ? = uncertain; N/A=not applicable *otherwise use yes or no. Only no, ? or N/A need qualification in the comments column*		

Individuals are able to move between 14 possible health states in the lifelong model and between 13 health states in the other models: on treatment ("On tx"); recurrent DVT ("rVTE – DVT"); recurrent PE ("rVTE – PE ± DVT"); intracranial bleeding event ("Major bleed – IC"); extracranial bleeding event ("Major bleed – EC"); clinically relevant non-major bleeding event ("CRNM bleed"); post intracranial bleed ("Post IC bleed"); off treatment post index PE ("Off Tx-post iPE"); off treatment post DVT ("Off Tx post DVT"); on treatment post DVT ("On treatment post DVT"); PE post historical DVT ("PE post DVT"); chronic thromboembolic pulmonary hypertension ("CTEPH"); long-term CTEPH ("Long-term CTEPH"); and death. A simplified schematic of the model structure is given in Figure 1, reproduced from MS Figure 12 page 113.

Figure 1 Simplified structure of the manufacturer's economic model



Patients enter the model following an index PE and receive treatment in the "On Tx" health state. They may then either: stay on treatment; experience a recurrent VTE (PE or DVT); experience an adverse event (CRNM bleed; major IC bleed; major EC bleed); move to be off treatment; enter a long-term complication state (e.g. CTEPH); or die.

Recurrent VTEs can be either PE or DVT. After recurrence patients are assumed to be treated for six months with LMWH+VKA and have a reduction in HRQoL for one month. Recurrent pulmonary embolism events are associated with excess mortality but recurrent DVT events are not. After one cycle in one of the recurrence states patients move to either an off-treatment state; an on-treatment state (in the lifelong model only); enter a long-term complication (CTEPH) state; or die (if the recurrent VTE was PE).

Patients who experience a DVT after an index PE are considered at risk of post thrombotic syndrome (PTS). In order to track patients at risk of PTS complications following a newly incident DVT there are states for "On treatment post-DVT" and "Off treatment post DVT". The "On treatment post-DVT" state is only used in the lifelong model and is not represented in the model schematic (Figure 1 and MS page 113). The consequences of PTS are applied as disutilities to patients in both the on- and off-treatment post DVT states. Patients may experience recurrent VTE or CTEPH whilst in either of the post DVT states but are unable to move from the On Treatment Post-DVT state to minor or EC bleeds. The expected costs and utilities associated with these movements (payoffs) are applied to patients in this state in order to reflect this restriction. Patients may however move from the On Treatment Post-DVT state to the IC bleed state (MS page 136).

Patients who experience CRNM bleeds are assumed to temporarily discontinue treatment for one month during the cycle in which the bleeding event takes place and have no reduction in utility. Patients experiencing major EC or IC bleeds are assumed to discontinue therapy for three months (EC bleed) or permanently (IC bleed) with a utility reduction which lasts for one month (EC bleed) or is lifelong (IC bleed). Patients do not transit through the EC bleed and minor (CRNM) bleed states but are assigned the relevant disutilities and costs for one cycle only before returning to another model state (MS page 113). Patients with major IC bleeds move to the "Post IC bleed" state and permanently discontinue treatment. Patients with EC bleeds may either stay off treatment, return to treatment, or enter the CTEPH state. Both types of major bleed are associated with excess mortality.

Sources used to develop and inform the structure of the model include NICE CG144[1] and EINSTEIN-PE (MS Section 7.2.1 page 111). A similar model structure was used in TA261 and this was found by the ERG for that appraisal to be generally satisfactory[11]. A lifelong treatment duration cohort was, however, included in the current model to reflect recommendations in CG144[1] and NICE TA261[25] to offer VKA beyond 3 months to patients with an unprovoked PE (MS Section 7.2.1 page 112). The current model also differs from the model used in TA261 by including 13/14 health states rather than eleven. The three additional health states in the current model are "Off treatment post DVT", "On treatment post DVT" and "PE post DVT".

The MS notes that two clinical experts were approached to provide comment on the initial model structure (MS Section 7.5.4 page 172). The MS does not give the criteria used to select the experts or the methods used to collate their opinions, although it notes that no iterations were performed. No declaration of interest was sought from either clinical expert so it is unclear if there was any conflict of interest (MS Section 7.5.4 page 172).

The model has a three month cycle length and a lifetime horizon of 40 years. A cycle length of three months was chosen with reference to the minimum treatment duration of three months and model horizon of 40 years (MS Table 27 page 117). A half-cycle correction was not used as the cycle length is short relative to the model horizon. The duration of treatment is assumed to be either 3, 6, or 12 months, or lifetime. No assumptions are made of a continuing effect of treatment after treatment cessation.

The model extrapolates the results of the EINSTEIN-PE trial in the case where lifelong treatment is assumed. The whole population HR for recurrent VTE of 1.12 was obtained from 12 months of trial data but is applied until three years in the lifelong treatment scenario. The relative hazards of bleeding events obtained from EINSTEIN-PE are also applied until three years. After three years the same probability of VTE whilst on treatment is used for both rivaroxaban and LMWH+VKA. The same transition probabilities for bleeding events are also used in both arms after three years.

The ERG clinical expert considers that the model is comprehensive and does not have any significant omissions. The ERG is satisfied that the structure of the model is broadly consistent with the current clinical understanding of PE and that the disease states and possible transitions reflect both the underlying biological processes and clinical pathway of care. There is one area of potential concern. The use of an “on treatment post DVT” state only in the lifelong model appears somewhat arbitrary and stems from the assumption that patients who experience a recurrent VTE are treated for six months with LMWH+VKA and cease treatment thereafter (with appropriate payoff). Clinical opinion sought by ScHARR[11] for TA261 indicated that patients with recurrent VTE are more likely to be treated on an ongoing basis. The ERG’s clinical expert also considered this to be likely, either with the same treatment or a different treatment. The effect of inclusion of only six months of LMWH+VKA cost after recurrence is unclear: rivaroxaban experiences slightly higher VTE recurrence rates than LMWH+VKA but on the other hand is associated with fewer bleeding events.

4.2.2 Patient Group

The MS states that the patient group included in the economic model base case is adults with an acute PE who match the licensed indication, EINSTEIN-PE trial population and the stated decision problem (MS Section 7.2.1 page 111). This definition is consistent with the patient groups relevant to the clinical evidence reviewed in Section 3.1. However the EINSTEIN-PE patient population which is used in the model base case does not entirely reflect the licensed indication for rivaroxaban as it excludes some patients for whom rivaroxaban is an appropriate treatment, including those with severe renal disease (creatinine clearance <30mL/min but >15mL/min). The trial did not include haemodynamically unstable patients and those to be treated with thrombolysis due to a massive PE (e.g. with a fibrinolytic agent) (MS page 55) but these patients are contraindicated for rivaroxaban. The patients in EINSTEIN-PE had a mean age of 58 years, 53% were male and had a mean weight of approximately 80kg (MS table 9 page 56). The mean age of 58 is younger than seen in some other published studies of PE and DVT[26] and an older cohort is examined by the ERG in scenario analysis described in Section 4.3 of this report.

The ERG clinical expert believes that the EINSTEIN-PE trial population is somewhat artificial and not wholly representative of the general treatment population. For example the general PE treatment population includes pregnant women but the SmPC advises that rivaroxaban should not be used in pregnant women. The MS estimates that 15% of PE patients are contraindicated for rivaroxaban (MS Section 2.2 page 26). The ERG clinical expert agrees that this is a reasonable estimate.

The NICE scope lists three patient subgroups of interest: underlying risk of bleeding; provoked/unprovoked PE; and active cancer. The manufacturer presents cost-effectiveness results by four intended treatment durations which are used as a proxy for both underlying risk of bleeding and provoked/unprovoked PE. However, the ERG clinical expert believes that there are no robust markers for determining length of treatment in advance which suggests that pre-specified treatment durations may not be a good proxy for other variables.

[redacted]. The manufacturer therefore considers that the “treatment duration subgroups are … representative of the subgroups requested” (MS page 268).

The EINSTEIN-PE trial included a small number of patients with active cancer (4.6% of participants) who in the standard care arm of the trial were assigned a regime of enoxaparin and either warfarin or acenocoumarol. (NB. VKA therapy is not indicated in patients with cancer. Cancer patients would be usually treated with LMWH monotherapy for at least six months.) The ERG clinical expert considers that the outcomes for this subset of cancer patients could, in theory, have been worse than those seen for other patients due to increased bleeding risk. [redacted] To further analyse this subgroup the manufacturer conducts a cost-minimisation study for active cancer patients comparing rivaroxaban to long-term LMWH rather than LMWH+VKA (MS Section 7.9.4 page 269).

In summary, the patient population considered in the model is not entirely representative of the general PE population as it is curtailed by both the licensed indication of rivaroxaban and the inclusion criteria of the EINSTEIN-PE trial. Nevertheless, the major patient groups within the rivaroxaban license are considered in the EINSTEIN-PE trial and so the model findings are likely to have broad validity.

4.2.3 Interventions and comparators

The scope specifies the comparator as initial treatment with an LMWH (such as enoxaparin, tinzaparin and dalteparin) or fondaparinux, with continued therapy with a VKA such as warfarin, acenocoumarol or phenindione or with an LMWH for people for whom a VKA is not considered an appropriate treatment.

The comparator used in the economic model is initial treatment with LMWH (enoxaparin) overlapped with therapy with a VKA (warfarin). This broadly matches the scope, although VKA was given to active cancer patients in EINSTEIN-PE, rather than LMWH monotherapy, which is the recommended treatment in this patient group. VKA is not considered an appropriate treatment for active cancer patients due to factors including drug interactions and increased risk of bleeding[27].

Fondaparinux is not included as a comparator in the economic model because EINSTEIN-PE did not incorporate it in any comparator arm and there is an absence of evidence of its efficacy with respect to PE treatment (MS page 43).

[redacted] The ERG clinical expert believes that enoxaparin is a reasonable comparator and notes that the different LMWH drugs are broadly comparable clinically. The MS considers dalteparin as a comparator to rivaroxaban in subgroup analysis of active cancer patients (MS Section 7.9 page 267).

The MS states that warfarin is the most frequently used VKA in clinical practice (MS page 32). This is confirmed by NICE CG144[1].

The ERG concludes that enoxaparin overlapping with warfarin is an appropriate combination of comparators to use in the economic model.

4.2.4 Clinical-effectiveness

The following clinical-effectiveness parameters are used in the manufacturer's economic evaluation (MS Section 7.3): probability of recurrent VTE whilst on treatment; probability of major bleeding whilst on treatment; probability of CRNM bleeding whilst on treatment; probability of CTEPH and of PTS; treatment discontinuation, probability of VTE after treatment cessation; and risk of mortality. These are discussed below in turn, but for a summary of the parameter values see MS Table 40 (page 143).

4.2.4.1 Probability of recurrent VTE on treatment

The probability of recurrent VTE whilst on treatment, the key clinical-effectiveness input parameter affected by the intervention, is taken from the EINSTEIN-PE trial where it was the primary efficacy outcome (see Section 3.3 of this report). The parameter enters the model as a probability based on a HR (for treatment duration up to 12 months). The manufacturer's clarification letter notes that there was no evidence of a deviation from the proportional hazards assumption for this outcome (manufacturer's clarifications, page 19). The probability of a recurrent VTE in the rivaroxaban arm is calculated by applying the appropriate treatment effect to the probability of recurrent VTE in the LMWH+VKA arm. A formula is reported on MS page

120 for deriving the probability from the rates of VTE occurrence from the trial. The ERG considers this an appropriate approach.

MS Table 28 provides the probability of recurrent VTE in patients in the LMWH+VKA arm for each of the intended treatment durations (and for each three-monthly period therein). The base case uses the three-monthly probabilities for this arm from this table and applies the whole population treatment effect (HR 1.12, 95% CI 0.75 to 1.68) to these. This differs from the approach initially taken in NICE TA261 where data from the whole trial population were used to derive baseline probabilities for the LMWH+VKA arm rather than data stratified by intended treatment duration[11]. However, the effect of using either a LMWH+VKA pooled population or intended treatment duration subgroups for the baseline probabilities may be readily examined in the current model as this option is user-specified. The Committee for NICE TA261 concluded that evidence of treatment effect should be based on the whole trial population. This is because of small numbers of patients in the intended treatment duration subgroups and insufficient evidence to demonstrate that rivaroxaban has a substantially different effectiveness across treatment durations [25]. EINSTEIN-PE has similarly low numbers in the intended treatment duration subgroups and the ERG believes that the approach adopted by the manufacturer to use the whole population treatment effect is therefore appropriate. For completeness the manufacturer provided data equivalent to that given in MS Table 28 for the rivaroxaban arm of the EINSTEIN-PE trial at the request of the ERG (see Table 8 in manufacturer's response to clarification questions document).

The model base case assumes that 37.2% of recurrent VTEs after an index PE are DVTs, and the remainder are PEs (MS Table 40 page 143). This proportion was obtained from EINSTEIN-PE and is varied in sensitivity analysis. Although there are considerable cost differences associated with treatment for PE and DVT the ERG is satisfied that model outcomes are not substantively affected by the assumed value of this proportion. It is possible that the proportion varies between treatment arms but this is not allowed for in the current model structure. Other studies have indicated that it is the nature of the initial VTE event (whether PE or DVT) that has most influence on the type of recurrent VTE event, with a recurrent PE more likely following an index PE than an index DVT,[28] rather than treatment *per se*.

As the EINSTEIN-PE trial was only of one year duration the manufacturer conducted a systematic review of long-term anticoagulation (MS Section 7.3.1,Table 29) to estimate the

probability of VTE for treatment with a VKA for greater than a year (lifelong treatment). Three studies, evaluating warfarin therapy, met the inclusion criteria, and these were meta-analysed in a separate 2006 publication by Streiff and colleagues[29] from which the pooled effect (0.7% per 100 patient years, 95% CI 0.3% to 1.1%) was taken. The MS reports the existence of heterogeneity between the three studies meta-analysed (though does not specify if this is clinical or statistical heterogeneity), but states this is the most robust source of evidence available for long-term anticoagulation. (However, the ERG note that there was no statistically significant heterogeneity in the subgroup of studies of continuous VKA treatment that are used to support the manufacturer's pooled estimate of 0.7%). The literature search appears to be reasonable in terms of the sources reported in MS page 121. Further details of the systematic review methodology are provided in an unpublished report (MS reference 115), written by IMS health on behalf of the manufacturer (NB. This report details the systematic reviews conducted by IMS for a number of the clinical-effectiveness parameters used in the manufacturer's submission).

4.2.4.2 Probability of bleeding

Other clinical-effectiveness parameters used in the model include the probability of major bleeding on treatment, and the probability of CRNM bleeds. These two parameters enter the model as probabilities based on a HR of 0.49 (95% CI 0.31 to 0.79) for major bleeds and a RR of 1.00 (95% CI 0.84 to 1.19) for CRNM bleeds, from the EINSTEIN-PE trial (for treatment duration up to 12 months). The same formula for deriving probabilities/risks from rates of occurrence is used as that for VTE recurrence (specified above – see MS page 125). As with recurrence of VTE described above, the base case uses the three monthly probabilities of major bleeds and CRNM bleeds for the LMWH+VKA arm and applies the whole population treatment effect (i.e. the HR and RR reported above, respectively) to these to obtain the probability of an event in the rivaroxaban arm (see MS Tables 30 and 31).

Notwithstanding their different patient populations, the ERG notes that the HR for major bleeding obtained in the rivaroxaban arm in the EINSTEIN-DVT[6] trial was 0.65 (0.33-1.3), somewhat higher than the HR of 0.49 (0.31-0.79) seen in EINSTEIN-PE. The ERG clinical expert has indicated that recent suggestion that DVT and PE may be two distinct conditions may explain these different bleeding rates. However, although the EINSTEIN-PE HR of 0.49 achieves statistical significance it is based on only 26 major bleeding events in the rivaroxaban

arm of that trial and may therefore not be entirely robust to generalisation. Alterative HRs for major bleeding are examined by the ERG in scenario analysis described in Section 4.3 of this report.

An assumption is made about the proportion of major bleeds which would be intracranial (IC): [redacted], on the basis of [redacted] of 68 major bleed events in EINSTEIN-PE being IC. There is a discrepancy with MS Table 16 which reports a total of 78 major bleeding events, and also with the trial publication[2] (Table 3) which reports a total of 15 IC events (proportion of IC bleeds therefore being 19.2%). However, this makes no substantive difference to outcome for 6 months and 12 months of treatment. A further note is that the proportion of major bleeds that are IC in the meta-analysis by Linkins and colleagues[30] (see below for further detail on this study) reported that 10% (95% CI 5 to 20) of major bleeds were IC in VTE patients. However, this was based on RCTs of VKA treatment rather than rivaroxaban so is not strictly comparable.

Three studies identified by the manufacturer's systematic review, and meta-analysed by Streiff and colleagues[29], were used to estimate the probability of major bleeding with lifelong treatment (MS page 124). Due to lack of data in the Streiff meta-analysis, lifelong estimates for CRNM bleeds are taken from the EINSTEIN-PE (assumed to be that experienced in the final six months of "all patients" in the trial (MS page 126). It is presumed this can only refer to the patients in the intended 12 months treatment group who completed the full treatment ([redacted] of 1809 patients in the 12 months intended treatment duration did not complete 12 months of treatment, as clarified by the manufacturer on request by the ERG, manufacturer's clarifications, page 13).

For lifelong treatment the whole population efficacy (recurrent VTE) and safety (major bleeding) HRs calculated from EINSTEIN-PE have been carried forward and applied to cycles from 12 to 36 months. This may be questionable as MS Figure 6 (MS page 71) indicates a sharply increasing hazard of recurrent VTE in the rivaroxaban arm towards the end of the 12 month study period. Furthermore the same hazards have been applied to both treatment arms from 36 months onwards in the 'Subsequent' transition matrix (MS Table 39 page 140). The MS states that when evaluating lifelong treatment all transition matrices are specific to each treatment arm (MS Section 7.3.2 page 141) but the ERG notes that this is not reflected in the 'Subsequent' matrix for lifelong treatment, which is the same in both treatment arms. This appears to be an

error in model wiring. The ERG corrects this error and examines alternative HRs for recurrent VTE in lifelong rivaroxaban treatment in scenario analyses described in Section 4.3.

4.2.4.3 Treatment discontinuation

In terms of treatment discontinuation the manufacturer assumes no difference between treatments, based on non-statistically significant differences in discontinuation in the EINSTEIN-PE trial (see Table 8 of this report, and MS Table 13). This is considered by the manufacturer to be a conservative assumption given, for example, the complex management with LMWH+VKA therapy and the challenges this presents for patient compliance. The criteria for discontinuation included were non-compliance, protocol violation, patient convenience, switching to a commercial drug, insufficient therapeutic effect and non-bleeding adverse events.

[redacted]

Patients who bleed whilst on anti-coagulation move to a bleeding state in the model and discontinue temporarily or permanently, depending on the type of bleed. Permanent treatment discontinuation probabilities are presented in MS Table 32 according to type of bleed (IC, EC etc) informed by data from the CSR and advice from Bayer clinicians (however no further information is given on how these probabilities were derived). The probabilities of permanent discontinuation per three month cycle were: IC bleeds (100%);

[redacted]

For lifelong treatment, estimates of discontinuation are based on a "brief review" of recent observational studies of cardiovascular medication (no further details given on methods of review, MS page 127). Fourteen papers were tabulated (MS Table 33), and a narrative discussion of the papers is given. Estimates used were taken from the UK database linkage study by Boggon and colleagues (2011)[31]: 3.6% discontinuation per 3 month timestep, (95% CI 1.9% to 6.9%), with no differential effect between arms assumed. These are same estimates used in NICE TA261 which were accepted by the Appraisal Committee.

4.2.4.4 Probability of recurrent VTE off treatment

The probability of VTE after treatment cessation is derived from manufacturer's systematic review of long-term trials and observational studies of anticoagulation (MS page 132). Of the 17 publications included, the chosen estimate was taken from the Prandoni and colleagues' cohort of Italian patients[7]. In this publication a total of 373 patients (22.9%) experienced a recurrent VTE, and the cumulative recurrence rate was 39.9% after a median follow-up of 10 years. Just over half of the cohort had an uprovoked VTE (53.1%). The MS gives a formula for a three month probability calculation (MS page 134), similar to the formulas for other clinical-effectiveness parameters mentioned above. The three month probability was estimated to be 1.26% (95% CI 1.09 to 1.46%). The same probability is applied to rivaroxaban and LMWH+VKA patients. The ERG notes that the index event experienced by the majority of patients in the cohort was DVT alone (66%), compared to DVT and PE (18%) and PE alone (16%). Furthermore, the likelihood of the recurrent VTE being a PE was statistically signficantly lower amongst patients with a DVT only index event. Therefore, this cohort cannot be considered wholly representative of the PE patient population (though this does not appear to have a significant impact on model outcomes).

4.2.4.5 Probability of VTE complications

The probabilities of CTEPH and PTS are based on the manufacturer's systematic review of trial-based and observational literature on rates of incidence of VTE complications (MS page 134) The CTEPH estimate was based on the study by Miniati and colleagues[32] (MS Table 37), selected from the systematic review as it was the study with the largest number of patients, and provided intermediate estimate of all the studies (meta-analysis was not conducted due to clinical heterogeneity). The cumulative risk from the study was converted into a constant risk applied in each model cycle with the first two years following the index or PE event, with 1.25% (95% CI 0.03 to 2.46) of PEs progressing to CTEPH during this period. The same risk was applied to recurrent PEs (it is not explicitly stated, but the ERG assumes this is within a two year period following recurrence).

The PTS estimate was based on the prospective cohort studies by Prandoni and colleagues from 41 studies in the systematic review providing data on PTS,[33;34] The MS describes the Prandoni studies as the longest and most robust studies. The impact of PTS was only modelled for newly incident DVTs (through inclusion of a post-DVT model state). The incidence of severe

PTS post DVT was estimated to be 8.1% (95% CI 5.8% to 10.4%) of patients based upon 5 year risk of severe PTS.

4.2.4.6 Mortality

The general underlying mortality risk was estimated from a cohort life table based on the Office for National Statistics 2008-2010 interim tables for England and Wales combined. Yearly mortality was calculated according to baseline patient characteristics (age, gender) from the EINSTEIN-PE trial (MS page 137).

For mortality associated with model events (e.g. DVT, PE, bleeding) the manufacturer conducted a systematic review to identify trial-based and observational literature (further details of the systematic review methodology are provided in an unpublished report, MS reference 115). A number of individual trials were identified, however, the manufacturer also identified an additional meta-analysis, by Linkins and colleagues[30], that was supplemental to the systematic review. Given the availability of this meta-analysis the individual trials were not considered further. The meta-analysis included 23,518 patients from 39 RCTs of VKA treatment for at least 6 months, of which 11 trials were of VTE patients. The meta-analysis appears to have been based on a reasonable quality systematic review, with the most recent literature search conducted in 2007.

Estimates for mortality from bleeding were taken from the Linkins and colleagues meta-analysis[30]. The proportion of bleeds that were fatal were 43.6% (95% CI 36.5 to 50.7) and 3.9% (95% CI 2.5 to 5.4) for IC and EC bleeds, respectively. Mortality estimates from CTEPH were from a UK specialist centre for pulmonary hypertension treatment. The three month mortality risk was 2.48%. The MS does not report a mortality estimate for patients who develop PTS and it is not explicitly stated why. However, the clinical advisor to the ERG commented that whilst PTS causes significant morbidity it does not directly cause mortality. PTS does not have much impact on the model outcomes so this is not considered to be an important issue.

The base case estimate for mortality from PE during the acute treatment phase was [redacted] based on 28 deaths occurring across the treatment arms in both the EINSTEIN-PE and DVT trials (as a proportion of 112 fatal or non-fatal PEs). Mortality after the

acute treatment phase was taken from Prandoni and colleagues[7] estimated to be 33.1% (95 % CI 25.0 to 41.2).

4.2.4.7 Summary

In summary, the MS provides a detailed description of, and justification for, the clinical-effectiveness parameter values used in the economic model. Many of the values were sourced from a series of systematic reviews conducted for the manufacturer by IMS health. Brief details of these reviews are given in the MS, with further information given in an unpublished report. The ERG has not thoroughly checked this report, but the reviews conducted appear to have been conducted to a high standard.

4.2.5 Patient outcomes

The MS describes a systematic review of HRQoL studies undertaken in order to identify evidence on utility associated with VTEs including events such as PE, DVT, bleeding, CTEPH and PTS in patient populations with index PEs, DVTs or VTEs generally. The review also attempted to identify evidence to suggest moderation of utilities according to treatment received (MS Section 7.4.5 page 150). The search strategy is described in MS Appendix 12 (MS page 325) and inclusion and exclusion criteria are given in MS Table 107 (MS page 330). Six studies were returned by the review although one was subsequently discarded as it did not provide utility data. Two further studies were added by the manufacturer to provide utilities for the population baseline and the post IC bleed state. The seven included studies are summarised in MS Table 42 (MS page 152).

The MS discusses the HRQoL studies found in the review and the rationale for choosing the studies used in the model (MS Section 7.4.9 page 156). No formal quality assessment of the included studies is described. The ERG notes that it is unclear how the study by Lenert and colleagues[35] meets the systematic review inclusion criteria given in MS Table 107 (MS page 330) as the population is healthy volunteers rather than patients with VTE. The quality of included studies appears variable. Some of the studies have a large sample size and use EQ-5D, for example Rivero-Arias[36]. Other studies are small and do not use EQ-5D, for example the study of O'Meara[37] which has a sample size of 36 (only 20 of whom with experience of DVT) and uses standard gamble. Many of the utility values used by the economic model are obtained from the Locadia study of patients' health state valuations in treatment of VTE[38] (Table 12 below). This study has a small select sample and uses time trade off (TTO), rather than EQ-5D.

The manufacturer considers this study preferable to others cited by NICE in CG92 which it states have unclear design and methodology[16] (MS refs 159 & 60).

HRQoL estimates are applied to the patients in the model in each cycle according to their model health state. The national EQ-5D study of Kind and colleagues (1998)[39] was used as the source for a baseline (population norm) utility value 0.825. The utility values for the DVT, PE, EC bleed, IC bleed and PTS states are calculated by applying a decrement in utility (as a multiplier) to the baseline utility value of 0.825 (MS Table 12 below). The duration of utility impact is assumed to be one month in the case of DVT, PE and EC major bleeds which is consistent with the approach taken in the cost-effectiveness model used in NICE CG92[16] and the model used in TA261[11]. The utility impact of an IC bleed is assumed to be of three months' duration whilst other events (PTS, CTEPH, post IC bleed, warfarin therapy) are associated with an ongoing impact on utility (MS Section 7.4.11 page 161-162).

The utility values used in the economic model differ slightly from those reported by ScHARR in their ERG report for NICE TA261[11] but the same sources appear to have been used.

The utility of a major EC bleed is assumed to match the utility reported in Locadia[38] for gastrointestinal (GI) bleed, and the utility of a major IC bleed is assumed to match the utility reported in Locadia[38] for haemorrhagic stroke. The utility of 0.33 for the IC bleed state appears particularly low and the ERG therefore conducted a brief search for further studies using EQ-5D in patients with cardiovascular disease. A prospective longitudinal study by Pickard and colleagues[41] gives a utility of 0.31 for IC bleed (stroke) patients at baseline, but this increases to 0.55 after one month, and to 0.61 by three months. Thus whilst the Locadia-given value of 0.33 appears reasonable at baseline, the ERG considers it should not be applied for three months as is done in the economic model. Given that rivaroxaban is associated with fewer IC bleeds than LMWH+VKA, a mid-value of 0.55 for the IC bleed health state utility would be a more conservative assumption and is examined by the ERG in scenario analysis described in Section 4.3.

Table 12 Estimates and source of utility values used in economic model. (Reproduced from MS Tables 42 and 43 page 152 & page 160.)

Model state	Point estimate	Sensitivity analyses		Sample size	Method of elicatation valuation and mapping	Source
		Lower	Upper			
Population norm	0.825	0.819	0.831	3395	EQ-5D visual analogue scale	Kind 1998[39]
Disutility due to warfarin therapy	0.012	0.016	0.006	48	Time trade off	Marchetti, 2001[20]
Post IC bleed	0.71	0.70	0.72	1283	EQ-5D	Rivero-Arias 2010[36]
CTEPH	0.56	0.53	0.59	308/869 with CTEPH	CAMPHOR scores and utility index	Meads 2008[40]
DVT	0.84	0.64	0.98	129	Ranking, direct rating and time trade off	Locadia 2004[38]
PE	0.63	0.36	0.86	129	Ranking, direct rating and time trade off	Locadia 2004[38]
EC bleed (GI bleed)	0.65	0.49	0.86	129	Ranking, direct rating and time trade off	Locadia 2004[38]
IC bleed (Haemorrhagic stroke)	0.33	0.14	0.53	129	Ranking, direct rating and time trade off	Locadia 2004[38]
PTS (Serious PTS)	0.93	0.76	1.00	30	Standard gamble	Lenert 1997[35]

The utility for severe PTS is taken from Lenert and colleagues[35]. This was a study of 30 healthy volunteers which used standard gamble to assess the utility of the PTS state. The MS notes that this study was preferable to three other studies which also provided utility estimates of the PTS state but which did not measure severe PTS specifically, which is the state in the economic model (MS refs 154-156). One of these three studies, Locadia and colleagues[38] reports a utility for the PTS state of 0.82 which is lower than the utility given for the severe PTS state in Lenert and colleagues[35]. This normalises to a utility of 0.86 for PTS whilst the Lenert study gives a utility of 0.93 for severe PTS. This suggests that the manufacturer has not been conservative in its choice of utility value for PTS, particularly as the Lenert study does not appear to meet the

inclusion criteria of the systematic search (as noted above), and patients on rivaroxaban are more likely to experience PTS.

The manufacturer assumes that the utility of the post IC bleed state is similar to the utility of patients post-stroke and uses a value of 0.713 taken from Rivero-Arias and colleagues[36]. This value was estimated using EQ-5D in a sample of 1,283 people, two years after the IC event. The ERG notes that utility of stroke patients in the Pickard study, six months after the event, was 0.62[41]. The Rivero-Arias study utility of 0.713 at a longer follow up time therefore seems plausible and is a conservative assumption as rivaroxaban is associated with lower risk of major bleeding than LMWH+VKA.

A disutility of 0.012 is associated with warfarin therapy but there is no disutility for rivaroxaban. The warfarin disutility comes from a TTO study conducted by Marchetti and colleagues[20] and was discussed and considered acceptable by NICE TA261[25]. The Committee for this appraisal also considered that although treatment with rivaroxaban could be associated with a small disutility, the relative difference in utility between the two treatments is at least as great as 0.012 and so this represents a conservative assumption in the economic model.

A utility value of 0.56 is assumed for patients with CTEPH. This is drawn from a study by Meads which used the CAMPHOR instrument in a sample of 308 patients[40]. The MS notes that utility values from this instrument are comparable to those from EQ-5D and so this utility was used without adjustment in the economic model (MS Section 7.4.9 page 158).

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

The ERG considers that the utilities used in the economic model are generally appropriate. A number of studies were used to obtain the required information and these employed various methods to value the health states. Some of the studies had small sample sizes. The resulting utilities may therefore not be entirely robust or consistent with each other but the ERG acknowledges that not all utilities were available from the same source using the NICE preferred instrument. However, the manufacturer's rationale for choosing a particular utility in preference to other available values does not always appear convincing, particularly for the IC bleed and PTS states.

4.2.6 Resource use

The MS describes a systematic review of the literature which was performed to identify resource use and cost data associated with the ongoing treatment of VTE (MS Section 7.5.3 page 164). The review took the form of an update to the review conducted for TA261[25]. Twenty included publications are summarised in MS Table 44 (MS page 166). The manufacturer does not formally appraise the quality of these studies but notes that two clinical experts were approached to provide validation on the parameter values tested (MS Section 7.5.4 page 172). Key resource use parameter estimates are summarised in MS Table 47 (MS page 180) which is reproduced below as Table 13.

Table 13 Key resource use estimates in economic model. Reproduction of MS Table 47 (MS page 180)

Resource item	Point estimate	Sensitivity			Rationale
		Lower	Upper	Distribution	
Acute treatment					
Number of days of acute treatment (ie LMWH) required by a PE patient	[redacted]	[redacted]	[redacted]	Dirichlet	EINSTEIN-PE CSR (Figure 14), SIGN guidelines[42].
Proportion of patients who self-inject LMWH	92%	64%	100%	Beta	From assumptions in NICE CG92[16]
Proportion of remaining patients who require nurse assistance at home	80%	56%	100%	Beta	From assumptions in the NICE CG92 model[16]
INR monitoring whilst on LMWH+VKA					
Visits in first 3 months	9	5	15	Gamma	UK observational research, BNF, SIGN[3;42]
Visits each 3 months thereafter	5	3	10	Gamma	
Recurrent VTEs: proportion treated as outpatients rather than inpatients					
Recurrent DVT patients	69%	50%	100%	Beta	Bayer Market Research
Incident PE patients	17%	0%	30%	Beta	
Other					
Proportion of patients requiring NHS-funded transportation	8.55%	6%	11%	Beta	Bayer/pH national survey
Proportion of CTEPH patients who require PEA	68.4%	64.2%	72.6%	Beta	321 of 469 patients from Condliffe 2008[43]

The economic model base case assumes that rivaroxaban treatment is 15 mg twice a day for the first 21 days, and 20 mg once a day thereafter (MS Table 2, page 19). The LMWH (enoxaparin) regime used by the model is the UK licensed dose of 1.5 mg/kg once a day (MS Section 7.7.7 page 174).

[redacted] This duration is calculated from the categorical data presented in MS Figure 14 (MS page 175) and uses an approximate midpoint of [redacted] to represent the >7 & ≤14 day category, and a value of [redacted] to represent the >14 day category.

[redacted].

The MS does not provide a breakdown of LMWH treatment lengths within the >7 & ≤14 day category but this would seem to the ERG more appropriate than using a single broad category which is the most populated category in MS Figure 14 by some margin.

[redacted]. Alternative LMWH treatment durations within the SIGN guideline of 6-10 days are investigated by the ERG in scenario analysis described in Section 4.3.

The UK licensed dose of enoxaparin differs from that used in the EINSTEIN-PE trial where patients were given a dose of 1.0 mg per kilogram of body weight twice daily. The manufacturer considers that outcome differences between the trial dosage and UK licensed dose would be minimal and the ERG clinical expert concurs that there is unlikely to be a difference in clinical outcome between these doses. Mean patient body weight is assumed to be 80kg (MS Table 48 page 182) which is consistent with participants in the EINSTEIN-PE trial.

Individual resource use components included in the initial outpatient treatment of PE are given in Table 45 (MS page 177). For patients managed in the outpatient setting, the manufacturer assumes that patients with DVTs require one Doppler ultrasound, one D-dimer and one emergency admission. Patients with PEs are assumed to require one CT angiography, one chest x-ray, one electrocardiogram, one D-dimer and one emergency admission.

90% of patients in EINSTEIN-PE required hospitalisation for their index event irrespective of their treatment (MS Table 46 page 178) but this parameter is not available as a separate model

input. Only one parameter is available to set the proportion of PE cases managed as an outpatient and this is set to 17% in the base case to reflect the proportion requiring hospitalisation for a PE recurrence, rather than the index event (Table 13). The MS notes that there is not a great consensus about this proportion (MS page 179). The model accounts for a reduction in the length of hospital stay for index PE patients on rivaroxaban who in EINSTEIN-PE had a mean length of stay of 8.6 days compared to a mean length of stay of 9.1 days for those on LMWH+VKA (MS Table 46 page 178). The saving associated with a shorter length of stay for rivaroxaban is understated by the model for the index PE event given that only 10% of LMWH+VKA patients do not require hospitalisation for their index event based on data from EINSTEIN-PE, rather than 17% as used in the model base case.

The ERG notes that it is overall favourable to rivaroxaban to assume a high proportion of patients treated for VTE on an outpatient basis. This is because treatment with LMWH as an outpatient incurs a cost which is applied through all model cycles, whilst the cost saving associated with reduced length of hospital stay on rivaroxaban therapy is only applied to the index event; and because rivaroxaban is associated with a higher incidence of recurrent VTE. Rivaroxaban is assumed in the economic model to be self-administered.

The model assumes, when the VTE is treated on an outpatient basis, that 92% of patients would be able to self-inject enoxaparin pre-filled syringes in their own homes when given appropriate education, and notes that this assumption is guided by evidence presented in NICE CG92 (Section 4.7.2)[16]. 80% of patients unable to self-inject are assumed to be treated by a district nurse in their own home, whilst the remainder (1.6% of patients overall) are assumed to be treated at a clinic (MS page 176). For those treated as an inpatient the model assumes no additional resource use for enoxaparin administration.

Warfarin is used to obtain resource use estimates for VKA as it was more widely used in EINSTEIN-PE than another VKA, acenocoumarol (MS page 176). The daily maintenance dose of warfarin is assumed to be 6 mg (MS page 182), the midpoint of the range given in BNF of 3-9 mg[3]. There is no wastage associated with the administration of rivaroxaban as two tablet sizes are available which may be used to give the correct dose. A 0.8 mL single syringe of enoxaparin gives the correct dose for an 80 kg patient and this is assumed by the model. However the BNF indicates that a 3 mL vial is available and this would be more cost-effective if vial sharing were feasible[3].

The manufacturer also estimates that 8.55% of patients would require NHS-funded transportation to the monitoring clinic based on results from a Bayer/pH survey.

For INR monitoring on LMWH+VKA therapy the model assumes 9 visits to primary or secondary healthcare in the first quarter, and 5 in each subsequent quarter (Table 13). These are the same frequencies presented by the manufacturer in TA261[25]. The MS notes that INR monitoring during EINSTEIN-PE was protocol driven and not necessarily generalizable to clinical practice in England and Wales (MS page 176).

[redacted] The ERG clinical expert concurs with 9 initial visits but estimates subsequent visit frequency at 3-4 per quarter, rather than 5. Clinicians consulted by ScHARR for NICE TA261 had different opinions: one clinical expert believed that six visits in the first 3 months and 2-3 thereafter would be more plausible[11]. The NICE Committee for TA261 concluded that a less intensive INR monitoring programme of 6 visits in the first three months followed by 3 visits every 3 months thereafter was reasonable and relevant. This regime is examined by the ERG in scenario analysis described in Section 4.3.

[redacted]

Based on a national survey of models of care, the MS assumes that INR monitoring takes place in a primary care setting in 66.45% of cases, and in a secondary care setting in the remaining 33.55% of cases (MS page 177). The survey collected data from a total of 78 Primary Care Trusts (PCTs) in England, three local health boards in Wales and one PCT from a health board in Scotland. The results of the survey conflict with the opinion of the ERG clinical expert who believes that generally most VKA monitoring is done in secondary care.

For INR monitoring visits in primary care the manufacturer assumes that half of the visits are handled by GPs and the remainder by nurses (MS page 182). The ERG clinical expert believes that in primary care monitoring would be done predominantly by a nurse (e.g. nurse-led

anticoagulation clinics) rather than by GPs. This is in broad agreement with the clinical experts consulted by ScHARR for TA261 who suggested that a 25%/75% GP/nurse split would be a more accurate assessment[11]. The assumption that a greater proportion of INR monitoring visits are handled by nurses would be unfavourable to rivaroxaban (see Section 4.2.7 of this report).

Apart from the original index event the economic model accounts for resource usage associated with recurrent PEs, incident DVTs, bleeding, PTS and CTEPH. Treatment of severe PTS is assumed to require in the first year three vascular surgery outpatient appointments and thereafter two GP visits per year, based the HTA report of Goodacre and colleagues[44]. The other states are assigned unit costs based on their severity and assumed location of treatment and, in the case of the CTEPH state, a requirement for pulmonary endodartectomy (PEA). Based on Condliffe and colleagues (2008)[43] it is assumed that 68.4% of CTEPH patients require a PEA (Table 13).

Overall the MS provides a comprehensive discussion of resource use estimates relevant to the decision problem. The ERG finds that the estimates are generally reasonable. However in some cases the manufacturer's assumptions are in disagreement with those of the ERG clinical expert and previous expert opinion sought by ScHARR in TA261[11]. The direction of the disagreement is in these cases favourable to rivaroxaban. These are explored by the ERG in scenario analyses in Section 4.3.

4.2.7 Costs

The unit cost of rivaroxaban used by the economic model is £2.10 per 15 mg or 20 mg tablet as given in BNF64[3] (MS Table 50 page 188). The daily acquisition cost for patients treated with rivaroxaban is therefore £4.20 for the first 21 days (15 mg twice a day) and £2.10 thereafter (20mg once a day). The cost of treatment in the first quarter totals £235.20 and £191.63 in subsequent quarters. Costs for enoxaparin and warfarin are also taken from BNF64[3]. The daily cost of enoxaparin is £9.77 assuming treatment with the UK licensed dose and a mean body weight of 80 kg (MS Table 48 page 182).
[redacted]. The daily cost of warfarin is £0.06 (MS Table 50 page 188).

The cost of INR monitoring in primary care is based on consultation costs from PSSRU[14]. The cost of monitoring delivered by a GP is £36 whilst the cost of monitoring delivered by a nurse is £12. The INR test is assumed to cost £3[45]. The overall unit cost of primary care INR monitoring is £26.55 based on the assumption that half of the monitoring is delivered by GPs and the remainder by nurses. INR monitoring in secondary care is assumed to be £25.69 for the first attendance and £21.57 for follow-up attendance based upon the average of consultant and non-consultant led anticoagulant services in NHS reference costs (MS Table 49 page 186). The ERG notes that the cost difference between primary and secondary care monitoring means that rivaroxaban is favoured when more monitoring is assumed to be carried out in primary care. This assumption is examined in scenario analysis described in Section 4.3.

All NHS reference costs assumed in the economic model are given in MS Table 49 (MS page 186). PEs and DVTs are assumed to be treated either on an inpatient basis, at a composite unit cost, or on an outpatient basis as the sum of the costs associated with multiple outpatient treatment components in line with NICE CG92[16] (MS page 179 and Table 45 page 177). The cost in the inpatient setting is calculated to be £785.67 for DVTs and £1511.29 for PEs (MS Table 49 page 186). The cost in the outpatient setting is estimated to be £275.75 for PEs and £184.81 for DVTs (MS Table 45 page 177 and Table 50 page 188). These costs are similar to those given in TA261 which clinical advisors believed to be based on reasonable assumptions[11].

The cost saving arising from the reduced length of hospital stay for the index event when treated with rivaroxaban is derived from a weighted average of appropriate NHS reference costs for excess bed-days (MS Table 49 page 187). The saving is calculated to be £88.46 (MS page 183).

The cost of the management of a major EC bleeding event is estimated by averaging NHS reference costs data for ten relevant healthcare resource groups (HRG) codes[15], giving £929.23 (MS Table 49 page 186-187). The cost associated with the management of a minor EC bleeding event is £128.48 which is taken from a single HRG code. It was assumed that the only costs associated with a minor bleed are for acute treatment, with full recovery in three months.

The cost associated with the management of an IC bleeding event is assumed to be £6,890.85 (MS Table 49 page 187). This is taken from NHS reference costs using data for the acute care of stroke followed by 14 days' rehabilitation. The duration of rehabilitation assumes a major

stroke, an assumption which the manufacturer bases on clinical opinion (MS page 184). Follow-on care after an IC bleed is assumed to be identical to the follow-on care for a major ischaemic stroke and is based on a costing by NICE[16] which is used to derived a cost of £1,260.09 per quarter.

The costs associated with bleeding events are similar to the bleeding event costs given in NICE TA261 which were considered by clinical advisors to be reasonable[11].

Based on the method of Goodacre in a previous HTA report[44] and using NHS reference costs[15], the cost of severe PTS is assumed to be £103.02 per three month cycle in the first year and £18.00 per cycle in subsequent years.

The management cost for CTEPH in the first three months is estimated as the weighted average of two relevant HRGs in NHS reference costs, giving £3,522.38[15] (MS page 185). The ongoing cost for the management of patients with CTEPH is assumed to be £3,844.54 per three month cycle. This is based on an estimate made in 2008 for NICE CG92[16], inflated by 3.0% per annum to 2011.

Uncertainty in unit cost estimates is handled in the economic model by applying an arbitrary user-specified range to drug costs per day. In the base case sensitivity analysis upper and lower limits are set to ±30% of the sourced cost for all drugs except rivaroxaban where no uncertainty is allowed for. For on-treatment management and monitoring costs upper and lower quartiles from NHS reference costs[15] are used where available as the upper and lower bounds for uncertainty. PSSRU-sourced costs are given an arbitrary range of ±30% in the base case.

The ERG has checked and verified costs and calculations and is satisfied that the unit costs used in the economic model are relevant and have been derived using appropriate methods. However, a significant cost which is not included in the manufacturer's model is the cost of reversing the effects of rivaroxaban and warfarin in the case of major bleeding or elective surgery. There is no specific antidote for rivaroxaban but the use of activated recombinant factor VII (rFVIIa) and prothrombin complex concentrate (PCC) should be considered for the management of severe and life-threatening bleeding in patients on rivaroxaban[46;47]. Vitamin K, fresh frozen plasma and PCCs are used to reverse the anticoagulant effect of warfarin[46]. The ERG clinical expert considers that reversal of warfarin is likely to need less PCC than reversal of

rivaroxaban, and that rFVIIa may be more effective for reversing rivaroxaban than PCC. NICE CG141 for upper gastrointestinal bleeding recommends offering PCC to patients who are taking warfarin and actively bleeding but does not recommend the use of rFVIIa except when all other methods fail[48]. The cost of treating a patient with rFVIIa is estimated as £19,303 for a patient weighing 70 kg[48]. Using the dose of PCC to reverse rivaroxaban documented in Eerenberg and colleagues[47], and cost assumptions from The Dudley Group of Hospitals NHS Trust[49], the ERG calculates a PCC cost for rivaroxaban patients of £1,680 which compares with a maximum cost for a warfarin patient of £1,260[49]. The ERG examines these additional cost assumptions in scenario analysis in Section 4.3.

4.2.8 Consistency/ Model validation

Internal consistency

The MS states that two clinical experts were approached to provide validation on the initial model structure and parameter values tested in the model (MS Section 7.5.4 page 172). Quality control of the model was also undertaken by the model developers (MS Section 7.8 page 267). The MS does not report any checklists used for internal validation.

The ERG has verified that the cost-effectiveness results given in the MS are reproducible and checked the wiring of the model for the key equations and assumptions. The ERG has also verified that the parameter inputs and model results match those reported in the MS.
Two model input errors were found. One relates to PSA and is described elsewhere in this report (Section 4.2.9). The second error concerns the five year probability of severe PTS which is applied in the model without conversion to a three month cycle length. These errors do not have a substantive impact on model outcome.

As noted in Section 4.2.1, in lifelong treatment the model uses the same probability of recurrent VTE for rivaroxaban and LMWH+VKA for cycles after 36 months. The same probabilities of bleeding events are also used after 36 months for the two treatments. This appears to be an error as the MS notes that all transition probabilities are treatment-specific in the lifelong model. The probabilities after 36 months are not explicitly stated in the MS (MS Section 7.3.2 page 141).

External consistency

The MS compares incidence of VTE and bleeding in the EINSTEIN-PE trial to incidence projected from the economic model by treatment arm and patient group for the 3, 6 and 12 month treatment duration analyses (Table 14). No validation of lifetime treatment is presented as the trial period was only 12 months. The MS states that the comparison indicates that results from the model are consistent with the trial. The ERG concurs that the model produces a good fit on most measures for the LMWH+VKA arm but observes that fits to the rivaroxaban arm are more discrepant. This is presumably largely a result of applying the whole population rivaroxaban treatment effect to the individual proportions obtained for the various patient groups and time points in the LMWH+VKA arm. In particular the model estimates that 1.8% of three month intended treatment patients on the rivaroxaban arm will experience a VTE recurrence compared to [redacted]% observed in the trial; and that 0.2% of six month intended treatment patients on the rivaroxaban arm will have a recurrent VTE by the 6 month timepoint, compared to [redacted]% observed in the trial (Table 14).

Table 14 Incidence of VTE and bleeding in the EINSTEIN-PE trial compared with incidence projected from the economic model. (Reproduction of MS Table 53 page 197.)

Patient group	Outcome	Timepoint	Rivaroxaban		LMWH+VKA	
			Model	Trial	Model	Trial
3 months						
	VTE	3 months	1.8%	[redacted]	1.6%	[redacted]
	Bleeding	3 months	8.6%	[redacted]	10.6%	[redacted]
6 months						
	VTE	3 months	1.8%	[redacted]	1.6%	[redacted]
		6 months	0.2%	[redacted]	0.2%	[redacted]
	Bleeding	3 months	7.2%	[redacted]	7.7%	[redacted]
		6 months	2.3%	[redacted]	2.6%	[redacted]
12 months						
	VTE	3 months	1.7%	[redacted]	1.5%	[redacted]
		6 months	0.4%	[redacted]	0.3%	[redacted]
		12 months	0.3%	[redacted]	0.3%	[redacted]
	Bleeding	3 months	6.9%	[redacted]	7.5%	[redacted]
		6 months	2.8%	[redacted]	2.9%	[redacted]
		12 months	2.9%	[redacted]	3.2 %	[redacted]

[redacted] the proportion of VTE recurrences in the rivaroxaban arm at the six month timepoint in the 12 month intended patient group at 0.4%, compared to [redacted]% observed in the trial (Table 14).

The MS states that the results of the model were compared against other studies and are consistent with the economic analysis of rivaroxaban for the treatment to DVT presented in TA261[25]. The model also captures the key events included in economic analyses for CG144[1] and other published VTE models (MS Section 7.8 page 266).

4.2.9 Assessment of Uncertainty

One-Way Sensitivity Analyses

Model methodological uncertainty was examined by running various one-way sensitivity analyses to examine a range of discount rates and two different time horizons (MS page 194). Structural assumptions such as inclusion of PTS and CTEPH states were also tested in one-way sensitivity analysis (MS Section 7.6.1 page 193). Heterogeneity was not examined although a range of different treatment lengths are considered. The effect of parameter uncertainty was examined using both deterministic and probabilistic sensitivity analysis.

A number of deterministic sensitivity analyses were performed. In all, 123 analyses were conducted for each of the four durations of treatment giving 496 analyses in total (MS Section 7.7.7 page 253) (NB. The MS states the total to be 496, but it would appear that this should be 492). Some of these analyses were multivariable rather than univariable. The variables subject to sensitivity analysis are described in MS Section 7.6.2 (MS page 193) and MS Table 52 (MS page 194) and included:

- Probabilities of clinical events on comparator
- Treatment effects (efficacy and safety) of comparator
- Utilities
- Resource usage
- Unit costs
- Discount rate

The ranges used for sensitivity analysis are clearly stated along with the parameter point estimates in the appropriate tables in the MS. The probabilities of clinical events on LMWH+VKA, and treatment effects of rivaroxaban, were varied by using the upper and lower 95% CI values. Utilities and disutilities were also set at upper and lower 95% CI values whilst resource usages were varied by fixed percentages. The assumed discount rate was varied from 0 to 6% and the time horizon was varied from five year to lifetime. Unit costs were varied by ±30% or according to the NHS Reference Cost interquartile range (IQR)[15] if this was available.

Results are presented in four tornado plots representing the four durations of treatment in MS Figures 15-18 (MS pages 254-257). These plots use the net monetary benefit measure (NMB) instead of ICER. The ICER is less meaningful in these results because of the strong dominance of rivaroxaban for patients not requiring lifelong treatment. NMB is an alternative framework to the ICER for comparing the cost-effectiveness of treatments, derived by a simple re-arrangement of the algebraic formulation of the cost-effectiveness decision rule.

For three months' treatment the MS states that the NMB at a WTP of £20,000 per QALY gained was positive in all analyses and largely insensitive to the assumptions made (MS Section 7.7.7 page 253). For six months' treatment the NMB was sensitive to the assumptions made around treatment effect for VTE recurrence and to a smaller extent the treatment effect for major bleeds (MS Section 7.7.7 page 254). For 12 months' treatment NMB was sensitive to assumptions around treatment effect for VTE and bleeds, and frequency and cost of monitoring visits. For lifetime treatment cost-effectiveness was most sensitive to changes in the frequency of INR monitoring visits but also sensitive to the probability of rivaroxaban discontinuation.

The manufacturer concludes that rivaroxaban is generally dominant at 3, 6 and 12 month treatment durations. However the ICER reaches £27,914 in the lifetime treatment case when three INR monitoring visits are assumed in each quarter after the first, rather than five as used in the model base case (MS page 256).

The ERG finds the one-way and multivariable deterministic sensitivity analyses reported by the MS to be comprehensive and satisfactory.

Scenario Analysis

No scenario analyses are described in the MS.

The ERG considers that several assumptions in the economic model base case are favourable to rivaroxaban and that in order to better gauge the uncertainty in the decision problem these should be varied simultaneously in a deterministic fashion. This scenario, presented in Section 4.3 (scenario f), assumes fewer INR monitoring visits; reduced LMWH treatment duration; a higher proportion of monitoring visits in secondary care; and a higher proportion of primary care monitoring visits handled by a nurse.

The ERG concurs with the manufacturer that insufficient evidence is available to inform the extent to which transition probabilities for lifelong treatment should vary after the first 12 months. However this uncertainty is not fully evaluated in the deterministic and probabilistic sensitivity analyses where the overall effect of treatment is varied but the possibility of a time-dependent treatment effect is not examined. The ERG believes that there is a requirement for a longer clinical trial to ensure that the HR for the effect of rivaroxaban does not diverge from the effect of LMWH+VKA as it appears to do at around 12 months from clinical evidence presented in MS Figure 6 (MS page 71). On the basis of MS Figure 6 the ERG conducted two lifetime treatment scenario analyses which assume HRs of 1.5 and 2.0 for the effect of rivaroxaban on recurrent VTE after 12 months' treatment. The ERG considers, based on data in MS Figure 6, that the HR after 12 months of treatment may be somewhat higher than 2.0 but chose to examine scenarios with only slight worsening of the HR and which maintained non-inferiority of rivaroxaban. The ERG also makes an adjustment to the lifelong treatment base case which assumes that the efficacy and safety HRs of rivaroxaban seen in EINSTEIN-PE are carried forward to model transitions on the rivaroxaban arm after 36 months, rather than using the same transition probabilities for both treatment arms as implemented in the base case (as explained in Section 4.2.4.2 of this report). These analyses are presented in Section 4.3.

The ERG also presents in Section 4.3 several scenario analyses with various assumptions about INR monitoring visits.

Probabilistic Sensitivity Analysis

The MS describes PSA conducted over 5,000 iterations (MS Section 7.6.3 page 195). The ERG verified that this takes approximately five minutes to run. Results are presented in MS Table 85 (MS page 258) and in Table 15 below. MS Table 85 shows that for six months of treatment at a threshold WTP of £20,000 per QALY gained there is a 95.9% probability that rivaroxaban is cost-effective. Lifelong treatment has a probability of being cost effective of 59.1% at a WTP threshold of £20,000 per QALY gained. Table 15 shows that based upon probabilistic mean costs and QALYs rivaroxaban dominates LMWH+VKA at all treatment durations except lifelong, where the ICER is £13,918 per QALY gained. The MS concludes that rivaroxaban has a high probability of being cost effective at a WTP threshold of £20,000 per QALY gained. Greater cost savings and increased incremental QALYs for rivaroxaban are associated with shorter treatment durations.

Table 15: Probabilistic mean costs and QALYs for patients for all evaluated treatment lengths (reproduced from MS Tables 86-89 page 258-263).

Technology	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£) (QALYs)
3 Months of Treatment					
Rivaroxaban	4,676.36	13.259	-	-	-
LMWH+VKA	5,061.04	13.221	384.68	-0.038	Dominated
6 Months of Treatment					
Rivaroxaban	4,700.66	13.244	-	-	-
LMWH+VKA	4,910.75	13.230	210.08	-0.014	Dominated
12 Months of Treatment					
Rivaroxaban	5,025.66	13.232	-	-	-
LMWH+VKA	5,146.66	13.210	121.00	-0.022	Dominated
Lifelong Treatment					
LMWH+VKA	9,718.55	12.356	-	-	-
Rivaroxaban	11,172.66	12.460	1,454.12	0.104	13,918

Variables included in PSA are described in MS Section 7.6.3 (MS page 195) and in MS Tables 28, 30, 31, 40, 43, 47 and 50. Model input probabilities are varied according to appropriate Beta distributions. The treatment effects of rivaroxaban are sampled from lognormal distributions. Utilities are sampled from Beta distributions and unit costs are sampled from Gamma

distributions. The ranges used in univariable sensitivity analysis are also used to define the parameters of the respective utility and cost PSA distributions. Dirichlet distributions based on data in MS Figure 14 (MS page 175) are used to sample values for number of days of acute treatment of DVT and PE with LMWH. MS Figure 14 is based on treatment lengths of whole days with the exception of treatment lengths of >7 but ≤14 days, and >14 days, which are considered as two broad categories. An approximate midpoint of the >7 & ≤14 days category ([redacted]) is assumed in the Dirichlet distribution, whilst a treatment length of [redacted] days is assumed in the Dirichlet distribution for the >14 days category. As noted in Section 4.2.6 the ERG believes it possible that the midpoint of the >7 & ≤14 category particularly may be somewhat higher than the mean treatment length within this category and in this case the PSA will sample systematically overstated LMWH treatment lengths, to the advantage of rivaroxaban.

The ERG found two errors in the PSA. The Beta distribution specified for PE off treatment mortality had alpha set to 0, and the PSA for this parameter did not read in a draw from a Beta distribution (which would have generated an error with alpha=0), but rather a value of 0. The draw for LMWH mean treatment length was also not wired in to subsequent model calculations and so uncertainty in this parameter is not reflected in PSA.

The ERG has re-run the lifelong treatment PSA based upon a corrected lifelong base case which carries forward the efficacy (prevention of recurrent VTE) and safety effects (bleeding events) of rivaroxaban after 36 months. This PSA was also run with revised assumptions concerning INR monitoring visits and is described in scenario analysis in Section 4.3.

The ERG believes that the methods of assessment of parameter uncertainty in the PSA are generally appropriate. However the possibility of correlation between parameters is not explored or reflected.

4.2.10 Comment on validity of results with reference to methodology used

The structure adopted for the economic model is reasonable and consistent with current clinical understanding of PE and previous economic evaluations of treatments for VTEs[25]. The methods of analysis are appropriate and conform to NICE methodological guidelines.

The parameters used for the model are generally appropriate. The population used in the model is drawn from the relevant trial (EINSTEIN-PE) and is broadly representative of the PE patient population in the UK. It is however not fully representative of this population as some patients eligible for rivaroxaban treatment were excluded from the trial and some PE patients are contraindicated for rivaroxaban.

4.3 Additional work undertaken by the ERG

In addition to the correction of minor model errors noted above the ERG has conducted the following scenario analyses:

a) Amendment to rivaroxaban efficacy and safety after 36 months in lifelong treatment
b) Variation to assumed frequency of INR monitoring visits
c) Reduction in mean LMWH treatment length
d) Reduction in rivaroxaban efficacy after 12 months in lifelong treatment
e) Higher hazard of major bleed on rivaroxaban
f) Reduced frequency of INR monitoring visits combined with greater proportion of monitoring visits in secondary care; greater proportion of primary care monitoring visits led by nurses; reduction in mean LMWH treatment length; reduction in rivaroxaban efficacy after 12 months in lifelong treatment; raised hazard of major bleed
g) Higher utility for intracranial bleed state
h) Higher mean age of model population
i) Costs of emergency anticoagulant reversal taken into account in cases of major bleeding

a) Amendment to rivaroxaban efficacy and safety after 36 months in lifelong treatment
Rivaroxaban becomes more cost-effective for lifelong treatment durations if its efficacy and safety effects (HRs of recurrent VTE and bleeding events respectively) are applied after 36 months of treatment instead of using the same transition probabilities as the LMWH+VKA arm. The ERG believes this was an unintended model wiring error and has accordingly corrected the lifelong base case ICER (Table 16). The ICER for lifelong rivaroxaban treatment compared to treatment with LMWH+VKA becomes £7,072 rather than £13,252 as given in the MS.

Table 16 ERG analysis on effect of amendment to rivaroxaban efficacy and safety after 36 months in lifelong treatment

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
Base case	Rivaroxaban	10,868	12.479	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,375	-0.104	13,252
Amended base case[1]	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,064	-0.150	7,072

[1] Rivaroxaban efficacy and safety adjusted to carry forward relative effects seen at other treatment durations (rather than use the same effects as LMWH+VKA for durations greater than 36 months)

b) Variation to assumed frequency of INR monitoring visits

The NICE Appraisal Committee for TA261 concluded that an INR monitoring programme of 6 visits in the first 3 months followed by 3 visits every 3 months thereafter was reasonable and relevant for the appraisal of rivaroxaban for the prevention of DVT, rather than the values assumed by the manufacturer of 9 visits in the first quarter and 5 visits in each subsequent quarter[25]. This programme of monitoring is examined here in Table 17 for each of three treatment durations (6 months, 12 months and lifelong). A programme of 2 visits in each quarter after the first is also examined in this table for the lifelong case (Section 4.2.6) [redacted].

It may be seen from Table 17 that rivaroxaban becomes relatively less cost-effective as fewer INR monitoring visits are assumed in the LMWH+VKA arm and the incremental costs associated with an LMWH+VKA regime decrease. However, rivaroxaban remains dominant for 6 months and 12 months of treatment. It is not cost-effective at a WTP of £20,000 for lifelong treatment with 2 monitoring visits per quarter, where the ICER is £22,912 (Table 17).

c) Reduction in treatment length with LMWH

Based on EINSTEIN-PE data and non-conservative assumptions (Section 4.2.6), the model base case assumes a mean LMWH treatment duration of [redacted] for PE patients. This is at the [redacted] of LMWH treatment durations recommended in the SIGN guideline where a range of 6-10 days is given[42].

Table 17 ERG analysis on effect of changes to assumed INR monitoring visits for patients requiring 6 months' treatment

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
6 Months of Treatment				
Base case (9 visits first quarter, 5 visits subsequent)	Rivaroxaban	4,546	11.992	-
	LMWH+VKA	4,759	11.979	-
	Incremental	213	-0.013	Dominated
6 visits in first quarter and 3 in each subsequent	Rivaroxaban	4,455	11.992	-
	LMWH+VKA	4,552	11.979	-
	Incremental	97	-0.013	Dominated
12 Months of Treatment				
Base case (9 visits first quarter, 5 visits subsequent)	Rivaroxaban	4,881	12.035	-
	LMWH+VKA	5,015	12.015	-
	Incremental	133	-0.020	Dominated
6 visits in first quarter and 3 in each subsequent	Rivaroxaban	4,793	12.035	-
	LMWH+VKA	4,721	12.015	-
	Incremental	-72	-0.020	3,542
Lifelong Treatment				
Amended base case (9 visits first quarter, 5 visits subsequent)	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,064	-0.150	7,072
6 visits in first quarter and 3 in each subsequent	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	7,871	12.375	-
	Incremental	-2,686	-0.150	17,857
6 visits in first quarter and 2 in each subsequent	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	7,110	12.375	-
	Incremental	-3,447	-0.150	22,912

Alternative assumed mean LMWH treatment durations within the SIGN guideline of 6-10 days are examined in Table 18. The cost-saving associated with these reduced treatment lengths is small and rivaroxaban still dominates LMWH+VKA.

Table 18 ERG analysis on effect of changes to mean LMWH treatment duration for patients requiring 6 months' treatment

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
Base case (9.7 days treatment)	Rivaroxaban	4,546	11.992	-
	LMWH+VKA	4,759	11.979	
	Incremental	213	-0.013	Dominated
Mean LMWH treatment duration 9 days	Rivaroxaban	4,541	11.992	-
	LMWH+VKA	4,747	11.979	-
	Incremental	206	-0.013	Dominated
Mean LMWH treatment duration 8 days	Rivaroxaban	4,533	11.992	-
	LMWH+VKA	4,729	11.979	
	Incremental	196	-0.013	Dominated
Mean LMWH treatment duration 6 days	Rivaroxaban	4,519	11.992	-
	LMWH+VKA	4,694	11.979	-
	Incremental	176	-0.013	Dominated

d) Reduction in rivaroxaban efficacy after 12 months in lifelong treatment

The lifelong treatment effect of rivaroxaban beyond the 12 months of EINSTEIN-PE trial data is highly uncertain as the trial was only for one year. MS Figure 6 (MS page 71) indicates a worsening of the relative hazard of recurrent VTE whilst on rivaroxaban compared to LMWH+VKA towards the end of the 12 month study period. It is plausible that the hazard might worsen further in the longer term particularly if adherence declines. The ERG clinical expert considers that adherence to a long-term regimen of rivaroxaban will in practice be far lower than the 80% plus in 94.2% patients seen in EINSTEIN-PE[2], because there is no requirement for INR monitoring (which would encourage patients to adhere to their treatment regimen).

To examine this uncertainty the ERG considered a HR for recurrent VTE whilst on rivaroxaban of 1.5 applied after 12 months of treatment in the lifelong case, combined with a HR of 1.123 for the first 12 months of treatment. This results in an ICER of £9,043 per QALY. A HR of 2.0 applied after 12 months of treatment nearly doubles the amended base case ICER to £14,090 per QALY (Table 19).

Table 19 ERG analysis on effect of variation to rivaroxaban recurrent VTE hazard ratio after twelve months, lifelong treatment

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
Amended base case HR=1.123 post 12 months tx	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,064	-0.150	7,072
Rivaroxaban rVTE HR=1.5 post 12 months tx	Rivaroxaban	10,567	12.494	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,074	-0.119	9,043
Rivaroxaban rVTE HR=2.0 post 12 months tx	Rivaroxaban	10,581	12.453	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,088	-0.077	14,090

e) Higher hazard of major bleed whilst on rivaroxaban

The relative hazard of major bleeding whilst on rivaroxaban compared to LMWH+VKA, obtained from EINSTEIN-PE trial, is much lower than the hazard seen in the EINSTEIN-DVT trial.[6] Cost-effectiveness outcomes are very sensitive to the assumed value of this parameter. Table 20 examines an HR for major bleed whilst on rivaroxaban of 0.65, equivalent to the HR obtained in EINSTEIN-DVT.[6] The upper limit of the 95% confidence interval for major bleed HR seen in EINSTEIN-PE, 0.79, is also examined.

Table 20 ERG analysis on effect of variation to rivaroxaban major bleed hazard, lifelong treatment

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
Amended base case HR=0.493	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,064	-0.150	7,072
Rivaroxaban major bleed HR=0.65	Rivaroxaban	10,858	12.482	-
	LMWH+VKA	9,628	12.360	-
	Incremental	-1,230	-0.122	10,070
Rivaroxaban major bleed HR=0.79	Rivaroxaban	11,123	12.443	-
	LMWH+VKA	9,746	12.346	-
	Incremental	-1,377	-0.097	14,177

These analyses are for the lifelong treatment case and indicate a progressive worsening of the ICER from £7,072 per QALY gained in the amended base case, to £14,177 per QALY gained when a major bleed HR for rivaroxaban of 0.79 is assumed.

f) Multiway scenario

This scenario combines the scenarios presented in (b), (c), (d) and (e) above with additional altered assumptions about the balance between INR monitoring visits carried out in primary and secondary care, and the balance between nurse-led and GP-led primary care visits. A 50:50 split is assumed between primary and secondary care INR monitoring, rather than the 66:34 split assumed in the model base case. It is also assumed that 75% of monitoring visits in primary care are nurse-led with the remainder being GP-led. This compares with the 50:50 split used in the model base case. ScHARR also explored this assumption in scenario analysis undertaken for TA261[11].

The results of this scenario are given in Table 21 for 6 months, 12 months and lifelong treatment durations. Rivaroxaban is relatively less cost-effective in this scenario as lower costs are incurred in the LMWH+VKA arm. However it remains dominant for the 6 month treatment duration and cost-effective at a WTP of £20,000 per QALY for the 12 month treatment duration. It is not cost-effective at a WTP of £20,000 per QALY for the lifelong treatment duration.

Table 21 ERG analysis on effect of various INR monitoring assumption changes, rivaroxaban hazard for rVTE of 1.5 after 12 months, and shorter mean LMWH treatment duration

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
6 Months of Treatment				
Base case	Rivaroxaban	4,546	11.992	-
	LMWH+VKA	4,759	11.979	-
	Incremental	213	-0.013	Dominated
Alternative[1]	Rivaroxaban	4,447	11.988	-
	LMWH+VKA	4,468	11.979	-
	Incremental	21	-0.009	Dominated
12 Months of Treatment				
Base case	Rivaroxaban	4,881	12.035	-
	LMWH+VKA	5,015	12.015	-
	Incremental	133	-0.020	Dominated
Alternative[1]	Rivaroxaban	4,794	12.030	-

	LMWH+VKA	4,618	12.015	-
	Incremental	-176	-0.015	11,590
Lifelong Treatment				
Amended base case	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,064	-0.150	7,072
Alternative[1]	Rivaroxaban	10,867	12.450	-
	LMWH+VKA	7,607	12.360	-
	Incremental	-3,260	-0.091	35,909

[1] Mean LMWH treatment duration for PE 8 days; 6 INR monitoring visits in first quarter and three in subsequent quarters; 50:50 split between primary and secondary care INR monitoring; 25% of primary care monitoring handled by GP and remainder by nurse; HR of 1.5 for recurrent VTE in rivaroxaban arm after 12 months; HR for major bleed on rivaroxaban of 0.65

g) Higher utility for intracranial bleed state

The economic model base case applies a utility of 0.33 to patients in the intracranial bleed state (Section 4.2.5). This was felt by the ERG to be somewhat low and an alternative utility for stroke patients after one month of 0.55, given in Pickard and colleagues[41] was used in scenario analysis. The results of this analysis are given in Table 22. A higher utility for the IC bleed does not appreciably change the total QALYs and model outcomes are hardly altered.

Table 22 ERG analysis on effect of change to intracranial bleed state utility from 0.33 (base case) to 0.55.

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
6 Months of Treatment				
Base case (IC bleed state utility=0.33)	Rivaroxaban	4,546	11.992	-
	LMWH+VKA	4,759	11.979	-
	Incremental	213	-0.013	Dominated
IC bleed state utility=0.55	Rivaroxaban	4,546	11.992	-
	LMWH+VKA	4,759	11.979	-
	Incremental	213	-0.013	Dominated
12 Months of Treatment				
Base case (IC bleed state utility=0.33)	Rivaroxaban	4,881	12.035	-
	LMWH+VKA	5,015	12.015	-
	Incremental	133	-0.020	Dominated
IC bleed state utility=0.55	Rivaroxaban	4,881	12.035	-
	LMWH+VKA	5,015	12.015	-

	Incremental	133	-0.020	Dominated
Lifelong Treatment				
Amended base case (IC bleed state utility=0.33)	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,064	-0.150	7,072
IC bleed state utility=0.55	Rivaroxaban	10,557	12.527	-
	LMWH+VKA	9,493	12.377	-
	Incremental	-1,064	-0.150	7,098

h) Higher mean age of model population

The economic model base case uses a population with a mean age of 58 years (Section 4.2.2). This is lower than the mean age of some other PE and DVT patient populations described in the literature[26]. An alternative mean age of 65 was examined in scenario analysis (Table 23). The table indicates that a higher mean age reduces the cost and QALY advantage of rivaroxaban relative to LMWH+VKA. However rivaroxaban remains dominant at 6 and 12 month treatment durations, and cost-effective at a WTP of £20,000 per QALY for the lifelong treatment duration.

Table 23 ERG analysis on effect of change to cohort mean age from 58 to 65

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
6 Months of Treatment				
Base case (mean age 58)	Rivaroxaban	4,546	11.992	-
	LMWH+VKA	4,759	11.979	-
	Incremental	213	-0.013	Dominated
Mean age 65	Rivaroxaban	4,174	10.229	-
	LMWH+VKA	4,375	10.217	-
	Incremental	201	-0.012	Dominated
12 Months of Treatment				
Base case (mean age 58)	Rivaroxaban	4,881	12.035	-
	LMWH+VKA	5,015	12.015	-
	Incremental	133	-0.020	Dominated
Mean age 65	Rivaroxaban	4,505	10.265	-
	LMWH+VKA	4,622	10.247	-
	Incremental	117	-0.019	Dominated
Lifelong Treatment				
Amended base case (mean age 58)	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	9,493	12.375	-

	Incremental	-1,064	-0.150	7,072
Mean age 65	Rivaroxaban	9,342	10.617	-
	LMWH+VKA	8,361	10.493	-
	Incremental	-981	-0.124	7,911

i) Cost of emergency anticoagulant reversal

There is currently no specific antidote to rivaroxaban and the cost of reversal of its effects in cases of acute bleeding and in preparation for emergency surgery is high (Section 4.2.7). Either prothrombin complex concentrate (PCC) or activated recombinant factor VII (rFVIIa) is advised in these cases[46]. For patients on warfarin with active gastrointestinal bleeding NICE CG141 recommends PCC[48]. The ERG has examined a scenario which applies the costs of PCC in both treatment arms in all cases of major bleeding (intracranial and extracranial). A second scenario assumes use of PCC for all major bleeds in the LMWH+VKA arm and rFVIIa for all major bleeds in the rivaroxaban arm. A third scenario extends the second scenario to also reflect an increased hazard of major bleed whilst on rivaroxaban (HR=0.65, as seen in EINSTEIN-DVT) and the NICE-preferred assumptions of INR monitoring visit frequency (6 in the first quarter and 3 in each subsequent quarter). Treatment with rFVIIa is assumed to cost £19,303 per patient whilst treatment with PCC is assumed to cost £1,260 for a patient on warfarin and £1,680 for a patient on rivaroxaban (see Section 4.2.7 for details). Results are given in Table 26.

The proportionate need for anticoagulant reversal drugs in clinical practice is uncertain but table 24 indicates that rivaroxaban remains cost-effective at a WTP to pay of £20,000 per QALY when anticoagulant reversal drug costs are applied to all cases of major bleeding and other base case assumptions remain unchanged. However, when the base case assumptions for INR monitoring visit frequency and HR of major bleed whilst on rivaroxaban and are also adjusted, in line with previous scenarios (Table 17 and Table 20, respectively), rivaroxaban is no longer cost-effective for either 12 months or lifelong treatment at a WTP of £20,000 per QALY (Table 24).

Table 24 ERG analysis on inclusion of anticoagulant reversal drug costs in cases of major bleeding

Scenario	Treatment	Total costs, £	Total QALYs	ICER (£/QALY gained)
12 Months of Treatment				
Base case (no anticoagulant reversal costs)	Rivaroxaban	4,881	12.035	-
	LMWH+VKA	5,015	12.015	-
	Incremental	133	-0.020	Dominated
PCC cost for major bleeds (both arms)	Rivaroxaban	4,900	12.035	-
	LMWH+VKA	5,042	12.015	-
	Incremental	142	-0.020	Dominated
rFVIIa cost (rivaroxaban), PCC cost (LMWH+VKA)	Rivaroxaban	5,089	12.035	-
	LMWH+VKA	5,042	12.015	-
	Incremental	-47	-0.020	2,328
Multivariable[1]	Rivaroxaban	5,102	12.030	-
	LMWH+VKA	4,748	12.015	-
	Incremental	-354	-0.015	23,364
Lifelong Treatment				
Amended base case	Rivaroxaban	10,557	12.526	-
	LMWH+VKA	9,493	12.375	-
	Incremental	-1,064	-0.150	7,072
PCC cost for major bleeds (both arms)	Rivaroxaban	10,740	12.526	-
	LMWH+VKA	9,707	12.375	-
	Incremental	-1,033	-0.150	6,868
rFVIIa cost (rivaroxaban), PCC cost (LMWH+VKA)	Rivaroxaban	12,662	12.526	-
	LMWH+VKA	9,707	12.375	-
	Incremental	-2,955	-0.150	19,642
Multivariable[1]	Rivaroxaban	13,615	12.482	
	LMWH+VKA	8,234	12.360	-
	Incremental	-5,381	-0.122	44,046

[1] Multivariable scenario assumes rFVIIa cost (rivaroxaban); PCC cost (LMWH+VKA); HR of major bleed=0.65; 6 INR monitoring visits in first quarter and 3 in subsequent quarters

Revised probabilistic sensitivity analysis for lifelong treatment

The ERG has re-run the manufacturer's PSA for lifelong treatment to reflect the amended base case for this treatment duration. 5,000 simulations were used. The revised probabilities that rivaroxaban is cost effective at various thresholds of WTP are given in Table 25. The ICER

calculated from the PSA mean costs and QALYs, £7,019 per QALY, is consistent with findings from the amended deterministic base case (ICER of £7,072, Table 16).

Table 25 Probability that rivaroxaban is cost-effective for lifelong treatment, amended base case

WTP per QALY (£)	Probability of cost-effectiveness
0	26.9%
10,000	53.4%
20,000	80.4%
30,000	90.0%
40,000	93.1%
50,000	94.1%

The ERG has also re-run the amended base case lifelong PSA using a mean of 6 INR monitoring visits in the first quarter and 3 in subsequent quarters. First quarter monitoring visits were assumed to vary between 8 and 5, and subsequent quarter monitoring visits were assumed to vary between 4 and 2. An HR of recurrent VTE after 12 months' treatment of 1.5 (95% CI 1.1-1.9) was also applied to the rivaroxaban arm. Results of this PSA are given in Table 26. The ICER associated with the mean costs and QALYs from this PSA is £22,787 per QALY gained.

Table 26 Probability that rivaroxaban is cost-effective for lifelong treatment, amended base case combined with fewer INR monitoring visits and higher hazard of recurrent VTE after 12 months

WTP per QALY (£)	Probability of cost-effectiveness
0	8.4%
10,000	17.8%
20,000	39.7%
30,000	61.5%
40,000	72.4%
50,000	78.0%

4.4 Summary of uncertainties and issues

- The number of INR monitoring visits for patients with VTE treated with a VKA in England and Wales is assumed in the economic model to be 9 in the first quarter and 5 in

subsequent quarters. The clinical advisor to the ERG suggests less intensive monitoring and the previous NICE Appraisal Committee for TA261 also concluded that less intensive monitoring would be more reasonable and relevant[25]. The model is highly sensitive to the assumed number of monitoring visits in subsequent quarters and under certain INR monitoring frequency assumptions lifelong treatment with rivaroxaban may not be cost-effective at a WTP of £20,000.

- There is much variation in the models of INR monitoring provision in England and Wales and the mean costs of providing such provision are therefore highly uncertain. This uncertainty particularly affects the cost-effectiveness of lifelong treatment which is more borderline than the cost-effectiveness of the shorter treatment durations.
- There is little evidence to inform the treatment effect of rivaroxaban relative to LMWH+VKA beyond 12 months. The ERG clinical expert believes that rivaroxaban patients may be less likely to comply with their regimen than those on long-term VKA because there is no requirement for regular monitoring. Rivaroxaban becomes much less cost-effective for lifelong treatment if higher hazard ratios are used for the treatment effect after 12 months.
- The relative hazard of major bleeding whilst on rivaroxaban compared to LMWH+VKA, obtained from EINSTEIN-PE, is much lower than the hazard seen in EINSTEIN-DVT. Although a significant difference between rivaroxaban and LMWH+VKA major bleeding risk was found in EINSTEIN-PE, this was based upon a relatively small number of events and the ERG believes that this hazard ratio should be applied with caution as cost-effectiveness outcomes are very sensitive to its assumed value.
- There is currently no specific antidote to rivaroxaban and the cost of the reversal of its effect in cases of major bleeding and elective surgery is potentially very high.

5 End of life

NICE end of life treatment criteria were not applicable and not included in the MS.

6 Innovation

The manufacturer describes the innovative nature of rivaroxaban for the treatment of PE and recurrent VTE in MS Section 4. The arguments for innovation generally repeat the assertions made elsewhere in the submission about the benefits to patients and to health services,

emphasising the novel single drug approach (e.g. easier drug administration, less requirement for monitoring, apparent patient treatment satisfaction). Many of these benefits have also been suggested by Consultees to the NICE appraisal process.

7 DISCUSSION

7.1 Summary of clinical-effectiveness issues

The assessment of clinical-effectiveness was based on a well-conducted systematic review of the literature. This yielded one included study – the large multi-national EINSTEIN-PE RCT, which compared rivaroxaban with LMWH+VKA treatment for up to a year. Overall this trial is of good methodological quality and low risk of bias, though due to nature of the treatment administration it was open-label. The trial found that rivaroxaban was associated with a slightly higher rate of recurrent VTE, though this was within the pre-specified margin for non-inferiority. Rivaroxaban can therefore be considered clinically comparable to the current standard treatment. There was a similar rate of clinically relevant bleeding between the two treatments, and a statistically significantly lower rate of major bleeding with rivaroxaban. There are also (limited) data to suggest greater patient satisfaction with rivaroxaban. The ERG concludes that, overall, the MS provides an unbiased estimate of the treatment effect.

However, the patient population in the trial may not be fully representative of the treatment population in general, particularly as patients with severe renal impairment were excluded. Furthermore, some patients, including those with an unprovoked PE may require long-term anticoagulation, however, the effectiveness and safety of rivaroxaban compared with LMWH+VKA treatment beyond 12 months has not yet been demonstrated. Given that in the EINSTEIN-PE trial just over two-thirds of patients had unprovoked PE this is a particular area of uncertainty.

7.2 Summary of cost-effectiveness issues

The MS includes evidence on the cost-effectiveness of rivaroxaban compared to LMWH+VKA for the treatment of PE and prevention of recurrent VTE. The model structure and methods adopted for the economic evaluation are reasonable and generally appropriate. The model

structure and parameter input values are consistent with the clinical disease pathways and the available clinical trial evidence.

In the analyses conducted by the manufacturer for treatment durations up to 12 months rivaroxaban leads to a saving in costs but also a gain in QALYs; it therefore dominates LMWH+VKA. However, the cost savings are moderate and range from £133 in the 12 month treatment case to £396 in the three month treatment case. The QALY gains are also modest and range from 0.02 in the 12 month treatment case to 0.027 in the three month treatment case.

There are uncertainties in the data and the assumptions which are made, particularly for treatment after 12 months. The dominance of rivaroxaban at treatment durations up to six months is robust to sensitivity analysis and scenario analysis. Rivaroxaban is less likely to dominate at 12 months' treatment duration but remains cost-effective at a WTP threshold of £20,000 per QALY. In some scenario and sensitivity analyses lifelong treatment is not cost-effective at a WTP threshold of £30,000 per QALY.

8 REFERENCES

(1) National Clinical Guideline Centre. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. http://www nice org uk/nicemedia/live/13767/59711/59711 pdf [2012 Available from: URL:http://www.nice.org.uk/nicemedia/live/13767/59711/59711.pdf

(2) Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; 366(14):1287-1297.

(3) Joint Formulary Committee. British National Formulary 64. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2012.

(4) Akl EA, Labedi N, Barba M, Terrenato I, Sperati F, Schünemann H. Anticoagulation for the long-term treatment of venous thromboembolic events in patients with cancer. *Cochrane Database of Systematic Reviews* 2011; 6(CD006650).

(5) Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011. The Cochrane Collaboration.

(6) Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363(26):2499-2510.

(7) Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematologica* 2007; 92(2):199-205.

(8) Bayer Healthcare. Protocol for study 11702. Oral direct factor Xa inhibitor rivaroxaban in the long-term prevention of recurrent symptomatic venous thrombolism in patients with symptomatic deep-vein thrombosis or pulmonary embolism. 2010.

(9) Snapin SM. Noninferiority trials. *Current Controlled Trials in Cardiovascular Medicine* 2000; 1(1):19-21.

(10) Schumi J, Wittes JT. Through the looking glass: Understanding non-inferiority. *Trials* 2011; 12(106).

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

(12) Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. Third edition. 2009. York Publishing Services Ltd., CRD.

(13) Patient reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic pulmonary embolism. 54th ASH Annual Meeting and Exposition; 12 Dec 8; Atlanta, GA: 2012.

(14) Curtis L. Unit Costs of Health and Social Care 2011. http://www pssru ac uk/pdf/uc/uc2010/uc2010 pdf [2011

(15) Department of Health. NHS reference costs 2010-2011. http://www dh gov uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_122803 [10 A.D. [cited 2010 June 7];

(16) National Clinical Guideline Centre - Acute and Chronic Conditions. Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital . http://www nice org uk/nicemedia/live/12695/47920/47920 pdf [2010 [cited 2013 Jan. 21]; Available from: URL:http://www.nice.org.uk/nicemedia/live/12695/47920/47920.pdf

(17) Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for treatment of pulmonary embolism. *Chest* 2005; 128(3):1601-1610.

(18) Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for secondary prophylaxis of cancer-related venous thromboembolism. *Thromb Haemost* 2005; 93(3):592-599.

(19) Dranitsaris G, Vincent M, Crowther M. Dalteparin versus warfarin for the prevention of recurrent venous thromboembolic events in cancer patients: a pharmacoeconomic analysis. *Pharmacoeconomics* 2006; 24(6):593-607.

(20) Marchetti M, Pistorio A, Barone M, Serafini S, Barosi G. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. *Am J Med* 2001; 111(2):130-139.

(21) Perez-de-Llano LA, Leiro-Fernandez V, Golpe R, Nunez-Delgado JM, Palacios-Bartolome A, Mendez-Marote L et al. Comparison of tinzaparin and acenocoumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study. *Blood Coagul Fibrinolysis* 2010; 21(8):744-749.

(22) Perlroth DJ, Sanders GD, Gould MK. Effectiveness and cost-effectiveness of thrombolysis in submassive pulmonary embolism. *Arch Intern Med* 2007; 167(1):74-80.

(23) Aujesky D, Smith KJ, Roberts MS. Oral anticoagulation strategies after a first idiopathic venous thromboembolic event. *Am J Med* 2005; 118(6):625-635.

(24) Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes (3rd edition). *Oxford University Press* 2005.

(25) National Institute for Health and Clinical Excellence. Technology Appraisal 261 (TA261) Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. http://www nice org uk/guidance/TA261 (accessed 10/12/12) [2012 Available from: URL:http://www.nice.org.uk/guidance/TA261

(26) Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; 158(6):585-593.

(27) Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; 349(2):146-153.

(28) Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. *J Thromb Haemost* 2010; 8(11):2436-2442.

(29) Streiff MB, Segal JB, Tamariz LJ, Jenckes MW, Bolger DT, Eng J et al. Duration of vitamin K antagonist therapy for venous thromboembolism: a systematic review of the literature. *Am J Hematol* 2006; 81(9):684-691.

(30) Linkins L, O'Donnell M, Julian JA, Kearon C. Intracranial and fatal bleeding according to indication for long-term oral anticoagulant therapy. *J Thromb Haemost* 2010; 8(10):2201-2207.

(31) Boggon R, van Staa TP, Timmis A, Hemingway H, Ray KK, Begg A et al. Clopidogrel discontinuation after acute coronary syndromes: frequency, predictors and associations with death and myocardial infarction--a hospital registry-primary care linked cohort (MINAP-GPRD). *Eur Heart J* 2011; 32(19):2376-2386.

(32) Miniati M, Monti S, Bottai M, Scoscia E, Bauleo C, Tonelli L et al. Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism. *Medicine (Baltimore)* 2006; 85(5):253-262.

(33) Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; 125(1):1-7.

(34) Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica* 1997; 82(4):423-428.

(35) Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. *J Am Med Inform Assoc* 1997; 4(1):49-56.

(36) Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. *Med Decis Making* 2010; 30(3):341-354.

(37) O'Meara JJ, III, McNutt RA, Evans AT, Moore SW, Downs SM. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. *N Engl J Med* 1994; 330(26):1864-1869.

(38) Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. *Thromb Haemost* 2004; 92(6):1336-1341.

(39) Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998; 316(7133):736-741.

(40) Meads DM, McKenna SP, Doughty N, Das C, Gin-Sing W, Langley J et al. The responsiveness and validity of the CAMPHOR Utility Index. *Eur Respir J* 2008; 32(6):1513-1519.

(41) Pickard AS, Johnson JA, Feeny DH, Shuaib A, Carriere KC, Nasser AM. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. *Stroke* 2004; 35(2):607-612.

(42) Scottish Intercollegiate Guidelines Network. Guideline 122. Prevention and management of venous thromboembolism. http://www sign ac uk/pdf/sign122 pdf [2010 [cited 2013 Jan. 21]; Available from: URL:http://www.sign.ac.uk/pdf/sign122.pdf

(43) Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2008; 177(10):1122-1127.

(44) Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S et al. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. *Health Technol Assess* 2006; 10(15):1-iv.

(45) National Institute for Health and Clinical Excellence. Anticoagulation therapy service - commissioning and benchmarking tool. http://www nice org uk/usingguidance/commissioningguides/anticoagulationtherapyservice/commissioningtool jsp [2011 [cited 2013 Jan. 21]; Available from: URL:http://www.nice.org.uk/usingguidance/commissioningguides/anticoagulationtherapyservice/commissioningtool.jsp

(46) Kazmi RS, Lwaleed BA. New anticoagulants: how to deal with treatment failure and bleeding complications. *Br J Clin Pharmacol* 2011; 72(4):593-603.

(47) Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124(14):1573-1579.

(48) National Clinical Guideline Centre. Acute upper gastrointestinal bleeding. Management. http://www nice org uk/nicemedia/live/13762/59548/59548 pdf [2012 Available from: URL:http://www.nice.org.uk/nicemedia/live/13762/59548/59548.pdf

(49) The Dudley Group of Hospitals NHS Trust. Policy for Use of PCC (Octaplex) for Reversal of Warfarin in Patients with Intracranial Haemorrhage/Major Bleeding. http://www dwmh nhs uk/sections/publications/documents/FOI28824268083 pdf [2007 [cited 2013 Feb. 4]; Available from: URL:http://www.dwmh.nhs.uk/sections/publications/documents/FOI28824268083.pdf