Bayer HealthCare
Bayer Schering Pharma

Single Technology Appraisal (STA) of rivaroxaban (Xarelto®) for the prevention of venous thromboemobolism (VTE) in adult patients undergoing elective hip or knee replacement surgery

8th October 2008

Please note commercial in confidence information has been removed from this document

Contents

List of appendices

Appendices are provided in a separate document; see file *Xarelto VTE prevention_STA form appendices.doc*

List of abbreviations

A&E	Accident and Emergency
CEA	Cost Effectiveness Analysis
CI	Confidence Interval
CT	Computed Tomography
CUA	Cost Utility Analysis
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
GCS	Graduated Compression Stockings
GP	General Practitioner
HFS	Hip Fracture Surgery
HRG	Healthcare Resource Group
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
INR	International Normalised Ratio
IPC	Intermittent Pneumatic Compression
JRP	Joint Recovery Programme
LMWH	Low Molecular Weight Heparin
LOS	Length of Stay
mITT	Modified Intention to Treat
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
od	Once daily
PE	Pulmonary Embolism
PSA	Probabilistic Sensitivity Analysis
PTS	Post Thrombotic Syndrome
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
RD	Risk Difference
RR	Relative Risk
RRR	Relative Risk Reduction
SD	Standard Deviation
SE	Standard Error
SG	Standard Gamble
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
THA	Total Hip Arthroplasty
THR	Total Hip Replacement
TKA	Total Knee Arthroplasty
TKR	Total Knee Replacement
UFH	Unfractionated Heparin
VAS	Visual Analogue Scale
VFP	Venous Foot Pump
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

Section A

1 Description of technology under assessment

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

Rivaroxaban (Xarelto®) is an oral direct factor Xa inhibitor, a type of anticoagulant.

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

Marketing authorisation was received for rivaroxaban on 1st October 2008.

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

Rivaroxaban is indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. The Summary of Product Characteristics is included as Appendix 1.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

The date of marketing authorisation will coincide with the UK launch of rivaroxaban.

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

Regulatory approval was sought through the EMEA centralised procedure, therefore approval throughout Europe will be the same as for the UK. Rivaroxaban has also been approved in Canada.

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

A submission for rivaroxaban was made to the SMC on 4th August 2008. The advice will be available on the SMC website on 8th December 2008.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Film-coated tablet each containing 10 mg of rivaroxaban

The following pack sizes will be available: 10 film-coated tablets, 30 film-coated tablets, and 100 film-coated tablets

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended dose of rivaroxaban is 10 mg taken once daily. The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery a treatment duration of 5 weeks is recommended.

- For patients undergoing major knee surgery a treatment duration of 2 weeks is recommended.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The list price is £4.50 per diem

1.10 What is the setting for the use of the technology?

It is anticipated that rivaroxaban will be prescribed and initiated whilst the patient is in hospital and the course of treatment will be completed post discharge.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No other aspects of care beyond routine clinical practice need to be considered.

2 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults undergoing elective hip or knee replacement surgery	Rivaroxaban is indicated for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.[1] Please see explanation following this table.
Intervention	Rivaroxaban	Rivaroxaban, an oral, direct factor Xa inhibitor. The recommended dose is one10 mg tablet taken once daily. ▪ For patients undergoing major hip surgery a treatment duration of 5 weeks is recommended. ▪ For patients undergoing major knee surgery a treatment duration of 2 weeks is recommended.[1]
Comparator(s)	Pharmacological methods of prophylaxis using one of the following drugs: ▪ Low molecular weight heparin ▪ Fondaparinux ▪ Dabigatran	Comparisons presented in the submission will include LMWH and dabigatran. LMWH is the main treatment currently used for the prevention of VTE in patients undergoing major orthopaedic surgery in the UK(8) and market research indicates enoxaparin is the most widely prescribed LMWH in orthopaedic departments in the UK(9). The principle comparison will therefore be against enoxaparin using a direct comparison based on the pivotal trials(10-12). Comparative data versus alternative LMWHs is not available however current literature suggests that LMWHs such as dalteparin and tinzaparin are indistinguishable

[1] Bayer. Rivaroxaban Summary of Product Characteristics, see Appendix 1.

		from enoxaparin(13) and the NICE guidelines recommend all LMWHs equally. A weighted comparison against all LMWHs will therefore be presented as a sensitivity analysis assuming equal efficacy between all LMWHs. A comparison with dabigatran will be presented as a sensitivity analysis based on an indirect comparison. Of the treatments recommended by NICE, LMWHs are the most commonly used (>98%), the market share of fondaparinux in orthopaedic departments is less than 2%(8;9). As agreed during the scoping phase fondaparinux will not be considered in the submission as this does not reflect routine clinical practice.
Outcomes	▪ Mortality ▪ Incidence of DVT/PE ▪ Post DVT complications including post thrombotic syndrome ▪ Length of hospital stay ▪ Health related quality of life ▪ Adverse effects of treatment including bleeding events (minor and major/clinically relevant bleeding) ▪ Joint outcomes (medium and long term) including joint infection	The outcomes listed will be presented in the submission with the exception of joint outcomes (medium and long term) including joint infection. This outcome was not collected in the pivotal trials.
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year. The reference case stipulates that the time horizon for estimating the clinical and cost effectiveness should be sufficiently long to reflect any differences in the costs or outcomes between the technologies being compared.	The economic evaluation will be a cost utility analysis, with the results presented as incremental cost per quality adjusted life year. The economic model will adopt a lifetime time horizon consisting of a 3 month acute phase followed by a longer time horizon that considers a chronic phase associated with long term complications resulting from VTE events.

	Costs will be considered from and NHS and Personal and Social Services Perspective	Alternative time horizons will be explored in a sensitivity analysis. Costs will be considered from an NHS and Personal and Social Services Perspective.
Special considerations, including issues related to equity or equality **Subgroups to be considered**	The duration of treatment with rivaroxaban in RCTs has been longer for patients undergoing elective hip surgery compared with those undergoing knee surgery. This, and other factors affecting clinical and cost effectiveness, would indicate that separate analysis of different types of surgery is necessary. There may also be subgroups of patients who can be identified as being at higher or lower risk of DVT and/or PE, for example as a result of co-morbidities. Guidance will only be issued in accordance with the marketing authorisation.	Analyses for hip and knee replacement will be presented separately. The economic evaluation will present the results for the entire population included in each of the pivotal studies. The studies were not powered to detect statistically significant differences in sub-groups.

Population: Explanation of licence versus trial populations

Rivaroxaban is licenced for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Replacement of the joint can be of several types:

- primary – the first time all (or part of) a joint is replaced
- revision – an operation that involves the removal and replacement of all or part of a previously-replaced joint
- re-operation other than revision - an operation following either a primary or revision operation that does not require any joint implants to be removed or replaced, for example, if an implant needs to be re-aligned or has become loose.

The National Joint Registry provides information about hip and knee replacements performed in England and Wales(8). The greatest number of operations is of the primary kind. In 2006 121,102 (92%) of the 131,378 operations recorded were primary operations; only 9,592 (7%) were revisions and 684 (0.5%) re-operations.

Of the 92% joint replacements that were primary operations, 90% of hip replacements and 91% of knee replacements were total joint replacements. A further 7% of operations were revisions of which total joint replacements were performed in 54% and 76% of hip and knee operations respectively. Overall, total joint replacements accounted for 88.5% of all joint replacement surgery performed.

The RECORD programme of clinical trials required all patients to undergo elective "total" hip or knee replacement (replacement of the whole joint). Any subjects who did not have a total hip or knee replacement were excluded from the mITT analyses. In the safety population for RECORD1 and 2 combined, primary unilateral hip replacement was performed in 6,496 or 94.3% of the subjects in the safety population. There were 254 subjects (3.7%) who underwent revision unilateral hip replacement. There were [redacted] subjects [redacted] who underwent primary bilateral hip replacement. In the RECORD 3 knee replacement trial, primary unilateral knee replacement was performed in 2313 or 94.1% of the subjects in the safety population. There were 54 subjects (2.2%) who underwent revision unilateral knee replacement. There were [redacted] subjects [redacted] who underwent primary bilateral knee replacement.

Very little medical literature is available on the risk of venous thromboembolism after the less common types of replacement of the hip or knee, such as partial joint replacement, hemi-arthroplasty, or revision arthroplasty.

With regard to the comparative risk of venous thromboembolism in primary total, partial, and revision total hip replacement, only one recent study was found which reported data(14). Zhan et al. screened more than eight million hospital discharge records from the 2003 Healthcare Cost and Utilization Project Nationwide Inpatient Sample and approximately nine million discharge abstracts from five state inpatient databases. Patients who had undergone total, partial, or revision hip replacement were identified with use of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes. In-hospital mortality, perioperative complications, readmissions, and the association between these outcomes and certain patient and hospital variables were analyzed. They identified approximately 200,000 total hip replacements, 100,000 partial hip replacements, and 36,000 revision total hip replacements. They found rates of venous thromboembolism (deep vein thrombosis or pulmonary embolism) to be 0.68% for total hip replacements, 1.36% for partial hip replacements, and 1.08% for revision total hip replacements.

Total joint replacements form the majority of hip and knee replacement operations. In the medical literature there is no information to suggest a difference in the pathophysiology of venous thromboembolism among the less common hip and knee replacement procedures from that in total joint replacement. It is therefore anticipated that rivaroxaban will be beneficial in these procedures as well.

Section B

3 Executive summary

This submission concerns the use of rivaroxaban (Xarelto), which has recently been licenced, for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (15).[2]

Rivaroxaban

Rivaroxaban is an oral highly selective direct factor Xa inhibitor. Factor Xa plays a central role in blood coagulation, activated by both the intrinsic and extrinsic coagulation pathways, catalysing the conversion of prothrombin to thrombin ultimately leading to fibrin clot formation and activation of platelets by thrombin. Selective inhibition of factor Xa by rivaroxaban is expected to terminate the amplified burst of thrombin generation created during the hypercoagulable state and be an effective strategy for the prevention of both arterial and venous thrombosis.

Rivaroxaban is an oral once daily, fixed dose treatment. Supplied as a film-coated tablet in packs of 10, 30 or 100 tablets, with each tablet containing 10 mg of rivaroxaban, the list price of treatment is £4.50 per diem.

Rivaroxaban will be licensed for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery. The recommended dose of rivaroxaban is 10 mg taken once daily. The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery a treatment duration of 5 weeks is recommended.
- For patients undergoing major knee surgery a treatment duration of 2 weeks is recommended.

VTE Prophylaxis: Current management and guidelines

In England and Wales, 65,532 hip replacement procedures, of which 10% were revisions or re-operations, and 65,846 knee replacement procedures, of which 8% were revisions or re-operations, were undertaken between 1 January and 31 December 2006(8).

Without thromboprophylaxis, patients undergoing major orthopaedic surgery are at high risk for both deep vein thrombosis (DVT) (incidence 40-60%) and symptomatic pulmonary embolism (PE) (incidence 2-5%)(16). The development of venous thromboembolic (VTE) complications is associated with substantial long term morbidity and is a leading cause of mortality in the UK(17). Without prophylaxis the rate of fatality from a PE after hip and knee replacement is approximately 0.4%(17). Applying this rate to the number of hip or knee replacements carried out in England and Wales in 2006 suggests that around 526 fatalities potentially could be avoided with thromboprophylaxis.

Current pharmacological thromboprophylactic treatment options include unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux and oral agents such as warfarin,

[2] The population included in the pivotal clinical trials are patients undergoing elective total hip or knee replacement. Data from the National Joint Registry, which collects information on all hip and knee replacement operations in England and Wales, demonstrates total joint replacement represents 89% of all hip and knee replacement operations(8). Patients undergoing the less common types of replacement of the hip or knee are also at risk of VTE. There is no reason to believe the risk differs from the baseline risk associated with all orthopaedic surgery of the hip or knee. There is no evidence to suggest the pathophysiology of VTE differs to that in total hip or knee replacement, therefore it is not anticipated that rivaroxaban would work any differently in this group of patients. Please see section 2 for additional information.

aspirin and dabigatran. UFH, LMWH products (including enoxaparin), and fondaparinux are administered parenterally making them inconvenient and costly for long term use post-discharge as this relies either on patients being able to self-administer or on costly district nurse administration. Whilst aspirin and warfarin are orally administered, the evidence base for aspirin is limited and inconclusive and warfarin has a narrow therapeutic window and unpredictable pharmacokinetics, necessitating frequent, inconvenient and costly monitoring and dose adjustments. Difficulties with existing therapy options often result in the duration of thromboprophylaxis being shorter in clinical practice than recommended in guidelines, leaving many patients at high risk of developing VTE, particularly on discharge from hospital (16;18-21).

Guidelines recommend the use of anticoagulants in the prevention of VTE in patients undergoing major orthopaedic surgery. Recent NICE guidelines (2007) recommend all patients undergoing elective major orthopaedic surgery should be offered either low molecular weight heparin (LMWH) or fondaparinux and patients having hip replacement with one or more risk factors for VTE should have their therapy continued for 4 weeks after surgery(22).

The main treatment currently in use for the prevention of VTE in patients undergoing hip or knee replacement surgery in the UK is low molecular weight heparin(23), of which enoxaparin is the most widely prescribed LMWH in orthopaedic departments in the UK (9). Of the treatments recommended by NICE, LMWHs are the most commonly used (>98%)(9;22). This will be the principle comparison included in the submission using a direct comparison based on the pivotal trials(10-12). The market share of fondaparinux in orthopaedic departments is less than 2% and is unlikely to change over the next few years, therefore it will not be considered in the submission as this does not reflect routine clinical practice (8;9). Dabigatran has also recently been approved by NICE as an option for the prevention for VTE in adults undergoing elective total hip or knee replacement (24). A comparison versus dabigatran is also considered in the submission using an indirect comparison.

Clinical Evidence

The clinical evidence for the use of rivaroxaban in the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery is derived from the RECORD programme, four randomised controlled trials (RCTs), directly comparing rivaroxaban with enoxaparin, the main product currently used in the UK in the same indication. It should be noted that the RECORD 1-3 trials use the European licenced dose of enoxaparin (40mg od) and the RECORD 4 trial uses the USA licenced dose (30mg bd).

In the phase III RCTs, RECORD 1(10), 3(12), and 4(25), rivaroxaban was demonstrated to have superior efficacy over enoxaparin after total hip replacement and total knee replacement. RECORD 2 also demonstrated superiority comparing 35 days rivaroxaban versus 12-14 days enoxaparin (4;11). Based on the composite primary endpoint of any DVT, non-fatal PE and death from all causes the relative risk reductions were 70-79% in total hip replacement and 31-49% in total knee replacement. Rivaroxaban was also demonstrated to have superior efficacy over enoxaparin in RECORD 1, 2 and 3 for the secondary endpoint major VTE. Superior efficacy was also shown for the symptomatic VTE endpoint in RECORD 2 and RECORD 3. Safety analyses from the RECORD programme of studies indicated a comparable safety profile of rivaroxaban to enoxaparin suggesting that the improved efficacy of rivaroxaban over enoxaparin is not at the expense of an increased risk of bleeding or other adverse events.

Dabigatran was investigated in three pivotal trials (26-28). RE-NOVATE and RE-MODEL, which compared dabigatran to enoxaparin 40mg od in hip and knee replacement, demonstrated non-inferiority to enoxaparin on the primary endpoint (total VTE and all cause mortality). A third study, RE-MOBILIZE, which compared dabigatran to the US dose of enoxaparin (30mg bd) in knee replacement failed to demonstrate non-inferiority to enoxaparin. These trials were used to perform an indirect comparison with rivaroxaban, using enoxaparin as a common comparator.

Rivaroxaban, a direct factor Xa inhibitor, is the first oral anticoagulant to demonstrate superiority over the LMWH enoxaparin, in preventing venous thromboembolic complications following elective hip or knee replacement surgery. It is an oral, once daily, fixed dose treatment with no monitoring requirements. Dabigatran, an oral direct thrombin inhibitor licensed earlier this year,

also offers the benefits of oral administration but demonstrated non-inferiority to enoxaparin(26-28).

Evidence of Cost Effectiveness

A systematic review of the cost effectiveness literature did not identify any published cost effectiveness studies relevant to the submission and therefore there is a requirement for a de novo economic evaluation. The economic evaluations identified through the systematic review were used to inform the approach to this evaluation. The review identified a paper which provides an overview of the pharmacoeconomic evaluations published on VTE prophylaxis in major orthopaedic surgery between 1984 and 2000(29). A key conclusion of the review by Sullivan et al. (2003) was that "the outcomes and costs of VTE-related care should be conducted over a timeframe that extends over several years, taking into account both the acute (from surgery up to 3 months) and chronic phases of the disease". The paper also makes several recommendations around endpoints that should be taken into account in the pharmacoeconomic evaluation of new drugs, and proposes elements for new pharmacoeconomic models for VTE prophylaxis. The development of the model followed these recommendations in terms of determining the structure, time horizon and the evaluated outcomes.

An economic model was built to assess the incremental cost per quality adjusted life year (QALY) of rivaroxaban compared to enoxaparin, LMWHs and dabigatran. The cost-effectiveness model is divided into three modules; prophylaxis, post-prophylaxis, and long-term complications. The first two modules constitute the acute phase, and are represented with a decision tree, while the third module represents the chronic phase and is developed as a Markov process. The prophylaxis module includes events recorded from the clinical trial (first 35 days for THR and 14 days for TKR patients post surgery). The post-prophylaxis module serves as an extension of the RECORD trials to reflect the risk of a symptomatic VTE event within the first 3 months, as recommended by Sullivan and colleagues (2003). The long-term complications module reflects the post-acute phase events and extrapolates any long-term complications, such as post thrombotic syndrome and recurrence resulting from symptomatic VTE events over the lifetime of the patient.

The key assumptions underlying the economic model are as follows:

- The phase III RECORD studies are the largest and most relevant data sources for the decision problem being addressed.
- All other LMWHs are bioequivalent to enoxaparin.
- An indirect comparison can be performed against dabigatran using enoxaparin as a common comparator.
- Patients are at risk of a first DVT or PE up to 90 days post-surgery. Patients who have experienced a VTE event are at risk of long term complications.
- The probability of DVT or PE events occurring beyond the duration of the clinical trial is the same regardless of prophylaxis method.
- Patients receiving LMWH require nurse training on self administration post discharge. Patients unable or unwilling to administer LMWH post discharge require district nurse administration.

The economic evaluation finds that rivaroxaban is highly cost effective, dominating enoxaparin, LMWHs and dabigatran in hip and knee replacement surgery over a range of scenarios. The model results are most sensitive to the probability of developing an initial VTE event and the probability of developing a symptomatic VTE during the prophylaxis module (up to 90 days post-surgery). The model is also sensitive to the cost of managing post-thrombotic syndrome; however sensitivity analyses indicate that the cost-effectiveness results are robust to a wide range of structural and data assumptions.

Whilst the resource use and cost of administration and monitoring of the injectable treatments has been taken into account, there is no evidence to quantify the costs associated with sharps disposal and needle stick injuries, these have therefore been excluded from the

evaluation. Similarly the model conservatively assumes there is no quality of life difference associated with the administration of an injectable versus an oral treatment.

Approximately 112,000 patients in England and Wales currently receive pharmacological thromboprophylaxis for the prevention of VTE in hip or knee replacement surgery. The introduction of rivaroxaban in England and Wales is associated with savings of £1.6 million over the next 5 years due to reductions in non-drug healthcare resource use associated with administration and monitoring.

Conclusion

A consistent body of good quality clinical evidence has found that in comparison with current standard treatment in the UK (enoxaparin), rivaroxaban is statistically superior at reducing VTE events and all cause mortality, with no increased risk of bleeding.

The economic modelling suggests that the superior efficacy and reduction in resource use associated with the administration and monitoring with injectable treatments is sufficient to offset the additional drug acquisition cost, such that rivaroxaban dominates, i.e. is cheaper and more effective than, enoxaparin, LMWHs and dabigatran.

As an oral agent with no coagulation monitoring requirements, rivaroxaban is not only more effective but also easier to use for both patients and healthcare professionals than other commonly used thromboprophylaxis treatments. Rivaroxaban therefore has the potential to simplify the care pathway in elective hip and knee replacement surgery, particularly where extended prophylaxis is required, and at the same time reduce the long term morbidity and costs associated with the treatment of VTE events.

4 Context

4.1 Overview of disease

Venous thromboembolism (VTE) is the forming of a blood clot in a vein (venous thrombosis) which may dislodge from its site of origin. Formation is associated with inactivity and certain surgical procedures and the risk rises with the duration of operation and period of immobility. VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common cause of mortality and morbidity(17). Each year there are approximately 25,000 deaths due to venous thromboembolism in England(17). This figure includes both patients admitted for medical care of serious illnesses as well as those admitted for surgery. Patients undergoing major orthopaedic surgery, which includes hip and knee replacement, represent a group that is at particularly high risk for VTE (>40% without prophylaxis)(16), and routine thromboprophylaxis has been the standard of care for many years.

Reliance on symptoms or signs of early DVT is an unreliable strategy to prevent clinically important thromboembolic events. Asymptomatic DVT is common and, in the absence of prophylaxis, affects at least half of all patients. Most of these thrombi are clinically silent, and resolve spontaneously without any long-term sequelae. However, for some patients, the presence of silent postoperative DVT, persistent venous injury, stasis due to prolonged decreased mobility, impairment of the endogenous anticoagulant or fibrinolytic systems, prolonged impairment of venous function, or a combination of these factors allows an existing small thrombus to propagate (or a new thrombus to develop). This thrombus then may produce symptoms as a result of venous occlusion (DVT) or embolisation to the lungs (PE). Symptomatic VTE often presents after orthopaedic patients are discharged from hospital and is a common cause for hospital readmission. Among some patients with post-hospital discharge DVT, the thrombus is present early after surgery, and, as thromboprophylaxis is discontinued, the silent DVT extends. For others who do not have DVT at hospital discharge, a new thrombosis may develop during recovery at home. This supports the need for extended prophylaxis (i.e. beyond hospital discharge and up to 5 weeks post-operatively), particularly in patients undergoing hip surgery.

The first manifestation of VTE may be sudden death, or be the cause of substantial long-term morbidity due to venous insufficiency and postthrombotic syndrome (PTS)(22). Symptoms of PTS can range from chronic persistent calf pain, discomfort, and swelling, which in severe cases (5-10% cases) can lead to ulceration of the legs(30). Recurrent VTE increases the risks of PTS.

With over 131,000 hip and knee replacements annually the personal and economic costs of venous thromboembolism in patients undergoing such surgery are significant(22).

VTE prophylaxis can reduce the risk of such events. Current measures include mechanical/physical prophylaxis (such as graduated elastic compression stockings, foot impulse devices and intermittent pneumatic compression) and pharmacological prophylaxis. The primary attraction of mechanical prophylaxis is the lack of bleeding potential. Both physical and pharmacological treatments have been shown to reduce the incidence of DVT in studies.

Numerous guidelines recommend the use of anticoagulants in the prevention of VTE in patients undergoing major orthopaedic surgery(22;31;32). Recent NICE guidelines recommend all patients undergoing elective major orthopaedic surgery should be offered either low molecular weight heparin or fondaparinux, and patients having a total hip replacement, with one or more risk factors for VTE, should have their therapy continued for 4 weeks after surgery. The recently updated American College of Chest Physicians' (ACCP) guidelines(32) recommend LMWH, fondaparinux or vitamin K antagonists. Similarly to NICE, the use of thromboprophylaxis with LMWH is recommended, and the duration of treatment should be at least 10 days and up to 35 days in patients undergoing hip or knee replacement(32). There is increasing evidence that extended prophylaxis (up to 35 days) significantly reduces VTE in total hip replacement procedures(16;20;21).

Current pharmacological thromboprophylactic treatment options include unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux and oral agents such as warfarin, aspirin and dabigatran. UFH, LMWH products (including enoxaparin), and fondaparinux are administered parenterally making them inconvenient and costly for long term use post-discharge as this relies on patients being able to self-administer or on costly district nurse administration. The use of LMWH is also associated with heparin induced thrombocytopenia (HIT). Whilst aspirin and warfarin are orally administered, the evidence base for aspirin is limited and inconclusive and warfarin has a narrow therapeutic window and unpredictable pharmacokinetics, necessitating frequent, inconvenient and costly monitoring and dose adjustments. Difficulties with existing therapy options often result in the duration of thromboprophylaxis being shorter in clinical practice than recommended in guidelines, leaving many patients at high risk of developing VTE, particularly on discharge from hospital (16;18-21).

The main treatment currently in use for the prevention of VTE in patients undergoing hip or knee replacement surgery in the UK is low molecular weight heparin, of which enoxaparin is the most widely prescribed LMWH in orthopaedic departments in the UK. The market share of fondaparinux in orthopaedic departments is less than 2% and is not considered part of routine clinical practice (9).

4.2 Rationale for development of the technology

As highlighted above, existing therapy options for prevention of VTE in patients undergoing hip or knee replacement surgery in the UK often result in inadequate prophylactic cover, particularly post-discharge (16;18-21). The availability of an oral once daily, fixed dose anticoagulant agent would meet a very high unmet need in this therapeutic area, especially with the trend for shorter hospital stays / earlier patient discharge. This addresses the inconvenience of parentally administered treatments, removes the risk of HIT and also, once daily fixed-dosing removes the necessity to monitor & adjust dosing.

Rivaroxaban, a direct factor Xa inhibitor, is the first oral anticoagulant to demonstrate superiority over the LMWH enoxaparin, in preventing venous thromboembolic complications in adult patients following elective total hip or knee replacement surgery. It is an oral, once daily, fixed dose treatment with no monitoring requirements. Dabigatran, an oral direct thrombin inhibitor licensed earlier this year, also offers the benefits of oral administration but demonstrated non-inferiority to enoxaparin(26;27).

4.3 Principle mechanism of action of rivaroxaban

Rivaroxaban is an oral highly selective direct factor Xa inhibitor. Activation of Factor X to Factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation. Selective inhibition of factor Xa by rivaroxaban is expected to terminate the amplified burst of thrombin generation created during the hypercoagulable state and be an effective strategy for the prevention of both arterial and venous thrombosis.

4.4 Suggested place with respect to currently available treatments for VTE prophylaxis in orthopaedic surgery

It is proposed that, due to its superior efficacy when compared to enoxaparin, the most widely used thromboprophylactic agent used in the prevention of VTE in hip or knee replacement surgery, rivaroxaban can directly replace this in the indication of hip or knee replacement surgery.

The benefits of this switch, in addition to improved efficacy, would be increased convenience for patients and healthcare professionals, facilitating the use of extended prophylaxis recommended by international guidelines, including NICE(16;22;32).

With regard to its place in respect of the recently launched dabigatran in the same indication, rivaroxaban will enhance the choice of agents available to clinicians in order that they can more successfully implement the NICE guidelines for extended prophylaxis and at the same time further reduce the incidence of thromboembolic events, including deaths, in patients undergoing major orthopaedic surgery.

4.5 Issues relating to current clinical practice

Without prophylaxis the rate of fatality from a PE after hip and knee replacement is approximately 0.4%. Hence there is clearly an argument for use of prophylaxis in this indication(17).

Within the Orthopaedic surgical community there is ongoing debate on the use of chemical prophylaxis. For example in the British Orthopaedic Association's (BOA's) Guide to Good Practice for Primary Total Hip Replacement (2006), no specific chemical thromboprophylaxis or dosing schedule is recommended.

The guide notes the efficacy of low dose heparin, LMWH and warfarin in reducing radiological DVT by 40 to 60%, however, points out concern regarding possible bleeding complications, which may put the surgical wound, implant or patient at risk. It states 'Some surgeons remain uncomfortable with routine chemical prophylaxis' and directs each unit to publish guidelines, which combine common sense with available evidence, with the surgeon and anaesthetist weighing up the current evidence, assessing individual risk factors and sharing with the patient their approach to the problem.

This is in contrast with the NICE guidelines published in 2007(22), which specifically recommend pharmacological thromboprophylaxis (LMWH or fondaparinux) in patients undergoing major orthopaedic surgery and also extended thromboprophylaxis in patients undergoing hip replacement surgery with one or more risk factors for VTE.

Despite availability of data from RCTs demonstrating the safety of pharmacological agents with respect to a low incidence of bleeding and major bleeding events, some clinicians remain unconvinced of the trade-off between safety and efficacy. This lack of consensus may lead to inadequate thromboprophylaxis cover (e.g. no thromboprophylaxis given at all, ineffective methods/agents used, or thromboprophylaxis is given for an insufficient duration). The underlying confusion in the UK is highlighted by the continuing use of aspirin as pharmacological thromboprophylaxis by some clinicians even though it is not a recommended agent(8).

LMWH is the main treatment currently used for the prevention of VTE in patients undergoing major orthopaedic surgery in the UK(8) and market research indicates enoxaparin is the most widely prescribed LMWH in orthopaedic departments in the UK(9).

The range of current pharmacological thromboprophylactic treatment options include unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux and oral agents such as warfarin, aspirin and dabigatran. UFH, LMWH products (including enoxaparin), and fondaparinux are administered parenterally making them inconvenient and costly for long term use post-discharge as this relies either on patients being able to self-administer or on costly district nurse administration. Whilst aspirin and warfarin are orally administered, the evidence base for aspirin is limited and inconclusive and warfarin has a narrow therapeutic window and unpredictable pharmacokinetics, necessitating frequent, inconvenient and costly monitoring and dose adjustments. Such difficulties with existing therapy options often result in the duration of thromboprophylaxis being shorter in clinical practice than recommended in guidelines, leaving many patients at high risk of developing VTE, particularly on discharge from hospital (16;18-21).

4.6 Relevant guidelines or protocols

- Venous thromboembolism: reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. NICE clinical guideline 46 (2007)(22).

  In addition to mechanical prophylaxis, patients at increased risk of VTE because they have individual risk factors and patients having orthopaedic surgery should be offered low molecular weight heparin (LMWH). Fondaparinux, within its licensed indications, may be used as an alternative to LMWH.

  Patients having hip replacement surgery with one or more risk factors for VTE should have their LMWH or fondaparinux therapy continued for 4 weeks after surgery.

- There is also a NICE guideline in development which will incorporate the above published NICE guideline as its 2-year review date is due during the new guideline development period. A single piece of guidance will be produced for all hospitalised patients after March 2009 (www.nice.org.uk).

- The SMC have issued the following advice in relation to orthopaedic surgery:
  - Non-recommendation of **bemiparin** for the prevention of thromboembolic events in patients undergoing orthopaedic surgery.
  - Recommendation of **dabigatran** etexilate for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
  - Recommendation for **fondaparinux** for the prevention of thromboembolic events in patients for whom antithrombotic therapy is appropriate.

- Scottish Intercollegiate Guidelines Network (SIGN). Guideline 62: Prophylaxis of Venous Thromboembolism, 2002, (33)

  Patients undergoing total hip or knee replacement (or other elective major orthopaedic surgery) can be considered for aspirin (150mg orally, started before surgery and continued for 35 days), unfractionated heparin (UFH) or LMWH. Or warfarin.

  The duration of UFH or LMWH prophylaxis should be 7-15 days after lower limb arthroplasty, extended to 4-5 weeks in very high-risk patients.

  NOTE: These guidelines are currently being updated. A consultation in 2005 suggested the following relevant revision(31):

  'More emphasis on LMWH and discussion regarding the role of fondaparinux, aspirin should not be recommended'

- Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-based Clinical Practice Guidelines (8th Edition)(32).

  *1.4.4. We recommend **against** the use of aspirin alone as prophylaxis against VTE for any patient group (**Grade 1A**).*

  3.1 Elective Hip Replacement
  3.1.1 For patients undergoing elective total hip replacement (THR), we recommend the routine use of one of the following anticoagulant options:
  LMWH (at a usual high-risk dose, started 12 h before surgery or 12 to 24 h after surgery, or 4 to 6 h after surgery at half the usual high-risk dose and then

increasing to the usual high-risk dose the following day); (2)fondaparinux (2.5 mg started 6 to 24 h after surgery); or (3) adjusted-dose VKA started preoperatively or the evening of the surgical day(international normalized ratio [INR] target, 2.5; INR range, 2.0 to 3.0) (all Grade 1A).
3.1.2 For patients undergoing THR, we recommend against the use of any of the following: aspirin, dextran, LDUH, GCS, or venous foot pump (VFP) as the sole method of thromboprophylaxis (all Grade 1A).
3.1.3 For patients undergoing THR who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with the VFP or IPC (Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

3.2 Elective Knee Replacement
3.2.1. For patients undergoing TKR, we recommend routine thromboprophylaxis using LMWH (at the usual high-risk dose), fondaparinux, or adjusted-dose VKA (INR target, 2.5; INR range, 2.0 to 3.0) (all Grade 1A).
3.2.2. For patients undergoing TKR, the optimal use of IPC is an alternative option to anticoagulant thromboprophylaxis (Grade 1B).
3.2.3. For patients undergoing TKR, we recommend against the use of any of the following as the only method of thromboprophylaxis: aspirin (Grade 1A), LDUH (Grade 1A), or VFP (Grade 1B).
3.2.4. For patients undergoing TKR who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with IPC (Grade 1A) or VFP (Grade 1B). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

Duration of Thromboprophylaxis
3.5.3.1. For patients undergoing THR, TKR, or HFS, we recommend thromboprophylaxis with one of the recommended options for at least 10 days (Grade 1A).
3.5.3.2. For patients undergoing THR, we recommend that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 1A). The recommended options for extended thromboprophylaxis in THR include LMWH (Grade 1A), a VKA (Grade 1B), or fondaparinux (Grade 1C).
3.5.3.3. For patients undergoing TKR, we suggest that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 2B). The recommended options for extended thromboprophylaxis in TKR include LMWH (Grade 1C), a VKA (Grade 1C), or fondaparinux (Grade 1C).

5 Equity and Equality

5.1 Identification of equity and equalities issues

Each year there are over 25,000 deaths due to venous thromboembolism (VTE) in England(17). Current guidelines recommend that in addition to mechanical prophylaxis, patients at increased risk of VTE and those undergoing orthopaedic surgery should be offered low molecular weight heparin (LMWH) or fondaparinux, and patients undergoing hip replacement with one or more risk factors for VTE should have their LMWH or fondaparinux therapy continued for 4 weeks after surgery(22).

Despite the publication of NICE guidelines, uptake of the VTE prophylaxis measures has been slow. For example one study found that although 99% of acute trusts were aware of the guidelines, only 32% carried out mandatory risk assessment for every hospitalised patient(34).

Rivaroxaban is an oral, once-daily direct Factor Xa inhibitor. Phase III trials have shown that rivaroxaban significantly reduces the risk of VTE in patients undergoing total knee replacement surgery and total hip replacement surgery compared with enoxaparin(10-12;35;36).

As an effective and convenient, once-daily oral treatment rivaroxaban offers a convenient treatment option that would aid the implementation of the current NICE guidelines as it is anticipated that the oral route of administration for rivaroxaban will be more acceptable than currently available subcutaneous injections of LMWH or fondaparinux.

Dabigatran etexilate is an oral direct thrombin inhibitor that was launched in the UK earlier this year. Dabigatran and rivaroxaban have not directly been compared in RCTs, however in head-to-head RCTs against enoxaparin dabigatran is shown to be non-inferior to enoxaparin, whereas rivaroxaban is superior. Dabigatran has recently been recommended by NICE for use as a thromboprophylactic in patients undergoing total hip or knee replacement. It would be in the interest of the NHS and general public for recommendations for both these products to be available as close together as possible.

No other issues relating to equity or equalities were identified.

6 Clinical Evidence

6.1 Identification of studies

In relation to the decision problem, a systematic search of the literature was undertaken to identify randomised placebo or active-controlled comparative studies investigating rivaroxaban as VTE prophylaxis during major orthopaedic surgery of the lower limbs. Major orthopaedic surgery of the lower limbs was defined as total hip or knee replacement. In addition, comparative studies that didn't include the intervention (rivaroxaban) were included in the wider initial search in case any indirect comparisons were necessary at a later stage. This required at least two of the following interventions to be included in any short-listed studies:

- rivaroxaban,
- enoxaparin or LMWH,
- dabigatran

As the search strategy followed the same approach as that undertaken by the National Institute for Health and Clinical Excellence (NICE) in their recent publication of guidelines for VTE prophylaxis(22), an assumption was made that the NICE review was complete to August 2006 and that the searches in this current systematic review would only search for new studies published since August 2006.

Five electronic bibliographic databases were searched, covering biomedical, science and health economic literature (Medline, Embase, Cinahl, The Cochrane Library including NHS EED, and Health Economic and Evaluations Database (HEED)).

Additional studies were identified during a search of abstracts from key orthopaedic surgery / haematology conferences and also the reference lists of relevant articles identified in the database searches were hand-searched. Further information on the databases searched, inclusion and exclusion criteria and search strategies can be found in Appendix 2 (section 10.2). Details of the cost-effectiveness literature search can be found in Section 7 and Appendix 3 (section 10.3).

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed according to the inclusion / exclusion criteria set out in section 6.2.2. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Where available the following data were reviewed: Baseline characteristics, Incidence of symptomatic and asymptomatic pulmonary embolism (PE) and deep vein thrombosis (DVT), number and cause of deaths, safety parameters, in particular bleeding, and adverse events.

6.2 Study Selection

6.2.1 Complete list of RCTs

A total of 6 individual RCTs comparing rivaroxaban with other therapies as a prophylaxis for VTE (see Table 1) were identified from the systematic review. Since carrying out the systematic review, some of these studies, having recently been completed, have now been published in full (RECORD 1(10), RECORD 2(11), RECORD 3(12)). Reference to the abstracts of these studies, initially identified in the systematic review, is still made in the table below for completeness. In addition, the final study in the RECORD programme (RECORD 4) has completed since the review. Results from RECORD 4 have not yet been fully published but were presented in May 2008 at the annual meeting of the European Federation of National Associations of Orthopaedics & Traumatology (EFORT)(36). Further details included in this submission on RECORD 4 are supplied from the full study report(35).

Table 1: RCTs involving rivaroxaban identified during the systematic review

Author	Study Title	No of patients / Interventions
Eriksson 2006a(2)	A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement.	n=873 Rivaroxaban 5, 10, 20, 30 or 40mg a day for 6-10 days vs Enoxaparin 40mg/day for 6-10 days
Eriksson 2006b(5)	Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement.	n=706 Rivaroxaban 2.5, 5, 10, 20 or 30mg b.i.d for 6-10 days vs Enoxaparin 40mg/day for 6-10 days
Eriksson 2007a(1) (abstract); Eriksson 2008(10) (full paper) Also known as RECORD 1	Oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty: The RECORD1 trial.	n=4541 Rivaroxaban 10mg od for 35 days vs Enoxaparin 40mg od for 35 days
Kakkar 2007(4) (abstract); Kakkar 2008(11) (full paper) Also known as RECORD 2	Thromboprophylaxis with Rivaroxaban Compared with Short-term thromboprophylaxis with Enoxaparin after Total Hip Arthroplasty: The RECORD 2 Trial.	n=2509 Rivaroxaban 10mg od for 35 days vs Enoxaparin 40mg od for 14 days
Lassen 2007 (7) (abstract); Lassen 2008(12) (full paper) Also known as RECORD 3	Rivaroxaban - An Oral, Direct Factor Xa Inhibitor - for Thromboprophylaxis after Total Knee Arthroplasty: The RECORD 3 Trial.	n=2531 Rivaroxaban 10mg od for 14 days vs Enoxaparin 40mg od for 14 days
Turpie 2008 (36) (EFFORT abstract); Bayer Schering Pharma 2008 (35) (Study Report) Also known as RECORD 4	RECORD 4 Study: REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE: a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement.	n=3148 Rivaroxaban 10mg od for 14 days vs Enoxaparin 30mg bid for 14 days

6.2.2 Inclusion and exclusion criteria

Included: Randomised, controlled trials (RCTs) involving patients aged 18 or over undergoing elective hip or knee replacement, comparing rivaroxaban with other therapies (including placebo).

Excluded: Phase II studies, open-label studies, dose-ranging studies, non-English language references.

See 10.2.6 for list of full inclusion and exclusion criteria for the overall search.

6.2.3 List of relevant RCTs

Eriksson 2006a and Eriksson 2006b studies (see Table 1) were rejected on the basis that they were phase II, dose-ranging studies. Eriksson 2006b also used a multiple dosing strategy (twice-daily dosing vs once-daily dosing). The relevant phase III RCTs included in this submission are listed in table 2. It should be noted that RECORD 4 uses the North American dosing for enoxaparin but the standard dose for rivaroxaban.

Table 2: Relevant RCTs involving rivaroxaban identified during the systematic review

Author	Study Title	No of patients / Interventions
Eriksson 2007a(1) (abstract); Eriksson 2008(10) (full paper) Also known as RECORD 1	Oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty: The RECORD1 trial.	n=4541 Rivaroxaban 10mg od for 35 days vs Enoxaparin 40mg od for 35 days
Kakkar 2007(4) (abstract); Kakkar 2008(11) (full paper) Also known as RECORD 2	Thromboprophylaxis with Rivaroxaban Compared with Short-term thromboprophylaxis with Enoxaparin after Total Hip Arthroplasty: The RECORD 2 Trial.	n=2509 Rivaroxaban 10mg od for 35 days vs Enoxaparin 40mg od for 14 days
Lassen 2007 (7) (abstract); Lassen 2008(12) (full paper) Also known as RECORD 3	Rivaroxaban - An Oral, Direct Factor Xa Inhibitor - for Thromboprophylaxis after Total Knee Arthroplasty: The RECORD 3 Trial.	n=2531 Rivaroxaban 10mg od for 14 days vs Enoxaparin 40mg od for 14 days
Turpie 2008 (36) (EFFORT abstract); Bayer Schering Pharma 2008 (35) (Study Report) Also known as RECORD 4	RECORD 4 Study: REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE: a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement.	n=3148 Rivaroxaban 10mg od for 14 days vs Enoxaparin 30mg bid for 14 days

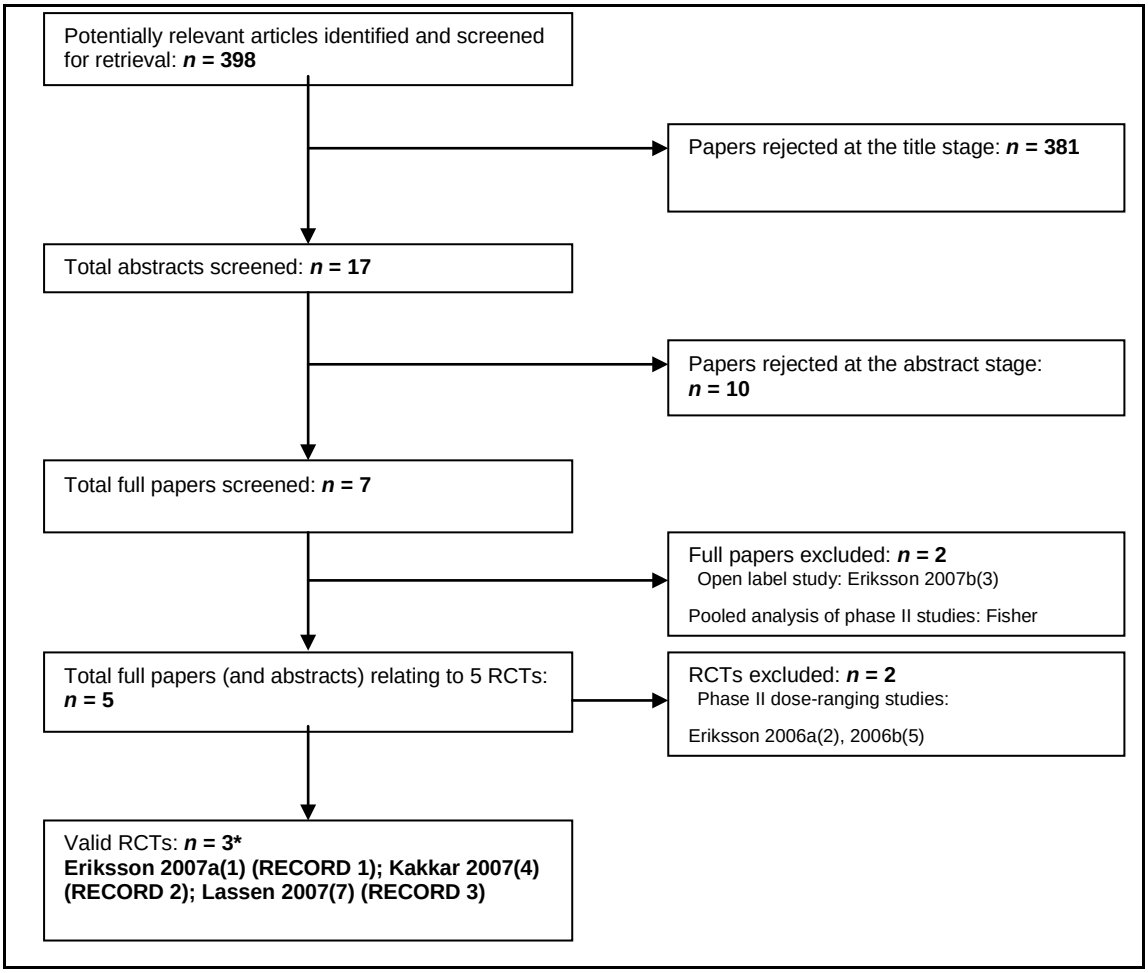
6.2.4 List of relevant non-randomised controlled trials

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

6.2.5 Ongoing studies

There are no ongoing studies relevant to the decision problem.

Figure 1: Flow chart of the clinical evidence screening process for rivaroxaban as VTE prophylaxis in orthopaedic surgery of the lower limbs



*RECORD 4 was not identified in the systematic review. It has recently being completed and presented in abstract form. Details of this North American study have been included for completeness.

6.3 Summary of methodology of relevant RCTs - RIVAROXABAN

6.3.1 Methods

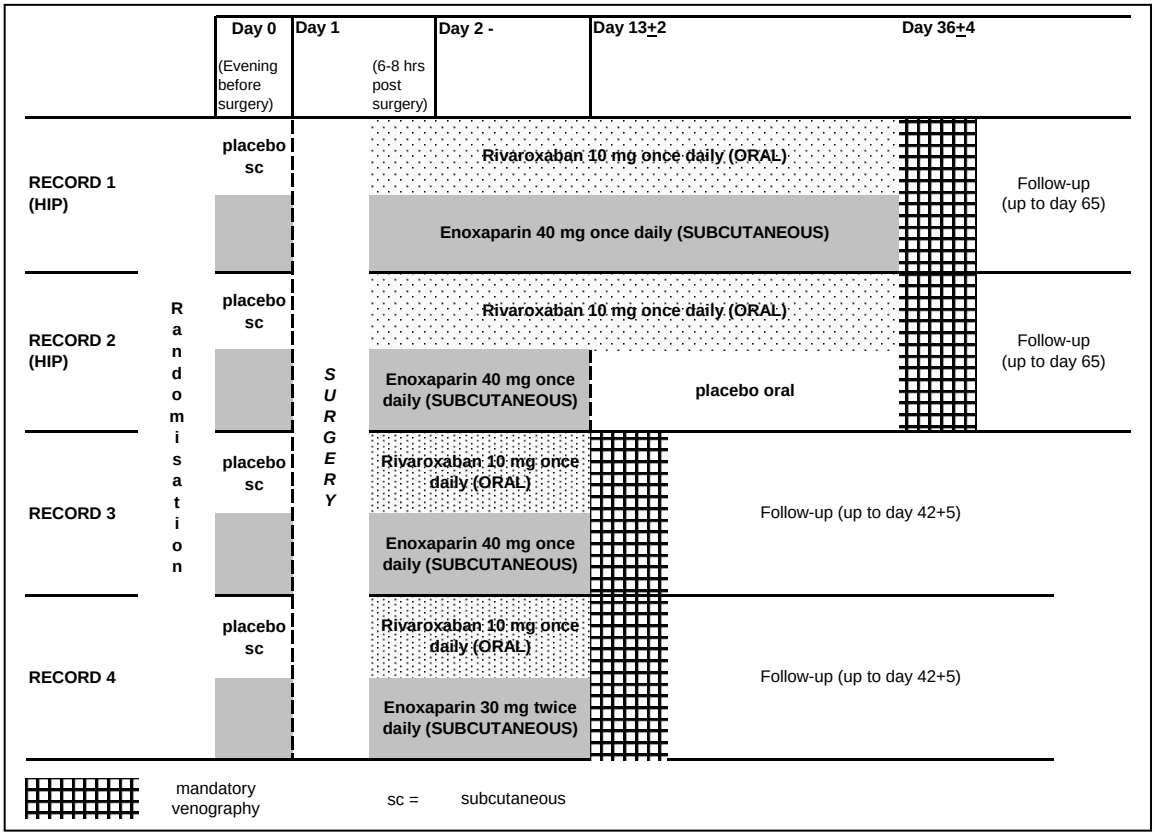
Table 3: Summary of methodology of relevant RCTs

Study	Indication	Study Design	Study Sites	Recruitment & follow-up period	Interventions	Patient numbers (randomised) (see section 6.3.3 Figure 3 to 6 CONSORT flow charts)
RECORD 1 (1;10;37)	TOTAL HIP REPLACEMENT	prospective, randomised, double-blind, parallel-group design, double-dummy, active comparator controlled multicentre phase III study	Argentina; Australia; Austria; Belgium; Brazil; Canada; Chile; Columbia; Czech Republic; Denmark; Germany; Finland; France; Greece; Hungary; Israel; Italy; Lithuania; Netherlands; Norway; Poland; Sweden; Slovakia; Spain; South Africa; Turkey; USA	Feb 2006 to March 2007 (last patient's last visit) Follow-up: 30 (+5) days after last treatment with study drug	• rivaroxaban 10mg od (day 1 to 35) plus placebo syringe (day 0 to 35)* • enoxaparin 40mg sc od (day 0 to 35) plus placebo tablet (day 0 to 35) [day 0 is the day before surgery]	n=4541 rivaroxaban n=2266 enoxaparin n=2275
RECORD 2 (4;11;38)			Australia; Brazil; Canada; China; Columbia; Denmark; Estonia; India; Indonesia; Latvia; Lithuania; Mexico; New Zealand; Norway; Peru; Portugal; South Africa; South Korea; Sweden; UK; USA	Feb 2006 to June 2007 (last patient's last visit) As per RECORD 1	• rivaroxaban 10mg od (day 1 to 35) plus placebo syringe (day 0 to 14)* • enoxaparin 40mg sc od (day 0 to 14) plus placebo tablet (day 0 to 35) [day 0 is the day before surgery]	n=2509 rivaroxaban n=1252 enoxaparin n=1257
RECORD 3 (7;12;39)	TOTAL KNEE REPLACEMENT		Germany; France; Poland; Italy; Spain; Canada; Belgium; Netherlands; Mexico; Sweden; Denmark; Norway; South Africa; Czech Republic; Israel; Austria; Columbia; China; Peru	Feb 2006 to January 2007 (last patient's last visit) As per RECORD 1	• rivaroxaban 10mg od (day 1 to 12±2) plus placebo syringe (day 0 to 12±2)* • enoxaparin 40mg sc od (day 0 to 12±2) plus placebo tablet (day 0 to 12±2) [day 0 is the day before surgery]	n=2531 rivaroxaban n=1254 enoxaparin n=1277
RECORD 4(35;36)			United States, Canada, Bulgaria, Denmark, India, Israel, Lithuania, Mexico, Pakistan, Poland, Sri Lanka, and Sweden .	[redacted] As per RECORD 1	• rivaroxaban 10mg od (day 1 to 12±2) plus placebo syringe bid (day 0 to 12±2)* • enoxaparin 30mg sc bid (day 0 to 12±2) plus placebo tablet (day 0 to 12±2) [day 0 is the day before surgery]	n=3148 rivaroxaban n=1584 enoxaparin n=1564

*placebo tablet was given on day 0

A computer generated randomisation list was prepared by Bayer and the randomisation number for each patient was provided through a telephone Interactive Voice Response System (IVRS). Randomisation was done stratified by centre using permuted blocks. The unique randomisation number of a patient was given by the number on the medication label. Placebo was identical in appearance and delivered under identical conditions and dosing regimen to active treatment in order to preserve blinding. Randomisation codes were kept in individual sealed envelopes and were only to be broken in the event of an emergency.

Figure 2: Summary of study design for RECORD 1,2,3 and 4



6.3.2 Study Population (2)– Inclusion and Exclusion Criteria – RIVAROXABAN RCTs

The following criteria were applied across RECORD 1(1;10;37;40), 2(4;11;38) 3(7;12;39), and 4(35).

Patients (males or females), aged ≥18 undergoing elective total hip replacement (RECORD 1 & 2) or elective total knee replacement (RECORD 3 and 4) were included in the studies. Patients were required to have given written consent prior to any study-specific screening procedures.

Any patients due to undergo staged total bilateral joint replacement were excluded. Also excluded were any patients with active bleeding or at high risk of bleeding contraindicating treatment with low molecular weight heparin (LMWH), any patients with contraindications to enoxaparin treatment or conditions prohibiting bilateral venography (e.g. amputation of one leg, allergy to contrast media). Other exclusion criteria were: pregnancy or breast-feeding, [redacted] concomitant use of HIV-protease inhibitors [redacted] planned intermittent pneumatic compression during active treatment period; [redacted] study; ongoing oral anticoagulant therapy that cannot be stopped in the opinion of the investigator; substantial liver disease; severe renal impairment (creatinine clearance <30ml per minute).Study Population (3)– Baseline characteristics (safety population) – RIVAROXABAN RCTs

Table 4: Study population

Study	Age (yrs)	Sex (female)	Weight (kg)	History of DVT or PE	Type of anaesthesia[#]			Duration of surgery (min)	Time to mobilisation (days)	Duration of initial hospital stay (days)
					General	General / Regional	Regional			
RECORD 1 (1;37)	R=63.1 (18-91) E=63.3 (18-93)	R=1220 (55.2%) E=1242 (55.8%)	R=78.1 (37-159) E=78.3 (40-132)	R=47 (2.1%) E=55 (2.5%)	R=661 (29.9%) E=648 (29.1%)	R=223 (10.1%) E=228 (10.3%)	R=1308 (59.2%) E=1330 (59.8%)	R=90.6 (27-480) E=91.3 (25-345)	[redacted]	[redacted]
RECORD 2 (4;38)	R=61.4 (13.2) E=61.6 (13.7)	R=667 (54.3%) E=651 (53%)	R=74.3 (15.8) E=75.2 (17.5)	R=10 (0.8%) E=20 (1.6%)	R=341 (27.8%) E=333 (27.1%)	R=77 (6.3%) E=91 (7.4%)	R=794 (64.7%) E=783 (63.7%)	R=95.0 (30-475) E=93.0 (28-595)	[redacted]	[redacted]
RECORD 3 (7;39)	R=67.6 (28-91) E=67.6 (30-90)	R=857 (70.2%) E=821 (66.3%)	R=80.1 (45-150) E=81.2 (41-157)	R=48 (3.9%) E=42 (3.4%)	R=227 (18.6%) E=242 (19.5%)	R=188 (15.4%) E=201 (16.2%)	R=786 (64.4%) E=774 (62.5%)	R=96.4 (26-500) E=97.1 (28-315)	[redacted]	[redacted]
RECORD 4(35;36)	R=64.4 (21-87) E=64.7 (24-89)	R=1007 (66%) E=967 (64.1%)	R=84.7 (38-190) E=84.4 (35-171.5.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data are mean (SD) or n (%) unless otherwise specified; R=rivaroxaban; E=enoxaparin; [#] Patients may have had more than one type of anaesthetic;

In each study, there were no notable differences between the two treatment groups with respect to demographic and baseline characteristics. The treatment groups were fairly well balanced and the study populations judged to be representative for a target population undergoing elective orthopaedic surgery in the UK. The proportion of females was 55.5% in RECORD 1, 54% in RECORD 2, 68% in RECORD 3 and 65.1 in RECORD 4. The mean age was 63, 61.5, 67.6 and 64.5 years with approximately 13, 13.2, 21 and 13.8% being >75 years of age, in the RECORD 1, RECORD 2, RECORD 3 and RECORD 4 trials, respectively.

6.3.2 Study Population (4) – Definition of populations used in the analysis

Randomised – number of patients screened and entered into each study given a randomisation code and assigned to a treatment

Safety Population – number of patients receiving ≤1 dose of assigned study drug

Modified intention-to-treat (MITT) – number of patients who were 1) valid for safety analysis; and 2) had also the appropriate surgery; and 3) had an adequate assessment of thromboembolism

An adequate assessment for thromboembolism was present if 1 of the following conditions was fulfilled:

- An adequate bilateral ascending venography performed in the appropriate timeframe. Performance of unilateral (left and right) venography on different days within the pre-specified time window were accepted.
- Confirmed symptomatic DVT up to the pre-specified number of days after surgery
- Confirmed symptomatic PE up to the pre-specified number of days after surgery
- Death during the pre-specified number of days after surgery

A venography performed early was considered adequate if a finding was present. A venography that was indeterminate for the proximal assessment was considered adequate if a distal finding was present. Similarly, a venography that was indeterminate for the distal assessment was considered adequate if a proximal finding was present; a unilateral venography (within the window or early) was considered adequate if a finding was present.

MITT major VTE - number of patients who were 1) valid for safety analysis; and 2) had also the appropriate surgery; and 3) had an adequate assessment of thromboembolism

An adequate assessment for thromboembolism of major VTE was present if at least one of the following conditions was fulfilled:

- An adequate bilateral ascending venography for the **proximal** segments was performed in the appropriate timeframe. Performance of unilateral (left and right) venography on different days within the pre-specified time window were accepted.
- Confirmed symptomatic **proximal** DVT up to the pre-specified number of days after surgery
- Confirmed symptomatic PE up to the pre-specified number of days after surgery
- Death during the pre-specified number of days after surgery

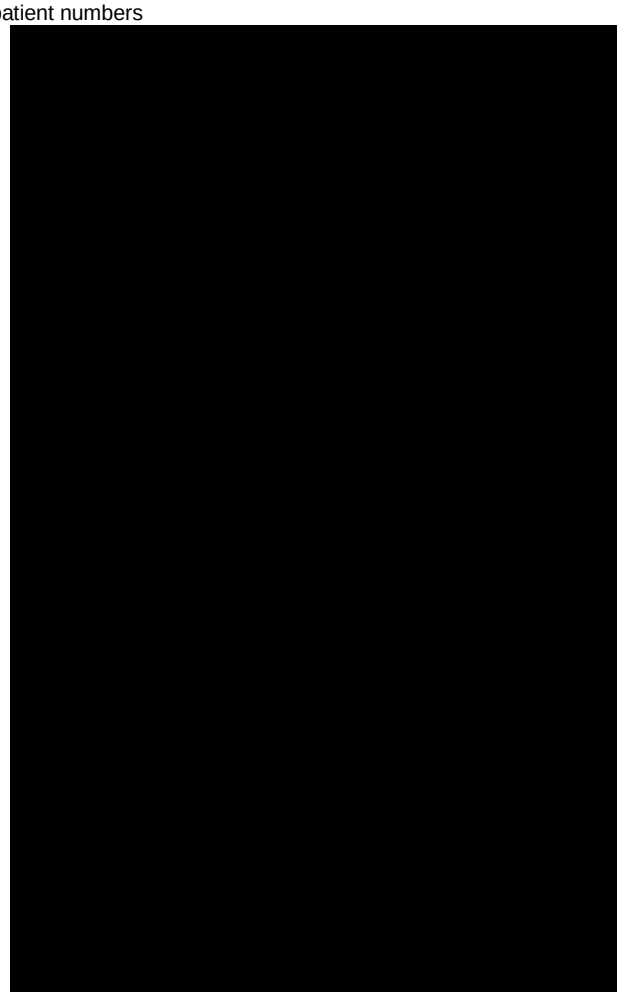
A venography performed early was considered adequate if a **proximal** finding was present; a unilateral venography (within the window or early) was considered adequate if a **proximal** finding was present.

The rate of the patients valid for the MITT analysis of major VTE was larger than the corresponding MITT population because the criteria for invalidation were less restrictive. For example, subjects with no confirmed symptomatic events (including death) who had a normal proximal DVT finding and a non-evaluable distal DVT finding (as obtained from a bilateral venography performed within 36 ± 6 days following surgery) would be invalid from MITT analyses of the primary endpoint but would be valid for MITT analyses of major VTE.

Per protocol (PP) – number of patients who 1) were valid for MITT analysis (except those included in the MITT analysis because of an early asymptomatic finding by venography as described above); and 2) had an adequate assessment of thromboembolism within the required timeframe; and 3) showed no major protocol deviations, defined as intake of prohibited anticoagulant concomitant medication, overall compliance <80% or >120%, start of first active post-operative dose later than 24 hours after surgery except for patients with spinal anaesthesia who had traumatic puncture for spinal anaesthesia.

6.3.3 Patient numbers – RIVAROXABAN RCTs

Figure 3 RECORD 1 – patient numbers



RECORD 1 Study flow

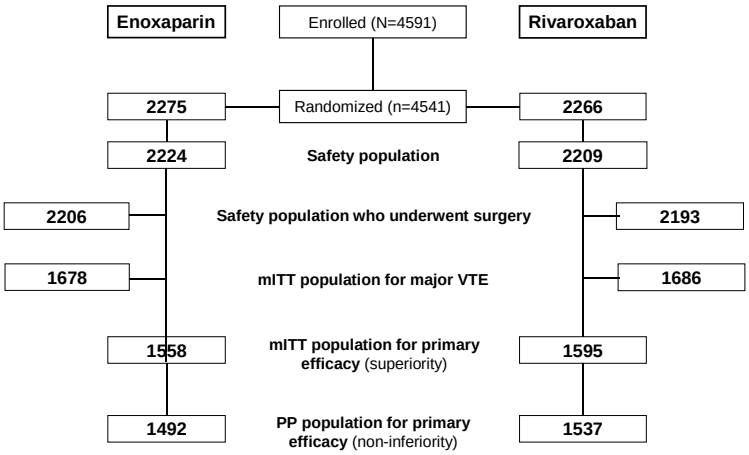


Figure 4 RECORD 2 – patient numbers

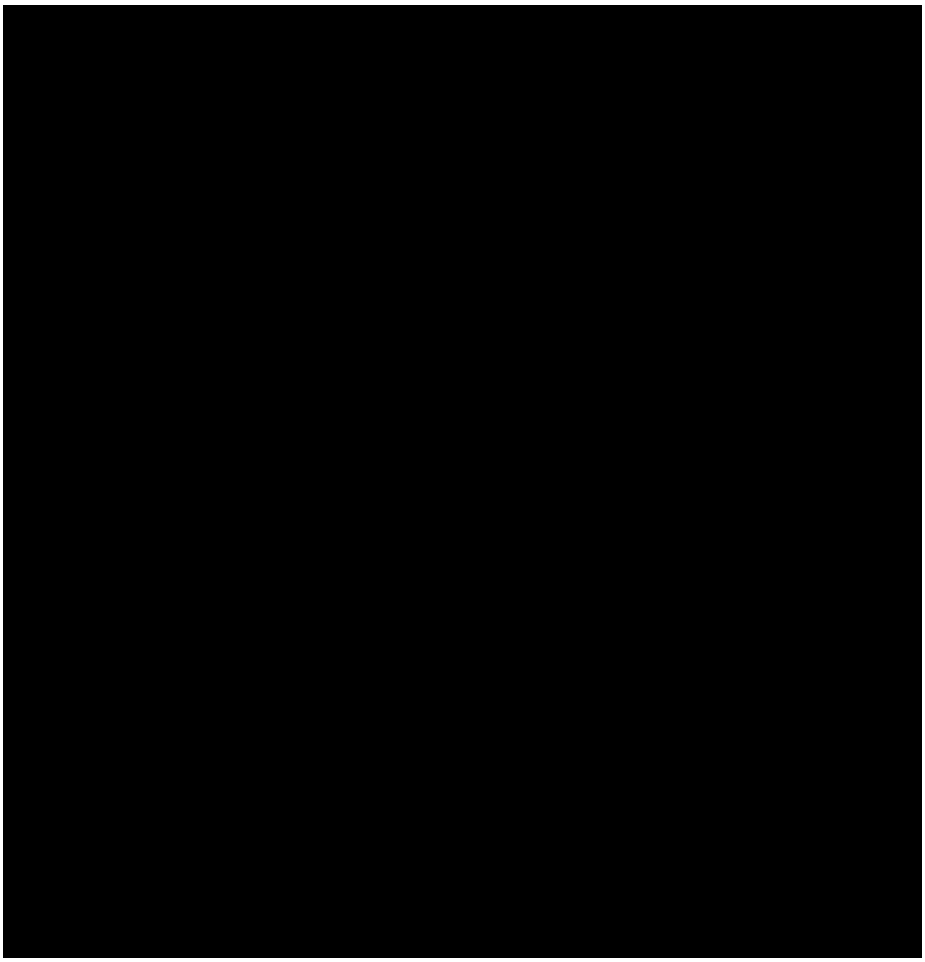
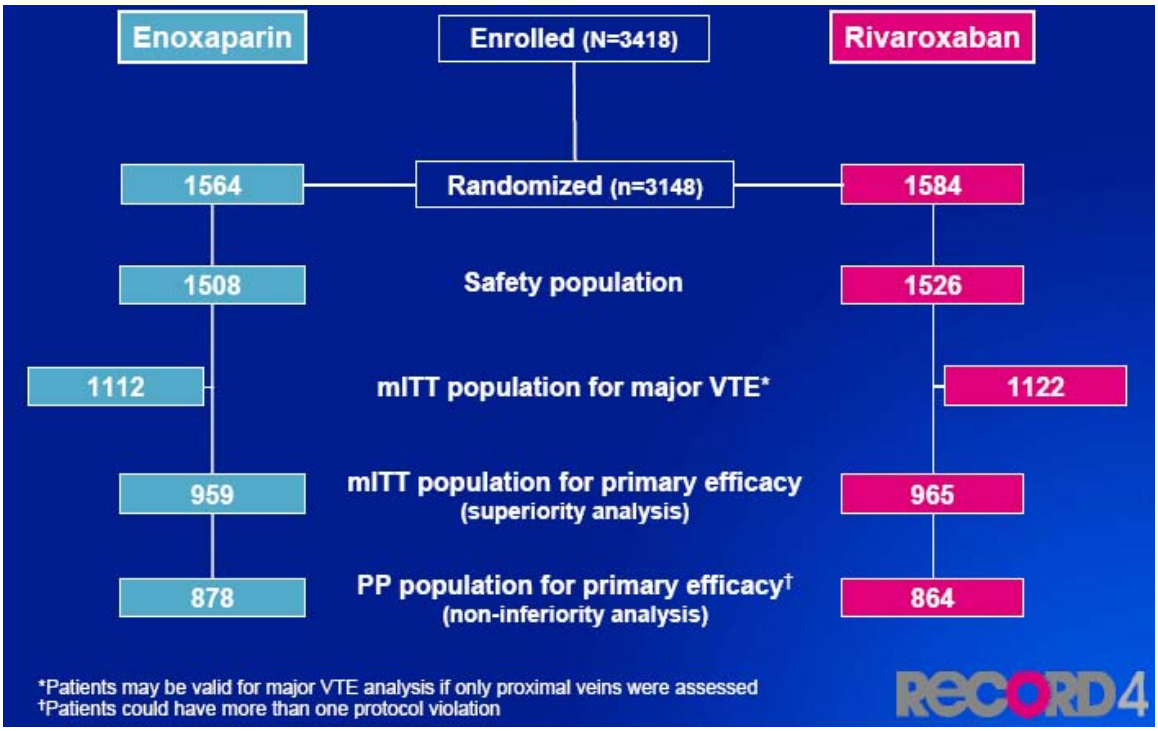


Figure 5 RECORD 3 – patient numbers

*Patients may be valid for major VTE analysis if only proximal veins were assessed;
†patients could have more than one protocol violation

Figure 6 RECORD 4 – patient numbers



6.3.4 Outcomes – RIVAROXABAN RCTs

The **primary endpoint** in RECORD 1, 2, 3 and 4 was defined as a composite endpoint of:

1. Any DVT (proximal and / or distal) and
2. Non fatal PE and
3. Death from all causes (10-12;35)

Secondary endpoints were:

1. Major VTE (Incidence of the composite endpoint comprising proximal DVT, non-fatal PE and VTE-related death) (10-12;35)
2. Incidence of symptomatic VTE (DVT,PE) during treatment and follow-up (at 65 days)(10-12;35)
3. Incidence of DVT (total, proximal, distal) (10-12;35)

The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug(10-12;35). Other safety endpoints were:

- Incidence of any treatment-emergent bleeding observed not later than 2 days after last intake of study drug(10-12;35)
- Incidence of non-major treatment-emergent bleeding observed not later than 2 days after last intake of study drug(10-12;35)
- Incidence of (any, non-major, major) post-operative bleeding(10-12;35)
- Treatment-emergent adverse events & Treatment-emergent serious adverse events(10-12;35)
- Deaths(10-12;35)
- Adjudicated cardiovascular events (on treatment / off treatment) (10-12;35).
-
-
-
-
- Laboratory parameters (10-12;35)
- SGOT/AST, SGPT/ALT, GGT, LDH, total bilirubin, direct & indirect bilirubin, alkaline phosphatase(1),

[redacted]

The analysis of the primary efficacy endpoint (and all secondary efficacy endpoints related to VTE) was solely based on the assessments made by venography, as assessed by the Independent Central Adjudication Committee (ICAC) and VTE Adjudication Committees (AC/VTE) who were blinded to the treatment. [redacted]
For diagnosis of PE, pulmonary angiography or a perfusion / ventilation lung scintigraphy combined with chest radiography or spiral CT were performed and images / films sent to AC/VTE.

[redacted]

The inclusion of an active control group was in line with medical standards as well as with the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease (CPMP/EWP/563/98)(41) and the endpoint measurement of bilateral venography was in accordance with CPMP recommendations for the assessment of drugs for prophylaxis of intra- and post-operative venous thromboembolic risk(42).

The choice of primary, secondary endpoints were in line with the recommendations set out by the CPMP in 2000(42). The CPMP stated that an important objective for the assessment of drugs for prophylaxis of intra- and post-operative venous thromboembolic risk is to demonstrate that the medicinal product decreases the number of patients developing DVTs within the prophylactic treatment period and recommends the use of bilateral venography as a suitable test for the detection and diagnosis of DVT(42).

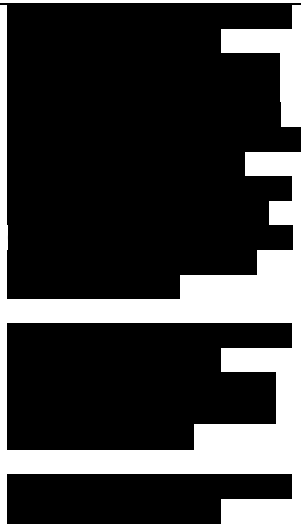
6.3.5 Statistical analysis and definition of study groups – RIVAROXABAN RCTs

See 6.3.2 Study Population for definition of study groups.

Table 5: Statistical analysis

Study	Primary Hypotheses	Statistical Analysis used	Power of study / Sample size	Analysis undertaken
RECORD 1 (10;37)	NON-INFERIORITY (PP population) H_0: Rivaroxaban is inferior to the comparator, i.e. the incidence of the primary efficacy endpoint in the rivaroxaban group is larger by more than 3.5% (absolute compared to the comparator group Vs H_1: Rivaroxaban is non-inferior to the comparator, i.e. the incidence of the primary efficacy endpoint in the rivaroxaban group is not larger by more than 3.5% (absolute) compared to the comparator group If non-inferiority test was met:- SUPERIORITY (MITT population) [redacted]	Primary outcome:- Stratified estimator Mantel-Haenszel weights and 2-sided 95% confidence interval (for non-inferiority). Non-stratified estimator & corresponding exact 2-sided 95% confidence interval (CI) (for superiority). Major VTE -most important secondary endpoint - the superiority test was preceded by non-inferiority test based on non-inferiority limit of δ=1.5%. [redacted] For major bleeding, between-treatment differences were estimated and corresponding 2-sided 95% CI calculated. Incidences of any bleeding, non-major bleeding, & treatment-emergent adverse events were tabulated & stratified by treatment group.	Assuming incidence rates of 8% for both treatment arms and a non-inferiority limit of 3.5%, a sample size of 1562 patients per treatment arm was deemed sufficient to show non-inferiority with a power of 95% and a one-sided type I error rate of 2.5%. A non-validity rate of approximately 25%, to allow primarily for non-evaluable venographies, meant that the total sample size required was 4200 patients.	For the primary efficacy analysis, the per protocol population was the primary population used for the test for non-inferiority of rivaroxaban compared to enoxaparin. The MITT population was performed as a supportive analysis in the test for superiority of rivaroxaban compared to enoxaparin. Use of the PP population for non-inferiority provides the more conservative estimate of primary outcome, as is the use of MITT for superiority *See 6.3.2 Study Population for definition of study groups*
RECORD 2 (11;38)	In the superiority test, the hypothesis of equality was rejected in favour of superiority if the upper limit of the 95% confidence interval determined for the treatment difference of rivaroxaban minus enoxaparin with respect to the incidence rates was below zero: H_0: The incidence of the primary efficacy endpoint is equal in the rivaroxaban group	The main analysis of the primary efficacy endpoint was estimated by measuring the difference in incidence rates between rivaroxaban and enoxaparin based on a stratified estimator using Mantel-Haenszel weights and the corresponding asymptotic two-sided 100 (1-α)% confidence interval using a significance level of α=5%. [redacted]	Assuming incidence rates of 11% for the comparator group, 914 patients per treatment group were required in order to detect a relative risk reduction of 40% (corresponding to an absolute risk reduction of 4.4% and thus to a rivaroxaban event rate of 6.6%) with a power of 90% and a two-sided type I error rate of 5%. A non-validity rate of approximately 25%, to allow primarily for non-evaluable venographies, meant that the total sample size required was 2500	For the primary efficacy analysis, the MITT population was the primary population used for the test for superiority of rivaroxaban compared to enoxaparin and the per protocol population used for supportive analysis.

Study	Primary Hypotheses	Statistical Analysis used	Power of study / Sample size	Analysis undertaken
	and the comparator group vs H_1: The incidence of the primary efficacy endpoint in the rivaroxaban group is smaller than in the comparator group.	[redacted] The incidence rates of the secondary efficacy endpoints as well as of the main safety endpoint were evaluated by estimating the difference in the incidence between treatment groups and calculating corresponding CIs using the same method as described for the primary efficacy analysis. The incidences of any bleeding, non-major bleeding, and treatment-emergent adverse events were tabulated and stratified by treatment group. Adverse events were descriptively analysed.	patients.	
RECORD 3 (12;39)	NON-INFERIORITY (PP population) H_0: Rivaroxaban is inferior to the comparator, i.e. the incidence of the primary efficacy endpoint in the rivaroxaban group is larger by more than 4% (absolute compared to the comparator group vs H_1: Rivaroxaban is non-inferior to the comparator, i.e. the incidence of the primary efficacy endpoint in the rivaroxaban group is not larger by more than 4% (absolute) compared to the comparator group If non-inferiority test was met:- SUPERIORITY (MITT population) H_0: The incidence of the primary efficacy endpoint is equal in the rivaroxaban group and the comparator group vs H_1: The incidence of the primary efficacy endpoint in the rivaroxaban group is smaller than in the comparator group	Primary outcome:- Stratified estimator Mantel-Haenszel weights and 2-sided 95% confidence interval (for non-inferiority). Non-stratified estimator & corresponding exact 2-sided 95% confidence interval (CI) (for superiority). Major VTE -most important secondary endpoint - the superiority test was preceded by non-inferiority test based on non-inferiority limit of δ=1.5%. The incidence rates of secondary efficacy endpoints were evaluated by estimating the difference in the incidence between treatment groups & calculating corresponding CIs using the same method as for primary efficacy analysis For major bleeding, between-treatment differences were estimated and corresponding 2-sided 95% CI calculated [redacted]	Assuming incidence rates of 27% for comparator group, a sample size of 860 patients per treatment arm was deemed sufficient in order to detect a relative risk reduction of 25% [redacted] with a power of 90% and a two-sided type I error rate of 5%. A non-validity rate of approximately 25%, to allow primarily for non-evaluable venographies, meant that the total sample size required was 2300 patients. This would mean the non-inferiority test (based on a non-inferiority limit of 4% [absolute]) preceding the superiority test has a power of 91% if an absolute risk reduction of 3% (corresponding to a relative risk reduction of 11%) under rivaroxaban is assumed. If an absolute risk reduction is assumed to be only 2% (corresponding to a relative reduction of 7%), a power of 80% would be maintained(12;39).	For the primary efficacy analysis, the per protocol population was the primary population used for the test for non-inferiority of rivaroxaban compared to enoxaparin. The MITT population was performed as a supportive analysis in the test for superiority of rivaroxaban compared to enoxaparin. Use of the PP population for non-inferiority provides the more conservative estimate of primary outcome, as is the use of MITT for superiority *See 6.3.2 Study Population for definition of study groups*

Study	Primary Hypotheses	Statistical Analysis used	Power of study / Sample size	Analysis undertaken
RECORD 4 (35)				

6.3.6 Critical appraisal of relevant RCTs

Table 6: Critical appraisal of relevant RCTs

	RECORD 1 (10)	**RECORD 2 (11)**	**RECORD 3 (12)**	**RECORD 4 (35)**
How was allocation concealed?	Bayer prepared computer-generated randomisation list. The randomisation number for each patient was provided through telephone interactive voice response system (IVRS).Unique randomisation number of patient was used on all medication labels (placebo & active treatment). Placebo & active treatments were identical in appearance and given under identical conditions. Randomisation codes kept in individual sealed envelopes.			
Randomisation Technique	Computer-generated randomisation list. Randomisation was done stratified by centre using permuted blocks of 4. The randomisation number for each patient was provided through telephone interactive voice response system (IVRS).			
Was a justification of sample size provided?	Yes, see section 6.3.5 Power of study/sample size			
Was follow-up adequate?	Yes. Period of recruitment: Feb 2006 to March 2007 (last patient's last visit) Follow-up: 30 (+5) days after last treatment with study drug	Yes. Period of recruitment :Feb 2006 to June 2007 (last patient's last visit) Follow-up: 30 (+5) days after last treatment with study drug	Yes. Period of recruitment: Feb 2006 to January 2007 (last patient's last visit) Follow-up: 30 (+5) days after last treatment with study drug	Yes. Period of recruitment: June 2006 to January 2008 (last patient's last visit) Follow-up: 30 (+5) days after last treatment with study drug
	Length of follow-up conforms with the EMEA draft guidelines 'GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR PROPHYLAXIS OF HIGH INTRA- AND POST-OPERATIVE VENOUS THROMBOEMBOLIC RISK'(43) where it is suggested the incidence of VTE (PE and / or DVT) should be monitored within a follow-up period after trial drug discontinuation, usually 4 to 6 weeks, standardised as completely as possible, and treated in a comparable way in all treatment arms of the trial.			
Were the individuals undertaking outcome assessment aware of allocation?	The main study endpoints were objectively assessed by independent adjudication committees blinded to the treatment.			
Parallel group or cross-over?	Parallel Group. No cross-over was built into RECORD 1,2, 3 or 4.			
Location effects	No UK participants. Majority of subjects were noted as 'White' (92%) and were drawn from Europe & the US. No location effect likely.	UK participants (n=218 [8.7%]). Majority of subjects were noted as 'White' (65%). No location effect likely.	No UK participants. Majority of subjects were noted as 'White' (81%) and were drawn from Europe & Canada. No location effect likely.	No UK participants. Majority of subjects were noted as 'White' (67%). No location effect anticipated.

	RECORD 1 (10)	RECORD 2 (11)	RECORD 3 (12)	RECORD 4 (35)
Dosage regimens	Rivaroxaban as per draft SPC (10mg tablet once daily). Enoxaparin as per standard practice & licenced dosage in UK (40mg by subcutaneous injection once daily).			Rivaroxaban as per draft SPC (10mg tablet once daily). Enoxaparin as per US dosage (30mg by subcutaneous injection twice daily).
Were study groups comparable?	Yes, demographic, baseline and surgical characteristics were similar across treatment groups in all studies			
Were the statistical analyses used appropriate?	Yes	Yes	Yes	Yes
Was an intention-to-treat (ITT) analysis undertaken?	Modified ITT See section 6.3.2	Modified ITT See section 6.3.2	Modified ITT See section 6.3.2	Modified ITT See section 6.3.2
Confounding factors?	None identified. The study design and selection and measurement of endpoints complies with the EMEA guideline for studies in this therapeutic area(43).			The dosage of enoxaparin is not the UK recommended dose.

6.4 Results of the relevant comparative RCTs

Primary Composite Efficacy Endpoint

In RECORD 1, MITT analysis in 3153 patients demonstrated a statistically significant difference (p<0.001) in the incidence of the composite primary endpoint, confirming superiority of rivaroxaban over enoxaparin (rivaroxaban n=18 (1.1%), enoxaparin n=58 (3.7%) 95% CI: -3.69%, -1.54%) in preventing VTE. The relative risk reduction was 70% [95% CI:49%; 82%](10).

For RECORD 2, a study designed to compare the efficacy of extended VTE prophylaxis with rivaroxaban with short-term enoxaparin prophylaxis, the MITT analysis in 1733 patients demonstrated a statistically significant difference (p<0.001) in the incidence of the composite primary endpoint. This confirmed superiority of the 35 days rivaroxaban regimen over the 14 days enoxaparin regimen (rivaroxaban n=17 (2.0%), enoxaparin n=81 (9.3%) 95% CI: -9.41%, -5.15%) in preventing VTE. The relative risk reduction was 78.9% [redacted]

[redacted]

Consequently, MITT analysis in 1702 patients demonstrated a statistically significant difference (p<0.001) in the incidence of the composite primary endpoint, confirming superiority of rivaroxaban over enoxaparin (rivaroxaban n=79 (9.6%), enoxaparin n=166 (18.9%) in preventing VTE. The relative risk reduction was 49% [95% CI: 35%, 61%](12).

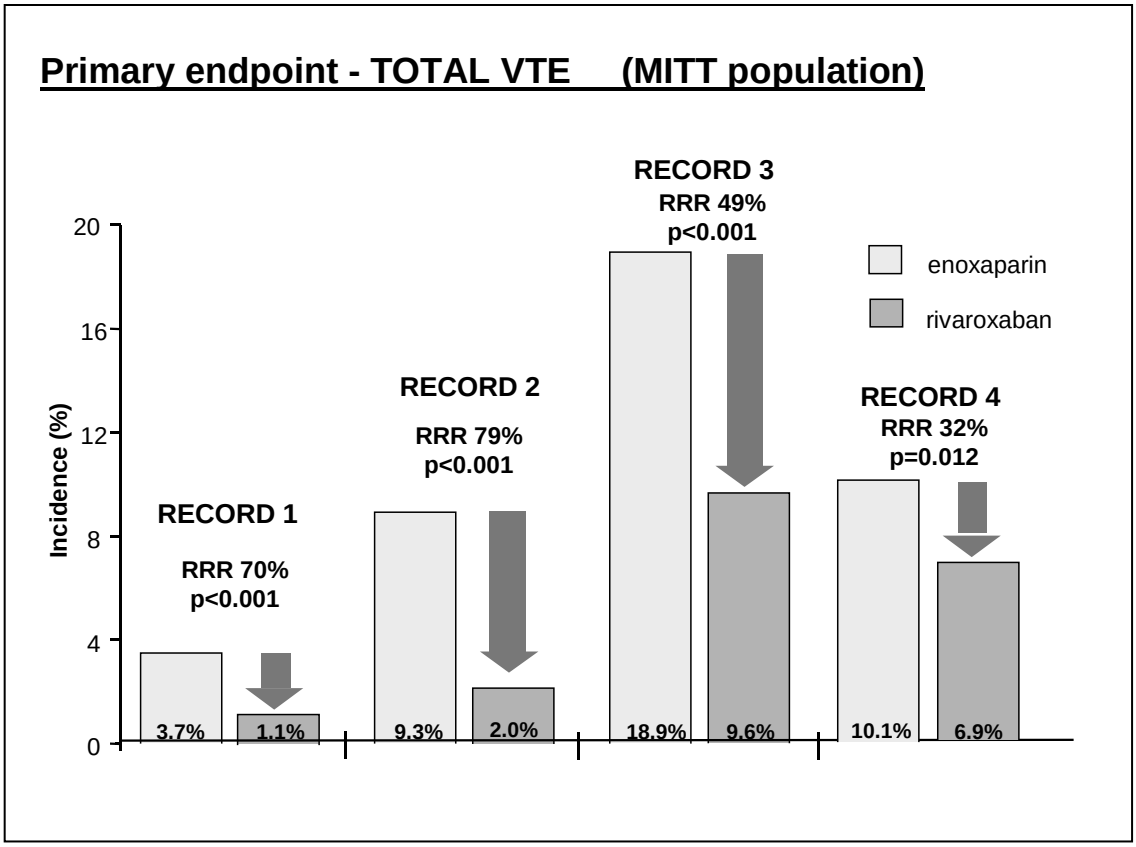
Rivaroxaban was again shown to be effective and statistically superior to enoxaparin in the prevention of the composite of total VTE and death in patients undergoing elective total knee replacement in the RECORD 4 study.

[redacted]In the MITT analysis, the composite primary endpoint occurred in 67 (6.9%) and 97 (10.7%) of patients randomised to rivaroxaban or enoxaparin, respectively (p=0.012), demonstrating superiority of rivaroxaban over enoxaparin (Point estimate of Mantel-Haenszel weighted difference to enoxaparin: -3.2% [95% CI: -5.67%, -0.71%]).

Table 7: Incidence of components of composite primary efficacy endpoint (MITT population)

	RECORD 1 (10;37)		RECORD 2 (11;38)		RECORD 3 (12;39)		RECORD 4 (35)	
	Rivaroxaban 10mg od n=1595 n (%)	Enoxaparin 40mg od n=1558 n(%)	Rivaroxaban 10mg od n=864 n (%)	Enoxaparin 40mg od n=869 n(%)	Rivaroxaban 10mg od n=824 n (%)	Enoxaparin 40mg od n=878 n(%)	Rivaroxaban 10mg od n=965 n (%)	Enoxaparin 30mg bid n=959 n(%)
Composite primary efficacy endpoint								
Any event	**18 (1.1) [0.7%, 1.8%]**	**58 (3.7) [2.8%, 3.8%] p<0.001**	**17 (2.0) [1.2,3.1]**	**81 (9.3) [7.5, 11.5] p<0.001**	**79 (9.6) [7.7%, 11.8%]**	**166 (18.9) [16.4%, 21.7%] p<0.001**	**67 (6.9) p=0.012**	**97 (10.1)**
Death of any cause	4 (0.3)	4 (0.3)	2 (0.2)	6 (0.7)	0	2 (0.2)	[redacted]	[redacted]
Non-fatal PEs	4 (0.3)	1 (<0.1)	1 (0.1)	4 (0.5)	0	4 (0.5)	[redacted]	[redacted]
Proximal and / or distal DVT	12 (0.8)	53 (3.4)	14 (1.6)	71 (8.2)	79 (9.6)	160 (18.2)	[redacted]	[redacted]
Components								
Proximal DVT	1 (<0.1)	31 (2.0)	5 (0.6)	44 (5.1)	9 (1.1)	20 (2.3)	[redacted]	[redacted]
Distal DVT	11 (0.7)	22 (1.4)	9 (1.0)	27 (3.1)	70 (8.5)	140 (15.9)	[redacted]	[redacted]
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unexplained death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 7 - Primary endpoint: Total VTE: any DVT, non-fatal PE and all-cause mortality up to day 36+6



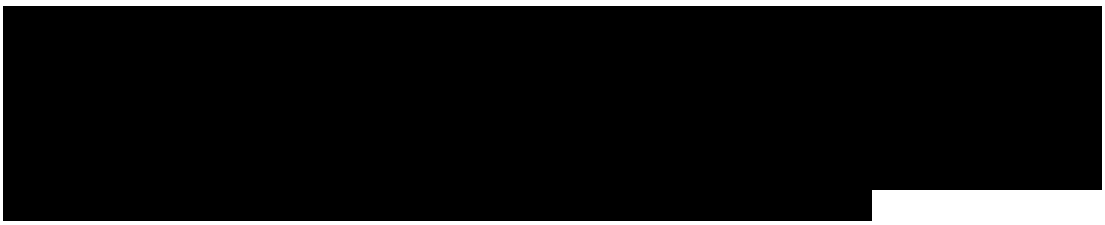
Key Secondary endpoints (see Table 8)

Major VTE (composite of proximal DVT, non-fatal PE, and VTE-related death)

RECORD 1: The major secondary endpoint, major VTE occurred in 4 (0.2%) patients receiving rivaroxaban compared to 33 (2.0% patients receiving enoxaparin. Superiority of rivaroxaban was thus demonstrated over enoxaparin (p<0.001; MITT population) with a relative risk reduction of 88% [95% CI: 66.0%; 96%](10).

RECORD 2: Major VTE occurred in 6 (0.6%) patients receiving rivaroxaban compared to 49 (5.1%) patients receiving the enoxaparin regimen. Superiority of rivaroxaban was thus demonstrated over enoxaparin (p<0.0001; MITT population with evaluable proximal veins)(11).

RECORD 3: The major secondary endpoint, major VTE occurred in 9 (1.0%) patients receiving rivaroxaban compared to 24 (2.6% patients receiving enoxaparin ([95%CI: -2.80%, -0.4%]; p=0.010; MITT population). Relative risk reduction 62% [95% CI:18, 82]; p=0.02(12).



Symptomatic VTE (DVT & PE)

RECORD 1: A lower incidence of symptomatic VTE was observed in patients treated with rivaroxaban compared with enoxaparin (n=6 (0.3%) vs n=11 (0.5%); relative risk reduction of 45%, p=0.22 - safety population)(10).

RECORD 2: The rivaroxaban regimen was statistically superior compared with enoxaparin (n=3 (0.2%) vs n=15 (1.2%); relative risk reduction 80%, p=0.004 - safety population) for symptomatic VTE(11).

RECORD 3: A statistically significantly lower incidence of symptomatic VTE was observed in patients treated with rivaroxaban compared with enoxaparin (n=8 (0.7%) vs n=24 (2.0%); relative risk reduction 66%, p=0.005 - safety population)(12).

RECORD 4: A lower incidence of symptomatic VTE was observed in patients treated with rivaroxaban 11 (0.7%) when compared with enoxaparin 18 (1.2%), (safety population)(35).

Table 8 - Incidence of secondary efficacy endpoints and their individual components as assessed by the central adjudication committee (MITT population)

	RECORD 1 (10;37)		RECORD 2 (11;38)		RECORD 3 (12;39)		RECORD 4 (35)	
Endpoint / subset	**Rivaroxaban 10mg od n=1595 n (%)**	**Enoxaparin 40mg od n=1558 n(%)**	**Rivaroxaban 10mg od n=864 n (%)**	**Enoxaparin 40mg od n=869 n(%)**	**Rivaroxaban 10mg od n=824 n (%)**	**Enoxaparin 40mg od n=878 n(%)**	**Rivaroxaban 10mg od n=965 n (%)**	**Enoxaparin 30mg bid n=959 n(%)**
Composite Endpoint II								
Any event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (VTE related)	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	[redacted]	[redacted]	[redacted]
Nonfatal PE	4 (0.3)	1 (<0.1)	1 (0.1)	4 (0.5)	0 (0.0)	[redacted]	[redacted]	[redacted]
DVT	12 (0.8)	53 (3.4)	14 (1.6)	71 (8.2)	79 (9.6)	160 (18.2)	[redacted]	[redacted]
Difference to enoxaparin								
Point estimate (%)	[redacted]		[redacted]		[redacted]		[redacted]	
95% CI (%)								
Deep vein thrombosis								
Any event	12 (0.8)	53 (3.4)	14 (1.6)	71 (8.2)	79 (9.6)	160 (18.2)	[redacted]	[redacted]
DVT, proximal	1 (<0.1)	31 (2.0)	5 (0.6)	44 (5.1)	9 (1.19)	20 (2.3)	[redacted]	[redacted]
DVT, distal	11 (0.7)	22 (1.4)	9 (1.0)	27 (3.1)	74 (9.0)	156 (17.8)	[redacted]	[redacted]
	-2.7 [a] [-3.7, -1.7] [a]		-6.48 [a] [-8.48, -4.48] [a]		[redacted]		[redacted]	
Pulmonary embolism								
Any event	4 (0.3)	2 (0.1)	[redacted]	[redacted]	0 (0.0)	4 (0.5)	[redacted]	[redacted]
Nonfatal PE	4 (0.3)	1 (<0..1)	1 (0.1)	4 (0.5)	0 (0.0)	4 (0.5)	[redacted]	[redacted]
Fatal PE	0 (0.0)	1 (<0.1)	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	[redacted]
	[redacted]		[redacted]		[redacted]		[redacted]	
Symptomatic VTE*								
Any event	6 (0.3)	11 (0.5) p=0.222	3 (0.2)	15 (1.2) p=0.004	8 (0.7)	24(2.0) =0.005	11 (1.1)	18 (1.9)
Nonfatal PE	4 (0.2)	1 (<0.1)	1 (<0.1)	4 (0.3)	0 (0.0)	4 (0.3)	[redacted]	[redacted]
Fatal PE	[redacted]	[redacted]	[redacted]	[redacted]	0 (0.0)	0 (0.0)	[redacted]	[redacted]
DVT, proximal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DVT, distal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	-0.2 [b] [-0.6, 0.1] [b]		-1.0 [b] [-1.8, -0.3] [b]		-1.3 [b] [-2.2, -0.4] [b]		[redacted]	

	RECORD 1 (10;37)		RECORD 2 (11;38)		RECORD 3 (12;39)		RECORD 4 (35)	
Endpoint / subset	**Rivaroxaban 10mg od n=1595 n (%)**	**Enoxaparin 40mg od n=1558 n(%)**	**Rivaroxaban 10mg od n=864 n (%)**	**Enoxaparin 40mg od n=869 n(%)**	**Rivaroxaban 10mg od n=824 n (%)**	**Enoxaparin 40mg od n=878 n(%)**	**Rivaroxaban 10mg od n=965 n (%)**	**Enoxaparin 30mg bid n=959 n(%)**
Death								
Any event	4 (0.3)	4 (0.3)	2 (0.2)	6 (0.7)	0 (0.0)	2 (0.2)	[redacted]	[redacted]
Death (VTE related)	[redacted]	[redacted]	[redacted]	1 (0.1)	[redacted]	[redacted]		
Death (not VTE related)				4 (0.5)				
Death (unexplained)	[redacted]	[redacted]	[redacted]	1 (0.1)	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]		[redacted]		[redacted]	
Symptomatic VTE (follow-up at 65 days THR, 45 days TKR)								
Any event	1 (<0.1)	3 (0.2)	1 (0.1)	1 (0.1)	3 (0.4)	3 (0.3)	[redacted]	[redacted]
Nonfatal PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Fatal PE								
DVT, proximal								
DVT, distal								
	[redacted]		[redacted]		[redacted]		[redacted]	
Death (follow-up)								
Any event	1 (<0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	[redacted]	[redacted]
Death (VTE related)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Death (not VTE related)								
Death (unexplained)								
	[redacted]		[redacted]		[redacted]		[redacted]	

CI=confidence interval; DVT=deep vein thrombosis; MITT=modified intent-to-treat; od=once daily; PE=pulmonary embolism; VTE=venous thromboembolism

*Symptomatic VTE reported on the basis of safety population who underwent surgery (RECORD 1: rivaroxaban n=2193; enoxaparin n=2206; RECORD 2: rivaroxaban n=1212, enoxaparin n=1207; RECORD 3: rivaroxaban n=1201, enoxaparin n=1217; RECORD 4: rivaroxaban n=1526 , enoxaparin n=1508)

[a] Point estimate and confidence intervals are based on Mantel-Haenszel-weighted difference in proportions, with weights based on sample sizes per strata (geographic region).

[b] Point estimate is based on observed rates and confidence intervals are based on an exact method (unstratified)

CONCLUSION

RECORD 1 is the largest study comparing a LMWH with an oral factor Xa inhibitor using an extended prophylaxis regimen. The results confirm that rivaroxaban was both clinically effective and statistically superior to subcutaneous enoxaparin 40 mg od in the prevention (35 vs 35 days) of VTE in patients undergoing elective total hip replacement. Rivaroxaban met the prespecified primary and secondary efficacy objectives. The relative risk reduction (unweighted relative risk) was 70% [95% CI:49%; 82%](10) for the primary efficacy endpoint. The clinical benefit of rivaroxaban was accompanied by a favourable safety profile, which was comparable to enoxaparin in terms of adverse event rates, treatment-emergent as well as during follow-up. The incidence of major and non-major clinically relevant bleeding events as well as all bleeding events was similar between the 2 treatment groups. The efficacy and safety results of this study support the beneficial use of rivaroxaban in the prevention of VTE for patients undergoing elective total hip replacement.

The RECORD 2 study demonstrated that extended prophylaxis with rivaroxaban prevented significantly more VTE than a 10-14 day treatment with subcutaneous enoxaparin in patients undergoing total hip replacement. The relative risk reduction (unweighted relative risk) was 79% for the primary efficacy endpoint, a composite of any DVT, non-fatal PE and death from all causes. As observed in RECORD 1, the safety profile of rivaroxaban was comparable to enoxaparin in terms of adverse event rates, incidence of major and non-major clinically relevant bleeding events as well as all bleeding events. This is important considering rivaroxaban was given for 35 days and enoxaparin was given for 14 days only.

As demonstrated in patients undergoing total hip replacement (RECORD 1 and RECORD 2 studies), the RECORD 3 study further confirms the efficacy of rivaroxaban in prevention of VTE in patients undergoing elective total hip and knee replacement (relative risk reduction 49%). Rivaroxaban 10 mg od was both clinically effective and statistically superior to enoxaparin 40 mg od in the prevention of VTE in patients undergoing elective total knee replacement. As in RECORD 1 and 2, the clinical benefit of rivaroxaban was accompanied by a favourable safety profile, which was comparable to enoxaparin. RECORD 4, which utilised the US dosing of enoxaparin, supports the superior efficacy of rivaroxaban when compared with enoxaparin in total knee replacement, with a relative risk reduction of 32% for the primary endpoint. The study also demonstrates a low rate of major and symptomatic VTE events in TKR and a comparable safety profile to enoxaparin.

In summary:

RECORD 1,2, 3 and 4 studies demonstrated the superior efficacy of rivaroxaban over enoxaparin:

- For extended thromboprophylaxis after total hip replacement (relative risk reduction 70% - RECORD 1)
- For extended prophylaxis compared to short duration enoxaparin prophylaxis after total hip replacement (relative risk reduction of 79% - RECORD 2)
- For thromboprophylaxis after total knee replacement (relative risk reduction 49% - RECORD 3; relative risk reduction 32% - RECORD 4)

Rivaroxaban showed:

- Superior efficacy for the primary composite endpoint (DVT, PE and all-cause mortality) in all studies
- Superior efficacy for secondary endpoints major VTE (RECORD 1,2 and 3)
- Superior efficacy was also shown for the symptomatic VTE endpoint in RECORD 2 and RECORD 3.
- The consistent benefit of rivaroxaban was not accompanied by any increase in major or any bleeding, indicating a favourable benefit-risk profile.

6.5 Meta-analysis

The results of the individual RECORD trials have been reported separately. Additionally, all available data were pooled and a meta-analysis was performed in order to demonstrate the clinical efficacy and safety of rivaroxaban versus enoxaparin. The RECORD 4 trial, which uses a US licenced dose of enoxaparin, was also included to the meta-analysis.

The results of the meta-analysis are presented below and have been used as a sensitivity analysis in the economic evaluation.

The meta-analysis of all of the RECORD trials was performed on the following outcomes:

- Primary efficacy endpoint (total VTE and all-cause mortality)
- Symptomatic VTE
- Non-fatal PE
- Fatal PE
- Major bleeding

The characteristics of each clinical trial are presented in table 9. The outcomes reported in each of the individual trials are summarised in table 10.

Table 9 RECORD trial characteristics

STUDY REFERENCE	DOSE AND DURATION OF INTERVENTION	PRIMARY END POINT(S)
RECORD 1(10)	Rivaroxaban: 10 mg, QD for 35 days Enoxaparin: 40mg QD for 35 days	Any DVT (proximal and/or distal), non-fatal PE, all cause mortality
RECORD 2 (11)	Rivaroxaban: 10 mg, QD for 35 days Enoxaparin: 40mg QD for 13 days	Any DVT (proximal and/or distal), non-fatal PE, all cause mortality
RECORD 3 (12)	Rivaroxaban: 10 mg, QD for 12 days Enoxaparin: 40mg QD for 12 days	Any DVT (proximal and/or distal), non-fatal PE, all cause mortality
RECORD 4 (35)	Rivaroxaban: 10 mg, QD for 12 days Enoxaparin: 30mg BID for 12 days	Any DVT (proximal and/or distal), non-fatal PE, all cause mortality

Table 10 RECORD trial results

	RECORD 1		RECORD 2		RECORD 3		RECORD 4	
	Rivaroxaban	**Enoxaparin**	**Rivaroxaban**	**Enoxaparin**	**Rivaroxaban**	**Enoxaparin**	**Rivaroxaban**	**Enoxaparin**
VTE	18/1595	58/1558	17/864	81/869	79/824	166/878	67/965	97/959
Symptomatic VTE	6/2193	11/2206	3/1212	15/1207	8/1201	24/1217	11/1524	18/1505
Non-fatal PE	4/1595	1/1558	1/864	4/869	0/824	4/878	[redacted]	[redacted]
Fatal PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeding	6/2209	2/2224	1/1228	1/1229	7/1220	6/1239	10/1526	4/1508

*The MITT population is not appropriate to reflect the incidence of symptomatic events since it includes only patients that had a venogram. The incidence of symptomatic VTE is reflected by the number of individuals that developed a symptomatic event in the safety population reduced by those patients who did not have surgery.

The four clinical trials were pooled together. Table 11 presents the results of the meta-analysis. The results of the statistical analysis match the measures of difference used in the economic evaluation; relative risk (RR) for VTE, symptomatic VTE and major bleeding, and risk difference (RD) for PE events. Each comparison consisted of one fixed effects model. If heterogeneity is observed between studies, a random effects model is used. [redacted] in the fixed effect meta-analysis. Details of the analysis of each outcome are presented below the table.

Table 11 RECORD program results (all trials pooled): Rivaroxaban vs. Enoxaparin

Outcome	RR (95% CI)	RD (%) (95% CI)
VTE	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		[redacted]
Major bleeding	[redacted]	

*random-effects model

Details of meta-analysis for each outcome:

VTE

RR - Fixed-effects model:

```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------
Eriksson et al 2 |
Kakkar et al 200 |
Lassen et al 200 |
RECORD 4         |
-----------------+-------------------------------------------------
  M-H pooled RR  |
-----------------+-------------------------------------------------
  Heterogeneity chi-squared =
  Test of RR=
```

There is significant heterogeneity between studies, therefore a random-effects model is more appropriate.

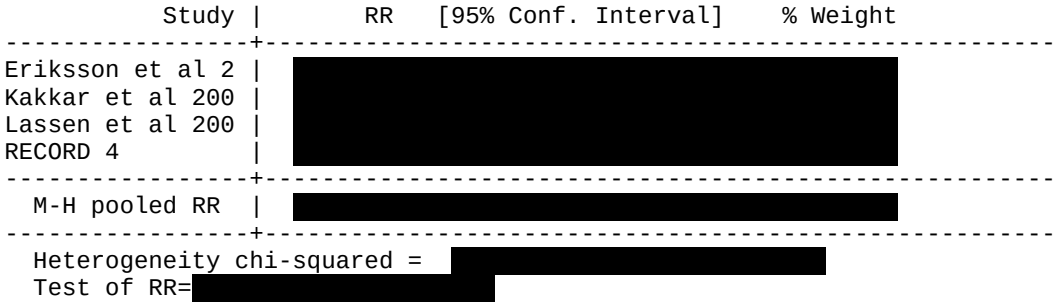
RR - Random-effects model:

```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------
Eriksson et al 2 |
Kakkar et al 200 |
Lassen et al 200 |
RECORD 4         |
-----------------+-------------------------------------------------
  D+L pooled RR  |
-----------------+-------------------------------------------------
  Heterogeneity chi-squared =
  Estimate of between-study variance Tau-squared =
  Test of RR=
```

[3] Statistical significance is observed by the range of the CI (if it is greater or less than one without overlapping).

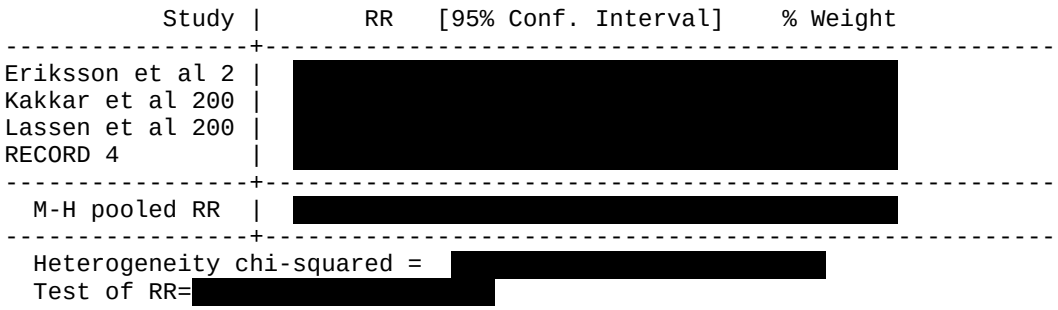
Symptomatic VTE

RR - Fixed-effects model:



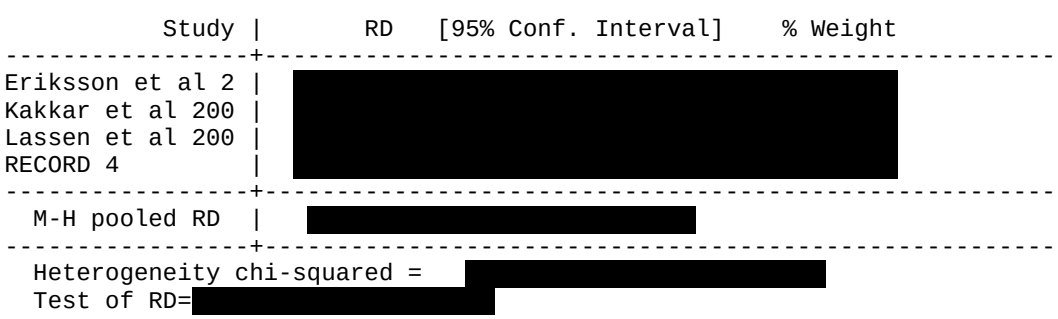
No significant heterogeneity.

RR - Random-effects model:



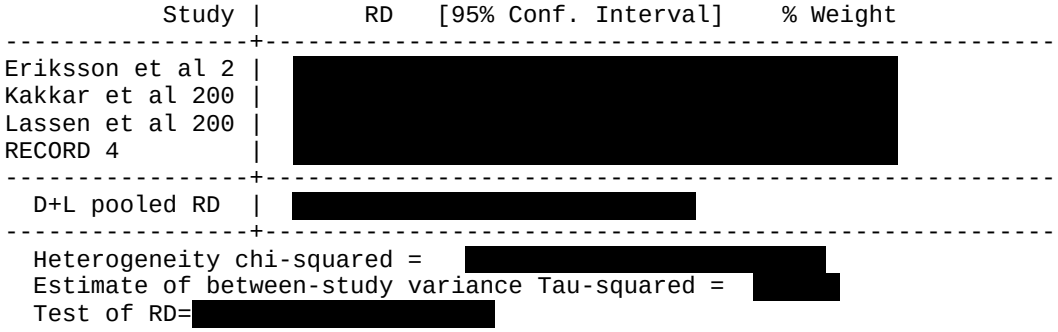
Non-fatal PE

RD - Fixed-effects model:



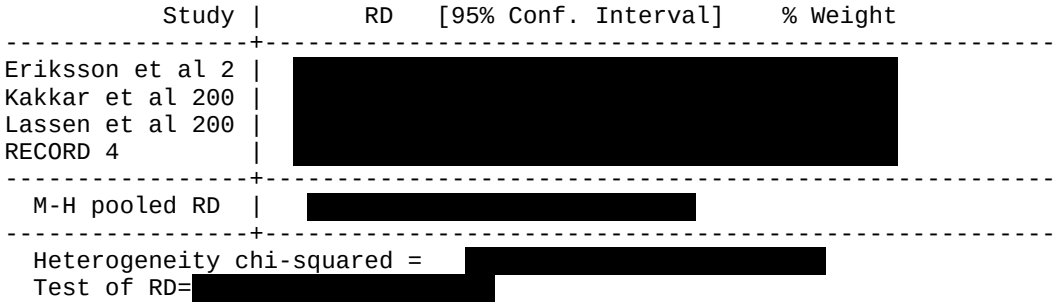
There is significant heterogeneity between studies, therefore a random-effects model is more appropriate.

RD - Random-effects model:



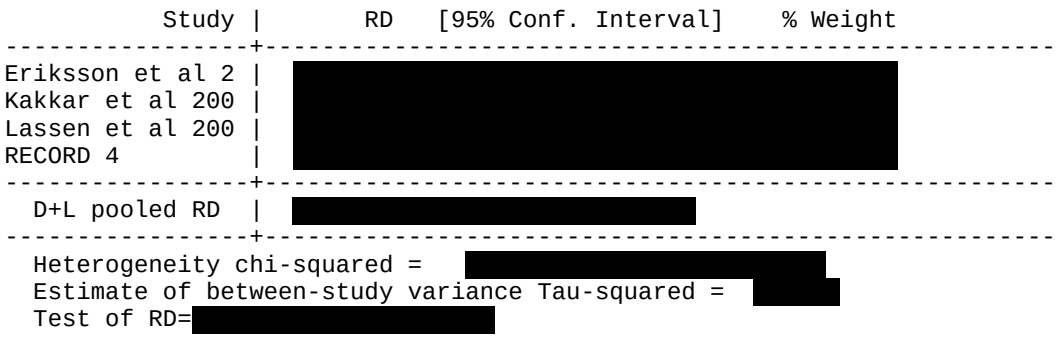
Fatal PE

RD - Fixed-effects model:



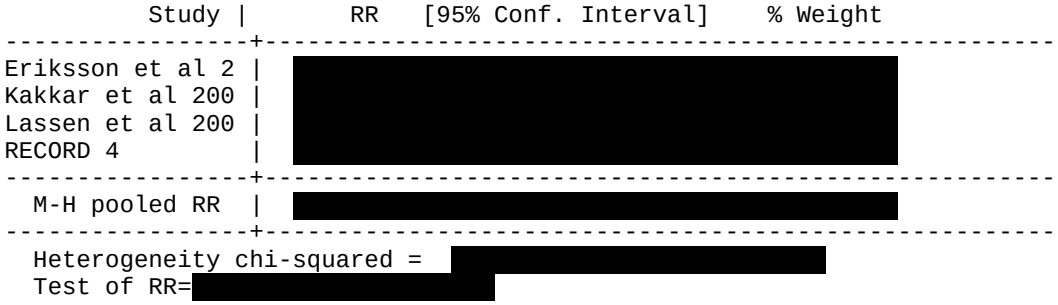
No significant heterogeneity.

RD - Random-effects model:



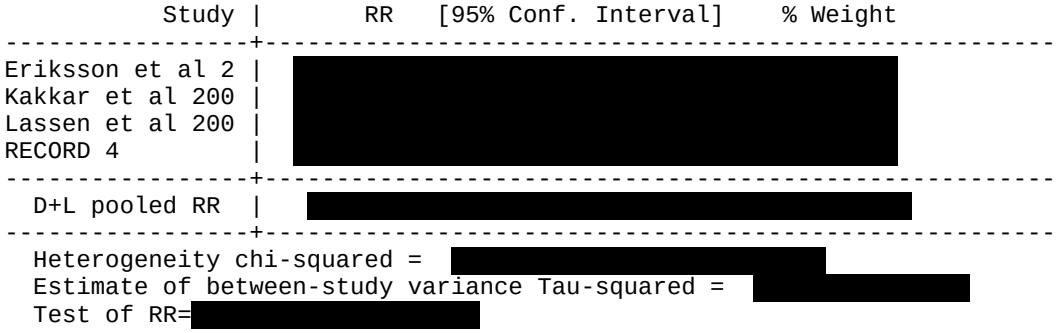
Major bleeding

RR - Fixed-effects model:



No significant heterogeneity.

RR - Random-effects model:



Additional analysis: Exploring heterogeneity across rivaroxaban studies

The differences in the duration and doses of the regimens of the comparator prophylaxis in the RECORD clinical trials prompted additional analysis on the impact of these differences to the meta-analysis . In particular, the inclusion of RECORD 2, where the duration of enoxaparin administration is not equal to rivaroxaban administration, might introduce a bias that favours rivaroxaban. Additionally, in RECORD 4 the enoxaparin dose regimen (30mg BID) does not match that of the other three clinical trials (40mg QD) with unclear direction of the introduced bias. The following analysis consists of two methods for each of the five outcomes included in the meta-analysis ; an influence analysis, and a meta-regression.

The first method investigates the influence of a single study on the overall meta-analysis estimate, by computing the pooled estimate without each study of interest in turn. No formal test of influence is given; the analysis follows some general recommendations to assess influence:

1. An individual study is suspected of excessive influence if the point estimate of its "omitted" analysis lies outside the confidence interval of the "total" pooled analysis.
2. A study is excessively influential if its "omitted" meta-analytic estimate differs in significance relative to the "total" pooled analysis.

The analysis uses the command *metainf* in Stata[4].

The second method extends a random effects meta-analysis to estimate the extent to which one or more covariates, with values defined for each study in the analysis, explain heterogeneity in the treatment effects. Here, the impact of 2 covariates was tested: data coming from RECORD 2 (dummy variable taking the value 1 for RECORD 2 and 0 for the other trials) and data coming from RECORD 4. The meta-regressions were performed using the command *metareg* in Stata.

In conclusion, in all outcomes (see below), both employed methods did not find that the inclusion of RECORD 2 or RECORD 4 introduces a significant bias in the pooled meta-analysis of all RECORD studies. In particular, in the influence analysis, the pooled effect without RECORD 2 or RECORD 4 fall within the confidence intervals of the total pooled estimates, and the conclusions in terms of significance do not change. The p-values associated with the meta-regressions are also not significant indicating that we cannot reject the null hypotheses that there is no difference in the outcome by adding RECORD 2 and RECORD 4.

VTE

Table 12 VTE Influence analysis – pooling performed using fixed effects

Fixed effects	ln(RR)	95% CI around ln(RR)	RR	95% CI around RR
Without RECORD 2	[redacted]	[redacted]	[redacted]	[redacted]
Without RECORD 4	[redacted]	[redacted]	[redacted]	[redacted]
All pooled	[redacted]	[redacted]	[redacted]	[redacted]

Table 13 VTE Influence analysis – pooling performed using random effects

Random effects	ln(RR)	95% CI around ln(RR)	RR	95% CI around RR
Without RECORD 2	[redacted]	[redacted]	[redacted]	[redacted]
Without RECORD 4	[redacted]	[redacted]	[redacted]	[redacted]
All pooled	[redacted]	[redacted]	[redacted]	[redacted]

Meta-regression analyses

p-value associated with influence of RECORD 2: [redacted]
p-value associated with influence of RECORD 4:

[4] It should be noted that the *metainf* results may differ slightly from the results shown in the indirect comparison section, as *metainf* uses a different method (inverse variance weighting, as opposed to Mantel-Haenszel) to pool the data.

Symptomatic VTE

Table 14 Symptomatic VTE - influence analysis – pooling performed using fixed effects

Fixed effects	ln(RR)	95% CI around ln(RR)	RR	95% CI around RR
Without RECORD2	[redacted]	[redacted]	[redacted]	[redacted]
Without RECORD 4	[redacted]	[redacted]	[redacted]	[redacted]
All pooled	[redacted]	[redacted]	[redacted]	[redacted]

The random-effects pooling gives identical results for this outcome.

Meta-regression analyses

p-value associated with influence of RECORD 2: [redacted]
p-value associated with influence of RECORD 4:

Non fatal PE

Table 15 Non fatal PE -influence analysis – pooling performed using fixed effects

Fixed effects	RD	95% CI around RD
Without RECORD 2	[redacted]	[redacted]
Without RECORD 4	[redacted]	[redacted]
All pooled	[redacted]	[redacted]

Table 16 Non fatal PE -influence analysis – pooling performed using random effects

Random effects	RD	95% CI around RD
Without RECORD 2	[redacted]	[redacted]
Without RECORD 4	[redacted]	[redacted]
All pooled	[redacted]	[redacted]

Meta-regression analyses

p-value associated with influence of RECORD 2: [redacted]
p-value associated with influence of RECORD 4:

Fatal PE

Table 17 Fatal PE - influence analysis – pooling performed using fixed effects

Fixed effects	RD	95% CI around RD
Without RECORD 2	[redacted]	[redacted]
Without RECORD 4	[redacted]	[redacted]
All pooled	[redacted]	[redacted]

The random-effects pooling gives identical results for this outcome.

Meta-regression analyses

p-value associated with influence of RECORD 2: [redacted]
p-value associated with influence of RECORD 4:

Major bleeding

Table 18 Major bleeding-influence analysis – pooling performed using fixed effects

Fixed effects	ln(RR)	95% CI around ln(RR)	RR	95% CI around RR
Without RECORD 2	[redacted]	[redacted]	[redacted]	[redacted]
Without RECORD 4	[redacted]	[redacted]	[redacted]	[redacted]
All pooled	[redacted]	[redacted]	[redacted]	[redacted]

The random-effects pooling gives identical results for this outcome.

Meta-regression analyses

p-value associated with influence of RECORD 2: [redacted]
p-value associated with influence of RECORD 4:

Additional analyses: Pooling studies by indication

The four RECORD clinical trials were also pooled by indication:

- THR: RECORD 1 and RECORD 2
- TKR: RECORD 3 and RECORD 4

The results of this analysis are used as a sensitivity analysis in the economic evaluation.

THR

Table 19 presents the results of the meta-analysis. The results of the statistical analysis match the measures of difference used in the economic evaluation; RR for VTE, symptomatic VTE and major bleeding, and RD for PE events. Each comparison consisted of one fixed effects model. If heterogeneity is observed between studies, a random effects model is used. [redacted] in the fixed effect meta-analysis. Details of the analysis of each outcome are presented below the table.

Table 19 THR results rivaroxaban vs. enoxaparin (RECORD 1 and RECORD 2 pooled)

Outcome	RR (95% CI)	RD (%) (95% CI)
VTE	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		[redacted]
Major bleeding	[redacted]	

Details of meta-analysis for each outcome:

VTE

RR - Fixed-effects model:

```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------
Eriksson et al 2 |  [redacted]
Kakkar et al 200 |  [redacted]
-----------------+-------------------------------------------------
  M-H pooled RR  |  [redacted]
-----------------+-------------------------------------------------
  Heterogeneity chi-squared =  [redacted]
  Test of RR=[redacted]
```

No significant heterogeneity.

Symptomatic VTE

RR - Fixed-effects model:

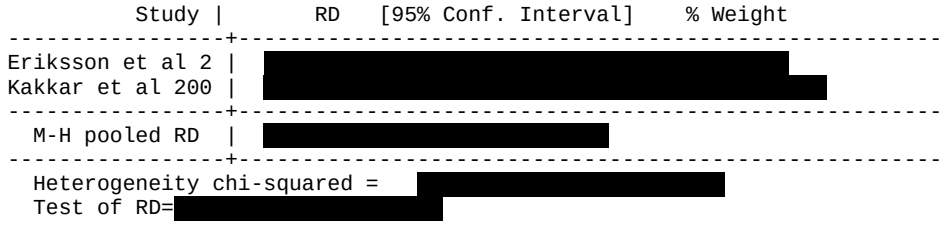
```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------
Eriksson et al 2 |  [redacted]
Kakkar et al 200 |  [redacted]
-----------------+-------------------------------------------------
  M-H pooled RR  |  [redacted]
-----------------+-------------------------------------------------
  Heterogeneity chi-squared =  [redacted]
  Test of RR=[redacted]
```

No significant heterogeneity.

[5] Statistical significance is observed by the range of the CI (if it is greater or less than one without overlapping).

Non fatal PE

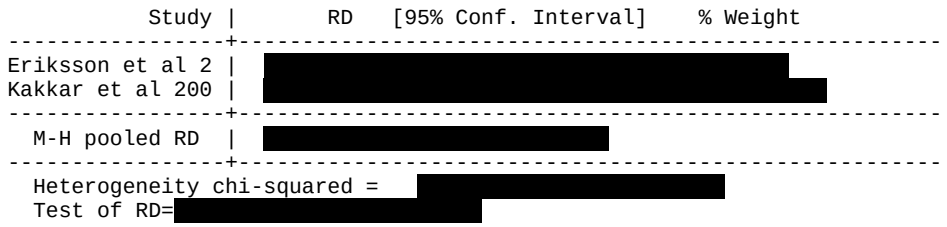
RD - Fixed-effects model:



No significant heterogeneity.

Fatal PE

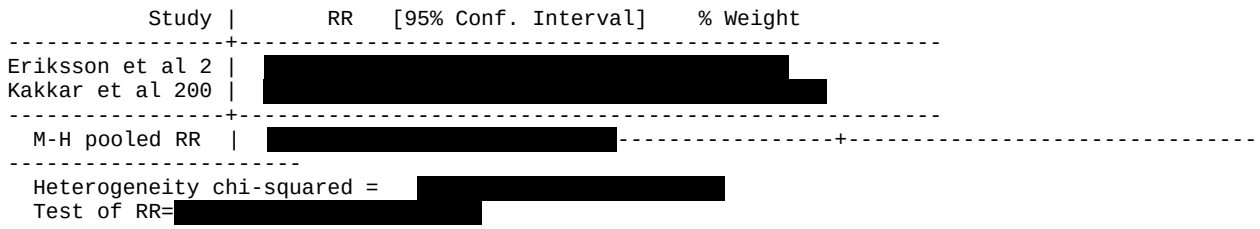
RD - Fixed-effects model:



No significant heterogeneity.

Major bleeding

RR - Fixed-effects model:



No significant heterogeneity.

TKR

Table 20 presents the results of the meta-analysis. The results of the statistical analysis match the measures of difference used in the economic evaluation; RR for VTE, symptomatic VTE and major bleeding, and RD for PE events. Each comparison consisted of one fixed effects model. If heterogeneity is observed between studies, a random effects model is used.

Details of the analysis of each outcome are presented below the table.

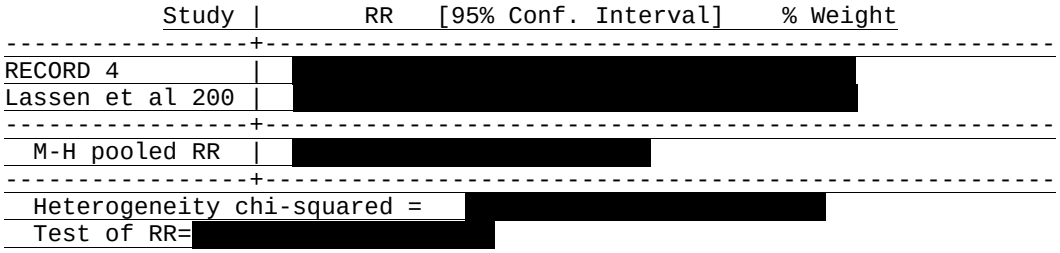
Table 20 TKR results rivaroxaban vs. enoxaparin (RECORD 3 and RECORD 4 pooled)

Outcome	RR (95% CI)	RD (%) (95% CI)
VTE		
Symptomatic VTE		
Non fatal PE		
Fatal PE		
Major bleeding		

Details of meta-analysis for each outcome:

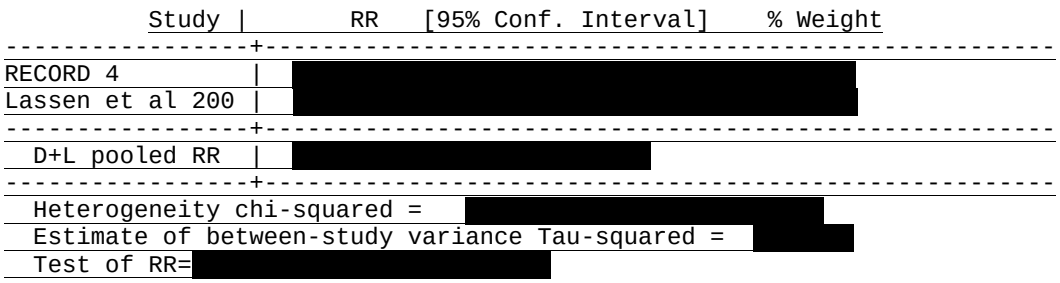
VTE

RR Fixed-effects model:



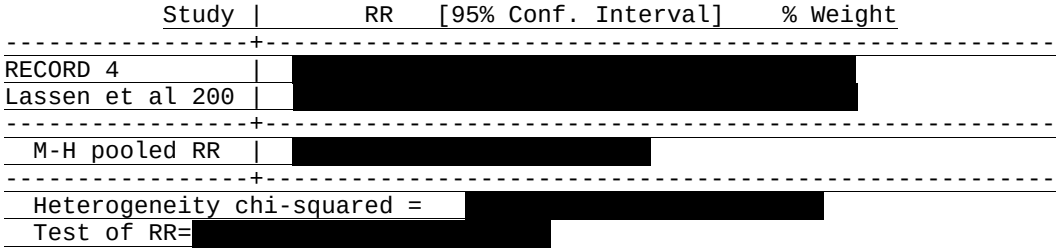
No significant heterogeneity

RR Random-effects model:



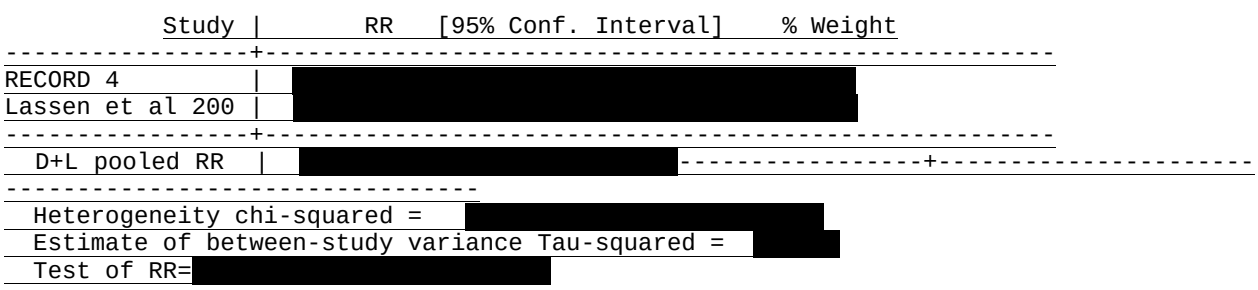
Symptomatic VTE

RR Fixed-effects model:



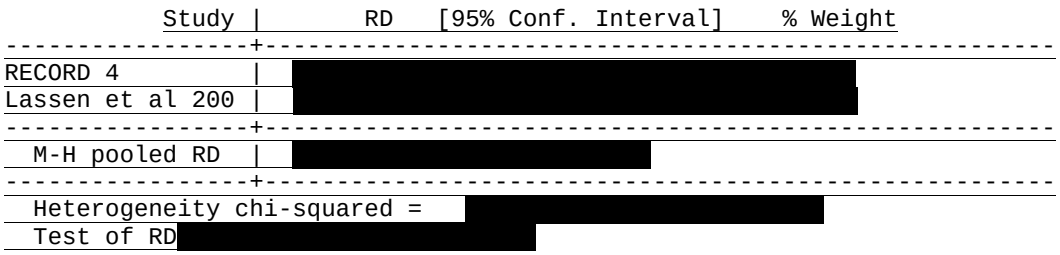
No significant heterogeneity

RR Random-effects model:



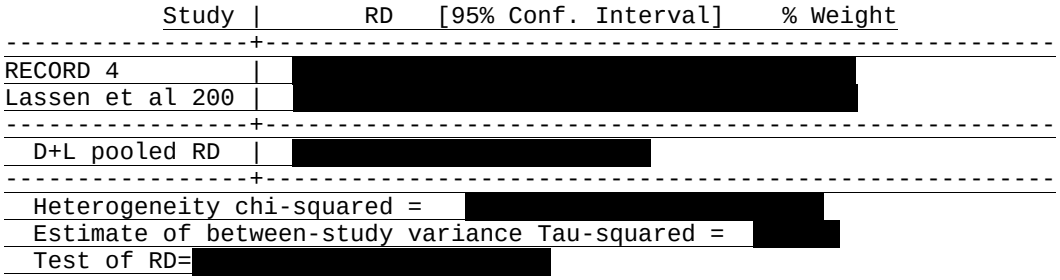
Non-fatal PE

RD Fixed-effects model:



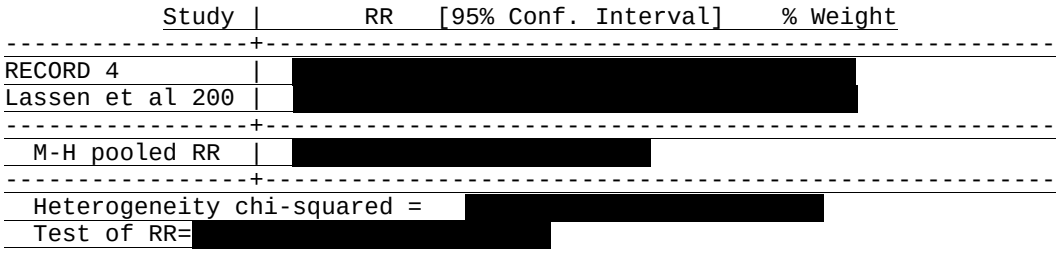
No significant heterogeneity

RD Random-effects model:



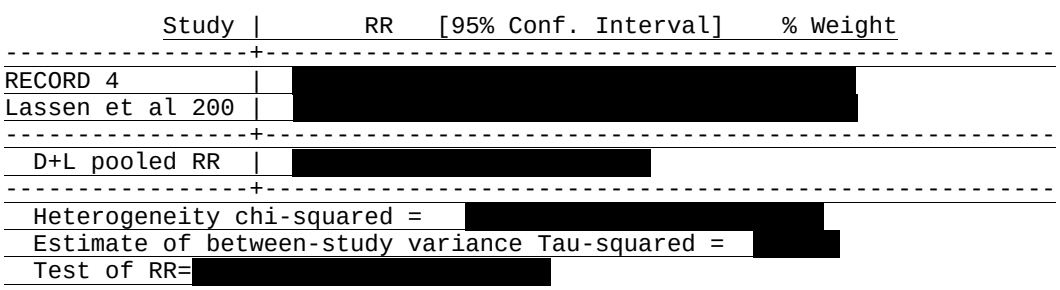
Major bleeding

RR Fixed-effects model:



No significant heterogeneity

RR Random-effects model:



6.6 Indirect/mixed treatment comparisons

The RECORD programme of studies utilised enoxaparin as the main comparator. LMWH is the main treatment currently used for the prevention of VTE in patients undergoing major orthopaedic surgery in the UK(8) and market research indicates enoxaparin is the most widely prescribed LMWH in orthopaedic departments in the UK(9).

Of the treatments recommended by NICE, LMWHs are the most commonly used (>98%), the market share of fondaparinux in orthopaedic departments is less than 2% and therefore will not be considered in the submission as this does not typically reflect routine clinical practice(9).

While preparing this submission, it was noted that a new oral thromboprophylactic called dabigatran etexilate received European marketing approval (March 2008) and was launched in the UK (April 2008). This was approved by NICE in September 2008. In light of the recent approval of dabigatran etexilate, it was considered appropriate to also carry out a comparison of rivaroxaban against dabigatran etexilate as a sensitivity analysis.

Due to lack of head-to-head clinical trial data between rivaroxaban and dabigatran an indirect comparison was employed. The comparator in the dabigatran studies in orthopaedic indications was also enoxaparin(26;27). The indirect comparison is performed by employing the adjusted indirect comparison method by Bucher and colleagues (1997), and using enoxaparin as the common comparator. The results of this analysis are presented below and have been used as a sensitivity analysis in the economic evaluation.

Dabigatran: Clinical Evidence

Dabigatran was included as a search term in the systematic review of the literature, carried out for this submission (see Appendix 2). In the systematic review, there were two sources of data identified for the use of dabigatran in elective major orthopaedic surgery, which could be used in the indirect comparison (RE-MODEL study & RENOVATE study). Since the systematic review a further study (RE-MOBILZE) has been published on-line(28). This has yet to be printed and therefore may be subject to revision.

1. **Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial(27)**

2. **Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial (RENOVATE)(26)**

3. **The oral thrombin inhibitor dabigatran etexilate vs the North American Enoxaparin Regimen for the prevention of venous thromboembolism after knee arthroplasty surgery (RE-MOBILIZE)(28)**

The rivaroxaban and dabigatran studies in total hip and knee replacement were similar in design – both randomised, controlled, double-blind studies, using enoxaparin subcutaneously as the control, with similar outcomes measured. Baseline demographics were also similar.

Key differences between the studies include (see Tables 21 to 23 for dabigatran data):

- RE-MODEL and RE-NOVATE did not involve patients from the USA and all dabigatran studies did not involve any patients from Asia [RECORD 1, 2 and 4 included patients from the USA. RECORD 2, 3 and 4 included patients from Asia]
- Efficacy and safety of drug treatment was tested in an overall greater number of patients receiving rivaroxaban (Total Hip Replacement n=3518; Total Knee Replacement n=2838) at a fixed dose of 10mg od. Dabigatran was assessed at two dose levels (220mg/day and 150mg/day). In the Total Hip replacement study 1157 patients received dabigatran 220mg daily and 1174 patients received dabigatran 150mg daily. Across the Total Knee Replacement studies, 1556 patients were treated with dabigatran 220mg daily and 1585 patients received 150mg dabigatran daily.
- Rivaroxaban was given for 35 days in Total Hip Replacement, whereas dabigatran was given for 28-35 days.

- Rivaroxaban was given for 12±2 days as thromboprophylaxis in Total Knee Replacement whereas dabigatran was given for 6-10 days in the RE-MODEL study and 12-15 days in the RE-MOBILIZE study.
- Across the Total Hip Replacement studies enoxaparin was given at the standard UK dose (40mg sc od) whereas for total knee replacement one study each of rivaroxaban and dabigatran employed UK enoxaparin doses (RECORD 3 and RE-MODEL) and one study each employed US enoxaparin dosing (RECORD 4 and RE-MOBILIZE).
- Enoxaparin was first given post-operatively in RE-MOBILIZE and pre-operatively in all other dabigatran and rivaroxaban studies. Therefore across the dabigatran studies, only 68% received enoxaparin in the same manner (i.e. pre-operatively) as those in the rivaroxaban studies.
- Patients entering the dabigatran studies were required to weigh > 40kg.
- Dabigatran was given at half the normal dose level (75mg or 110mg) 1-4 hours postoperatively (i.e. day 1), whereas rivaroxaban was given at its usual fixed dose of 10mg on day 1.
- When reviewing the results for the two treatments, the efficacy event rates are higher in the dabigatran/enoxaparin studies than they are in RECORD studies, in particular for the primary efficacy outcome and symptomatic VTE. This is with the exception of enoxaparin event rates in RECORD 2, where rates for the primary outcome are highest for enoxaparin. This may be explained by the fact that enoxaparin was only administered for up to 14 days in RECORD 2 (vs 28-25 days in dabigatran RE-NOVATE study and 35 days in RECORD 1), in an indication (hip replacement) where extended prophylaxis is now demonstrated to be more effective.
- Major bleeding rates were higher in the dabigatran / enoxaparin studies than observed in the rivaroxaban / enoxaparin RECORD studies.
- In all studies, rivaroxaban showed superior efficacy to enoxaparin for the primary composite endpoint. It was also shown to be superior for secondary endpoints of major VTE in RECORD 1, 2, and 3 and for symptomatic VTE in RECORD 2 and 3. Dabigatran, on the other hand, was only demonstrated to be non-inferior to enoxaparin in RE-NOVATE and RE-MODEL and in the RE-MOBILIZE study was inferior to enoxaparin.

Table 21 – Methods – DABIGATRAN RCTs

Study	Indication	Study Design	Study Sites	Recruitment & follow-up period	Interventions	Patient numbers (randomised) (see also Figures 8 to 10)
RE-NOVATE (26)	TOTAL HIP REPLACEMENT	prospective, randomised, double-blind, non-inferiority, active controlled multicentre phase III study	Europe; Australia; South Africa;	Patients were enrolled between December 2004 and April 2006. The maximum duration of the study including follow-up was 450 days from enrolment.	• Dabigatran 220mg od (day 1 to 35) plus placebo syringe (day 0 to day 28-35)* • Dabigatran 150mg od (day 1 to 35) plus placebo syringe (day 0 to day 28-35)* • enoxaparin 40mg sc od (day 0 to 35) plus placebo tablet (day 1 to day 28-35) [day 0 is the day before surgery]	n=3494 dabigatran 220mg n=1157 dabigatran 150mg n=1174 enoxaparin n=1162
RE-MODEL (27)	TOTAL KNEE REPLACEMENT			Patients were enrolled between November 2004 and March 2006. Duration of study including follow-up not reported.	• Dabigatran 220mg od (day 1 to day 6-10) plus placebo syringe (day 0 to day 6-10)* • Dabigatran 150mg od (day 1 to day 6-10) plus placebo syringe (day 0 to day 6-10)* • enoxaparin 40mg sc od (day 0 to day 6-10) plus placebo tablet (day 1 to day 6-10) [day 0 is the day before surgery]	n=2101 dabigatran 220mg n=694 dabigatran 150mg n=708 enoxaparin n=699
RE-MOBILIZE (28)			United States, Canada, Mexico, UK	Patients were enrolled between November 2004 and June 2006. Duration of study including follow-up not reported.	• Dabigatran 220mg od (day 1 to day 12-15) plus placebo syringe (day 0 to day 12-15)* • Dabigatran 150mg od (day 1 to day 12-15) plus placebo syringe (day 0 to day 12-15)* • enoxaparin 30mg sc bid (day 1 to day 12-15) plus placebo tablet (day 1 to day 12-15) [day 0 is the day before surgery]	n=2615 dabigatran 220mg n=862 dabigatran 150mg n=877 enoxaparin n=876

* The first dabigatran dose was halved (110mg or 75mg)

Inclusion & Exclusion criteria – DABIGATRAN RCTs [Note – full study report not available](26;27)

Patients (males or females), aged ≥18 undergoing elective total hip replacement (RE-NOVATE) or elective total knee replacement (RE-MODEL, RE-MOBILIZE) were included in the studies. Patients were also required to weigh >40kg. Signed, informed consent.

Exclusion criteria included: any bleeding diathesis; history of acute intracranial disease or haemorrhagic stroke; major surgery, trauma, uncontrolled hypertension, or myocardial infarction in the past 3 months; gastrointestinal or urogenital bleeding, or ulcer disease in the past 6 months; severe liver disease; alanine or aspartate aminotransferase concentrations greater than two times the upper limit of the normal range in the past month; severe renal insufficiency (creatinine clearance less than 30 mL/min); use of long-acting non-steroidal anti-inflammatory drugs (also contraindicated during treatment); childbearing potential; allergy to radiopaque contrast media or heparin; and active malignant disease. If spinal or epidural anaesthesia was done, less than three attempts or non-traumatic placement was required for patient eligibility.

Table 22 - Baseline characteristics – DABIGATRAN RCTs (safety population)

Study	Age (yrs)	Sex (female)	Weight (kg)	History of DVT or PE	Type of anaesthesia[#]			Duration of surgery (min)	Time to mobilisation (days)	Duration of initial hospital stay (days)**
					General	Combination	Neuraxial alone			
RE-NOVATE (26)	D220 =65 (10) D150 =63 (11) E=64 (11)	D220=636 (56%) D150=667 (57%) E=651 (56%)	D220 =79 (15) D150 =79 (15) E=78 (15)	D220=40 (3%) D150=29 (2%) E=30 (3%)	D220=293 (26%) D150=276 (24%) E=278 (24%)	D220=95 (8%) D150=110 (10%) E=90 (8%)	D220=746 (66%) D150=766 (66%) E=773 (68%)	D220 =85 (29) D150 =85 (29) E=87 (29)	Not Reported	D220 =9 (7-12) D150 =9 (7-12) E=9 (7-12)
RE-MODEL (27)	D220 =67 (9) D150 =68 (9) E=68 (9)	D220=441 (65%) D150=451 (64%) E=478 (69%)	D220 =82 (15) D150 =83 (15) E=82 (15)	DVT R=30 (3.6%) E=25 (2.8%) PE R=7 (0.8%) E=6 (0.7%)	D220=149 (22%) D150=167 (24%) E=152 (22%)	D220=195 (29%) D150=204 (29%) E=202 (30%)	D220=331 (49%) D150=325 (47%) E=330 (48%)	D220 =91 (28) D150 =91 (30) E=90 (28)	Not Reported	Not Reported
RE-MOBILIZE (28)	D220 =66.2 (9.5) D150 =65.9 (9.5) E=66.3 (9.6)	D220=486 (56.7%) D150=507 (58.2%) E=504 (58.1%)	D220 =88.4 (19.1) D150 =87.6 (20) E=88 (19.2)	Not reported	D220=453 (52.9%) D150=470 (54%) E=449 (51.7%)	Not reported	Spinal D220=397 (46.3%) D150=399 (45.8%) E=412 (47.5%)	D220 =91 (28) D150 =91 (30) E=90 (28)	Not Reported	Not Reported

Data are mean (SD) or n (%) unless otherwise specified; D=dabigatran; E=enoxaparin; [#] Patients may have had more than one type of anaesthetic; ** Data are median

In each study, there were no notable differences between the two treatment groups with respect to demographic and baseline characteristics.

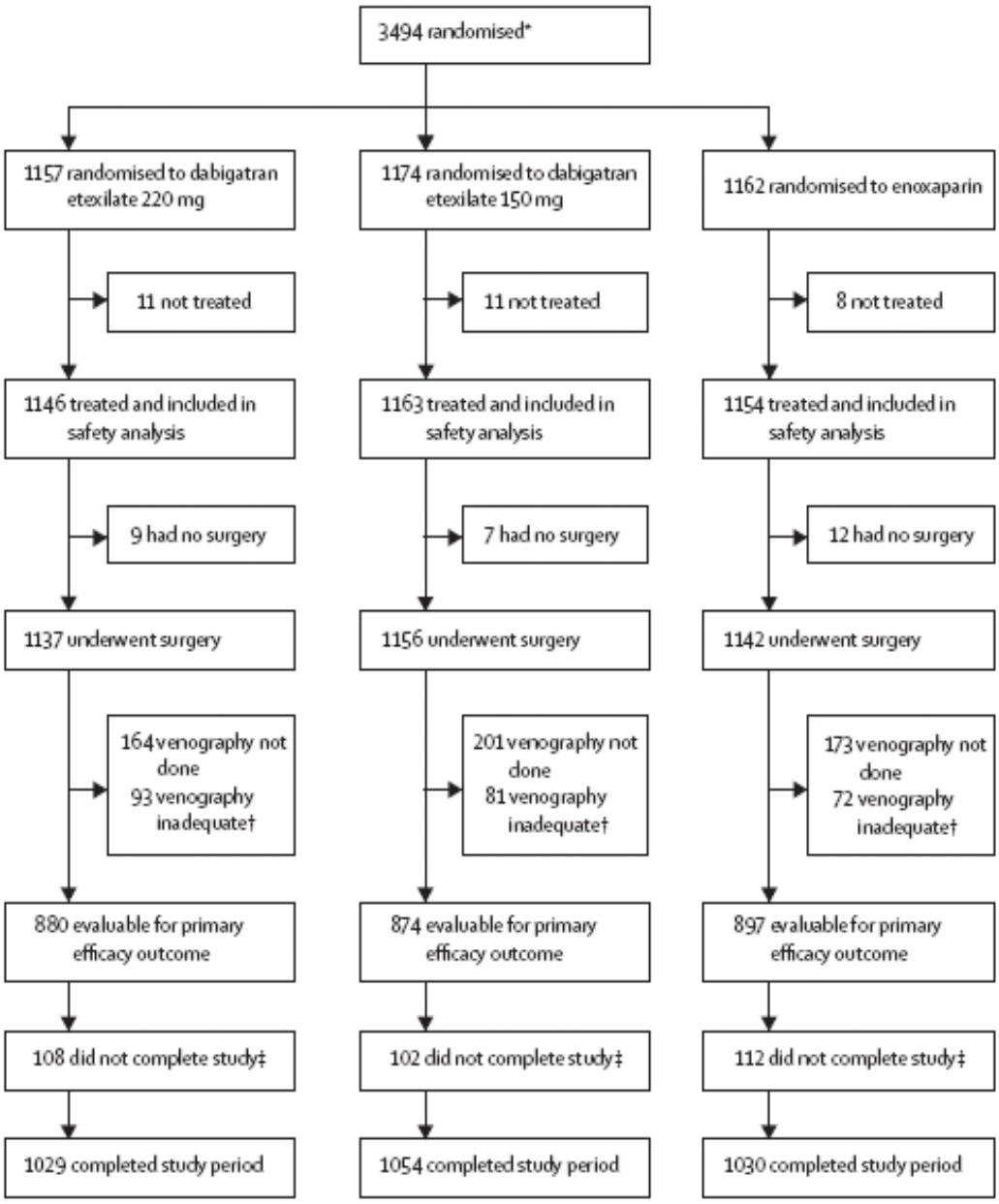
Outcomes

The main (primary) outcome in the dabigatran studies is the same as the primary efficacy outcome in the rivaroxaban RCTs, as is the main secondary outcome 'Major VTE'. Information on all outcomes measured is not available in the dabigatran publications accessible to the public.

Critical appraisal of relevant RCTs (DABIGATRAN)

Allocation was concealed in the dabigatran studies. Patients were randomly assigned to one of three treatment groups, using a computer-generated central scheme stratified by study centre. Randomisation was performed in blocks of six. A justification of sample size was provided and follow-up of patients was deemed to be adequate. Diagnostic tests for venous thromboembolic events were initially assessed locally, then by an independent central adjudication committee blinded to treatment allocation. The results of the independent committee were used in the primary analysis. The study was of a parallel group design with no crossover. The RE-NOVATE and RE-MODEL studies were carried out at centres in Europe, Australia, and South Africa. RE-MOBILIZE was performed in centres from the United States, Canada, Mexico and the UK. It is not reported in the RE-NOVATE and RE-MODEL publications whether there were any participants from the UK or whether there is likely to be a location effect in relation to the decision problem. The dosage of dabigatran used in the study is as described on the Summary of Product Characteristics. In RE-NOVATE and RE-MODEL studies, enoxaparin dosing is as per standard practice & licenced dosage in UK .The RE-MOBILIZE study uses enoxaparin dosing based on common practice in the United States and different to that recommended in the UK. Study groups were comparable and the statistical analyses adequate. Efficacy analyses were done by modified intention-to-treat (MITT). The only apparent confounding factors is the non-standard (to the UK) dosage of enoxaparin used in the RE-MOBILIZE study.

Figure 8 RE-NOVATE study – Patient numbers



*119 patients were not randomised to treatment since they did not meet the inclusion or exclusion criteria (n=25), withdrew informed consent (n=53), experienced an adverse event before randomisation (n=3), or due to other reasons (n=38). †Venography was considered adequate by the central adjudication committee if films were provided that visualised the proximal and distal deep veins in both legs. If deep-vein thrombosis was seen in any one of the veins visualised, the patient was considered to be suitable for the efficacy outcome even if the venous system was not visualised entirely. ‡The main reasons for premature study discontinuation included consent withdrawal, adverse events, and non-compliance with protocol.

Figure 9 RE-MODEL study – Patient numbers

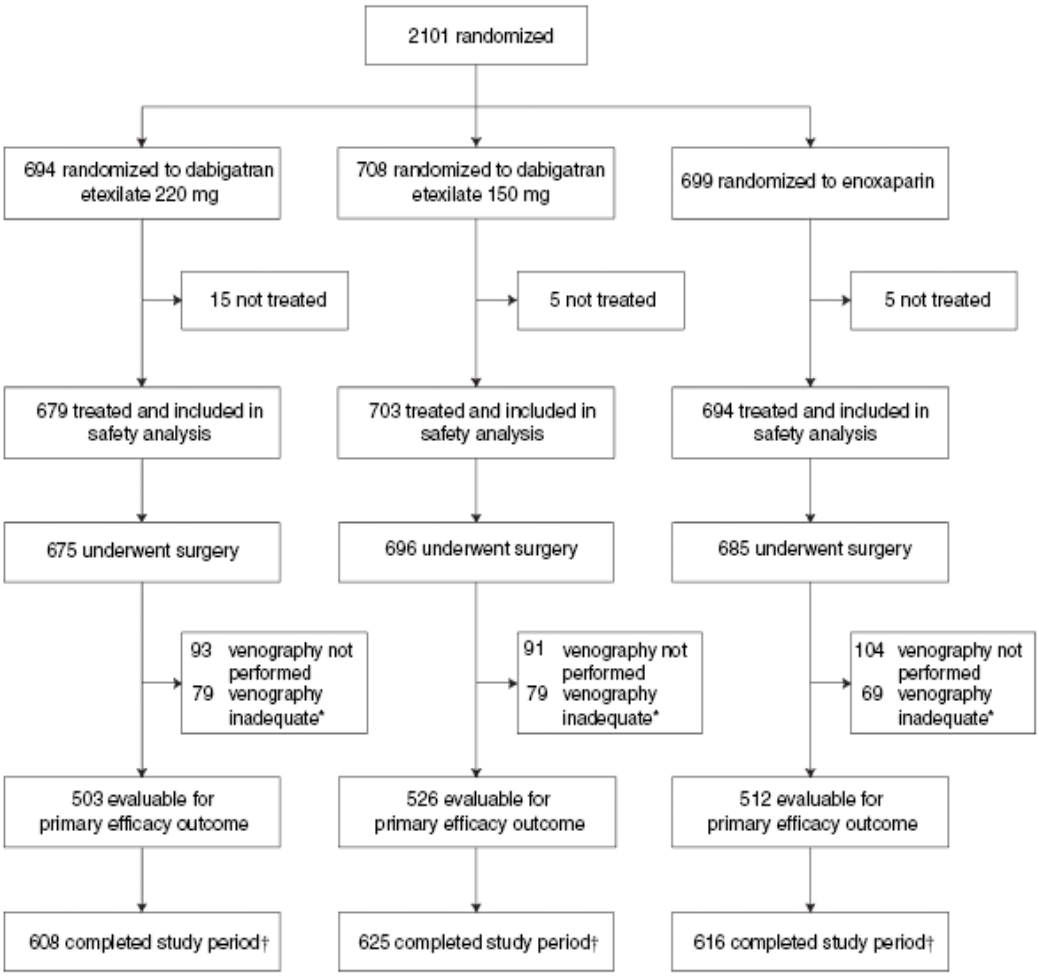
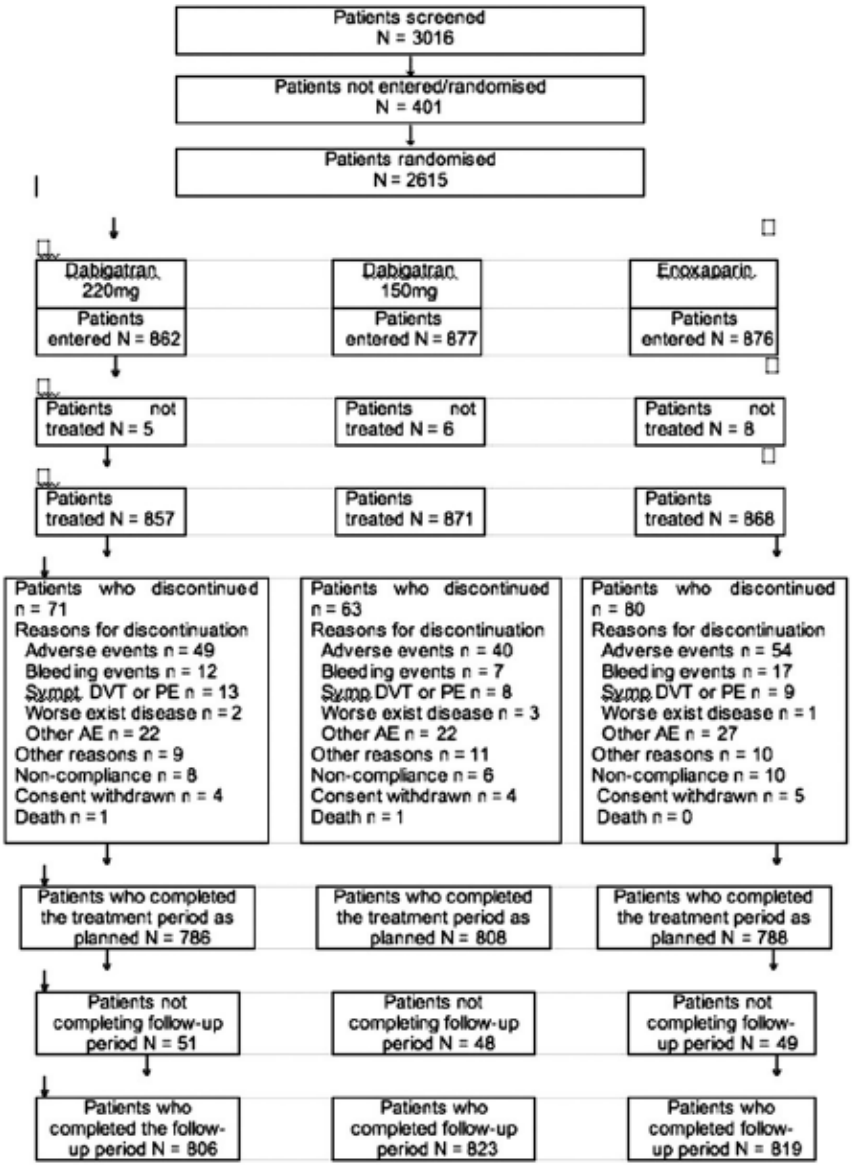


Fig. 1. Randomization and progression of patients in the trial. *Venography was considered adequate by the central adjudication committee if films were provided visualizing the proximal and distal deep veins in both legs. If deep vein thrombosis was seen in any one of the veins visualized, the patient was considered to be suitable for the efficacy outcome even if the venous system was not visualized entirely. †The main reasons for premature study discontinuation included consent withdrawal, adverse events, and non-compliance with protocol.

Figure 10 RE-MOBILIZE study - patient numbers



Outcomes – DABIGATRAN RCTs

Table 23: Incidence of components of composite primary efficacy endpoint & reported secondary outcomes

	RENOVATE(26)			**RE-MODEL(27)**			**RE-MOBILIZE (28)**		
	Dabigatran 220mg n (%)	Dabigatran 150mg n (%)	Enoxaparin 40mg od n(%)	Dabigatran 220mg n (%)	Dabigatran 150mg n (%)	Enoxaparin 40mg od n(%)	Dabigatran 220mg n (%)	Dabigatran 150mg n (%)	Enoxaparin 30mg bid n(%)
Composite primary efficacy endpoint									
Any event (Total VTE & all-cause mortality)	**53/880 (6) [4.5%,7.6%]** **Abs Diff vs Enox -0.7% [-2.9,1.6%] p<0.0001**	**75/874 (8.6) [6.7%,10.4%]** **Abs Diff vs Enox 1.9% [-0.6,4.4%] p<0.0001**	**60/897 (6.7) [5.1%,8.3%]**	**183/503 (36.4) [32.2,40.6%]** **Abs diff vs enox -1.3% [-7.3,4.6%] p=0.0003**	**213/526 (40.5) [36.3,44.7%]** **Abs diff vs enox 2.8% [-3.1,8.7%] p=0.017**	**193/512 (37.7) [33.5,41.9%]**	**188/604 (31.1)** **P=0.234**	**219/649 (33.7)** **P=0.0009**	**163/643 (25.3)**
Proximal and / or distal DVT*	40/874 (4.6)	63/871 (7.2)	56/894 (6.3)	181/503 (36)	208/524 (39.7)	184/511 (36)			
Proximal DVT	18/905 (2.0)	28/885 (3.2)	32/914 (3.5)	13/506 (2.6)	18/525 (3.4)	16/510 (3.1)	14/604 (2.3)	20/649 (3.1)	10/643 (1.6)
Distal DVT	22/874 (2.5)	35/871 (4.0)	24/894 (2.7)	168/503 (33.4)	190/524 (36.3)	168/511 (32.9)	167/604 (27.6)	198/649 (30.5)	148/643 (23.0)
Non Fatal PE							6/604 (1)	0 (0)	5 (0.8)
Symptomatic DVT*	**6/1137 (0.5)**	**9/1156 (0.8)**	**1/1142 (0.1)**	**1/675 (0.1)**	**3/696 (0.4)**	**8/685 (1.2)**	**7**	**6**	**5**
Symptomatic PE*	**5/1137 (0.4)**	**1/1156 (0.1)#**	**3/1142 (0.3)**	**0/675 (0)**	**1/696 (0.1)**	**1/685 (0.1)#**	**6**	**0**	**5**
Death	**3/1137 (0.3)+**	**3/1156 (0.3)+#**	**0/1142 (0)**	**1/675 (0.1)**	**1/696 (0.1)*** **	**1/685 (0.1)#**	**1 (0.2)*** * **0 (0)##**	**0 (0)*** * **1 (0.2)##**	**0 (0)*** * **0 (0)##**
Major VTE & VTE-related mortality*** **	**28/909 (3.1) [2.0%,4.2%]** **Abs diff vs enox -0.8% [-2.5,0.8%] p=0.33**	**38/888 (4.3) [2.9%,5.6%]** **Abs diff vs enox 0.4% [-1.5,2.2%] p=0.71**	**36/917 (3.9) [2.7,5.2%]**	**13/506 (2.6) [1.2,3.9%]** **Abs diff vs enox -1.0% [-3.1,1.2%] p=0.38**	**20/557 (3.8) [-2.0,2.6%]** **Abs diff vs enox 0.3 [-2.0,2.6%] p=0.82**	**18/511 (3.5) [1.9,5.1%]**	**21/618 (3.4)** **Abs diff vs enox 1.2% [-0.7,3.0%] p=0.21**	**20/656 (3)** **Abs diff vs enox 0.8% [-0.9,2.5%] p=0.36**	**15/668 (2.2)**
Symptomatic DVT, PE or death during follow-up	**1∞**	**1∞**	**1∞**	**0.6%**	**0.4%**	**0.3%**	**5**	**6**	**6**

* Includes events that occurred within 3 days of last dose of study medication. Patients could have events included in more than one category.
#Fatal pulmonary embolism, same patient. +Venous thromboembolism could not be excluded in one patient in the dabigatran etexilate 220mg group and two patients in the dabigatran etexilate 150mg group. **Includes proximal DVT and PE. ***Includes all deaths where VTE cannot be excluded. ##Death not associated with VTE. ∞ Deaths in follow-up not reported.

Methods

The adjusted indirect comparison(44) (Bucher et al. 1997) derives the indirect estimates by comparing the effects of each treatment versus the common comparator, and therefore retains the benefits of randomisation from the original trial data.

The analysis is performed on the summary statistics of the direct comparisons as reported from the clinical trials (rivaroxaban vs enoxaparin, dabigatran vs enoxaparin).

For the relative risk (RR), the logRR derived from the direct comparisons and their variances is used. This is done on the log scale as the transformation makes these quantities asymptotically normally distributed and statistically independent.

The estimate of the treatment effect is then obtained by calculating the difference between the two log relative risks (RR):

Equation 1 Diff = ln RR (rivaxoraban) – ln RR (dabigatran)

And as the two logRR are independent, the standard error of this estimated effect is calculated as follows:

Equation 2 $SE(Diff) = [Var(\ln RR\ rivaxoraban) + Var(\ln RR\ dabigatran)]^{1/2}$

and the 95% confidence interval is derived as:

Equation 3 Diff ± 1.96*SE(Diff)

Back transformations of these quantities give the RR for the indirect comparison and its 95% confidence interval.

The same method is applied for the indirect comparison of the risk difference (RD). However, no log-transformation is needed and the calculations are performed on the original scale.

Statistical significance of the outcome is observed by the range of the confidence interval:

- If it crosses 1 for RR
- If it crosses 0 for RD.

Meta-analysis of dabigatran trials

The meta-analysis of RECORD trials is presented in the beginning of section 6.5. In order to perform the indirect comparison, a meta-analysis was also conducted on the available dabigatran trials (see tables 24-25). Details of the analysis of each outcome are presented below the tables.

Table 24 Dabigatran trials meta-analysis (RE-NOVATE, RE-MODEL and RE-MOBILIZE)

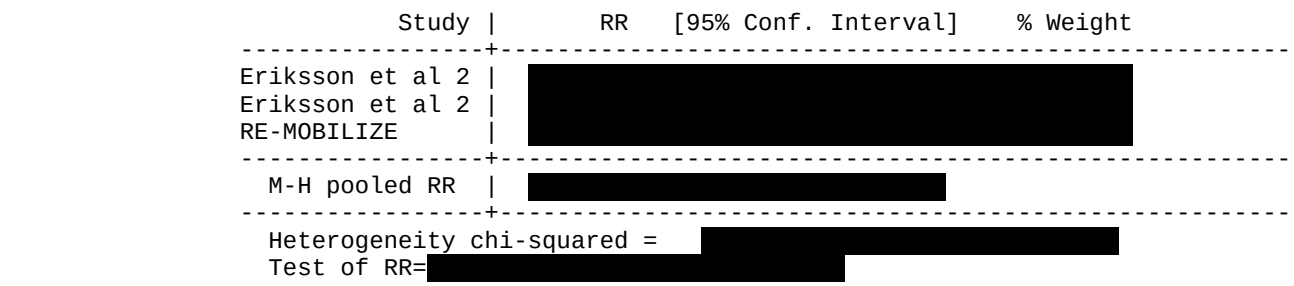
Outcome	RR (95% CI)	RD (%) (95% CI)
VTE	[redacted]	
Total DVT	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		[redacted]
Major bleeding	[redacted]	

*Random effects model

Details of meta-analysis for each outcome:

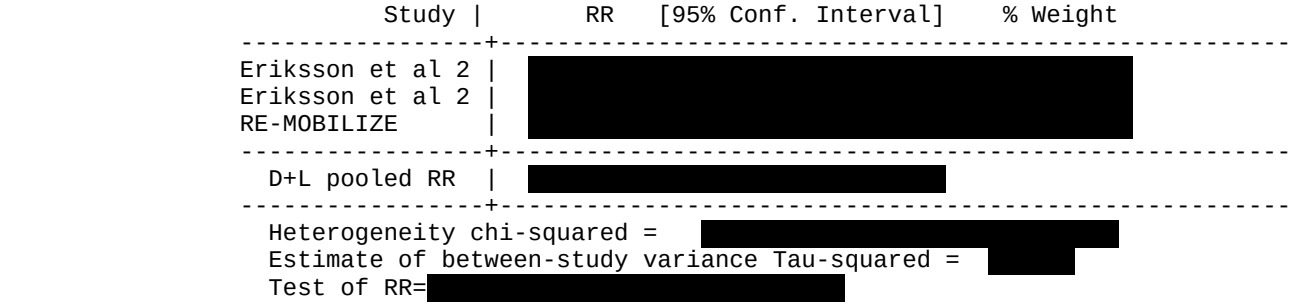
VTE

RR - Fixed-effects model:



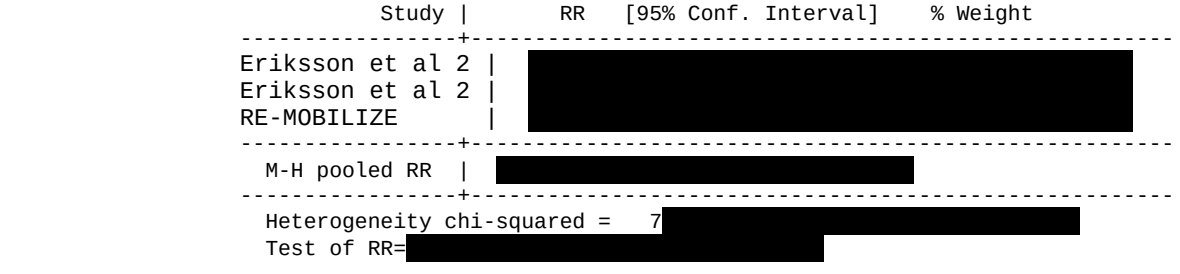
No significant heterogeneity.

RR - Random-effects model:



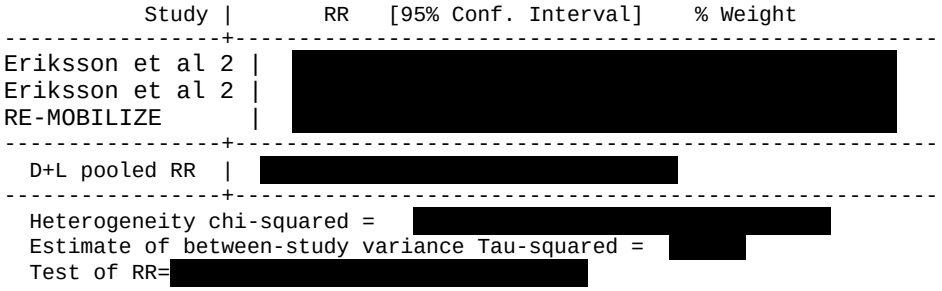
Symptomatic VTE

RR - Fixed-effects model:



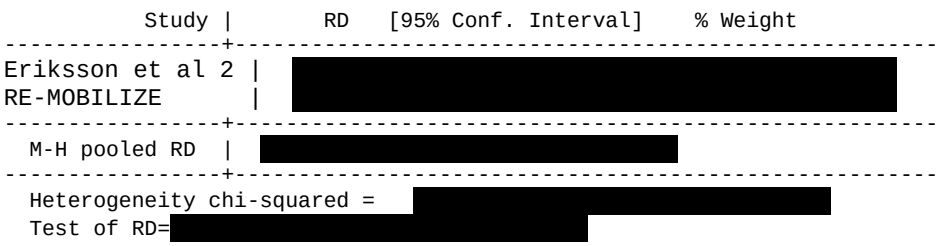
There is significant heterogeneity between studies, therefore a random-effects model is more appropriate.

RR - Random-effects model:



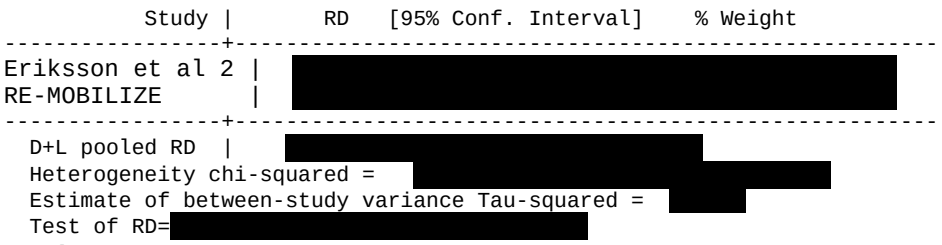
Non-fatal PE

RD - Fixed-effects model:



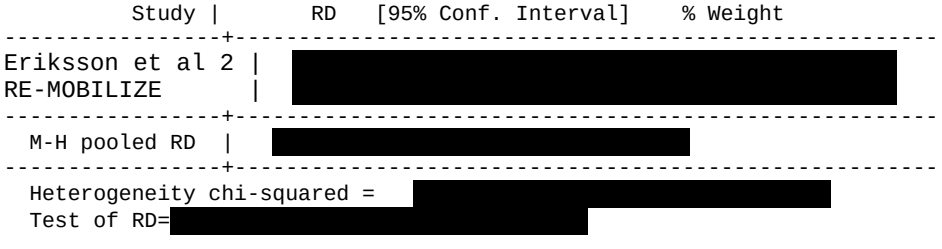
No significant heterogeneity.

RD - Random-effects model:



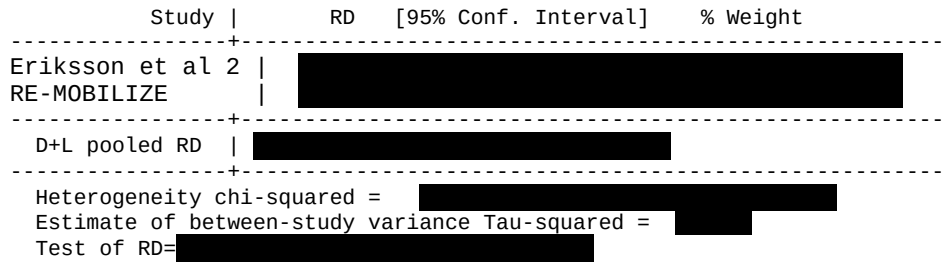
Fatal PE

RD - Fixed-effects model:



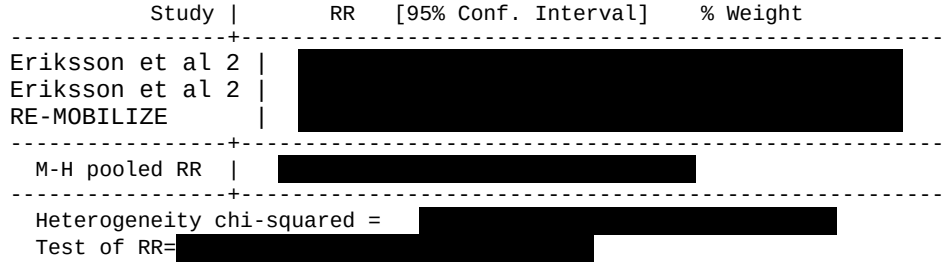
No significant heterogeneity.

RD - Random-effects model:



Major bleeding

RR - Fixed-effects model:



No significant heterogeneity.

RR - Random-effects model:

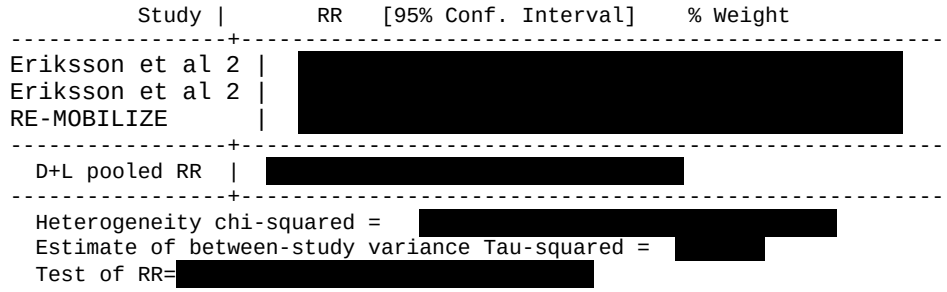


Table 25 Dabigatran TKR meta-analysis (RE-MODEL and RE-MOBILIZE)

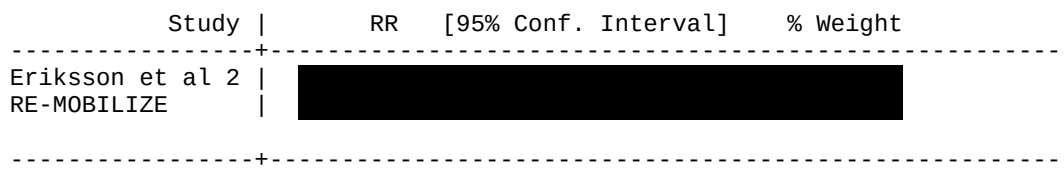
Outcome	RR (95% CI)	RD (%) (95% CI)
VTE		
Symptomatic VTE		
Non fatal PE		
Fatal PE		
Major bleeding		

* Random-effects model

Details of meta-analysis for each outcome:

VTE

RR Fixed-effects model:



```
  M-H pooled RR  |
-----------------+------------------------------------------------------
  Heterogeneity chi-squared =
  Test of RR=
```

There is significant heterogeneity between studies, therefore a random-effects model is more appropriate.

RR Random-effects model:

```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+------------------------------------------------------
Eriksson et al 2 |
RE-MOBILIZE      |
-----------------+------------------------------------------------------
  D+L pooled RR  |
-----------------+------------------------------------------------------
  Heterogeneity chi-squared =
  Estimate of between-study variance Tau-squared =
  Test of RR=
```

Symptomatic VTE

RR Fixed-effects model:

```
          Study |       RR   [95% Conf. Interval]    % Weight
-----------------+------------------------------------------------------
Eriksson et al 2 |
RE-MOBILIZE      |
-----------------+------------------------------------------------------
  M-H pooled RR  |                 -----------------+---------
-----------------------------------------------
  Heterogeneity chi-squared =
  Test of RR=
```

No significant heterogeneity.

RR Random-effects model:

```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+------------------------------------------------------
Eriksson et al 2 |
RE-MOBILIZE      |
-----------------+------------------------------------------------------
  D+L pooled RR  |
-----------------+------------------------------------------------------
  Heterogeneity chi-squared =
  Estimate of between-study variance Tau-squared =
  Test of RR=
```

Fatal PE

RD Fixed-effects model:

```
           Study |       RD   [95% Conf. Interval]    % Weight
-----------------+------------------------------------------------------
Eriksson et al 2 |
RE-MOBILIZE      |
-----------------+------------------------------------------------------
  M-H pooled RD  |
-----------------+------------------------------------------------------
  Heterogeneity chi-squared =
  Test of RD=
```

No significant heterogeneity.

RD Random-effects model:

```
           Study |       RD   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Eriksson et al 2 |
RE-MOBILIZE      |
-----------------+-------------------------------------------------------
  D+L pooled RD  |
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =
  Estimate of between-study variance Tau-squared =
  Test of RD=
```

Major bleeding

RR Fixed-effects model:

```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Eriksson et al 2 |
RE-MOBILIZE      |
-----------------+-------------------------------------------------------
  M-H pooled RR  |
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =
  Test of RR=
```

No significant heterogeneity.

RR Random-effects model:

```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Eriksson et al 2 |
RE-MOBILIZE      |
-----------------+-------------------------------------------------------
  D+L pooled RR  |
-----------------+-------------------------------------------------------
  Heterogeneity chi-squared =
  Estimate of between-study variance Tau-squared =
  Test of RR=
```

Indirect comparison

The pooling of RECORD and dabigatran studies allows the use of meta-regression analysis for these indirect comparisons, along the lines of Thompson and Sharp (1999)(45). Analyses were run in Stata SE version 8.1, using the command *metareg*.

This approach extends a random-effects meta-analysis to estimate the degree to which one or more covariates account for differences between treatment effects. In the case of an indirect comparison, type of treatment is one of these covariates. In this analysis, no other covariates were considered.

The regression model used by *metareg* relates the treatment effect to the study-level covariates, assuming a normal distribution for the residual errors with both a within-study and an additive between-studies component of variance, denoted τ^2. While the within-study variance or standard error is supplied by the user, τ^2 is estimated either by an iterative procedure, using an estimate which is based on one of restricted maximum likelihood method. This estimated between-studies variance τ^2 is a measure of the residual heterogeneity having adjusted for the covariates.

As with the previous method, analyses were run on RRs for VTE, symptomatic VTE and bleeding, and RDs for PE. An estimate of the differences between rivaroxaban and its comparators is reported for each model, as well as a ninety-five percent two-sided confidence interval and a p-value.

Results

In the comparison with RECORD 1, VTE and symptomatic VTE events were associated with a [redacted] and [redacted] relative risk reduction (RRR), respectively, for patients treated with rivaroxaban versus dabigatran when undergoing THR surgery (Table 26). In the comparison with RECORD 2, VTE and symptomatic VTE events were associated with a [redacted] and [redacted] RRR, respectively, for patients treated with rivaroxaban versus dabigatran (Table 27). In the comparison with RECORD 3, rivaroxaban was associated with [redacted] RRR of VTE events versus dabigatran (Table 28). In the comparison where all data are included for both agents (meta-regression); rivaroxaban was associated with [redacted] RRR of VTE events (Table 29). In the comparison that includes RECORD 1, RECORD 2 and RE-NOVATE (meta-regression); rivaroxaban was associated with [redacted] RRR of VTE events against dabigatran (Table 30). In the comparison that includes RECORD 3, RECORD 4, RE-MODEL and RE-MOBILIZE (meta-regression); rivaroxaban was associated with [redacted] RRR of VTE events against dabigatran (Table 31).

Table 26 Indirect comparison: RECORD 1 and RE-NOVATE

Outcome	RR (95% CI)	RD (%) (95% CI)
VTE	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		
Major bleeding	[redacted]	

Table 27 Indirect comparison: RECORD 2 and RE-NOVATE

Outcome	RR (95% CI)	RD (%) (95% CI)
VTE	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		
Major bleeding	[redacted]	

Table 28 Indirect comparison: RECORD 3 and RE-MODEL

outcome	RR (95% CI)	RD (%) (95% CI)
VTE	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		[redacted]
Major bleeding	[redacted]	

Table 29 Indirect comparison: all RECORD trials and all dabigatran trials

Outcome	RR (95% CI) and p-value	RD (%) (95% CI) and p-value
VTE	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		[redacted]
Major bleeding	[redacted]	

Table 30 Indirect comparison: RECORD 1, RECORD 2 and RE-NOVATE

Outcome	RR (95% CI) and p-value	RD (%) (95% CI) and p-value
VTE	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		
Major bleeding	[redacted]	

Table 31 Indirect comparison: RECORD 3, RECORD 4, RE-MODEL and RE-MOBILIZE

Outcome	RR (95% CI) and p-value	RD (%) (95% CI) and p-value
VTE	[redacted]	
Symptomatic VTE	[redacted]	
Non fatal PE		[redacted]
Fatal PE		[redacted]
Major bleeding	[redacted]	

6.7 Safety

Comprehensive evidence of the safety of rivaroxaban when compared with enoxaparin, a subcutaneous low molecular weight heparin, is provided by safety analyses and adverse event reporting from four large phase III, randomised, controlled trials (RECORD 1, RECORD 2, RECORD 3 and RECORD 4)(10-12;35-39). The design, methodologies, all clinical and safety endpoints and efficacy results from these studies are detailed in earlier in this section.

The total number of patients valid for the safety analyses from these studies was 12383 (n=6183 rivaroxaban; n=6200 enoxaparin). Results indicated a comparable safety profile of rivaroxaban to enoxaparin suggesting that the improved efficacy of rivaroxaban over enoxaparin outlined in Section 6.4 is not at the expense of an increased risk of bleeding or other adverse events. This is a key requirement for any new anticoagulant.

Table 32: Patients valid for safety analysis from phase III studies with rivaroxaban(10-12)

	Rivaroxaban 40mg po od		**Enoxaparin 40mg sc od**	
Treatment duration	**35 days**	**14 days**	**35 days**	**14 days**
Total Hip Replacement				
RECORD 1	2209		2224	
RECORD 2	1228			1229
Total Knee Replacement				
RECORD 3		1220		1239
RECORD 4		1526		1508
	Rivaroxaban		**Enoxaparin**	
Treatment duration	**35 days**	**14 days**	**35 days**	**14 days**
TOTAL patients	**3437**	**2746**	**2224**	**3976**

In all studies, the main safety endpoint - the incidence of treatment-emergent major bleeding - showed comparable rates for patients treated with rivaroxaban 10mg compared to enoxaparin 40mg(10-12;35). The rate of clinically relevant bleeding was similarly low between rivaroxaban and enoxaparin groups across all studies (see Table 33). Clinically relevant non-major bleeding and haemorrhagic wound complications (e.g. bleeding into joints) were also low and occurred in a similar number of patients in the two treatment groups. In RECORD 1 there was one fatal bleeding in the rivaroxaban group, however, the patient never actually received rivaroxaban treatment. One intraocular bleeding event (in a patient with Gaucher's disease and a history of intraocular bleeding) which resolved without discontinuation of study medication. Other surgical complications such as haematomas and seromas were also low across the two treatment groups(see Table 34).

In addition to bleeding as a safety endpoint, the incidences of cardiovascular events and adverse events were compared across the two treatments, rivaroxaban and enoxaparin. All adverse events were coded by MedDRA (Medical Dictionary for Regulatory Activities) version 10.0. Treatment-emergent adverse events were defined as those events starting after first application of double-blind study drug up to 2 days after cessation of double-blind study drug. As summarised in Table 35, the incidence of treatment-emergent adverse events including those that were considered to be treatment related was similar between the treatment groups(1;4;7;10-12). This was observed across all 4 RCTs. There was no evidence that rivaroxaban significantly increased cardiovascular adverse events. Wound-related infections were also similar across treatment groups.

In all 4 studies clotting parameters (eg PT, PiCT [prothrombinase-induced clotting time]) were affected as expected by the mode of action of rivaroxaban and there was no evidence of reactivation of coagulation after treatment cessation.

Table 33: Safety results from RECORD 1, 2, 3 and 4

	RECORD 1(10)			RECORD 2(11)			RECORD 3(12)			RECORD 4(35;36)		
	Rivaroxaban 10mg od 35±4 days n=2209 (%)	Enoxaparin 40mg od 35±4 days n=2224 (%)	p	Rivaroxaban 10mg od 35±4 days n=1228 (%)	Enoxaparin 40mg od 12±2 days n=1229 (%)	p	Rivaroxaban 10mg od 12±2 days n=1220 (%)	Enoxaparin 40mg od 12±2 days n=1239 (%)	p	Rivaroxaban 10mg od 12±2 days n=1526 (%)	Enoxaparin 30mg bid 12±2 days n=1508 (%)	p
Any bleeding	**133 (6)**	**131 (5.9)**	**0.94**	**81 (6.6)**	**68 (5.5)**	**0.25**	**60 (4.9)**	**60 (4.8)**	**0.93**	**160 (10.5)**	**142 (9.4)**	
Major bleeding*	**6 (0.3)**	**2 (0.1)**	**0.178**	**1 (0.1)**	**1 (0.1)**		**7 (0.6)**	**6 (0.5)**	**0.77**	**10 (0.7)**	**4 (0.3)**	**0.110**
Fatal	**1****	**0**		0	0		0	0		**1*****	**0**	
Into a critical organ	**1**	**0**		0	1		0	1		**1**	**2**	
Leading to re-operation	**2**	**1**		0	0		5	4		**4^**	**0**	
Leading to fall in haemoglobin§	**2**	**1**		1	0		1	0		**4^**	**0**	
Leading to transfusion of >2 units of blood§	**2**	**1**		1	0		1	0		**5**	**2****	
Non-major bleeding	**128 (5.8)**	**129 (5.8)**		**80 (6.5)**	**67 (5.5)**		**53 (4.3)**	**54 (4.4)**		**155 (10.2)**	**138 (9.2)**	
Clinically relevant non-major bleeding	65 (2.9)	54 (2.4)		40 (3.3)	33 (2.7)		33 (2.7)	28 (2.3)		**39 (2.6)**	**30 (2.0)**	
-Haemorrhagic wound complications#	34 (1.5)	38 (1.7)		20 (1.6)	21 (1.7)		25 (2.0)	24 (1.9)		[redacted]	[redacted]	
Other non-major bleeding	71 (3.2)	77 (3.5)		43 (3.5)	36 (2.9)		22 (1.8)	31 (2.5)		**124 (8.1)**	**112 (7.4)**	

* Major bleeding events could qualify for more than one sub-category **event occurred before intake of first active dose ***1 patient had fatal post-operative upper GI bleed and a fall in haemoglobin leading to transfusion ^all 4 patients had a fall in haemoglobin leading to transfusion
§extra-surgical-site bleeding #composite of excessive haematoma & surgical-site bleeding

Table 34: Incidence of haematomas and seromas in RECORD 1,2, 3 and 4

	RECORD 1(10)		RECORD 2(11)		RECORD 3(12)		RECORD 4(35)	
	Rivaroxaban 10mg od 35±4 days n=2209 (%)	Enoxaparin 40mg od 35±4 days n=2224 (%)	Rivaroxaban 10mg od 35±4 days n=1228 (%)	Enoxaparin 40mg od 12±2 days n=1229 (%)	Rivaroxaban 10mg od 12±2 days n=1220 (%)	Enoxaparin 40mg od 12±2 days n=1239 (%)	Rivaroxaban 10mg od 12±2 days n=1526 (%)	Enoxaparin 40mg od 12±2 days n=1508 (%)
Haematoma Haematoma evacuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Seroma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 35: Adverse events reports in RECORD 1,2, 3 and 4

	RECORD 1 (1;10)		RECORD 2(4;11)		RECORD 3(7;12)		RECORD 4(35;36)	
	Rivaroxaban 10mg od 35±4 days n=2209 (%)	Enoxaparin 40mg od 35±4 days n=2224 (%)	Rivaroxaban 10mg od 35±4 days n=1228 (%)	Enoxaparin 40mg od 12±2 days n=1229 (%)	Rivaroxaban 10mg od 12±2 days n=1220 (%)	Enoxaparin 40mg od 12±2 days n=1239 (%)	Rivaroxaban 10mg od 12±2 days n=1526 (%)	Enoxaparin 40mg od 12±2 days n=1508 (%)
Any Adverse Event (all)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**1319 (86.4)**	**1312 (87)**
On treatment	1413 (64.0)	1439 (64.7)	768 (62.5)	807 (65.7)	776 (63.6)	844 (68.1)	1222 (80.1)	1216 (80.6)
Drug-related	270 (12.2)	265 (11.9)	245 (20.0)	249 (20.3)	146 (12.0)	161 (13.0)	310 (20.3)	295 (19.6)
During follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular adverse events	**11 (0.5)**	**10 (0.4)**	**8 (0.7)**	**4 (0.3)**	**4 (0.3)**	**9 (0.7)**	**7 (0.5)**	**11 (0.7)**
On treatment	5 (0.2)	9 (0.4)	3 (0.2)	4 (0.3)	4 (0.3)	3 (0.2)	2 (0.1)	7 (0.5)
During follow-up*	7 (0.3)	1 (<0.1)	4 (0.3)	0 (0.0)	0 (0.0)	6 (0.5)	5 (0.3)	3 (0.2)
Wound-related infections (all)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**6 (0.4)**	**6 (0.4)**
On treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4 (0.3)	3 (0.2)
During follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Death	**5 (0.2)**	**5 (0.2)**	**2 (0.2)**	**8 (0.7)**	**0 (0.0)**	**6 (0.5)**	**6 (0.4)**	**6 (0.4)**

*Events occurring more than 1 day after the last intake of study drug

In light of the liver function abnormalities produced by ximelagatran, an oral thrombin inhibitor now withdrawn from research, hepatotoxicity risk was closely monitored in the RCTs comparing rivaroxaban with enoxaparin. Across the RECORD 1,2, 3 and 4 studies, based on liver enzyme levels, there was no evidence of any liver safety issues(10-12;35;36). The incidence rates of abnormal liver function tests were similar in both treatment groups in all studies, however the number of patients with significant post-operative abnormalities in liver function tests was too small in any one study to draw a conclusion regarding any potential effect of treatment on hepatic function.

A pharmacokinetic/pharmacodynamic analysis between rivaroxaban concentration and prothrombin time (PT) using a 'close-to-linear' model indicated a steeper slope in patients with reduced renal or hepatic function. In subjects with mild, moderate and severe renal impairment rivaroxaban area-under-curve (AUC) increased by 44%, 52% and 64%, respectively, while the AUC of factor Xa increased by 50, 86 and 100% and AUC of PT increased by 33, 116, and 144%, respectively compared to subjects with normal renal function. The group of patients with severe renal impairment included subjects with creatinine clearance 15-30ml/min. A higher exposure and increase in factor Xa could be expected in patients with creatinine clearance <15 ml/min. Rivaroxaban AUC was increased by 15% in patients with mild hepatic impairment (Child Pugh A) and by 127% in those with moderate hepatic impairment (Child Pugh B). On this basis, the SPC recommends caution in patients with severe renal impairment (creatinine clearance 15-30 ml/min) and use in patients with creatinine clearance <15ml/min is not recommended. Rivaroxaban is also contraindicated in patients with hepatic disease, which is associated with coagulopathy and clinically relevant bleeding risk. Caution is advised for cirrhotic patients with moderate hepatic impairment (Child Pugh B) and patients with increased risk for bleeding are to be monitored.

Please refer to the SPC for further information on the safety profile of rivaroxaban (see Appendix 1).

There have been no reports of accidental or intentional overdose with rivaroxaban, however, there is a potential for increased bleeding related to overdose. No specific antidote is known. The SPC recommends several steps to help manage events of haemorrhage including the use of activated charcoal and the use of pro-coagulants, such as activated prothrombin complex concentrate, prothrombin complex concentrate, and recombinant factor VIIa. There is no experience in the use of these substances in rivaroxaban-treated patients. Formal clinical investigations to demonstrate the effectiveness of the existing pro-coagulatory drugs in this setting is not feasible and might be unethical.

6.8 Non-RCT evidence

Not applicable. All evidence supplied from RCTs.

6.9 Interpretation of clinical evidence

6.9.1

Following major orthopaedic surgery such as total hip or knee replacement, the incidence of DVT is approximately 40-60%(16). Over 25% of the thrombi formed involve the proximal deep veins. These thrombi are more likely to produce symptoms and to result in pulmonary embolism (PE), which can be fatal. In clinical practice therefore, the objective of pharmacological prophylaxis will be to prevent or at least reduce the risk of DVT, which consequently is closely associated with a reduction in PE and reduced death rates from PE(22).

The use of a composite outcome including both asymptomatic and symptomatic VTE is controversial(46). Some clinicians argue that there is considerable imbalance between asymptomatic events, accounting for the vast majority of events and which often resolve without any clinical consequence, and symptomatic VTE events. However, as symptomatic VTE is relatively rare and difficult to detect clinically in a reliable manner, the American College of Chest Physicians (ACCP) consensus statement(16) and the European Health

Authorities (EMEA)(42) recommend the use of a composite outcome combining clinical events with asymptomatic DVT. Although asymptomatic DVT, as measured by venography is not typically assessed in clinical practice, the assessment of the frequency of DVT in this way in clinical studies provides a good indication of the efficacy of thromboprophylactic agents. This method is common to all studies investigating thromboprophylactic agents.

The RECORD study programme assessed a wide range of outcomes based on the incidence of DVTs (proximal, distal, any), PE (fatal and non-fatal), VTE-related death and all-cause mortality(10-12;35;37-39). These correlate well with the objective of thromboprophylaxis in clinical practice. The detection and diagnosis of DVTs was measured by bilateral ascending venography, a highly sensitive test which also provides hardcopy images for blinded study adjudication(16;42). The clinical (primary and secondary) endpoints included all those recommended by the EMEA. For confirmatory studies designed to show superiority to an existing agent the primary endpoint had to be a composite endpoint consisting of I) proximal DVTs or any DVTs ii) symptomatic and well documented non-fatal PE and iii) death from all causes. In studies designed to show non-inferiority the endpoint should be a composite of proximal DVTs, symptomatic and well documented non-fatal PE and VTE related deaths(42). In RECORD 1-4 studies, rivaroxaban showed superior efficacy for the primary composite endpoint (DVT, PE and all-cause mortality), reducing the risk of VTE by 70%, 79%, 49% and 32%. Superior efficacy of rivaroxaban was also demonstrated for secondary endpoints major VTE when compared with enoxaparin in RECORD 1-3 and for symptomatic VTE in RECORD 2 and RECORD 3.

In addition to the clinical benefits, by very nature of the thromboprophylactic mode of action of these drugs, there is a possibility of an increased risk of bleeding. This needs to be a major feature of safety monitoring during any study, in order that these agents can be used safely in clinical practice with a good risk-benefit profile. The safety endpoints in the RECORD studies were based on guidance from the EMEA, and included monitoring, recording and analysis of all bleeding events in study participants. Rivaroxaban was observed to have a low and similar incidence of major bleeding, and all bleeding events, as enoxaparin.

The use of enoxaparin as the comparator in the RECORD programme is considered an appropriate representation of the LMWH class and relevant to UK clinical practice. This is supported by market research that suggests that of the treatments recommended by NICE, LMWHs are the most commonly used (98%) and enoxaparin represents 71% of LMWH use (9). Furthermore, the recent NICE guidelines propose recommendations that assume each LMWH preparation available in the UK to be bioequivalent(22) by recommending all LMWHs equally.

It is also likely that the RECORD studies over exaggerate the effectiveness of enoxaparin (versus an oral therapy) since compliance and delivery of treatment, particularly during the extended prophylaxis period out of hospital will be much better in the study for a treatment requiring subcutaneous injection than in a normal clinical setting.

6.9.2

There are no reasons to suggest that results described within the submission from RECORD 1, 2, 3 and 4 would not be applicable to the patient population within routine clinical practice in England and Wales. Rivaroxaban was used as per its approved indication and dosing in all patients in these studies.

The duration of enoxaparin prophylaxis used in the RECORD studies is longer than the recommended specified duration of use for enoxaparin of 7-10 days. However it is still valid within enoxaparin's indication for prophylaxis of venous thromboembolism because it can be used 'until the risk of thromboembolism has diminished' (see enoxaparin SmPC(47)). In addition, a longer duration is recommended by NICE and the ACCP(22;32). Results from The Scottish Arthroplasty Project Audit of Consultant Practice (2003) suggest a third of clinicians only maintain thromboprophylaxis during inpatient stay for total hip or knee replacement patients(23). However, in the same audit, it was noted that extended prophylaxis was increasing with over 60% clinicians extending prophylaxis, following hip or knee replacement

surgery, to 6 weeks or longer. This is based on evidence that patients have an increased risk of thromboembolism up to 6 weeks following surgery and that VTE rates can be reduced with continued thromboprophylaxis when the patient leaves hospital(21;48). There is no reason to suggest that duration of thromboprophylaxis for major orthopaedic surgical indications in England and Wales is different to that of Scottish clinical practice. Indeed Guidelines produced by the National Institute for Health and Clinical Excellence (NICE) support the use of extended prophylaxis (4 weeks) in patients undergoing hip replacement surgery with one or more VTE risk factors(22) and updated guidance from the American College of Chest Physicians (ACCP) recommend thromboprophylaxis following elective hip or knee replacement surgery for at least 10 days and continuing up to 35 days(32). In addition, draft guidelines from the European Agency for the Evaluation of Medicinal Products (EMEA) suggest a duration of post-operative thromboprophylaxis for total hip replacement of 5-6 weeks and, for total knee replacement, a duration of 10-14 days(43). The duration of thromboprophylaxis selected in the RECORD studies is therefore in line with the most up to date national guidelines developed by clinical experts and rivaroxaban is shown in these studies to be significantly more effective than enoxaparin, the most widely used LMWH in orthopaedic surgery departments in the UK (9).

It should be noted that the enoxaparin dosing in RECORD 4 was not the European / UK standard dose or regimen. RECORD 4 took place primarily in North America where thromboprophylactic regimens vary from those practiced in Europe. In RECORD 4, enoxaparin was administered twice a day at a dose of 30mg per injection. This varies from the approved 40mg once-daily injection in the UK.

A notable feature of RECORD studies was the relatively high number of patients excluded from the efficacy analysis due to inadequate assessment of thromboembolism. A total of 12,729 patients were randomised in the studies, and 8512 patients were available for modified-intention-to-treat (MITT) analysis of the main study endpoint. Reasons for exclusion were similar between rivaroxaban and enoxaparin groups and do not limit study conclusions. This finding is commonplace in studies within these indications, which require venography to assess clinical outcomes(46). Design of the RECORD study programme pre-empted non-evaluable patients and the non-evaluable rate in the RECORD trials is in line with other thromboprophylaxis studies. In RECORD 1, 3 and 4 recruitment was increased beyond the planned number of patients to maintain statistical power(10;12;35). Sensitivity analyses also showed the missing data did not affect study power or bias the outcomes(11;12).

The oral formulation of rivaroxaban also makes it easier to use as extended thromboprophylaxis for both patients and healthcare professionals than subcutaneous enoxaparin however, the double-blind double-dummy design of the RECORD studies masks the potential benefits of an oral therapy versus a treatment requiring subcutaneous injection. Benefits of an oral therapy include patient and clinician convenience and also removes the need for painful and bruising injections.

7 Cost Effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A systematic review of the economic literature relating to pharmacological VTE prophylaxis in patients undergoing hip and knee replacement was conducted in order to identify existing economic evaluations. The search strategy focused on the cost-effectiveness studies of VTE prophylaxis (comparisons between enoxaparin/LMWH, rivaroxaban and dabigatran) specifically in hip and knee replacement patients. No additional exclusion criteria were applied.

A systematic literature review of the economic literature was previously conducted by NICE, as part of the clinical guidelines on VTE prevention in all surgical patients, in order to identify any applied study estimating the cost or cost-effectiveness of any of the prophylaxis regimens covered in the guidelines[6] (22). This review identified studies up to up to 7 August 2006, and it was assumed that the review was complete up to this date. Searches in this current systematic review were therefore limited to new studies published since August 2006.

The following databases were searched for identification of economic papers (to April 2008)

- Medline (Dialog Datastar)
- Embase (Dialog Datastar)
- The Cochrane Library Issue 1, 2008 (including NHS EED)
- Health Economic and Evaluations Database (HEED)

The full search strategy is shown in Appendix 3, section 10.3.

7.1.2 Description of identified studies

The original NICE review identified 65 studies, of which we excluded 24 which were not related to a THR or TKR population, or did not include any pharmacological method of prophylaxis. The update of the NICE review identified an additional 13 studies for review. Details of the 54 studies reviewed are provided in Appendix 4

The search for relevant pharmacoeconomic literature revealed no studies of direct relevance to the rivaroxaban submission. No publications included relevant UK pharmacoeconomic analyses of rivaroxaban and therefore there is a requirement for a de-novo economic evaluation. The economic evaluations identified through this review were used to inform the approach to this evaluation.

Details of the studies identified are provided in Appendix 4. Further discussion of the structure of previously published economic models is provided in section 7.2.6

[6] Graduated elastic compression stockings, Intermittent pneumatic compression devices, Foot pumps or foot impulse devices, Electrical stimulation, Vena caval filters, Aspirin or antiplatelet therapy, Low-dose unfractionated heparin, Low molecular weight heparin (LMWH), Fondaparinux, Oral anticoagulants (e.g. warfarin, coumarin), Dextrans, Early mobilisation, Foot elevation, Hydration, Placebo or no intervention

7.2 De novo economic evaluation(s)

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

Rivaroxaban is licensed for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. The model assumes that a 10mg rivaroxaban tablet is administered once daily, beginning 6 to 8 hours after wound closure.

The duration of the treatment is dependent upon the type of surgery. For patients undergoing major hip surgery, treatment duration of 5 weeks is recommended while treatment duration of 2 weeks is recommended for patients undergoing major knee surgery. The duration of prophylaxis administration in the model reflects the average time as observed from the phase III clinical trials (see table 36).

Table 36 Duration of administration

Rivaroxaban	10mg per day RECORD 1: 33.4 days RECORD 2: 33.5 days RECORD 3: 11.9 days
Enoxaparin	40mg per day RECORD 1: 33.7 days RECORD 2: 12.4 days RECORD 3: 12.5 days

Source: Average duration from RECORD trials (Eriksson et al., 2008; Kakkar et al., 2008; Lassen et al., 2008)

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

No treatment continuation rule was assumed.

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

Rivaroxaban is licensed for the prevention of VTE in patients undergoing elective hip or knee replacement surgery. In accordance with the licensed indication, the economic evaluation includes patients undergoing elective THR or TKR.

The population included in the pivotal clinical trials are patients undergoing elective total hip or knee replacement. Data from the National Joint Registry, which collects information on all hip and knee replacement operations in England and Wales, demonstrates total joint replacement represents 89% of all hip and knee replacement operations(8). Patients undergoing the less common types of replacement of the hip or knee are also at risk of VTE. There is no reason to believe the risk differs from the baseline risk associated with all orthopaedic surgery of the hip or knee. There is no evidence to suggest the pathophysiology of VTE differs to that in total hip or knee replacement, therefore it is not anticipated that rivaroxaban would work any differently in this group of patients. Please see section 2 for additional information.

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

Analyses for hip and knee replacement are presented separately.

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

No other subgroups were identified.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

The cohort enters the model at the point of admission for surgery and exits at death. The type of prophylaxis (model arm) does not impact the model entry and exit time points of the cohort.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The main treatment currently in use in the prevention of VTE in patients undergoing major orthopaedic surgery in the UK is low molecular weight heparin (8) and is recommended by existing clinical guidelines(22;32;33). The comparator therapy used to conduct the economic evaluation is enoxaparin, which is the most widely prescribed LMWH in orthopaedic departments the UK(9) and was the comparator in the phase III RECORD programme.

Current literature suggests that LMWHs such as dalteparin and tinzaparin are indistinguishable from enoxaparin(13;49;50), and the NICE guidelines recommend all LMWHs equally. A sensitivity analysis was run in order to investigate the cost-utility of rivaroxaban vs LMWHs assuming equal efficacy between all LMWHs.

Dabigatran, launched in April 2008, is a new oral anti-coagulant for the prevention of VTE in elective total hip replacement and total knee replacement patients. This has recently been recommended by NICE for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (July 2008), therefore the cost-utility of rivaroxaban vs dabigatran is also investigated in the sensitivity analysis.

Although the NICE guidelines also recommend that fondaparinux may be used as an alternative to LMWH, the market share of fondaparinux in orthopaedic departments is less than 2% and therefore will not be considered in the submission as this does not reflect routine clinical practice(9). A comparison will not be made against mechanical prophylaxis alone as this does not reflect current guidelines and clinical practice.

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The viewpoint of the analysis is the NHS and Personal Social Services in England and Wales.

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. What time horizon was used in the analysis, and what was the justification for this choice?

The time horizon of the analysis reflects a lifetime horizon in order to capture all important differences in costs and effects between the compared technologies. The cohort entry age is assumed to be 64 years old (average of the baseline age of the RECORD program cohort).

The model extrapolates patient outcomes until 100 years of age where approximately 99.6% of the cohort are dead. Alternative time horizons are tested as a sensitivity analysis:

1. One year analysis including events occurring in the acute phase only (3 months[7]).
2. Five years analysis(29).

7.2.6 Framework

7.2.6.1 Please provide the following.

- A description of the model type.
- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
- A list of all variables that includes their value, range (distribution) and source.
- A separate list of all assumptions and a justification for each assumption.

Model type and schematic

The cost-effectiveness model is divided into three modules; prophylaxis, post-prophylaxis, and long-term complications. The first two modules constitute the acute phase, and are represented with a decision tree (Figure 11) while the third module represents the chronic phase and is developed as a Markov process (Figure 12). The prophylaxis module includes events recorded from the clinical trial (first 35 days for THR and 14 days for TKR patients post surgery). The post-prophylaxis module serves as an extension of the RECORD trials to reflect the risk of a symptomatic VTE event within the first 3 months, as recommended by Sullivan and colleagues (2003)(29). The long-term complications module reflects the post-acute phase events and extrapolates any long-term complications resulting from symptomatic VTE events.

[7] Since events occurring in the acute phase (3 months) may require treatment for up to 6 months, the analysis of the acute phase models costs and utilities over a one year time horizon to include all relevant outcomes.

Figure 11 Model structure – Acute phase

Figure 12 Chronic phase (Markov model)

Variables list
In order to facilitate the review of the model and cross-referencing of the model parameters' calculations and sources, all model variables are presented at each relevant part in the following sections.

Key assumptions list

- An asymptomatic VTE event does not incur any cost: *A reasonable assumption since asymptomatic events would not be detected (and hence would not be treated) in clinical practice.*
- An asymptomatic VTE event does not have any impact on the cohort's quality of life: *A reasonable assumption due to the asymptomatic nature of the event.*
- Patients are at risk of a first DVT or PE up to 90 days post-surgery: *Based on Sullivan et al., 2003*
- During the acute phase (i.e. the first 90 days post-surgery), the probability of DVT or PE events occurring beyond the duration of the clinical trial is the same regardless of prophylaxis method: *A necessary assumption due to the absence of prophylaxis specific data.*
- The Markov model assumes that transitions occur within the period of one year (annual cycles). *A necessary assumption that fits the available data from the literature.*
- Transitions that occur during the acute phase are not discounted: *A reasonable assumption since these events occur within the first 90 days.*
- All events occur at the end of the model cycle and health state rewards are adjusted by half-cycle correction to prevent from overestimating from the actual accrued costs and benefits: *A standard assumption in CE calculations using Markov state transition models.*
- In the long-term complications module, the model assumes the same background mortality risk for all individuals in the model regardless of the health state: *A reasonable assumption since PTS has not been associated with increased mortality*

- Patients with a DVT only are at the same risk of PTS as patients with both a DVT and a PE: *A necessary assumption due to lack of clinical data*
- All recurrent VTE events are DVTs: *A model simplifying assumption*
- In the long-term complications phase, the model assumes the same risk of events for both comparators: *In the absence of prophylaxis specific data for these variables this is a necessary assumption.*
- If the results of the clinical trial or indirect comparison do not show any statistically significant difference between the two arms the model assumes parity between the two comparators: *An assumption which was tested in sensitivity analysis.*
- Patients experiencing major bleeding have zero utility for the duration of hospitalisation for bleeding, and full utility for the remainder of the year: *Following the approach taken by NICE (2007(22)) this conservative assumption is made because of a lack of published annual utility for these patients*
- In hospital drug administration and monitoring is carried out by a band 5 nurse: *In line with the assumption made by NICE (2007)*.
- DVT diagnosis is confirmed by a Doppler ultrasound: *In line with the assumption made by NICE (2007)*
- PE diagnosis is confirmed by a CT pulmonary angiography, a chest X-ray and an ECG: *In line with the assumption made by NICE (2007)*
- 10% of patients will be incorrectly suspected of having DVT and 2% of having a PE: *In line with previous economic evaluations*
- Only patients with asymptomatic VTE develop symptomatic VTE during the post-prophylaxis module: *A necessary assumption due to lack of clinical evidence to determine whether all patients who develop their first symptomatic VTE after the clinical trial period had asymptomatic VTE or not*. *This assumption is tested in sensitivity analysis.*
- Patients enter the model aged 64: *Based on the mean age of patients in the RECORD trials*
- Dalteparin and tinzaparin have the same efficacy and safety profile as enoxaparin: *This assumption is implicitly made by the NICE clinical guidelines which recommend all LMWHs equally, and is supported by current literature(13;49;50).*
- A proportion of patients are assumed to receive a therapeutic adjunct such as physiotherapy or elastic stockings alongside pharmacological prophylaxis, and this is reflected in the efficacy of rivaroxaban, enoxaparin and dabigatran: *All patients in the RECORD trials were permitted a therapeutic adjunct, as were patients in the dabigatran trials on which the indirect comparison was based*.
- The length of stay of the primary hospitalisation is not affected by the choice of pharmacological prophylaxis: *It is possible that patients receiving oral rivaroxaban may not need to be admitted the day before surgery since the first dose is administered post-operatively, unlike subcutaneous injections of LMWH which is initiated 12 hours pre-operatively. However, no difference is conservatively assumed in the base case analysis*.
- In the post-prophylaxis module, all PEs are non-fatal: *A necessary assumption due to lack of clinical data*

7.2.6.2 Why was this particular type of model used?

A multi modular approach was selected for the economic analysis. This was deemed essential in order to capture all potential benefits of the two comparators during both the acute and the chronic phase of the condition. The acute phase was modelled through a decision tree analysis, where the risk of VTE events or bleeding is populated by the observed clinical trial data and asymptomatic events are extrapolated to symptomatic during a three month acute phase at which patients are still at risk of an initial VTE event. In the chronic phase, all symptomatic events are extrapolated to reflect the risk of long-term complications by a state transition model. Markov models are suitable to represent events that recur over time. Given the nature of the long-term complications a Markov model is used to represent the cohort transitions through the various phases.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

In order to determine the most appropriate model structure, a literature review was conducted to identify existing economic analyses of pharmacological VTE prophylaxis in patients undergoing hip or knee replacement, and determine the current best practice (Appendix 3 and Appendix 4). The review identified 54 potentially relevant economic analyses.

The review also identified a paper which provides an overview of the pharmacoeconomic evaluations published on VTE prophylaxis in major orthopaedic surgery between 1984 and 2000, and discusses changes in the understanding of the natural history of VTE and changes in medical practice, and how these changes affect the way economic evaluations of VTE prophylaxis in major orthopaedic surgery should be conducted(29). A key conclusion of the review by Sullivan et al. (2003) was that "the outcomes and costs of VTE-related care should be conducted over a timeframe that extends over several years, taking into account both the acute (from surgery up to 3 months) and chronic phases of the disease". This recommendation is reflected in the more recent economic studies, identified in the literature search, which include both an acute phase and a chronic phase.

Sullivan and colleagues (2003) also make several recommendations around endpoints that should be taken into account in the pharmacoeconomic evaluation of new drugs, and propose elements for new pharmacoeconomic models for VTE prophylaxis.

The development of the model followed these recommendations in terms of determining the model structure, time horizon and the evaluated outcomes.

ACUTE PHASE

In particular, the acute phase can be divided into two sections:

- the prophylaxis module; that reflects the observed clinical trial data
- the post-prophylaxis module; which extrapolates observed asymptomatic events to symptomatic events, post the clinical trial timeframe.

Prophylaxis module

Based on the conducted literature review of economic studies (Appendix 4) most previously published economic models use a decision tree structure for the acute phase. One of the first economic evaluations of VTE prophylaxis in this population was conducted by Oster et al. (1987)(51), and this has been used as the basis of the acute phase for many subsequent evaluations(52-57) although all of these analyses have expanded the structure used by Oster et al. (1987) to reflect the natural history of the disease (such as the inclusion of long-term complications), and current clinical management patterns. Although many publications(58-61) do not explicitly state that they are basing their model on the paper by Oster et al.(51), the structure of the acute phase is remarkably similar between these publications and those which are based on Oster et al.

In 2007, the National Institute for Health and Clinical Excellence (NICE) published guidelines for reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery(22). These guidelines contain details of an economic model developed by the NICE guideline group to determine the most cost-effective thromboprophylaxis strategy for different surgical scenarios. This model differs slightly in its structure of the acute model phase from the majority of published economic evaluations. The key difference is that it appears that in the NICE model, patients who experience a major bleeding event do not appear to be at risk of experiencing any subsequent or concomitant VTE events, and patients who have previously experienced a VTE event do not appear to be at risk of a major bleeding event. This contrasts with most other economic evaluations which do not incorporate any relationship between the risk of bleeding and the risk of a VTE event. Discussions with clinical experts concluded that the risk of VTE is not affected by major bleeding and vice versa.

The structure of the prophylaxis module follows Oster and colleagues (1987) modified to fit the clinical trial data.

The prophylaxis module reflects the incidence of events observed in the RECORD trial. The probability of developing a VTE event or having prophylaxis related bleeding is based on the

phase III clinical trials, the RECORD studies, which compare rivaroxaban directly with enoxaparin, and on the indirect comparison of rivaroxaban vs dabigatran.

The RECORD study results were used to populate the model with the incidence of; prophylaxis related bleeding, VTE, symptomatic VTE, non-fatal PE, and fatal PE for rivaroxaban and enoxaparin (Table 37). The event probabilities used in the analysis of rivaroxaban vs dabigatran 220mg are also shown in Table 37 and are based on the results of the indirect comparison presented in section 6.

Following prophylaxis related bleeding the model assumes that the cohort has the same risk of fatal bleeding regardless of the prophylaxis (model arm) (Table 38). The incidence of any VTE event includes the risk of symptomatic and asymptomatic events; the latter of which are observed via a venography at the end of the clinical trial. The model assumes that an asymptomatic VTE event does not incur any cost nor does it have any impact on the cohort's quality of life. The incidence of PE is calculated as the composite endpoint of non-fatal PE and fatal PE. The clinical trials did not record the incidence of asymptomatic PE.

An analysis of the relative risk of rivaroxaban versus enoxaparin revealed that major bleeding and PE events were either very few or very similar to suggest a significant difference between the two methods of prophylaxis. Whenever that is the case, the model assumes parity between the two comparators (see Table 37). This assumption is tested in sensitivity analysis where the observed rates are applied to the model.

The model also assumes a proportion of patients that will have a false positive test for DVT and PE based on the literature (Table 38).

Table 37 Prophylaxis Module: event probabilities

	RIVAROXABAN	ENOXAPARIN	DABIGATRAN 220MG
RECORD 1			
VTE	0.0113	0.0372	0.0332
Symptomatic VTE	0.0027	0.0027*	0.0137
Non fatal PE	0.0025	0.0025*	0.0025*
Fatal PE	[redacted]	[redacted]	[redacted]
Major bleeding	0.0027	0.0027*	0.0027*
RECORD 2			
VTE	0.0197	0.0937	0.0855
Symptomatic VTE	0.0025	0.0124	0.0354
Non fatal PE	0.0012	0.0012*	0.0012*
Fatal PE	[redacted]	[redacted]	[redacted]
Major bleeding	0.0008	0.0008*	0.0008*
RECORD 3			
VTE	0.0959	0.1880	0.1809
Symptomatic VTE	0.0067	0.0196	0.0067*
Non fatal PE	0.0000	0.0000*	0.0000*
Fatal PE	[redacted]	[redacted]	[redacted]
Major bleeding	0.0057	0.0057*	0.0057*

Source: RECORD program, indirect comparison

*If the results of the clinical trial do not show any statistically significant difference between the two arms the model assumes parity between the two comparators. This assumption is tested in sensitivity analysis. Details of the statistical significance and the relative risks are presented in appendix 5

Table 38 Prophylaxis module Non-RECORD related probabilities

EVENT	PROBABILITY	SOURCE
Proportion of patients with a false positive VTE test: DVT	0.1000	Harrison et al., 1997; Drummond et al., 1994; Menzin et al., 1995; Bergqvist et al., 1996; Hawkins et al., 1998
Proportion of patients with a false positive VTE test: PE	0.0200	Harrison et al., 1997; Drummond et al., 1994; Menzin et al., 1995; Bergqvist et al., 1996; Hawkins et al., 1998
Probability of death following major bleeding	0.0079	NICE, 2007 (Muntz, 2004)

Post-prophylaxis module

The review of existing economic analyses identified a small number of models (including the NICE, 2007 model(22)) which use a short time frame for the acute phase equal to the duration of the clinical trial from which the efficacy data is obtained. However, the majority of

the models identified in the literature search use a three month time horizon for the acute phase(52;54;56-61)

Additionally, Sullivan et al. (2003) recommend that since symptomatic VTE has been reported in patients undergoing THR or TKR at 90 days post-surgery, the time horizon of the acute phase should extend up to 3 months for initial events(29). [redacted]

Please refer to section 7.2.6.8 for details on the extrapolation method.

CHRONIC PHASE
Sullivan and colleagues (2003) suggest that three months post-surgery, patients are no longer at risk of a VTE event. However, patients who have experienced a DVT are at risk of developing post-thrombotic syndrome (PTS) and all patients who experienced a VTE event are at risk of having a recurrent VTE.

The review of the economic literature identified nine economic evaluations that modelled long-term complications up to 5 years or beyond(22;52;53;55-62). The majority of these studies identified used a decision tree for the entire analysis, although three studies(22;53;55) used a markov model for the chronic phase.

A Markov process was added to the economic model to reflect the risk that the cohort who developed a symptomatic VTE event can later have PTS and recurrent VTE(63;64). Patients may be at risk of developing these long-term complications for several years after their initial VTE event(63-65).

Please refer to section 7.2.6.8 for details on the extrapolation method.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

Please see section 7.2.6.3 for details.

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model reflects all essential features of the condition except medium and long-term joint outcomes. This outcome was not collected in the pivotal trials.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

In accordance with other economic evaluations the model adopts a multi-modular approach, a 3-month acute phase, during which patients are at risk of an initial VTE event, followed by a chronic phase. The chronic phase of the model includes long-term complications that were estimated using a Markov process with one-year cycles. The length of the cycle is appropriate considering the available data that inform the model transition probabilities.

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

Half-cycle correction was implemented in the model.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

ACUTE PHASE

Prophylaxis module

No extrapolation was implemented.

Post-prophylaxis module

The RECORD trial reports the incidence of symptomatic VTE during a 65 day (THR) and 42 day (TKR) follow up period. However, premature drop outs reduced the proportion of the trial cohort in the follow- up period by around 3%. The follow-up period does not match the recommended by Sullivan and colleagues (2003)(29) acute phase period (90 days), and includes fewer patients than the modified intention to treat (mITT) population. [redacted]

[redacted]

Table 39 Post-prophylaxis module probabilities

EVENT	PROBABILITY		SOURCE
	THR	TKR	
Risk of asymptomatic VTE developing into symptomatic VTE	[redacted]	[redacted]	Quinlan et al., 2007
Risk of asymptomatic VTE developing into PE	[redacted]	[redacted]	Calculated from White et al., 1998
Proportion PEs that are fatal after RECORD	0.0000	0.0000	Assumption

*Please refer to appendix 6 for details on the calculations

CHRONIC PHASE

As previously mentioned, the chronic phase (long-term complications module) reflects events occurring in the post-acute phase, and extrapolates any long-term complications associated with symptomatic VTE events over a lifetime horizon.

The Markov model contains three health states (see Figure12):

- No PTS
- PTS
- Death (absorbing state)

The cohort starts the long-term complications module in the No-PTS health state. In this health state the cohort is divided into three parts:

1. Individuals without VTE event or asymptomatic DVT event (by the end of the post-prophylaxis module).
2. Individuals who experienced a symptomatic DVT event at previous modules (prophylaxis or post-prophylaxis)

3. Individuals who experienced a PE event at previous modules (prophylaxis or post-prophylaxis)

The proportion of the cohort that falls within the first category is only at risk of death based on background mortality. The proportion of the cohort that falls within the second and third category is at risk of long-term complications. The proportion of the cohort who experienced a DVT event at previous modules is at risk of developing PTS only or dying based on background mortality. In addition, approximately 37% of PE patients also have DVT(67;68) so are at risk of PTS or dying based on background mortality. This value was varied in one way sensitivity analysis. The remaining PE patients are only at risk of dying based on background mortality.

All individuals who experienced DVT or PE in previous modules (prophylaxis or post-prophylaxis) are also at risk of recurrent VTE. The incidence of recurrent VTE is modelled as a transitory event rather than a health state. Costs are therefore assigned only for the duration of treatment, and the effect of developing recurrent VTE is modelled as a disutility. Within the scope of this analysis the model assumes that all recurrent VTE events are DVT events.

The risk of developing long-term complications may vary depending on time and is therefore modelled with time-dependant transition probabilities (see table 40). The method of estimating the applied transition probabilities from their sources is reported in appendix 6. The model assumes the same risk of developing PTS for patients with a DVT only, and for patients with both a DVT and PE event. The model assumes the same background mortality risk for all individuals in the model regardless of the health state (see table 41).

The occurrence of new PTS or recurrent VTE events is assumed to last for the first 5 years post-surgery.

During the long-term complications phase the cohort accrue cost and utility corresponding to whether or not they develop PTS based on state membership. All events occur at the end of the model cycle and health state rewards are adjusted by half-cycle correction.

In the absence of data indicating any difference in the long-term profile between particular pharmacological methods of prophylaxis, the model assumes the same profile for all comparators in the post-prophylaxis module and the long-term complications phase. That is, the same event risk is applied to both model arms.

Table 40 Long-term complications transition probabilities

VARIABLE	PROBABILITY	SOURCE
Probability of developing PTS: year 1	0.18 (0.13-0.22)	Prandoni et al., 1997(64); reported
Probability of developing PTS: year 2	0.0792 (0.06-0.08)	Prandoni et al., 1997; reported
Probability of developing PTS: year 3 to year 5	[redacted]	Prandoni et al., 1997; Calculated
Probability of recurrent VTE: year 1 and year 2	[redacted]	Prandoni et al., 1997; Calculated
Probability of recurrent VTE: year 3 to year 5	[redacted]	Prandoni et al., 1997; Calculated

*Please refer to appendix 6 for details on the calculations

Table 41 Background mortality risk

AGE	MORTALITY RISK	AGE	MORTALITY RISK	AGE	MORTALITY RISK
64	0.012102	77	0.0468065	90	0.183364
65	0.0131145	78	0.0519245	91	0.201319
66	0.0144355	79	0.0580565	92	0.2224975
67	0.015943	80	0.0643465	93	0.2476425
68	0.017519	81	0.072119	94	0.265814
69	0.0194025	82	0.079718	95	0.2975885
70	0.0211635	83	0.088386	96	0.3222535
71	0.0239275	84	0.0958365	97	0.35066
72	0.0267645	85	0.1065635	98	0.3777865
73	0.029713	86	0.119263	99	0.398315
74	0.033555	87	0.138931	100	0.4416345
75	0.0373635	88	0.152946		
76	0.04185	89	0.170372		

Source: Statistics.gov.uk

7.2.7 Clinical evidence

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The base-case analysis is rivaroxaban vs enoxaparin, and the baseline risk of disease progression is obtained from the three phase III trials of rivaroxaban versus enoxaparin which are relevant to the UK. The details of these studies are as follows:

- RECORD 1 – 10 mg rivaroxaban (QD) vs 40 mg enoxaparin (QD) after total hip replacement (non-inferiority study with subsequent step up to superiority)
- RECORD 2 – 10 mg rivaroxaban (QD) vs 40 mg enoxaparin (QD) after total hip replacement (superiority study)
- RECORD 3 – 10 mg rivaroxaban (QD) vs 40 mg enoxaparin (QD) after total knee replacement (non-inferiority study with subsequent step up to superiority)

Further details of these studies can be found in section 6.

The RECORD study results were used to populate the model with the incidence of prophylaxis related bleeding, VTE, symptomatic VTE, non-fatal PE, and fatal PE. The events observed in the RECORD clinical trials are shown in Table 42. The incidence of any VTE event includes the risk of symptomatic and asymptomatic events; the latter of which are observed via a venography at the end of the clinical trial. The clinical trials did not record the incidence of asymptomatic PE.

Table 42 Events observed in RECORD clinical trials

	RIVAROXABAN	ENOXAPARIN
RECORD 1		
VTE	18/1595	58/1558
Symptomatic VTE*	6/2193	11/2206
Non fatal PE	4/1595	1/1558
Fatal PE	[redacted]	[redacted]
Major bleeding	6/2209	2/2224
RECORD 2		
VTE	17/864	81/869
Symptomatic VTE*	3/1212	15/1207
Non fatal PE	1/864	4/869
Fatal PE	[redacted]	[redacted]
Major bleeding	1/1228	1/1229
RECORD 3		
VTE	79/824	166/878
Symptomatic VTE*	8/1201	24/1217
Non fatal PE	0/824	4/878
Fatal PE	[redacted]	[redacted]
Major bleeding	7/1220	6/1239

Source: RECORD program (Eriksson et al., 2008(10); Kakkar et al., 2008(11); Lassen et al., 2008)(12).
*Symptomatic VTE events are reported on the basis of the safety population that underwent surgery.

The observed event rates were used to derive the relative risk (RR) and risk difference (RD) of rivaroxaban versus enoxaparin. When the relative risks or risk differences were not statistically significant, the model assumes parity between the compared prophylaxis methods. This was tested in a sensitivity analysis. The RR and RD of rivaroxaban vs. enoxaparin are presented in appendix 5.

7.2.7.2 How were the relative risks of disease progression estimated?

The baseline risk of VTE and bleeding events is calculated from the relevant clinical trial. Moreover, in the prophylaxis module, the probability of a false positive diagnosis and death following major bleeding were based on published literature and were consistent with previously published economic evaluations. Please refer to section 7.2.6.4, Table 37 and Table 38 for details on the calculated probabilities in the prophylaxis module.

In the chronic phase, the long-term complications module extrapolates all symptomatic events for the occurrence of PTS, recurrent VTE and background mortality for the cohort's lifetime. Details on the estimated probabilities and mortality risk are presented in section 7.2.6.8, Table 40 and Table 41. Further details on the calculation method of the transition probabilities from Prandoni and colleagues (1997)(64) are presented in appendix 6.

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The outcomes included in the economic model are VTE related events in the short term and its long term complications such as PTS and VTE recurrence. Consistent with previously published economic evaluations(22;70), patients experiencing a DVT or a PE were assigned the utility of that event for the duration of VTE treatment while patients experiencing non-fatal prophylaxis related major bleeding were assigned the utility of that event for the duration of their hospitalisation. Since PTS is a chronic event, patients in the PTS health state were assigned the utility of PTS for the duration of the analysis or until they die.

The model assumes that prophylaxis related major bleeding is fatal in a proportion of patients based on published literature, and that all patients are at risk of a fatal PE based on the RECORD trial results. All patients are also at risk of background mortality based on UK life tables.

Further details of the utility values used the analysis and their sources can be found in section 7.2.8.

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

No significant differences in adverse events were observed between rivaroxaban and enoxaparin in the RECORD trials. However, following the recommendations by Sullivan et al. (2003)(29), and previously published economic evaluations(22;52;56-61;70-72), the model includes prophylaxis related major bleeding.

7.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

All parameters were based on published data.

7.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

All assumptions have been stated in the relevant section.

7.2.8 Measurement and valuation of health effects

7.2.8.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

In line with NICE's recommendations, the primary outcome measure in this analysis was quality adjusted life years (QALYs).

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The outcomes included in the economic model are prophylaxis related major bleeding, VTE related events in the short term, and its long term complications such as PTS and recurrence. Such events impact on quality and quantity of life. Health related quality of life is a multidimensional construct that includes symptoms, toxicity associated with treatment, and functional, emotional and social factors that reflect the well being of the patient. With this in mind the primary outcome measure is the cost per QALY gained.

7.2.8.3 How were health effects measured and valued?

The RECORD clinical trials did not collect any health-related quality of life data. The economic model therefore uses utility values identified in a systematic literature review (appendix 7). The utility values for symptomatic DVT and PE were weighted for the expected time with the event. The model applies the DVT utility for 3 months and the PE utility for 6 months(70).

Although NICE's guidelines state that utilities should be measured using the EQ-5D where possible, no appropriate utilities which were elicited using this questionnaire were identified in the systematic literature search. The cost utility model therefore incorporates utilities reported in Lenert & Soetikno 1997 and Haentjens et al 2004 which were the most appropriate utilities identified in the systematic literature review(70;73).

As none of the studies identified in the initial search strategy were specific to a population who had just undergone THR or TKR surgery, an additional search to identify utility values for this population was conducted. A general utility search identified over 2,000 studies for review. Since the NICE state that utilities should be measured using the EQ-5D where possible, the utility search for THR/TKR patients was limited to those studies using the EQ-5D questionnaire.

The systematic literature review of VTE related utilities in a THR and TKR population highlighted some published utilities relevant to this area. The cost utility model uses the best available evidence and incorporates utilities for VTE related events reported in Lenert & Soetikno (1997)(73) and Haentjens et al (2004)(70), and weights these utilities by the THR and TKR specific utilities reported by Brunenberg et al. (2005)(74). Although Lenert and Soetikno (1997) also provide a utility value for prophylaxis related major bleeding, it is not clear from the study what time period this utility should be applied for. As a conservative assumption, it is therefore assumed that patients will have zero utility for the duration of hospitalisation for bleeding, and full utility for the remainder of the year). The duration of hospitalisation is assumed to be 2.7 days based on the length of stay reported in the NHS reference costs for the relevant Healthcare Resource Groups (HRGs).

The utilities used in the model are shown in Table 43. For events occurring within the first year post-surgery, all utility values are adjusted to account for the fact that patients will have reduced utility as a result of having undergone major surgery(74). Sensitivity analyses were also conducted on the utility following THR/TKR using alternative sources and methods of utility calculation (Table 44). From the study by Brunenberg et al. 2005, the weighted average 52 week EQ-5D score across the Joint Recovery Programme (JRP) and usual care arms is

shown in Table 44. In addition, using the weighted average 7, 12, 26 and 52 week EQ-5D scores, an annual score was calculated assuming that patients experienced the 7-week utility score for the first 7 weeks post-surgery, the 12 week score for the next 5 weeks, the 26 week score for the following 14 weeks and the 52 week score for the remainder of the year. The resulting value was used in sensitivity analysis along with alternative values from other sources for the THR population Table 44).

For subsequent years (i.e. years 2-5), the average quality of life in the United Kingdom as measured by Kind et al. (1998)(75) using the EQ-5D was used for patients with no event following the approach taken by NICE (2007)(22).

Table 43 Annual utilities used in the Cost Effectiveness Model

	REPORTED UTILITY	ADJUSTED FOR THR	ADJUSTED FOR TKR	SOURCE
No VTE Event	[redacted]	[redacted]	[redacted]	[redacted]
Prophylaxis related bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Asymptomatic DVT	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic DVT	[redacted]	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent VTE	[redacted]	[redacted]	[redacted]	[redacted]
Long Term Utility – (No VTE Event)	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]

Table 44 Surgery specific utility values (1 year)

	THR	TKR
Brunenberg et al. (2005)	0.704*	0.66*
Brunenberg et al. (2005)	0.701†	0.645†
Ostendorf et al. (2004a)(76)	0.75	-
Ostendorf et al. (2004b)(77)	0.76	-
Malchau et al. (2005)(78)	0.75	-

*weighted average of the JRP and Usual Care arms; † Calculated utility based on 7, 12, 26 and 52 week scores

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 7.2.11).

The clinical trials did not include any generic or condition-specific preference based measures.

7.2.8.5 Were any health effects excluded from the analysis? If so, why were they excluded?

It has been suggested that the method of administration (injection versus oral) may have some effect on patients' utility. However, as no data has been identified to support this hypothesis disutility associated with injections is not included in the model.

As discussed in section 7.2.7.4 with the exception of prophylaxis related major bleeding, disutility associated with prophylaxis related adverse events were not included in the economic model.

7.2.9 Resource identification, measurement and valuation

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The costs and resources used in the model are presented in Table 45.

Table 45 Cost and Resource use

	RESOURCE USE	COST	SOURCE
PROPHYLAXIS DRUG COST			
Rivaroxaban	10mg per day RECORD 1: 33.4 days RECORD 2: 33.5 days RECORD 3: 11.9 days	£4.50 per day	Bayer
Enoxaparin	40mg per day RECORD 1: 33.7 days RECORD 2: 12.4 days RECORD 3: 12.5 days	£4.20 per day	(22;79)
Dabigatran	110mg for first day, 220mg per day thereafter THR analyses: 31.5 days TKR analyses: 8 days	Day 1: £2.20; £4.20 per day thereafter	(22;79)
PROPHYLAXIS RELATED ADMINISTRATION			
Rivaroxaban	2-3 minutes nurse time per day during hospitalisation	£2 per day	(22) (Assumed same as other oral prophylaxis)
Enoxaparin	2-3 minutes nurse time per injection during hospitalisation 8% of patients require daily visits from a district nurse post-discharge 92% patients require 30 mins nurse time for training to self-inject	£2 per day £24 per injection £20 per training session	(22;80)
Dabigatran	2-3 minutes nurse time per day during hospitalisation	£2 per day	(22) (Assumed same as other oral prophylaxis)
PROPHYLAXIS RELATED MONITORING			
Rivaroxaban	No monitoring assumed		
Enoxaparin	In hospital: Full blood count at baseline, then every 2-4 days until day 14 Outpatient: no monitoring assumed	£2.35 per test	(22;81)
Dabigatran	One liver function test	£2.33	Assume same as INR test.(81)
PROPHYLAXIS RELATED BLEEDING			
Non-fatal bleeding	HRG Codes FA16Z, FB06Z, FC08A, FC08B, FC08C Cost of Stroke (3%*£8,099[a])	£833.11 £273.59	(22;82;83)
Fatal Bleeding		£0	(22)

	RESOURCE USE	COST	SOURCE
VTE DIAGNOSIS			
DVT inpatient	Doppler ultrasound (Radiology Services - RA22Z)	£64	(22;82)
DVT outpatient	Doppler ultrasound (Radiology Services - RA22Z) 1 outpatient visit (Consultant Led Follow up Attendance Outpatient Face to Face speciality code: 303)	£60 £102.54	(22;80;82)
PE Inpatient	Angiography (Radiology Services - RA10Z) Chest X-ray (Radiology Services - RA28Z) ECG (Diagnostic Services DA13)	£128 £29 £22	(22;82;84)
PE outpatient	Angiography (Radiology Services - RA10Z) Chest X-ray (Radiology Services - RA28Z) ECG (Diagnostic Services DA13) A&E visit – (weighted average of codes VB01Z to VB09Z)	£106 £28 £22 £120	(22;80;82;84)
DVT TREATMENT			
Inpatient Treatment	Hospitalisation (weighted average of EB11Z elective and non-elective) Drug treatment: 5mg warfarin for 107[b] days; 1.5mg/kg enoxaparin for 7 days Graduated compression stockings (6 pairs over 2 years) Anticoagulation clinic visits (7 visits for proximal DVT, 5 visits for distal DVT) [Speciality Code: 324] Ambulance transport (10% visits)	£235.77 per day for 4 days Warfarin: £0.02 per day; Enoxaparin: £6.69 £9.72 per pair First visit £24.01[c]; Follow-up visits £18.72[c] £53 per journey	(22;79;82)
Outpatient Treatment	Drug treatment: 5mg warfarin for 107[b] days; 1.5mg/kg enoxaparin for 7 days Enoxaparin administration (8% patients) Anticoagulation clinic visits (7 visits for proximal DVT, 5 visits for distal DVT) (Speciality Code: 324) Ambulance transport (10% visits) Graduated compression stockings (6 pairs over 2 years)	Warfarin: £0.02 per day; Enoxaparin: £6.69 £24 per injection First visit £24.01[c]; Follow-up visits £18.72[c] £53 per patient journey £9.72 per pair	(22;79;80;82)
PE TREATMENT			
Inpatient Treatment	Hospitalisation (weighted average of EB11Z elective and non-elective) ICU - Service Code XC07ZTHE (10% hospitalised patients) Drug treatment: 5mg warfarin for 180 days; 1.5mg/kg enoxaparin for 7 days Graduated compression stockings (6 pairs over 2 years) Anticoagulation clinic visits (6 visits) (Speciality Code: 324) Ambulance transport (10% visits)	£250.96 per day for 6 days £1,180 per day for 7 days Warfarin: £0.02 per day; Enoxaparin: £6.69 £9.72 per pair First visit £24.01[c]; Follow-up visits £18.72[c] £53 per patient journey	(22;79;82)
Outpatient Treatment	Drug treatment: 5mg warfarin for 180 days; 1.5mg/kg enoxaparin for 7 days Enoxaparin administration (8% patients) Anticoagulation clinic visits (6 visits) (Speciality Code: 324) Ambulance transport (10% visits)	Warfarin: £0.02 per day; Enoxaparin: £6.69 £24 per injection First visit £24.01[c]; Follow-up visits £18.72[c] £53 per patient journey	(22;79;80;82)

	RESOURCE USE	COST	SOURCE
	Graduated compression stockings (6 pairs over 2 years)	£9.72 per pair	
LONG-TERM COMPLICATIONS			
Diagnosis of PTS	Assume included in cost of treatment	0	
Treatment of PTS		£2864.75	(85)
Treatment of recurrent VTE	Assume same as treating DVT post-discharge (see above for cost breakdown)	£347.57 per event	Assumption

[a] Inflated to 2007 prices
[b] Patients with proximal DVT receive warfarin therapy for 180 days, and patients with distal DVT receive warfarin for 90 days (NICE, 2007). The ratio of proximal DVTs to all DVTs was estimated from the RCTs in our review that reported the incidence of both: (308/13130)/(1641/13040) = 19%
[c] Weighted average of consultant led / non-consultant led / multiprofessional visits
[d] Converted to £ and inflated to 2007 prices

7.2.9.2 How were the resources measured?

Resource use was based on the economic model produced by NICE (2007) in their recently published VTE guidelines(22). As with the NICE model, this economic analysis is performed from the perspective of the NHS and personal and social services. Details of costs and resource use are summarised in Section 7.2.9.1. Unit cost data are taken from the NHS reference costs and the Unit Costs of Health and Social Care publication by the Personal Social Services Research Unit(80).

The length of stay (LOS) for THR and TKR was 7.8 and 7.2 days respectively based on Hospital Episode Statistics (HES) data for 2006/07. The mean LOS for THR patients was calculated based on the weighted average LOS for the 4-character main operation and primary diagnosis codes W37.1 (Total prosthetic replacement of hip joint using cement), W38.1 (Total prosthetic replacement of hip joint not using cement) and W39.1 (Other total prosthetic replacement of hip joint). The mean LOS for TKR patients was calculated based on the weighted average LOS for the 4-character main operation and primary diagnosis codes W40.1 (Total prosthetic replacement of knee joint using cement), W41.1 (Total prosthetic replacement of knee joint not using cement, and W42.1 (Other total prosthetic replacement of knee joint). Enoxaparin is administered 12 hours before surgery, while the first dose of rivaroxaban is given post-surgery. It is therefore anticipated that rivaroxaban patients may require one less day in hospital compared with enoxaparin patients. This potential cost saving is not included in the base case analysis, and the LOS is assumed to be equal for all methods of prophylaxis.

The cost of prophylaxis is obtained from the British National Formulary(79) and the duration of prophylaxis is taken from the clinical trial on which the safety and efficacy data are based. The model uses this information to calculate the in-hospital drug costs, post-discharge drug costs and the total drug cost per course. The model also includes administration and monitoring costs associated with each method of prophylaxis. Administration and monitoring have been calculated based on the resource use shown in Table 45 which was obtained from NICE (2007)(22). The cost of a full blood count and an INR test were obtained from the Newcastle upon Tyne Hospital Trusts Diagnostic Service Tariff (2007)(81) while the cost of a nurse's time was obtained from Unit Costs of Health and Social Care 2007(80). It was assumed that any inpatient drug administration and monitoring would be carried out by a band 5 nurse. Based on NICE (2007), it was assumed that 8% of enoxaparin patients were unable to self administer and that the remaining patients who self-inject received 30 minutes of nurse time for training. Although it is acknowledged that there may be some monitoring costs incurred once patients have been discharged from hospital, NICE (2007) note that these costs are difficult to quantify, and did not therefore include them in the model. Following this approach, it has been conservatively assumed that patients do not incur any outpatient monitoring costs related to enoxaparin for either the prophylaxis or treatment of VTE events.

The cost of bleeding is based on data provided in the NHS Reference costs (2007)(82). It was assumed that 21% of patients with a bleeding event will require re-operation(86). The elective

and non-elective inpatient costs for the three bleeding related HRG codes (FC08A, FCO8B and FC08C - Gastrointestinal Bleed with major, intermediate and without CC) were weighted based on the number of finished consultant episodes in order to obtain a weighted average cost for bleeding without re-operation. The cost of bleeding with re-operation was calculated in a similar manner using the elective and non-elective inpatient costs for HRG codes FA16Z (very major procedure for gastrointestinal bleed), and FB06Z (major or therapeutic procedure for gastrointestinal bleed). The costs of bleeding with and without re-operation were combined to produce an average cost of prophylaxis related major bleeding of £833.11. Based on NICE (2007), it is also assumed that prophylaxis related major bleeding will result in a stroke in 3% of patients. NICE (2007) assign a cost of £7744 for patients experiencing a stroke based on Grieve et al (2000)(83). Inflating this cost to 2007 prices using the HCHS Pay and Prices Index(80) provides a cost of £8099. A cost of £273.59 (£8099*3%) is therefore added to the average cost of bleeding obtained from the NHS Reference Costs(82). Those patients who experience a fatal bleeding event will incur no costs(22).

Unlike previous reference costs published by the NHS, the 2007 version uses the HRG4.0 grouper which distinguishes between inpatient and outpatient radiography. The cost of diagnosis is therefore different depending on whether the patient is diagnosed while still in hospital following THR/TKR surgery, or post discharge. The clinical trial report did not record whether an event occurred during hospitalisation or post-discharge. Therefore the proportion of events in the prophylaxis module that occur post-discharge is estimated based on Hull et al. 2000(87). Hull and colleagues (2000) present results from an RCT and report that 19.7% of patients experience an event in the overall period, and that 4.8% of patients experience an event in the post discharge period. Based on this result the estimated proportion of events that occur post-discharge is 24%, which is applied to both DVT and PE events. Based on NICE (2007), diagnosis of a DVT is assumed to be confirmed by a Doppler ultrasound while a PE would be confirmed by a CT pulmonary angiography, a chest X-ray and an ECG. The cost of diagnosis was calculated based on the NHS Reference Costs (2007)(82). Patients who are diagnosed with a DVT after they have been discharged will incur the additional cost of an outpatient visit, while patients diagnosed with a PE post-discharge will incur the cost of a visit to accident and emergency (A&E). The model assumes that 10% of patients will be incorrectly suspected of having DVT and 2% of having a PE (i.e. a false positive diagnosis) based on Harrison et al. (1997)(88), Drummond et al. (1994)(89), Menzin et al. (1994)(90), Menzin et al. (1995)(91), Bergqvist et al. (1996)(92) and Hawkins et al. (1998)(93). This rate will be the same for all types of procedure and prophylaxis and affects only cost calculations. These patients will incur the cost of the initial diagnostic test but no treatment costs.

Patients may either be treated for both DVT and PE in hospital, or as an outpatient attending an anticoagulation clinic. NICE (2007) report that 10% of patients with DVT and 90% of patients with PE will require an extended hospital stay. It is therefore assumed that 10% of all patients with DVT are treated in hospital, while the remainder attend an anticoagulation clinic. Similarly, it is assumed that 90% of patients with a PE receive treatment as a hospital in-patient with the remaining 10% attending the anticoagulation clinics. Of the patients who are treated in hospital, it is assumed that 10% will be treated in the intensive care unit (ICU) based on NICE (2007). The length of stay for DVT and PE patients who are not suitable for home treatment but do not require ICU treatment will be 4 and 6 days respectively, based on the weighted average length of stay for patients with DVT (elective and non-elective), and PE with major, intermediate or no complications (elective and non-elective)(82). The costs associated with the additional hospitalisation are combined with the drug costs used for the treatment of DVT and PE. No costs associated with warfarin monitoring were assumed. It is assumed that once patients are discharged from hospital following DVT or PE treatment, they will attend an anticoagulation clinic for follow-up treatment.

For those patients who are treated as outpatients, it is assumed patients with a distal DVT will have 5 anticoagulation clinic visits, and patients with proximal DVT or PE will have 7 visits. Following the method used by NICE (2007), the proportion of DVT patients who have a proximal DVT (19%) was estimated from the RCTs of pharmacological prophylaxis and THR

or TKR population. It is also assumed that 5-10% of anticoagulation clinic visits will involve ambulance transport to the clinic. This is based on expert opinion and data from the Portsmouth and North Middlesex hospitals 2005/6 as reported by NICE (2007)(22). Costs were obtained from Curtis and Netten (2007)(80). All patients with DVT or PE will also wear graduated compression stockings (NICE, 2007)(22).

The cost of treating PTS was obtained from MacDougall et al. (2006)(85) who conducted a retrospective observational cohort study to determine the direct medical costs of patients with PTS. The authors found that annualised median total costs for the PTS group were $20,569 compared with $15,838 in matched controls with DVT and/or PE but no PTS. The cost of PTS is therefore estimated to be $4,726. Costs were converted to pounds and inflated to 2007 values. The authors also report the mean total costs in the PTS and no PTS groups, however the difference between the two groups was $11,667. This value was considerably higher than expected, and is likely to be due to a very small number of patients who incur very high costs. As a conservative measure, the median cost difference was therefore used in the base case analysis with the mean cost difference being used in a sensitivity analysis.

It was assumed that the cost of PTS diagnosis was included in the treatment cost.

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

During the RECORD trials detailed resource utilisation data was not routinely collected. Resource utilisation and costs for the analysis were therefore based on the published literature, including the NICE Guidelines on the prevention of VTE(22), the NHS Reference Costs(82), the Personal Social Services Research Unit (PSSRU)(80), the British National Formulary(79) and Newcastle upon Tyne Hospital Trust tariffs (2007)(81).

7.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

All resources used to treat the disease were taken into account for the duration of the analysis. Further details of the assumptions made regarding the treatment of subsequent events are provided in section 7.2.9.2

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

The costs and their sources are presented in Table 30. Further details regarding the selection of this source are provided in section 7.2.9.2.

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

The model assumes a cost per day of £4.50 for rivaroxaban and £4.20 for enoxaparin. Dabigatran is assumed to cost £2.20 for the first day and £4.20 per day thereafter. No price discounts are presented.

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

The introduction of rivaroxaban does not require any additional infrastructure to be put in place.

7.2.9.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

All resources are measured and valued in line with the reference case.

7.2.9.9 Were resource values indexed to the current price year?

Costs were based on the current version of the BNF(79), NHS reference costs(82) and PSSRU(80) where possible. Any costs obtained from published sources were inflated to current prices using the Hospital and community health services (HCHS) pay and price inflation index reported by Curtis (2007)(80).

7.2.9.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

The model makes several assumptions relating to the administration and monitoring of prophylaxis. It was assumed that all inpatient drug administration and monitoring would be carried out by a band 5 nurse. This assumption is necessary in order to assign a cost to nurse time. After discharge, it was conservatively assumed that patients do not incur any outpatient monitoring costs related to enoxaparin for either the prophylaxis or treatment of VTE events due to difficulties in quantifying the resource use. Similarly, the model conservatively does not assign any costs associated with monitoring warfarin in the treatment of VTE. Excluding items from the cost of a VTE event favours the comparator since fewer rivaroxaban patients experience a VTE event. In line with the NICE analysis, the model assumes that 8% of enoxaparin patients were unable to self administer and that the remaining patients who self-inject received 30 minutes of nurse time for training.

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

In line with NICE guidelines, both costs and effects were discounted using an annual discount rate of 3.5%.

7.2.11 Sensitivity analysis

7.2.11.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

In addition to the probabilistic sensitivity analysis (PSA) described in Section 7.2.11.3, a range of univariate and scenario-based sensitivity analyses were also performed.

7.2.11.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

One way sensitivity analysis was conducted on a number of model inputs.

- **Time period**: Sullivan et al. 2003 recommend that both the acute (from surgery up to 3 months) and chronic phases of the disease should be taken into account. A patient cohort lifetime horizon was used for the base case, and sensitivity analysis was conducted taking into account only the acute phase of the disease (3 months). Since events occurring in the acute phase of the disease may require treated for up to six months, costs and utilities are modelled over a one year time horizon in order to include all relevant costs(29). Sensitivity analysis was conducted on a 5 year time horizon.
- **Extrapolation method**: The base case assumption is that only patients with asymptomatic VTE develop symptomatic VTE during the post-prophylaxis module. However, there is no clinical evidence to determine whether all patients who develop their first symptomatic VTE after the clinical trial period had asymptomatic VTE or not. Therefore, sensitivity analysis was conducted assuming that all patients who did not develop a symptomatic VTE event (i.e. both patients with No VTE event, and those

with an asymptomatic event) during the prophylaxis module are at risk of a VTE during the post-prophylaxis module.

- **Rate of asymptomatic to symptomatic:** The ratio of asymptomatic to symptomatic VTE was obtained from Quinlan et al. (2007)(66). In order to explore the sensitivity of the model results to this ratio, sensitivity analysis was conducted in which the ratio was varied based on the confidence intervals reported in this paper. Quinlan et al. (2007) also reported the values based on trials adjudicated at McMaster and in Gothenberg only. Sensitivity analysis was also run based on these results.
- **Drug costs**: In order to determine the effect drug costs have on the model results, a sensitivity analysis was run with these costs excluded.
- **Discount rates**: In line with NICE guidelines, discount rates were varied from 0% to 6%
- **Duration of hospitalisation**: The base case duration of hospitalisation following THR and TKR was the average length of stay as reported in the NHS Reference Costs(82). In order to test the sensitivity of results to this input, the duration was varied by ±2 days. Since enoxaparin patients require their first dose 12 hours before surgery, they may incur an additional day of hospitalisation compared with patients receiving rivaroxaban. An additional sensitivity analysis exploring the impact of this additional stay was conducted using the weighted average cost per day of patients undergoing minor or intermediate hip or knee procedures based on NHS reference costs.
- **Efficacy and Safety data**: Although the clinical trials reported differences in efficacy and safety between the two arms, this was non-statistically significant for some endpoints. For the basecase analysis it was assumed there was no difference between the two methods of prophylaxis where the difference was not statistically significant. However, it could be argued that the non-significance of these results is due to low numbers and does not indicate that there is no difference between the drugs. Therefore, a sensitivity analysis was run using the actual relative risk and risk differences reported in the direct comparison with enoxaparin and the indirect comparison with dabigatran, regardless of whether these values were statistically significant.
- **Proportion of VTE patients with symptomatic VTE and PE:** None of the RECORD clinical trials identified a statistically significant difference in PE rates between rivaroxaban and enoxaparin arms and the RECORD 1 clinical trial did not identify any statistically significant difference in symptomatic VTE rates. The base case analysis therefore assumes that the probability of these events is the same in the enoxaparin arm as in the rivaroxaban arm. As an alternative assumption for the non-significant values, a sensitivity analysis was run in which the proportion of VTE patients who had a symptomatic VTE or a PE in the rivaroxaban arm was applied to the enoxaparin arm in order to estimate the number of patients with a symptomatic VTE or PE based on the probability of total VTE. This sensitivity analysis was not conducted for the RECORD 3 analysis since no patients in the rivaroxaban arm experienced a PE.
- **Switch to no prophylaxis**: An additional scenario analysis was conducted assuming patients are stopping current treatment after discharge from hospital. The cohort in the study drug arm of the model (rivaroxaban) receive 35 days of prophylaxis (THR) or 14 days or prophylaxis (TKR), whereas in the comparator arm (enoxaparin) receive prophylaxis only for the period of hospitalisation.
  The cost of treatment is calculated based on the number of days patients receive each drug for at each scenario;
    - THR; 35 days of prophylaxis with rivaroxaban versus 7.8 days with enoxaparin
    - TKR; 14 days of prophylaxis with rivaroxaban versus 7.3 days for enoxaparin

  The efficacy of the enoxaparin arm under this scenario is based on estimates by Eikelboom et al (2001)(21) and Hull et al. (2000)(87). The model assumes that 76% of all VTE events occur during hospitalisation (calculated from the data reported by Hull et al., 2000). Moreover, Eikelboom et al., (2001) conducted a meta-analysis of all randomised trials assessing the efficacy and safety of extended duration prophylaxis

compared with placebo or untreated control in patients undergoing elective hip or knee replacement surgery. This study reported a reduction in VTE events in patients with extended duration prophylaxis compared with the control group (odds ratio 0.38). This odds ratio was used to calculate the increase in VTE events during the post-switch period when patients switch to no prophylaxis. The VTE event risk during the pre-switch period was then added to the risk during the post-switch period in order to estimate the VTE event risk for the prophylaxis period.
An additional sensitivity analysis was also conducted in which the costs of enoxaparin were reduced to reflect the reduced duration of prophylaxis, but no efficacy adjustment was made.

- **Utility values following THR**: Since more than one source reporting the utility following THR was identified in the literature review (see section 7.2.8), a sensitivity analysis was run using the value of 0.74 which was reported by Ostendorf et al (2004)(76;77) and Malchau et al. (2005)(78)
- **Utility values weighted by time**: it may be argued that calculating the weighted average utility over time is a more accurate estimate of the annual utility than the one year utility score reported by Brunenberg et al. (2005). Therefore, a sensitivity analysis was run using the weighted average utility estimates reported in Table 44.
- **Utility of PTS**: The utility assigned to patients with PTS is expected to be a key driver of the model results. A sensitivity analysis varying the utility value using the lower and higher 95% confidence interval was therefore conducted.
- **Proportion of PE patients who also have DVT**: The base case analysis assumes that 37% of PE patients also have a DVT. In order to assess the impact this assumption has on the model, this was varied from 0% to 100% in sensitivity analysis.
- **Cost of PTS:** Several estimates of the annual cost of treating PTS were identified. The base case analysis was based on the median cost reported by MacDougall et al. (2006) was used as this was the most recently published source(85). The authors of this study also reported that the mean annual cost of PTS was $11,667. As a conservative assumption this was not used in the base case analysis, however this value was used in sensitivity analysis in order to asses the impact on the results.
  The cost of PTS used in the NICE analysis was based on a study by Bergqvist et al. (1997)(94) who conducted an observational study of patients who were diagnosed with a DVT or PE between 1970 and 1985 in a Swedish hospital. Patients were followed up for 10 to 15 years, and data on the use of health care resources due to complications or events related to VTE over this time was recorded. NICE use a cost of £4,000 for PTS based on this analysis, although it is not clear exactly how this value was calculated. A sensitivity analysis was run using an annual cost of PTS of £278.89 (£4000 inflated to current prices and divided by 15).
  Caprini et al. (2003) estimated the costs of diagnosis and treatment of PTS based on patient care protocols defined by the literature and applying US-specific costs(95). The authors estimated a cost per year for treating mild/moderate PTS of $839 in the first year and $341 in subsequent years, while the cost per year for treating severe PTS is $3817 in the first year and $933 in subsequent years. The difference between the first and subsequent years was assumed to be the cost of diagnosis. These costs were inflated to current prices, converted to pounds and used in the sensitivity analysis. These costs were not used in the base case analysis since the treatment protocol on which these costs are based does not take recurrent events such as recurrent ulcers into account, and may therefore be an underestimate of the actual cost.
- **Probability of PTS**: Since the probability of PTS was expected to be a key driver of the model results, a sensitivity analysis was run in which the probability of PTS in each year was varied based on the upper and lower confidence intervals for year 1. Prandoni et al. (1997) only report these values in the form of a graph(64). The values read from the graph should therefore be considered to be estimates.
- **Probability of recurrent VTE**: Prandoni et al. (1997) also present a graph which indicates the upper and lower confidence intervals of the cumulative incidence of

recurrent VTE. These values were used to estimate upper and lower values for the probability of recurrent VTE for year 1 and a sensitivity analysis was conducted in order to test the impact of using different probabilities of recurrent VTE in the model.

- **Indirect comparison vs dabigatran 220mg (Bucher et al. 1997)(44):** Dabigatran has recently been recommended by the SMC for the primary prevention of VTE in adult patients who have undergone elective total hip or total knee replacement surgery. A sensitivity analysis comparing rivaroxaban with dabigatran 220mg was therefore conducted. This analysis uses results from the adjusted indirect comparison(44). Further details of this analysis are provided in section 6. The duration of dabigatran prophylaxis administration in the indirect comparison matches the average of the reported clinical trials; THR: 28-35 days –average 31.5 and TKR 6-10 days –average 8 days.
- **Comparison vs LMWHs:** Since the NICE clinical guidelines recommend all LMWHs equally, a sensitivity analysis was conducted versus a mix of enoxaparin, dalteparin and tinzaparin. The relative market share was based on data from IMS Health, and was used to weight the average prophylaxis related drug cost(9). This analysis assumes that all LMWHs have the same efficacy and safety profile as enoxaparin based on published literature(13;49;50).
- **RECORD 4 data:** Since the RECORD 4 trial does not reflect clinical practice in England and Wales, it is less relevant than the other RECORD trials and was not therefore considered in the base case analysis. However, a sensitivity analysis was conducted comparing rivaroxaban with both enoxaparin and dabigatran (220mg) using the results of this trial.
- **Pooled data from all RECORD trials**: The base case analysis considers each of the RECORD trials individually. Additional sensitivity analyses were conducted based on the results of the pooled analyses (as described in section 6). Sensitivity analyses were conducted based on the THR studies (RECORD 1 and 2 combined), the TKR studies (RECORD 3 and 4 combined) and all available studies (RECORD 1, 2, 3 and 4 combined).

7.2.11.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

In order to address uncertainty around the model inputs a probabilistic sensitivity analysis was performed. Table 46 presents the parameters of the model that were sampled and the corresponding distributions that were fitted. The PSA was calculated by one thousand samples.

Table 46 PSA Inputs

VARIABLE	DISTRIBUTION	NOTES
Costs		
Nurse cost in hospital	Gamma	Mean £40; Lowest and highest Nurse salary reported assumed to be limits for the 99% confidence interval (CI). Nurse cost post discharge linked to this variable.
Full blood count	Gamma	Mean £2.34; Assumed 99% CI limits (0-mean*2) Liver function test linked to this variable.
Proportion of pts that develop symptomatic event post-discharge	Beta	Mean 0.24; Assume Beta(a,b) parameters by imposing the following percentiles; 50% mean, 25% & 75% -/+ 0.10
Major bleed event w/o reoperation	Normal	Mean £727.84; variance calculated by $s^2 = \frac{\sum f_i (M_i - \bar{x})^2}{n-1}$ where f_i and M_i are frequency and midpoint of class i, respectively*. Major bleed with reoperation linked to this variable.
Proportion of major bleeds that need reoperation	Beta	Mean 0.20; Assume Beta(a,b) by imposing the following percentiles; 50% mean, 25% & 75% -/+ 0.10
Proportion of major bleeds that lead to chronic morbidity (i.e. non-fatal strokes)	Beta	Mean 0.03; Assume Beta(a,b) by imposing the following percentiles; 50% mean, 25% & 75% -/+ 0.015
Doppler ultrasound (outpatient)	Normal	The interquartile range based on the individual data submissions made by providers is used as a proxy for the actual interquartile range in order to calculate the standard deviation (SD) and SE. A normal distribution is used because the unit cost is based on a large number of observations (over 24,000). The cost of inpatient Doppler ultrasound is linked to this variable.
Outpatient visit	Normal	Similar to the above.
Angiography (outpatient)	Normal	The interquartile range based on the individual data submissions made by providers is used as a proxy for the actual interquartile range in order to calculate the SD and SE. A normal distribution is used because the unit cost is based on a large number of observations (over 59,000). The cost of inpatient angiography is linked to this variable.
Chest x-ray	Normal	The interquartile range based on the individual data submissions made by providers is used as a proxy for the actual interquartile range in order to calculate the SD and SE. A normal distribution is used because the unit cost is based on a large number of observations (over 3 million).
ECG	Normal	The interquartile range based on the individual data submissions made by providers is used as a proxy for the actual interquartile range in order to calculate the SD and SE. A normal distribution is used because the unit cost is based on a large number of observations (over 53,000).
Cost of A&E visit	Normal	Mean £120.28; variance calculated by $s^2 = \frac{\sum f_i (M_i - \bar{x})^2}{n-1}$ where f_i and M_i are frequency and midpoint of class i, respectively*.
ICU treatment	Normal	The interquartile range based on the individual data submissions made by providers is used as a proxy for the actual interquartile range in order to calculate the SD and SE. A normal distribution is used because the unit cost is based on a large number of observations (over 16,000).

VARIABLE	DISTRIBUTION	NOTES
Proportion of pts that need ICU treatment	Beta	Mean 0.10; Assume Beta(a,b) by imposing the following percentiles; 50% mean, 25% & 75% -/+ 0.025.
Proportion of people who require additional hospital stay for DVT	Beta	Mean 0.10; Assume Beta(a,b) by imposing the following percentiles; 50% mean, 25% & 75% -/+ 0.025
Anticoagulation clinic follow-up visit cost	Normal	Mean £18.72; variance calculated by $s^2 = \frac{\sum f_i (M_i - \bar{x})^2}{n-1}$ where f_i and M_i are frequency and midpoint of class i, respectively*. Anticoagulation clinic first visit cost linked to this variable.
Cost per additional days in hospital for PE	Normal	Mean £251; variance calculated by $s^2 = \frac{\sum f_i (M_i - \bar{x})^2}{n-1}$ where f_i and M_i are frequency and midpoint of class i, respectively*. Hospital cost for DVT linked to this variable.
Proportion of people who require additional hospital stay for PE.	Beta	Mean 0.90; Assume Beta(a,b) by imposing the following percentiles; 50% mean, 25% & 75% -/+ 0.05
Treatment of PTS	Gamma	Mean £2865; Assume SE ¼ of the mean
Utility values		
THR -No VTE event (utility of perfect health after operation)	Beta	Brunenberg et al. 2005(74) using SD and N reported for the usual care group. All VTE events in the THR population linked to this variable.
TKR -No VTE event (utility of perfect health after operation)	Beta	Brunenberg et al. 2005 using SD and reported for the usual care group. All VTE events in the TKR population linked to this variable.
Prophylaxis related bleeding days in hospital	Gamma	Mean 2.7; variance calculated by $s^2 = \frac{\sum f_i (M_i - \bar{x})^2}{n-1}$ where *fi* and *Mi* are frequency and midpoint of class *i*, respectively*.
PTS	Beta	Lenert et al. 1997(73) as reported 0.93 (0.76-1)
Recurrent VTE	Beta	Mean 0.84; Assume Beta(a,b) by imposing the following percentiles; 50% mean, 25% 0.8 & 75% 0.95
Event probabilities – prophylaxis period		
Prophylaxis related major bleeding	Lognormal	Fitted to the RR and the CI in each comparison.
VTE	Lognormal	Fitted to the RR and the CI in each comparison. All other VTE outcomes linked to this parameter.
Event probabilities – extrapolation period		
Proportion of patients with a false positive VTE test: DVT	Beta	Mean 0.10; Assume Beta(a,b) by imposing the following percentiles; 50% mean, 25% & 75% -/+ 0.025
Proportion of patients with a false positive VTE test: PE	Beta	Mean 0.02; Assume Beta(a,b) by imposing the following percentiles; 25% 0.015, 50% mean, 75% 0.025
Probability of death following major bleeding	Beta	Mean 0.008; Assume Beta(a,b) by imposing the following percentiles; 25% 0.0075, 50% mean, 75% 0.0085
Risk of VTE after RECORD THR	Beta	Assume Beta(a,b) by imposing the following percentiles; 25% 0.0068, 50% mean, 75% 0.0078. The risk of PE is linked to this variable.
Risk of VTE after RECORD TKR	Beta	Assume Beta(a,b) by imposing the following percentiles; 25% 0.0065, 50% mean, 75% 0.0075. The risk of PE is linked to this variable.
In THR, risk of asymptomatic VTE developing into symptomatic	Beta	(66); 0.20 (0.163-0.263) The risk of PE is linked to this variable.

VARIABLE	DISTRIBUTION	NOTES
In TKR, risk of asymptomatic VTE developing into symptomatic	Beta	(66); 0.05 (0.023-0.071) The risk of PE is linked to this variable.
Event probabilities – long-term complications period		
Probability of developing PTS: year 1	Beta	(64); 0.18 (0.13-0.22) CI read from figure. Assume N=200. All PTS probabilities for following years linked to this variable.
Probability of recurrent VTE: year 1	Beta	(64); 0.09 (0.08-0.16) CI read from figure. Assume N=400. All PTS probabilities for following years linked to this variable.

*The source of the cost data does not provide any measure of variation within each group. The employed method estimates overall variability across the groups using the formula for grouped data. This assumes that all estimates within group *i* have the value *Mi.* This assumption is likely to underestimate overall variability of the parameter.

7.2.12 Statistical analysis

7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

Please see section 7.2.7.2 and appendix 6 for an explanation.

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

As described above, the probabilities used in the long-term complications module are time dependent and can be seen in Table 40.

7.2.13 Validity

The economic model was developed by IMS Health, an independent health economics consultancy. The completed model was firstly validated by a senior member of staff not involved in the model development. The model was then further validated by another independent health economics consultancy (Pharmerit).

7.3 Results

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

THR Population Record 1 (rivaroxaban 35 days vs enoxaparin 35 days)

The costs calculated in the model are outlined in Table 47.

Table 47 Cost Breakdown (THR - RECORD 1)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
ACUTE PHASE			
Prophylaxis related costs*	£165.90	£234.67	-£68.77
Cost of events	£23.55	£27.88	-£4.34
LONG-TERM COMPLICATIONS MODULE			
Cost of events	£27.60	£73.97	-£46.37

*Prophylaxis related costs include drug, administration and monitoring costs

Table 47 shows that rivaroxaban is associated with reduced costs in terms of prophylaxis related costs, the cost of treating VTE events, and the cost of treating long-term complications.

The results of the cost-effectiveness analysis of rivaroxaban versus enoxaparin in a THR population based on the RECORD 1 trial data over a lifetime horizon are shown in Table 48.

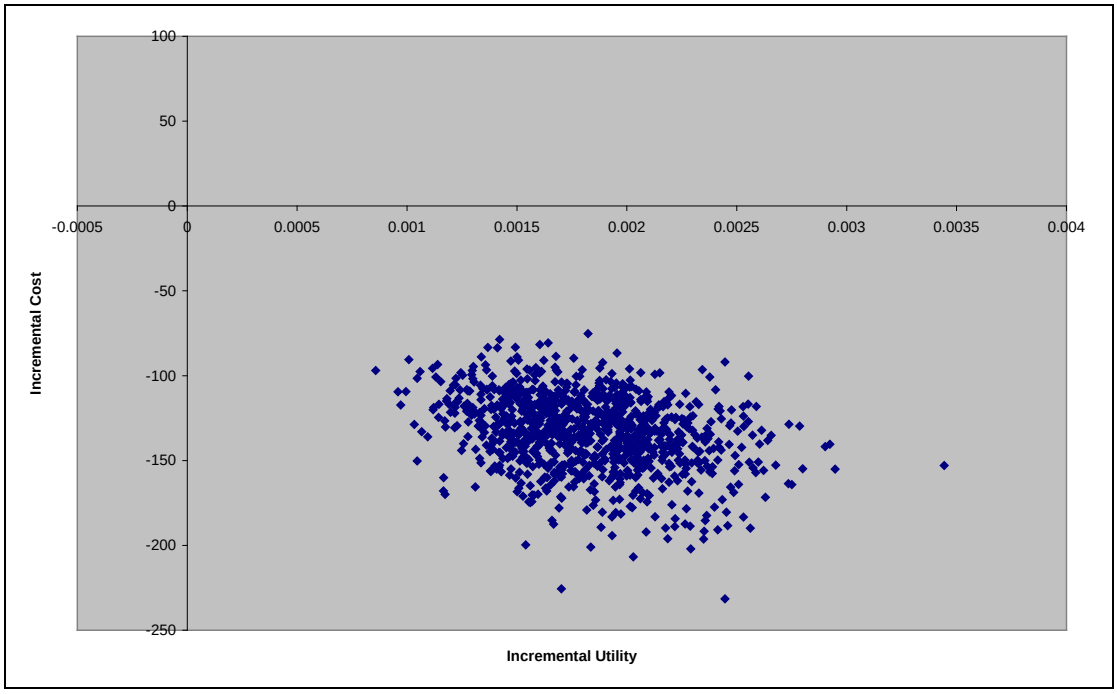
Table 48 Model results: rivaroxaban vs enoxaparin (THR – RECORD 1)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£224.87	£357.45	-£132.58
QALY	13.79901	13.79724	0.0018
Cost per QALY			**Rivaroxaban dominates**

Table 48 shows that based on the RECORD 1 clinical trial, rivaroxaban will cost less and results in more QALYs than enoxaparin over a lifetime horizon. Based on this analysis, rivaroxaban therefore dominates enoxaparin as prophylaxis in a THR population.

Figure 13 shows the cost utility analysis plane for the THR population based on RECORD 1.

Figure 13 THR RECORD 1: Cost Utility Analysis Plane (rivaroxaban v enoxaparin)



All PSA samples fall within the SE quadrant where rivaroxaban is less costly and more effective than enoxaparin; it dominates.

THR Population Record 2 (rivaroxaban 35 days vs enoxaparin 12-14 days)

The costs calculated in the model are outlined in Table 49.

Table 49 Cost Breakdown (THR - RECORD 2)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
ACUTE PHASE			
Prophylaxis related costs*	£166.35	£104.31	£62.04
Cost of events	£20.01	£34.91	-£14.90
LONG-TERM COMPLICATIONS MODULE			
Cost of events	£48.62	£262.76	-£214.14

*Prophylaxis related costs include drug, administration and monitoring costs

Table 49 shows that rivaroxaban is associated with higher prophylaxis related costs due to the shorter duration of enoxaparin prophylaxis. However, the cost of treating VTE events, and the cost of treating long-term complications is lower in the rivaroxaban arm.

The results of the cost-effectiveness analysis of rivaroxaban versus enoxaparin in a THR population based on the RECORD 2 trial data over a lifetime horizon are shown in Table 50.

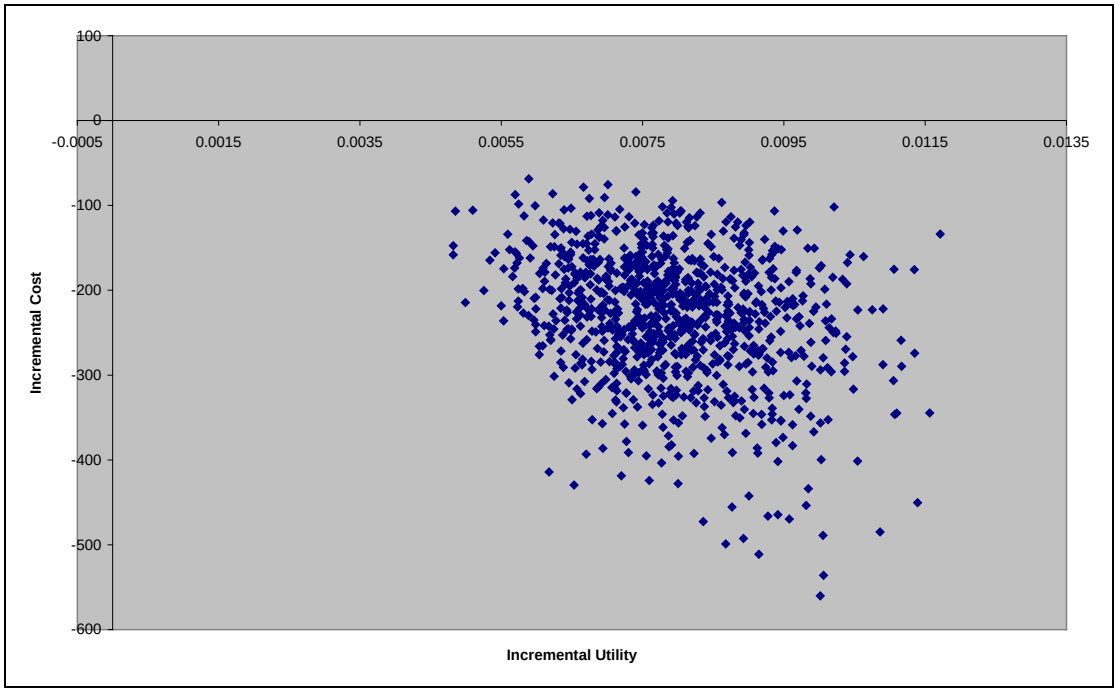
Table 50 Model results: rivaroxaban vs enoxaparin (THR – RECORD 2)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£248.72	£476.19	-£227.46
QALY	13.79861	13.79075	0.0079
Cost per QALY			**Rivaroxaban dominates**

Table 50 shows that based on the RECORD 2 clinical trial, rivaroxaban will cost less and results in more QALYs than enoxaparin over a lifetime horizon. Based on this analysis, rivaroxaban therefore dominates enoxaparin as VTE prophylaxis in a THR population.

Figure 14 shows the cost utility analysis plane for the THR population based on RECORD 2.

Figure 14 THR RECORD 2: Cost Utility Analysis Plane (rivaroxaban v enoxaparin)



All PSA samples fall within the SE quadrant where rivaroxaban is less costly and more effective than enoxaparin; it dominates.

TKR Population Record 3 (rivaroxaban 14 days vs enoxaparin 14 days)

The costs calculated in the model are outlined in Table 51.

Table 51 Cost Breakdown (TKR)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
ACUTE PHASE			
Prophylaxis related costs*	£68.15	£104.88	-£36.73
Cost of events	£25.55	£34.18	-£8.63
LONG-TERM COMPLICATIONS MODULE			
Cost of events	£100.82	£260.84	-£160.02

*Prophylaxis related costs include drug, administration and monitoring costs

Table 51 shows that rivaroxaban is associated with lower costs in terms of prophylaxis related costs, the cost of treating VTE events, and the cost of treating long-term complications.

The results of the cost-effectiveness analysis of rivaroxaban versus enoxaparin in a TKR population based on the RECORD 3 trial data over a lifetime horizon are shown in Table 52.

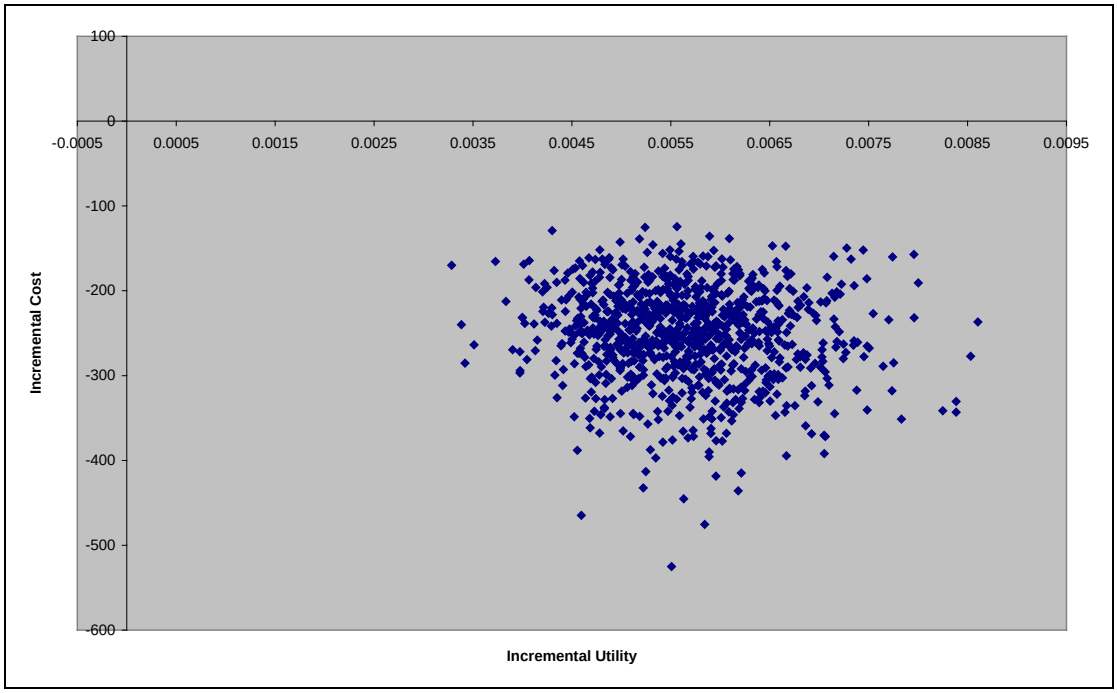
Table 52 Model results: rivaroxaban vs enoxaparin (TKR)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£222.98	£473.54	-£250.56
QALY	13.67062	13.66498	0.0056
Cost per QALY			**Rivaroxaban dominates**

Table 52 shows that rivaroxaban will cost less and results in more QALYs than enoxaparin over a lifetime horizon. Based on this analysis, rivaroxaban therefore dominates enoxaparin as prophylaxis in a TKR population.

Figure 15 shows the cost utility analysis plane for the TKR population based on RECORD 3.

Figure 15 TKR RECORD 3: Cost Utility Analysis Plane (rivaroxaban v enoxaparin)



All PSA samples fall within the SE quadrant where rivaroxaban is less costly and more effective than enoxaparin; it dominates.

7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

Data for the THR and TKR populations are presented separately in section 7.3

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

The results of the one way sensitivity analyses for the base case analysis of rivaroxaban vs enoxaparin in a THR population based on the RECORD 1 trial data are shown in Table 53

Table 53 One way sensitivity analysis results: Total Hip Replacement (RECORD 1)

	Sensitivity Analysis	**Source**	**Incremental Cost**	**Incremental QALYs**	**Results**
Base Case			**-£132.58**	**0.0018**	**Rivaroxaban dominates**
1.	Time Period: Acute phase (up to 3 months)	Sullivan et al., 2003(29)	-£73.10	0.0002	Rivaroxaban dominates
2.	Time Period: 5-years	Assumption	-£86.12	0.0006	Rivaroxaban dominates
3.	Extrapolation method: No symptomatic VTE to symptomatic VTE	White et al., 1998(69)	-£68.44	0.0000	Rivaroxaban is cost savin
4.	Risk of symptomatic to asymptomatic VTE: lower limit (26.3%)	Quinlan et al., 2007(66)	-£150.91	0.0023	Rivaroxaban dominates
5.	Risk of symptomatic to asymptomatic VTE: higher limit (16.3%)	Quinlan et al., 2007(66)	-£119.55	0.0014	Rivaroxaban dominates
6.	Drug costs: excluded	Assumption	-£141.34	0.0018	Rivaroxaban dominates
7.	Discount rates: Costs: 0%, Effects: 0%	Assumption	-£156.32	0.0023	Rivaroxaban dominates
8.	Discount rates: Costs: 6%, Effects: 6%	Assumption	-£121.75	0.0015	Rivaroxaban dominates
9.	Duration of hospitalisation: +2 days	Assumption	-£128.74	0.0018	Rivaroxaban dominates
10.	Duration of hospitalisation: -2 days	Assumption	-£136.42	0.0018	Rivaroxaban dominates
11.	Duration of hospitalisation: 1 extra day for enoxaparin (£786)	Assumption	-£918.58	0.0018	Rivaroxaban dominates
12.	Efficacy and Safety data: accept non-significant data	Direct comparison	-£159.63	0.0100	Rivaroxaban dominates
13.	Proportion of VTE patients with symptomatic VTE and PE: assume same as rivaroxaban	RECORD 1(10)	-£167.97	0.0031	Rivaroxaban dominates
14.	Switch to no prophylaxis after discharge: enoxaparin costs and efficacy adjusted	Assumption	£2.73	0.0030	£914 per QALY
15.	Switch to no prophylaxis after discharge: enoxaparin costs adjusted only (efficacy remains as per RECORD study)	Assumption	£25.93	0.0018	£14,616 per QALY
16.	Utility values following THR: 0.75	Ostendorf et al. (2004)(76;77); Malchau et al. (2005)(78)	-£132.58	0.0018	Rivaroxaban dominates
17.	Utility values weighted by time: 0.701	Brunenberg et al. (2005)(74)	-£132.58	0.0018	Rivaroxaban dominates
18.	Utility of PTS: upper value (1)	Lenert et al., 1997(73)	-£132.58	0.0006	Rivaroxaban dominates
19.	Utility of PTS: lower value (0.76)	Lenert et al., 1997(73)	-£132.58	0.0046	Rivaroxaban dominates

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£132.58**	**0.0018**	**Rivaroxaban dominates**
20.	0% PE patients also have DVT	Assumption	-£126.85	0.0017	Rivaroxaban dominates
21.	100% PE patients also have DVT	Assumption	-£141.49	0.0020	Rivaroxaban dominates
22.	Cost of PTS: £7,072.16	MacDougall et al., 2006(85)	-£218.67	0.0018	Rivaroxaban dominates
23.	Cost of PTS: £278.89	NICE, 2007(22)	-£79.66	0.0018	Rivaroxaban dominates
24.	Cost of PTS: Diagnosis £758.68, Treatment £344.05	Caprini et al., 2003(95)	-£82.87	0.0018	Rivaroxaban dominates
25.	Probability of PTS: upper value (year 1: 0.22)	Prandoni et al., 1997(64)	-£144.29	0.0020	Rivaroxaban dominates
26.	Probability of PTS: lower value (year 1: 0.13)	Prandoni et al., 1997(64)	-£117.28	0.0014	Rivaroxaban dominates
27.	Probability of recurrent VTE: upper value (year 1: 0.16)	Prandoni et al., 1997(64)	-£133.44	0.0018	Rivaroxaban dominates
28.	Probability of recurrent VTE: lower value (year 1: 0.08)	Prandoni et al., 1997(64)	-£132.48	0.0018	Rivaroxaban dominates
29.	Comparison vs LMWHs	BNF, 2008(79); IMS Health(9)	-£123.48	0.0018	Rivaroxaban dominates

Table 53 shows that rivaroxaban dominates enoxaparin and a mix of LMWHs in this population over a range of assumptions.

Sensitivity analysis 3 involved changing the method of extrapolation to assume that all patients who did not develop a symptomatic VTE event during the clinical trial (i.e. those with no VTE and those with an asymptomatic VTE) are at risk of developing a VTE during the post-prophylaxis module. Since the direct comparison found no statistically significant differences in symptomatic VTE events between rivaroxaban and enoxaparin, the proportion of the cohort at risk of developing a VTE during the post-prophylaxis module was the same in both arms. Consequently, there was no difference in the proportion of patients who had experienced a symptomatic VTE during the acute phase of the model, which meant that there was no difference in the proportion of patients at risk of long-term complications. The model therefore found no differences in effectiveness between rivaroxaban and enoxaparin over a lifetime horizon when this method of extrapolation was used. As in the base case analysis, rivaroxaban was associated with lower costs due to lower prophylaxis related costs which was driven by the cost of enoxaparin administration thus this sensitivity analysis indicates that rivaroxaban is cost saving compared to enoxaparin.

Analysis 13 was conducted in order to assess the impact of our assumption that where there is no statistically significant difference in events, we assume the same number of events occurring in both arms. Assuming instead that the probability of symptomatic VTE and PE depends on the probability of total VTE does not change the overall result (i.e. rivaroxaban still dominates), although the incremental costs and QALYs increase compared with the base case analysis indicating that the base case assumption was conservative.

Analyses 14 and 15 assumed that all enoxaparin patients discontinue prophylaxis on discharge. Using this assumption, rivaroxaban no longer dominates as the cost of the rivaroxaban arm is now higher than the enoxaparin arm due to the lower drug costs incurred in the enoxaparin arm as a result of the shorter duration, although rivaroxaban still results in higher QALYs. Under this assumption when only the cost of enoxaparin is adjusted, and the efficacy is based on

35 days treatment, the cost per QALY is £14,616, and when we also adjust the efficacy of enoxaparin in order to reflect the reduced duration of prophylaxis the cost per QALY is £914.

Although it appears from Table 53 that using different utility values following THR does not affect the results at all (analyses 15 and 16), the results are actually different but the impact on the results is so small that it is not apparent at the level shown in the table. The model is therefore not sensitive to the source or method used to derive these values.

The results of the one way sensitivity analyses for total hip replacement based on the RECORD 2 trial data are shown in Table 54

Table 54 One way sensitivity analysis results: Total Hip Replacement (RECORD 2)

	Sensitivity Analysis	**Source**	**Incremental Cost**	**Incremental QALYs**	**Results**
Base Case			**-£227.46**	**0.0079**	**Rivaroxaban dominates**
1.	Time Period: Acute phase (up to 3 months)	Sullivan et al., 2003(29)	£47.14	0.0008	£58,337 per QALY
2.	Time Period: 5-years	Assumption	-£13.33	0.0024	Rivaroxaban dominates
3.	Extrapolation method: No symptomatic VTE to symptomatic VTE	White et al., 1998(69)	-£68.05	0.0034	Rivaroxaban dominates
4.	Rate of symptomatic to asymptomatic VTE: lower limit (26.3%)	Quinlan et al., 2007(66)	-£272.77	0.0091	Rivaroxaban dominates
5.	Rate of symptomatic to asymptomatic VTE: higher limit (16.3%)	Quinlan et al., 2007(66)	-£195.25	0.0070	Rivaroxaban dominates
6.	Drug costs: excluded	Assumption	-£326.13	0.0079	Rivaroxaban dominates
7.	Discount rates: Costs: 0%, Effects: 0%	Assumption	-£337.10	0.0102	Rivaroxaban dominates
8.	Discount rates: Costs: 6%, Effects: 6%	Assumption	-£117.45	0.0068	Rivaroxaban dominates
9.	Duration of hospitalisation: +2 days	Assumption	-£232.62	0.0079	Rivaroxaban dominates
10.	Duration of hospitalisation: -2 days	Assumption	-£231.30	0.0079	Rivaroxaban dominates
11.	Duration of hospitalisation: 1 extra day for enoxaparin (£786)	Assumption	-£1013.46	0.0079	Rivaroxaban dominates
12.	Efficacy and Safety data: accept non-significant data	Direct comparison	-£224.65	0.0091	Rivaroxaban dominates
13.	Proportion of VTE patients with PE: assume same as rivaroxaban	RECORD 2(11)	-£202.65	0.0075	Rivaroxaban dominates
14.	Switch to no prophylaxis after discharge: enoxaparin costs and efficacy adjusted	Assumption	-£315.27	0.0115	Rivaroxaban dominates
15.	Switch to no prophylaxis after discharge: enoxaparin costs adjusted only (efficacy remains as per RECORD study)	Assumption	-£199.31	0.0079	Rivaroxaban dominates
16.	Utility values following THR: 0.75	Ostendorf et al. (2004)(76;77); Malchau et al. (2005)(78)	-£227.46	0.0080	Rivaroxaban dominates
17.	Utility values weighted by time: 0.701	Brunenberg et al. (2005) (74)	-£227.46	0.0078	Rivaroxaban dominates
18.	Utility of PTS: upper value (1)	Lenert et al., 1997(73)	-£227.46	0.0025	Rivaroxaban dominates
19.	Utility of PTS: lower value (0.76)	Lenert et al., 1997(73)	-£227.46	0.0208	Rivaroxaban dominates
20.	0% PE patients also have DVT	Assumption	-£213.31	0.0076	Rivaroxaban dominates

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£227.46**	**0.0079**	**Rivaroxaban dominates**
21.	100% PE patients also have DVT	Assumption	-£246.50	0.0083	Rivaroxaban dominates
22.	Cost of PTS: £7,072.16	MacDougall et al., 2006(85)	-£625.34	0.0079	Rivaroxaban dominates
23.	Cost of PTS: £278.89	NICE, 2007(22)	£17.07	0.0079	£2,173 per QALY
24.	Cost of PTS: Diagnosis £758.68, Treatment £344.05	Caprini et al., 2003(95)	£2.24	0.0079	£285 per QALY
25.	Probability of PTS: upper value (year 1: 0.22)	Prandoni et al., 1997(64)	-£281.40	0.0091	Rivaroxaban dominates
26.	Probability of PTS: lower value (year 1: 0.13)	Prandoni et al., 1997(64)	-£156.92	0.0063	Rivaroxaban dominates
27.	Probability of recurrent VTE: upper value (year 1: 0.16)	Prandoni et al., 1997(64)	-£230.33	0.0081	Rivaroxaban dominates
28.	Probability of recurrent VTE: lower value (year 1: 0.08)	Prandoni et al., 1997(64)	-£227.05	0.0078	Rivaroxaban dominates
29.	Comparison vs LMWHs	BNF, 2008(79); IMS Health(9)	-£224.12	0.0079	Rivaroxaban dominates

As with the results of the RECORD 1 analysis, table 54 shows that rivaroxaban dominates enoxaparin and a mixed group of LMWHs in this population over a range of assumptions using the RECORD 2 clinical data.

If we only consider events occurring in the acute phase of the model, rivaroxaban is more costly than enoxaparin although it results in more QALYs. The incremental cost per QALY in this analysis is £58,337 (analysis 1). Since this analysis does not consider any long-term complications occurring as a result of a VTE event, the majority of costs incurred in this analysis are the prophylaxis drug costs. Since the purpose of the RECORD 2 clinical trial was to compare extended duration rivaroxaban (35 days) with short duration enoxaparin (10-14 days), the prophylaxis related costs were significantly lower in the enoxaparin arm due to the reduced duration of prophylaxis.

As with the RECORD 1 analysis, assuming the same proportion of VTE patients have a PE as in the rivaroxaban arm does not change the overall result (analysis 13). However, while the incremental costs and QALYs increased in the RECORD 1 analysis, the opposite effect was observed in the RECORD 2 analysis with a slight decrease in the incremental results.

Analyses 23 and 24 indicate that assuming a lower cost of PTS results in rivaroxaban being more costly than enoxaparin over a lifetime horizon resulting in a cost per QALY of up to £2,173. The annual cost of PTS on which this analysis was based reflects reimbursed prices (not costs) in one Swedish hospital around 20 years ago. It is therefore unclear how well this cost will reflect current costs and practices in England and Wales.

The results of the one way sensitivity analyses for total knee replacement based on the RECORD 3 trial data are shown in Table 55.

Table 55 One way sensitivity analysis results – Total Knee Replacement

	Sensitivity Analysis	**Source**	**Incremental Cost**	**Incremental QALYs**	**Results**
Base Case			**-£250.56**	**0.0056**	**Rivaroxaban dominates**
1.	Time Period: Acute phase (up to 3 months)	Sullivan et al., 2003(29)	-£45.36	0.0005	Rivaroxaban dominates
2.	Time Period: 5-years	Assumption	-£90.54	0.0017	Rivaroxaban dominates
3.	Extrapolation method: No symptomatic VTE to symptomatic VTE	White et al., 1998(69)	-£77.54	0.0013	Rivaroxaban dominates
4.	Rate of symptomatic to asymptomatic VTE: lower limit (7.1%)	Quinlan et al., 2007(66)	-£271.98	0.0062	Rivaroxaban dominates
5.	Rate of symptomatic to asymptomatic VTE: higher limit (2.3%)	Quinlan et al., 2007(66)	-£228.96	0.0050	Rivaroxaban dominates
6.	Drug costs: excluded	Assumption	-£251.61	0.0056	Rivaroxaban dominates
7.	Discount rates: Costs: 0%, Effects: 0%	Assumption	-£332.50	0.0074	Rivaroxaban dominates
8.	Discount rates: Costs: 6%, Effects: 6%	Assumption	-£213.18	0.0048	Rivaroxaban dominates
9.	Duration of hospitalisation: +2 days	Assumption	-£246.72	0.0056	Rivaroxaban dominates
10.	Duration of hospitalisation: -2 days	Assumption	-£254.40	0.0056	Rivaroxaban dominates
11.	Duration of hospitalisation: 1 additional day for enoxaparin (£818)	Assumption	-£1,068.56	0.0056	Rivaroxaban dominates
12.	Efficacy and Safety data: accept non-significant data	Direct comparison	-£221.11	0.0052	Rivaroxaban dominates
13.	Switch to no prophylaxis after discharge: enoxaparin costs and efficacy adjusted	Assumption	-£322.03	0.0089	Rivaroxaban dominates
14.	Switch to no prophylaxis after discharge: enoxaparin costs adjusted only (efficacy remains as per RECORD study)	Assumption	-£218.74	0.0056	Rivaroxaban dominates
15.	Utility values weighted by time: 0.701	Brunenberg et al. (2005) (74)	-£250.56	0.0057	Rivaroxaban dominates
16.	Utility of PTS: upper value (1)	Lenert et al., 1997(73)	-£250.56	0.0017	Rivaroxaban dominates
17.	Utility of PTS: lower value (0.76)	Lenert et al., 1997(73)	-£250.56	0.0153	Rivaroxaban dominates
18.	0% PE patients also have DVT	Assumption	-£244.36	0.0055	Rivaroxaban dominates
19.	100% PE patients also have DVT	Assumption	-£260.22	0.0058	Rivaroxaban dominates
20.	Cost of PTS: £7,072.16	MacDougall et al., 2006(85)	-£548.00	0.0056	Rivaroxaban dominates

	Sensitivity Analysis	Source	Incremental Cost	Incremental QALYs	Results
Base Case			**-£250.56**	**0.0056**	**Rivaroxaban dominates**
21.	Cost of PTS: £278.89	NICE, 2007(22)	-£67.83	0.0056	Rivaroxaban dominates
22.	Cost of PTS: Diagnosis £758.68, Treatment £344.05	Caprini et al., 2003(95)	-£78.84	0.0056	Rivaroxaban dominates
23.	Probability of PTS: upper value (year 1: 0.22)	Prandoni et al., 1997(64)	-£290.82	0.0065	Rivaroxaban dominates
24.	Probability of PTS: lower value (year 1: 0.13)	Prandoni et al., 1997(64)	-£197.88	0.0045	Rivaroxaban dominates
25.	Probability of recurrent VTE: upper value (year 1: 0.16)	Prandoni et al., 1997(64)	-£252.64	0.0058	Rivaroxaban dominates
26.	Probability of recurrent VTE: lower value (year 1: 0.08)	Prandoni et al., 1997(64)	-£250.26	0.0056	Rivaroxaban dominates
27.	Comparison vs LMWHs	BNF, 2008(79); IMS Health(9)	-£247.19	0.0056	Rivaroxaban dominates

The sensitivity analysis in table 55 indicates that rivaroxaban costs less and results in more QALYs than enoxaparin and a mix of LMWHs over a range of sensitivity analyses.

Additional analyses

The base case analyses were performed based on the results of the three RECORD trials which are most relevant for England and Wales. However, additional analyses were performed based on the RECORD 4 clinical trial data and also using pooled data from the four RECORD studies and the results are presented in Table 56. Further details of the methods used to pool the results of these studies are presented in section 6.

Table 56 Rivaroxaban vs enoxaparin additional analyses - results

Population	Incremental Cost	Incremental QALYs	Results
TKR – RECORD 4	-£53.17	0.0005	Rivaroxaban dominates
THR – RECORD 1 & 2 pooled	-£182.00	0.0043	Rivaroxaban dominates
TKR – RECORD 3 & 4 pooled	-£178.11	0.0037	Rivaroxaban dominates
THR & TKR (RECORD 1,2,3 & 4 pooled)	-£202.89	0.0047	Rivaroxaban dominates

The additional analyses shown in Table 55 indicate that rivaroxaban is cost-effective when compared with enoxaparin in both a THR and TKR population. These results corroborate the findings of the base case analyses.

Indirect Comparison – Rivaroxaban vs Dabigatran

Additional analyses were also run in order to estimate the cost-effectiveness of rivaroxaban vs dabigatran. These analyses used efficacy and safety data obtained from the indirect comparison described in section 6.

The results of the cost-effectiveness analysis of rivaroxaban versus dabigatran (220mg) in THR over a lifetime horizon based on data from the RECORD 1 clinical trial and Eriksson et al. (2007a)(26) are shown in Table 57.

Table 57 Model results: rivaroxaban vs dabigatran (THR – RECORD 1)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£224.86	£396.22	-£171.36
QALY	13.79901	13.79400	0.0050
Cost per QALY			**Rivaroxaban dominates**

The results of the cost-effectiveness analysis of rivaroxaban versus dabigatran (220mg) in THR over a lifetime horizon based on data from the RECORD 2 clinical trial and Eriksson et al. (2007a) (26) are shown in Table 58.

Table 58 Model results: rivaroxaban vs dabigatran (THR – RECORD 2)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£248.72	£749.36	-£500.64
QALY	13.79861	13.78483	0.0138
Cost per QALY			**Rivaroxaban dominates**

The results of the cost-effectiveness analysis of rivaroxaban versus dabigatran (220mg) in TKR over a lifetime horizon based on data from the RECORD 3 clinical trial, Eriksson et al. (2007b)(27), and RE-MOBILIZE (2008)(28) are shown in Table 59.

Table 59 Model results: rivaroxaban vs dabigatran (TKR – RECORD 3)

	RIVAROXABAN	ENOXAPARIN	INCREMENTAL
Cost	£222.96	£259.59	-£36.63
QALY	13.67062	13.66934	0.0013
Cost per QALY			**Rivaroxaban dominates**

The analyses presented in Table 57 to Table 59 indicate that rivaroxaban is associated with lower costs and higher quality of life when compared with dabigatran in both a TKR and a THR population.

As in the comparison with enoxaparin, additional analyses were performed using pooled data from the four RECORD studies. The results of these analyses are presented in Table 60.

Table 60 Rivaroxaban vs dabigatran (220mg) additional analyses - results

Population	Trials	Incremental Cost	Incremental QALYs	Results
THR	RECORD1, RECORD 2 & RENOVATE	-£282.42	0.0080	Rivaroxaban dominates
TKR	RECORD 3, RECORD 4, REMODEL & REMOBILIZE	-£28.46	0.0010	Rivaroxaban dominates
THR & TKR	RECORD1, RECORD 2, RECORD 3, RECORD 4, RENOVATE, REMODEL & REMOBILIZE	-£82.39	0.0026	Rivaroxaban dominates

The analyses presented in Table 60 also indicated that rivaroxaban dominates dabigatran across a range of population groups.

7.3.3.2 What are the key drivers of the cost effectiveness results?

There are three key drivers of the cost-effectiveness results:

1) The probability of developing an initial VTE event, and the probability of developing a symptomatic VTE during the prophylaxis module
2) The assumption that patients with an asymptomatic VTE during the clinical trial period are at risk of developing a symptomatic VTE up to 90 days post-surgery (particularly in the analysis based on RECORD 1 data in which no statistically significant difference in symptomatic VTE events was observed).
3) The cost of PTS (since PTS is a chronic condition)

However, the sensitivity analyses shown above indicate that the cost-effectiveness results are very stable and none of the model inputs have a substantial impact on the results.

7.3.4 Interpretation of economic evidence

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

No previous analyses examining the cost-effectiveness of rivaroxaban have been conducted.

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

This economic evaluation applies to all adult patients undergoing elective total hip or knee replacement surgery as this is the population included in the pivotal clinical trials. Rivaroxaban is licenced for adult patients undergoing elective hip and knee replacement surgery. Data from the National Joint Registry, which collects information on all hip and knee replacement operations in England and Wales, demonstrates total joint replacement represents 89% of all hip and knee replacement operations(8). Patients undergoing the less common types of replacement of the hip or knee are also at risk of VTE. There is no reason to believe the risk differs from the baseline risk associated with all orthopaedic surgery of the hip or knee. There is no evidence to suggest the pathophysiology of VTE differs to that in total hip or knee replacement, therefore it is not anticipated that rivaroxaban would work any differently in this group of patients. Please see section 2 for additional information.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The evaluation has several strengths. In particular, the model structure is based on published recommendations and previously conducted economic evaluations and therefore represents best practice of economic modelling in this area. As far as possible, the economic evaluation is based on clinical trial data with the prophylaxis module replicating exactly what happened in the trial. Subsequent events are then modelled over a lifetime horizon. The cost and resource use assumptions in the model are very thorough, and as the sensitivity analysis indicates, the overall model results are not sensitive to changes in the model parameters and are therefore very robust.

However, the nature conducting an economic evaluation means that some assumptions are necessary due to imperfect information. Although the model is based on clinical trial data, due to the small number of events observed in the clinical trials, the probability of some events occurring is numerically different between prophylaxes but is not statistically significant. These differences are therefore not captured in the base case analysis but are however explored in a sensitivity analysis. An additional sensitivity analysis was also conducted using an alternative assumption based on the relationship between total VTE and symptomatic VTE/PE and this was not found to change the overall result.

Moreover, the data used to extrapolate the clinical trial results over a longer time horizon are based on published literature, and the key source for the occurrence of long-term complications(64) was based on an observational study published over ten years ago when the diagnosis and treatment of VTE events was different from today. The impact of using different probabilities for long-term complications was tested in sensitivity analysis and was not found to alter the overall conclusion.

An assumption is also necessary in order to project the symptomatic events that would develop if venography and treatment was not performed at the end of the RECORD trials since the true relationship between asymptomatic and symptomatic DVT is uncertain(96;97) Nuijten et al. 2003) and tests for asymptomatic VTE are not normally part of routine practice. Furthermore, if asymptomatic VTE is detected, it will be treated; hence, clinical trial follow up does not reflect what happens in routine practice where VTE is normally undetected and hence untreated. It is highly unlikely that RCTs would identify the rate of asymptomatic events developing to symptomatic since all VTE events would be treated once detected. Such an assumption allows the economic model to capture the full impact of differential VTE-related morbidity, and health related quality of life (HRQoL) impairment associated with each comparator. Several sensitivity analyses were conducted around this assumption.

Ideally all utility data would have come from one source. However, a systematic literature review was unable to identify any such source, thus the utility data used in the model is based on several sources and some assumptions were necessary in order to apply these values to the model. The utility values were tested in sensitivity analyses and did not change the overall conclusion.

Moreover, except from a few exceptions, the probabilistic analysis is largely based on assumptions for the variable range and type of distributions. The review of the model inputs did not identify appropriate forms for the probabilistic distributions. In such cases, the applied distributions are fitted to cover the extreme values that would likely to occur in real life, and therefore ensuring that the full range of uncertainty is explored.

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The model results are very robust. However, the quality of data on which the utility values are based is not ideal. A utility study including all of the relevant model health states would improve the uncertainty around the validity of these values. Similarly, a longer follow-up study would provide more data on the long-term complications associated with VTE events. Nevertheless, additional analysis would improve the accuracy of the model but is not expected to change the overall result (i.e. that rivaroxaban dominates enoxaparin).

Ideally, all cost-effectiveness analyses would have been based on head to head randomised controlled trials. This was not possible for the analyses of rivaroxaban vs dabigatran since no such trials have been conducted; hence these analyses are based on an indirect comparison. Similarly, the analysis comparing rivaroxaban with LMWHs as a group is based on the efficacy and safety data for enoxaparin. While the clinical literature suggests that all LMWHs share the same efficacy and safety profile, the results of this analysis would be strengthened if it were based on a clinical trial comparing rivaroxaban with each of the LMWHs.

8 Assessment of factors relevant to the NHS and other parties

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

The estimated projected annual budget for the NHS in England and Wales in a world with and without rivaroxaban for RECORD 1 and 2 trials is shown in Table 61and Table 62 (representing the THR populations) and RECORD 3 trial is shown in Table 63 (representing the TKR population). The total budget (i.e. for THR and TKR populations combined) assuming THR patients receive RECORD 1 dosing is shown in Table 64 while the budget assuming THR patients receive RECORD 2 dosing is shown in Table 65. The scenario with current market share assumes that current prescribing trends continue.

For the purposes of this analysis, the costs included within the budget are drug acquisition, administration and monitoring costs only.

Table 61 THR patients only: Estimated annual budget assuming RECORD 1 dosing (35 days rivaroxaban and LMWH)

Scenario with current market share					
	2009	2010	2011	2012	2013
enoxaparin	£6,823,498	£6,777,265	£6,729,763	£6,680,386	£6,628,798
dalteparin	£1,233,582	£1,225,224	£1,216,636	£1,207,709	£1,198,383
tinzaparin	£1,183,125	£1,175,108	£1,166,872	£1,158,311	£1,149,366
aspirin	£304,607	£305,101	£305,578	£306,010	£306,381
fondaparinux	£173,548	£174,885	£176,229	£177,563	£178,878
dabigatran	£99,945	£201,431	£304,468	£409,030	£515,074
Total	**£9,818,305**	**£9,859,015**	**£9,899,546**	**£9,939,009**	**£9,976,881**
Scenario with rivaroxaban					
rivaroxaban	£0	£290,119	£818,574	£1,767,367	£2,848,732
enoxaparin	£6,823,498	£6,530,238	£6,032,773	£5,175,529	£4,203,193
dalteparin	£1,233,582	£1,180,565	£1,090,631	£935,655	£759,872
tinzaparin	£1,183,125	£1,132,276	£1,046,021	£897,384	£728,791
aspirin	£304,607	£300,469	£292,508	£277,792	£260,898
fondaparinux	£173,548	£174,885	£176,229	£177,563	£178,878
dabigatran	£99,945	£201,431	£304,468	£409,030	£515,074
Total	**£9,818,305**	**£9,809,984**	**£9,761,204**	**£9,640,319**	**£9,495,437**
Incremental Cost	**£0**	**-£49,031**	**-£138,341**	**-£298,690**	**-£481,443**

In a THR population assuming RECORD 1 trial dosing, the introduction of rivaroxaban is expected to reduce costs over the next 5 years. These costs saving are a result of savings in administration and monitoring costs. Since rivaroxaban is an oral prophylaxis, patients receiving rivaroxaban would not incur any administration costs in an outpatient setting. When the duration of prophylaxis is equal, the savings in administration costs outweigh the increase in prophylaxis drug costs (rivaroxaban has a higher drug acquisition costs per course compared to LMWHs).

Table 62 THR patients only: Estimated annual budget assuming RECORD 2 dosing (35 days rivaroxaban, 12 days LMWH)

Scenario with current market share					
	2009	2010	2011	2012	2013
enoxaparin	£3,061,723	£3,040,978	£3,019,664	£2,997,508	£2,974,360
dalteparin	£577,011	£573,102	£569,085	£564,909	£560,547
tinzaparin	£535,991	£532,359	£528,628	£524,749	£520,697
aspirin	£304,607	£305,101	£305,578	£306,010	£306,381
fondaparinux	£173,548	£174,885	£176,229	£177,563	£178,878
dabigatran	£99,945	£201,431	£304,468	£409,030	£515,074
Total	**£4,752,825**	**£4,827,856**	**£4,903,651**	**£4,979,770**	**£5,055,938**
Scenario with rivaroxaban					
rivaroxaban	£0	£290,119	£818,574	£1,767,367	£2,848,732
enoxaparin	£3,061,723	£2,930,136	£2,706,922	£2,322,274	£1,885,985
dalteparin	£577,011	£552,213	£510,146	£437,655	£355,432
tinzaparin	£535,991	£512,955	£473,879	£406,542	£330,164
aspirin	£304,607	£300,469	£292,508	£277,792	£260,898
fondaparinux	£173,548	£174,885	£176,229	£177,563	£178,878
dabigatran	£99,945	£201,431	£304,468	£409,030	£515,074
Total	**£4,752,825**	**£4,962,208**	**£5,282,726**	**£5,798,223**	**£6,375,163**
Incremental Cost	**£0**	**£134,352**	**£379,075**	**£818,453**	**£1,319,224**

In the case of RECORD 2 trial dosing the introduction of rivaroxaban is expected to increase costs in the THR population. This is because of the longer duration of prophylaxis of rivaroxaban (35 days) compared to LMWH (12 days). Although 35 days rivaroxaban is more costly when compared with 12 days LMWH, the RECORD 2 clinical trial has shown that the increased duration of prophylaxis will prevent more VTE events. The cost savings associated with the prevention of VTE events have been considered in the cost-effectiveness analysis

Table 63 TKR patients only: Estimated annual budget assuming RECORD 3 dosing (12 days rivaroxaban and LMWH)

Scenario with current market share					
	2009	2010	2011	2012	2013
enoxaparin	£2,757,268	£2,736,453	£2,715,092	£2,692,941	£2,669,865
dalteparin	£521,905	£517,965	£513,921	£509,729	£505,361
tinzaparin	£483,187	£479,539	£475,796	£471,914	£467,870
aspirin	£318,383	£318,974	£319,549	£320,078	£320,544
fondaparinux	£42,928	£43,259	£43,591	£43,921	£44,246
dabigatran	£34,446	£69,423	£104,935	£140,973	£177,521
Total	**£4,158,116**	**£4,165,613**	**£4,172,884**	**£4,179,555**	**£4,185,407**
Scenario with rivaroxaban					
rivaroxaban	£0	£117,210	£330,709	£714,027	£1,150,906
enoxaparin	£2,757,268	£2,631,300	£2,418,401	£2,052,362	£1,637,348
dalteparin	£521,905	£498,061	£457,763	£388,478	£309,923
tinzaparin	£483,187	£461,112	£423,804	£359,658	£286,931
aspirin	£318,383	£314,320	£306,417	£291,724	£274,843
fondaparinux	£42,928	£43,259	£43,591	£43,921	£44,246
dabigatran	£34,446	£69,423	£104,935	£140,973	£177,521
Total	**£4,158,116**	**£4,134,685**	**£4,085,620**	**£3,991,144**	**£3,881,717**
Incremental Cost	**£0**	**-£30,928**	**-£87,264**	**-£188,411**	**-£303,690**

Assuming RECORD 3 trial dosing, the introduction of rivaroxaban is expected to reduce costs over the next 5 years in the TKR population. This is because the savings in administration and monitoring costs outweigh the higher drug acquisition costs of rivaroxaban when comparing equal duration of prophylaxis.

The total cost for both THR and TKR combined will vary depending on the duration of LMWH prophylaxis received by the THR population. The total cost is therefore calculated assuming each of the THR dosing regimes individually.

Table 64 Total estimated annual budget for THR and TKR – THR patients receive RECORD 1 dosing (35 days rivaroxaban and LMWH)

	2009	2010	2011	2012	2013
Current Market share	£13,976,421	£14,024,628	£14,072,430	£14,118,564	£14,162,288
With rivaroxaban	£13,976,421	£13,944,669	£13,846,824	£13,631,463	£13,377,155
Incremental Cost	**£0**	**-£79,959**	**-£225,606**	**-£487,100**	**-£785,133**

If we assume that THR patients receive 35 days LMWH, the introduction of rivaroxaban will result in a decrease in direct costs over the next five years

Table 65 Total estimated annual budget for THR and TKR - THR patients receive RECORD 2 dosing (35 days rivaroxaban, 12 days LMWH)

	2009	2010	2011	2012	2013
Current Market share	£8,910,941	£8,993,469	£9,076,535	£9,159,324	£9,241,345
With rivaroxaban	£8,910,941	£9,096,893	£9,368,346	£9,789,367	£10,256,880
Incremental Cost	**£0**	**£103,424**	**£291,811**	**£630,043**	**£1,015,535**

Assuming that THR patients receive 35 days rivaroxaban and only 13 days of LMWH (as in the RECORD 2 trial) total direct costs will increase over the next 5 years.

8.2 What number of patients were assumed to be eligible? How was this figure derived?

The number of patients undergoing THR and TKR in 2006/07 was obtained from the National Joint Registry for England and Wales (4th annual report)(8) and population estimates for England and Wales were obtained from the Office of National Statistics(98) (Table 66). Combining this data indicates an annual incidence of 0.121% and 0.122% for THR and TKR respectively. If we assume that the incidence of THR and TKR remains constant, the number of operations will increase in line with population growth (Table 66).

Table 66- Estimated number of patients undergoing surgery

	2007	2008	2009	2010	2011	2012	2013
Total Population (000s)	54,074	54,481	54,896	55,319	55,744	56,166	56,582
Patients undergoing THR	65,532	66,025	66,528	67,041	67,556	68,067	68,571
Patients undergoing TKR	65,846	66,342	66,847	67,362	67,880	68,393	68,900

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

The analysis assumes that patients receive either rivaroxaban, LMWH, fondaparinux, aspirin or dabigatran. Patients who do not receive any of these prophylaxes are assumed to receive no pharmacological prophylaxis and do not therefore incur any costs. The projected proportion of patients receiving no pharmacological prophylaxis remains constant over time (see section 8.4 for the proportion of patients receiving no prophylaxis). It is assumed that patients receiving LMWH consist of those receiving enoxaparin, dalteparin and tinzaparin. Although aspirin is not recommended for use in England and Wales, market share data indicate that it is used in clinical practice for some patients. Dabigatran has also been included in the analysis since it has recently been approved by NICE.

8.4 What assumption(s) were made about market share (where relevant)?

Current market share was obtained from the National Joint Registry 4th annual report (2007)(8). The breakdown for LMWH was based on IMS data outlining the use of LMWHs in orthopaedic surgery wards in the UK which showed that 71% of LMWH patients receive enoxaparin, 16% receive dalteparin and 13% receive tinzaparin(9).

Table 67- Current market share

	THR	TKR
Rivaroxaban	0.0%	0.0%
Low Molecular Weight Heparin (LMWH)	60.0%	57.0%
Aspirin	25.0%	26.0%
Fondaparinux	1.0%	1.0%
No prophylaxis	14.0%	16.0%

It is assumed that the market share of rivaroxaban will increase over the next five years as shown in Table 68. It is also assumed that dabigatran will be introduced gradually over the next five years and will represent 5% of the market share by 2013. Market share will be taken primarily from patients currently receiving LMWH (85%), although some will be taken from those receiving aspirin (15%). Since the current market share of fondaparinux is so low (1%), it is assumed that this will not change following the introduction of rivaroxaban.

Table 68- Projected market share with Rivaroxaban

	2008	2009	2010	2011	2012	2013
Market share of rivaroxaban	0.0%	2.5%	7.0%	15.0%	24.0%	35.0%

8.5 What unit costs were assumed? How were these calculated?

The duration of rivaroxaban and enoxaparin prophylaxis was based on the RECORD trials. Three separate analyses have therefore been conducted based on the duration of prophylaxis in each of the RECORD trials. For THR patients, the duration of rivaroxaban was 35 days in both the RECORD 1 and RECORD 2 trials, while enoxaparin prophylaxis was given for 35 days in the RECORD 1 trial and 12 days in the RECORD 2 trial. All TKR patients received both rivaroxaban and enoxaparin for 12 days in the RECORD 3 trial. The model assumes that the duration of prophylaxis with other LMWHs is equal to that of enoxaparin. Aspirin prophylaxis was assumed to be given for 35 days based on the SIGN guidelines (2002)(33). Based on the fondparinux product label, TKR patients were assumed to receive prophylaxis for 7 days while THR patients were assumed to receive extended duration prophylaxis of 28 days based on the NICE guidelines (2007)(22). The duration of dabigatran prophylaxis was based on the mean recommended dose in the clinical trials.

Drug costs were obtained from the British National Formulary (BNF)(79). The cost per course associated with each method of prophylaxis is shown Table 69.

Table 69 Drug costs associated with each method of prophylaxis (RECORD 1&2&3)

			RECORD 1 dosing		RECORD 2 dosing		RECORD 3 dosing	
	Daily Dose	Cost per day	Days	Cost per Course	Days	Cost per Course	Days	Cost per Course
Rivaroxaban	10mg	£4.50	35	£157.50	35	£157.50	12	£54.00
Enoxaparin	40mg	£4.20	35	£147.00	35	£54.60	12	£50.40
Dalteparin	5000units	£2.82	35	£98.70	35	£36.66	12	£33.84
Tinzaparin	4500units	£3.83	35	£134.05	35	£49.79	12	£45.96
Aspirin	150mg	£0.08	35	£2.83	35	£2.83	35	£2.83
Fondaparinux	2.5mg	£6.66	28	£186.48	28	£186.48	7	£48.62
Dabigatran	220mg	£4.20	32	£132.30	32	£132.30	8	£33.60

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve day case or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

The cost and resource use associated with administration and monitoring were obtained from published sources(80)(81) Please see section 7.2 for further information.

Table 70 Administration costs associated with each method of prophylaxis

				Total administration cost		
	Inpatient Cost (per day)[1]	Outpatient Cost (per day)	Training Cost	RECORD 1 dosing	RECORD 2 dosing	RECORD 3 dosing
Rivaroxaban	£2.00	£0.00	£0.00	£15.60	£15.60	£15.60
Enoxaparin	£2.00	£1.92	£20.00	£87.82	£87.82	£43.66
Dalteparin	£2.00	£1.92	£20.00	£87.82	£87.82	£43.66
Tinzaparin	£2.00	£1.92	£20.00	£87.82	£87.82	£43.66
Aspirin	£2.00	£0.00	£0.00	£15.60	£15.60	£15.60
Fondaparinux	£2.00	£1.92	£20.00	£74.38	£74.38	£0[3]
Dabigatran	£2.00	£0.00	£0.00	£15.60	£15.60	£15.60

[1] 2-3 minutes of nurse time per day during hospitalisation
[2] 8% patients receiving injectable prophylaxis require a district nurse visit
[3] TKR patients receive fondaparinux for 7 days. Since the duration of hospitalisation is 7.3 days, patients will not receive fondaparinux prophylaxis post-discharge and will therefore not incur any outpatient administration costs.

Table 71 Monitoring costs associated with each method of prophylaxis

	Inpatient Cost	Outpatient Cost[2]	Total monitoring costs
Rivaroxaban	£0.00	£0.00	£0.00
Enoxaparin	£9.40[1]	£0.00	£9.40
Dalteparin	£9.40[1]	£0.00	£9.40
Tinzaparin	£9.40[1]	£0.00	£9.40
Aspirin	£0.00	£0.00	£0.00
Fondaparinux	£0.00	£0.00	£0.00
Dabigatran	£2.33[3]	£0.00	£0.00

[1] Full blood count at baseline, then every 2-4 days until day 14
[2] Assume no outpatient monitoring
[3] One liver function test

Since we assume no monitoring costs post-discharge the total monitoring costs do not differ with the dosing regimen.

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

Most patients receiving parenteral prophylaxes such as the LMWHs and fondaparinux require training prior to hospital discharge to enable them to self-inject. In addition, it is estimated that 8% patients are unable to self-inject and therefore require a district nurse visit to administer the drug(22). Since rivaroxaban, dabigatran and aspirin are administered orally, no district nurse visits or training is required to aid administration resulting in resource savings.

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

Unlike LMWH which is initiated 12 hours pre-operatively, rivaroxaban is initiated post-operatively. The introduction of rivaroxaban therefore has the potential to reduce the length of hospital stay due to THR or TKR, although this has not been included in the current analysis. Additionally, current methods of prophylaxis (LMWH and fondaparinux) are administered by subcutaneous injection and may therefore incur costs associated with sharps disposal or needle stick injury. Such potential cost savings associated with the introduction of an oral method of prophylaxis such as rivaroxaban are not included in this analysis.

The budget impact model does not include any cost savings associated with the prevention of VTE events – although these have been considered in the cost-effectiveness analysis

9 References

(1) *Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Oral rivaroxaban compared with subcutaneous enoxaparin for extended thromboprophylaxis after total hip arthroplasty: The RECORD1 trial. Blood (ASH Annual Meeting Abstracts) 2007;110.*

(2) *Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation 2006;114:2374-81.*

(3) *Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. Dose-escalation study of rivaroxaban (BAY 59-7939) - an oral, direct Factor Xa inhibitor - for the prevention of venous thromboembolism in patients undergoing total hip replacement. Journal of Thrombosis and Haemostasis 2007;120(5):685-93.*

(4) *Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended Thromboprophylaxis with Rivaroxaban Compared with Short-term thromboprophylaxis with Enoxaparin after Total Hip Arthroplasty: The RECORD 2 Trial. Blood (ASH Annual Meeting Abstracts) 2007;110.*

(5) *Eriksson BI, Borris L, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. Journal of Thrombosis and Haemostasis 2006;4(1):121-8.*

(6) *Fisher WD, Eriksson BI, Bauer KA, Borris L, Dahl OE, Gent M, et al. Rivaroxaban for thromboprophylaxis after orthopaedic surgery: Pooled analysis of two studies. Thromb Haemost 2007;97(6):931-7.*

(7) *Lassen MR, Turpie AGG, Rosencher N, Borris LC, Ageno W, Lieberman JR, et al. Rivaroxaban - An Oral, Direct Factor Xa Inhibitor - for Thromboprophylaxis after Total Knee Arthroplasty: The RECORD 3 Trial. Blood (ASH Annual Meeting Abstracts) 2007;110.*

(8) *National Joint Registry. 4th Annual Report. National Joint Registry 2007 [cited 8 A.D. Aug 9];Available from: URL: http://www.njrcentre.org.uk/*

(9) *IMS Health. Market Research, HPAI data, MAT to December 2007. 2008.*

(10) *Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. New England Journal of Medicine 2008;358(26):2765-75.*

(11) *Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet 2008;372(9632):31-9.*

(12) *Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus Enoxaparin for thromboprophylaxis after total knee arthroplasty. New England Journal of Medicine 2008;358:2776-86.*

(13) *White RH, Ginsberg JS. Low-molecular-weight heparins: are they all the same? Br J Haematol 2003;121(1):12-20.*

(14) *Zhan C, Kaczmarek R, Loyo-Berrios N, Sangl J, Bright RA. Incidence and Short-Term Outcomes of Primary and Revision Hip Replacement in the United States. J Bone Joint Surg Am 2007;89:526-33.*

(15) *European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use Summary of Positive Opinion for Xarelto. 2008. Report No.: EMEA/CHMP/357818/2008.*

(16) *Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of Venous thromboembolism: The seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:338-400.*

(17) *House of Commons Health Committee. The prevention of venous thromboembolism in hospitalised patients. Second report of session 2004-2005. 2005.*

(18) *Turpie AGG. Oral, direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. Arterioscler Thromb Vasc Biol 2007;27:1238-47.*

(19) *Warwick D, Friedman RJ, Agnelli G, Gil-Garay E, Johnson K, Fitzgerald G, et al. Insufficient duration of venous thromboembolism prophylaxis after total hip or knee replacement when compared with the time course of thromboembolic events. Journal of Bone & Joint Surgery (Br) 2007;89B(6):799-807.*

(20) *Hull RD, Pineo GF, Stein PD, Mah AF, MacIsaac SM, Dahl OE. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med 2001;135(10):858-69.*

(21) *Eikelboom JW, Quinian DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomized trials. Lancet 2001;358:9-15.*

(22) *National Collaborating Centre for Acute Care [Commissioned by National Institute for Health & Clinical Excellence]. Venous Thromboembolism: Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism in inpatients undergoing surgery. 2007. Report No.: NICE Clinical Guideline 46.*

(23) *Scottish Arthroplasty Project. Thromboprophylaxis - a comparison of practice in Scotland with England and Wales. 2004.*

(24) *TA157: Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults. National Institute for Health and Clinical Effectiveness (NICE) 2008Available from: URL: http://www.nice.org.uk/nicemedia/pdf/TA157Guidance.pdf*

(25) *Bayer Healthcare Pharmaceutical. Amendment A to RECORD 4 Study: REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE: a controlled, double-bline, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement. Study number 11355. 2008. Report No.: MRR A41857.*

(26) *Eriksson BI, Dahl OE, Rosencher N, Kurth AA, Van Dijk CN, Frostick SP, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949-56.*

(27) *Eriksson BI, Dahl OE, Rosencher N, Kurth AA, Van Dijk CN, Frostick SP, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. Journal of Thrombosis and Haemostasis 2007;5:2178-85.*

(28) *The RE-MOBILIZE Writing Committee. The oral thrombin inhibitor dabigatran etexilate vs the North American Enoxaparin Regimen for the prevention of venous*

thromboembolism after knee arthroplasty surgery. The Journal of Arthroplasty. In press 2008.

(29) Sullivan SD, Kahn SR, Davidson BL, Borris L, Bossuyt P, Raskob G. Measuring the outcomes and pharmacoeconomic consequences of venous thromboembolism prophylaxis in major orthopaedic surgery. Pharmacoeconomics 21[7], 477-496. 2003. Ref Type: Journal (Full)

(30) Kahn SR, Ginsberg JS. The post-thrombotic syndrome: current knowledge, controversies, and directions for future research. Blood Rev 2002;16(3):155-65.

(31) Scottish Intercollegiate Guidelines Network (SIGN). Proposed Review of SIGN Guideline 2005 consultation form - SIGN 62: Prophylaxis of venous thromboembolism. 2005.

(32) Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008;133:381-453.

(33) Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of venous thromboembolism. A national clinical guideline. 2002. Report No.: Guideline Number 62.

(34) All Party Parliamentary Thrombosis Group. Thrombosis: Awareness, management and prevention. Available at http://www dvtreport com/ 2007

(35) Bayer Healthcare Pharmaceutical. Amendment A to RECORD 4 Study: REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE: a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement. Study number 11355. 2008. Report No.: MRR A41857.

(36) Turpie AGG, Bauer KA, Berkowitz SD, Cushner FD, Davidson BL, Gent M, et al. Comparison of rivaroxaban - an oral, direct Factor Xa inhibitor - and subcutaneous enoxaparin for thromboprophylaxis after total knee replacement. 8 A.D. May 30; 2008.

(37) Bayer Healthcare AG. RECORD1 Study: Regulation of Coagulation in ORthopedic Surgery to prevent DVT and PE, controlled, double-blind, randomized study of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement. Study number 11354. 2007. Report No.: MRR00233.

(38) Bayer Healthcare AG, B. RECORD 2 Study: REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE, Controlled, Double-Blind, Randomized Study of BAY59-7939 in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip Replacement. Study number 011357. 2007. Report No.: MRR-00234.

(39) Bayer Healthcare AG. RECORD 3 Study: REgulation of Coagulation in ORthopedic Surgery to Prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in subjects undergoing elective total knee replacement. Study number 11356. 2007. Report No.: MRR-00218.

(40) Bayer Healthcare AG. RECORD 1 Study: REgulation of Coagulation in ORthopedic Surgery to prevent DVT and PE, controlled, double-blind, randomized study of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement. Clinical Study Protocol 11354 version 1.10. 2005.

(41) *Committee for Proprietary Medicinal Products (CPMP). Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease. 1999. Report No.: CPMP/EWP/563/98.*

(42) *Committee for Proprietary Medicinal Products (CPMP). Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk. 2000. Report No.: CPMP/EWP/707/98:European Agency for the Evaluation of Medicinal Products (EMEA).*

(43) *Committee for Proprietary Medicinal Products (CPMP). DRAFT Guideline on clinical investigation of medicinal products for prophylaxis of high intra- and post-operative venous thromboembolic risk. 2006. Report No.: CPMP/EWP/707/98 Rev 1.*

(44) *Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology 50, 683-691. 1997.*
Ref Type: Journal (Full)

(45) *Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med 18[20], 2693-2708. 1999.*
Ref Type: Journal (Full)

(46) *Thabut G, Estellat C, Boutron I, Samama CM, Ravaud P. Methodological issues in trials assessing primary prophylaxis of venous thrombo-embolism. Eur Heart J 2006;27:227-36.*

(47) *Sanofi-Aventis. Clexane (Enoxaparin), Summary of Product Characteristics. http://emc medicines org uk/ 2008 [cited 2008 Oct 5];*

(48) *Cohen AT, Bailey CS, Alikan R, Cooper DJ. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty: a meta-analysis. Thromb Haemost 2001;85:940-1.*

(49) *Lopez LM. Low-molecular-weight heparins are essentially the same for treatment and prevention of venous thromboembolism [review]. Pharmacotherapy 21[6 pt 2], 56S-61S. 2001.*
Ref Type: Journal (Full)

(50) *Anderson DR, O'Brien B, Nagpal S. Economic evaluation comparing low molecular weight heparin with other modalities for the prevention of deep vein thrombosis and pulminary embolism following total hip or knee arthroplasty. Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1998.*

(51) *Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep vein thrombosis in major orthopedic surgery. JAMA 257[2], 203-208. 1987.*
Ref Type: Journal (Full)

(52) *Annemans L, Minjoulat-Rey MC, De Knock M. Cost consequence analysis of fondaparinux versus enoxaparin in the prevention of venous thromboembolism after major orthopaedic surgery in Belgium. Acta Clin Belg 59[6], 346-357. 2004.*
Ref Type: Journal (Full)

(53) *Botteman MF, Caprini J, Stephens JM, Nadipelli V, Bell CF, Pashos CL. Results of an economic model to assess the cost-effectiveness of enoxaparin, a low-molecular-weight heparin, versus warfarin for the prophylaxis of deep vein thrombosis and associated long-term complications in total hip replacement surgery in the United States. Clin Ther 24[11], 1960-1986. 2002.*
Ref Type: Journal (Full)

(54) *Dranitsaris G, Kahn SR, Stumpo C, Paton TW, Martineau J, Smith R, et al. Pharmacoeconomic analysis of fondaparinux versus enoxaparin for the prevention of thromboembolic events in orthopedic surgery patients. Am J Cardiovasc Drugs 4[5], 325-333. 2004.*
Ref Type: Journal (Full)

(55) *Levin LA, Bergqvist D. Cost effectiveness of desirudin compared with a low molecular weight heparin in the prevention of deep vein thrombosis after total hip replacement surgery. Pharmacoeconomics 19[5 pt 2], 589-597. 2001.*
Ref Type: Journal (Full)

(56) *Sullivan SD, Davidson BL, Kahn SR, Muntz JE, Oster G, Raskob G. Cost effectiveness of desirudin compared with a low molecular weight heparin in the prevention of deep vein thrombosis after total hip replacement surgery. Pharmacoeconomics 22[9], 605-620. 2004.*
Ref Type: Journal (Full)

(57) *Sullivan SD, Kwong L, Nutescu E. Cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against venous thromboembolism in patients undergoing hip fracture surgery. Value Health 9[2], 68-76. 2006.*
Ref Type: Journal (Full)

(58) *Bjorvatn A, Kristiansen F. Fondaparinux sodium compared with enoxaparin sodium: a cost-effectiveness analysis. Am J Cardiovasc Drugs 5[2], 121-130. 2005.*
Ref Type: Journal (Full)

(59) *Gordois A, Posnett J, Borris L, Bossuyt P, Jonsson B, Levy E, et al. The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery. Journal of Thrombosis and Haemostasis 1[10], 2167-2174. 2003.*
Ref Type: Journal (Full)

(60) *Lundkvist J, Bergqvist D. Cost-effectiveness of extended prophylaxis with fondaparinux compared with low molecular weight heparin against venous thromboembolism in patients undergoing hip fracture surgery. Eur J Health Econ 8[4], 313-323. 2007.*
Ref Type: Journal (Full)

(61) *Lundkvist J, Bergqvist D, Jonsson B. Cost-effectiveness of fondaparinux vs. enoxaparin as venous thromboembolism prophylaxis in Sweden. Eur J Health Econ 4[4], 254-262. 2003.*
Ref Type: Journal (Full)

(62) *O'Brien BJ, Anderson DR, Goeree R. Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after total hip replacement. CMAJ 150[7], 1083-1090. 1994.*
Ref Type: Journal (Full)

(63) *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 92[2], 199-205. 2007.*
Ref Type: Journal (Full)

(64) *Prandoni P, Villalta S, Bagatella P, Rossi I, Marchiori A, Piccioli A, et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica 82[4], 423-428. 1997.*
Ref Type: Journal (Full)

(65) *Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med 160[6], 769-774. 2000.*
Ref Type: Journal (Full)

(66) *Quinlan DJ, Eikelboom JW, Dahl OE, Eriksson BI, Sidhu PS, Hirsch J. Association between asymptomatic deep vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery. Journal of Thrombosis and Haemostasis 5[7], 1438-1443. 2007.*
Ref Type: Journal (Full)

(67) *Pengo V, Lensing AWA, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of Chronic Thromboembolic Pulmonary Hypertension after Pulmonary Embolism. New England Journal of Medicine 350[22], 2257-2264. 2004.*
Ref Type: Journal (Full)

(68) *Matisse Investigators. Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism. New England Journal of Medicine 349[18], 1695-1702. 2003.*
Ref Type: Journal (Full)

(69) *White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Arch Intern Med 158[14], 1525-1531. 1998.*
Ref Type: Journal (Full)

(70) *Haentjens P, De Groote K, Annemans L. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Arch Orthop Trauma Surg 124[8], 507-517. 2004.*
Ref Type: Journal (Full)

(71) *Dahl OE, Pleil AM. Investment in prolonged thromboprophylaxis with dalteparin improves clinical outcomes after hip replacement. Journal of Thrombosis and Haemostasis 1[5], 896-906. 2003.*
Ref Type: Journal (Full)

(72) *Honorato J, Gomez-Outes A, Navarro-Quilis A, Martinez-Gonzalez J, Rocha E, Planes A. Pharmacoeconomic analysis of bemiparin and enoxaparin as prophylaxis for venous thromboembolism in total knee replacement surgery. Pharmacoeconomics 22[13], 885-894. 2004.*
Ref Type: Journal (Full)

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

(74) *Brunenberg DE, Van Steyn MJ, Sluimer JC, Bekebrede LL, Bulstra SK, Joore MA. Joint recovery programme versus usual care: An economic evaluation of a clinical pathway for joint replacement surgery. Med Care 43[10], 1018-1026. 2005.*
Ref Type: Journal (Full)

(75) *Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. Br Med J 316[7133], 736-741. 1998.*
Ref Type: Journal (Full)

(76) *Ostendorf M, Buskens E, Van Stel H, Schrijvers A, Marting L, Dhert W. Waiting for total hip arthroplasty: Avoidable loss in quality time and preventable deterioration. J Arthroplasty 19[3], 302-309. 2004.*
Ref Type: Journal (Full)

(77) *Ostendorf M, Van Stel HF, Buskens E, Schrijvers A, Marting L, Verbout AJ. Patient-reported outcome in total hip replacement. A comparison of five instruments of health status. J.Bone Joint Surg.B 86[6], 801-808. 2004.*
Ref Type: Journal (Full)

(78) *Malchau H, Garellick G, Eisler T, Karrholm J, Herberts P. Presidential guest address: The Swedish Hip Registry: Increasing the sensitivity by patient outcome data. Clin Orthop Relat Res 441, 19-29. 2005.*
Ref Type: Journal (Full)

(79) *BNF. British National Formulary (BNF) 2008 [cited 2008 Apr 1];55Available from: URL: http://www.bnf.org/bnf/*

(80) *Curtis L. Unit Costs of Health and Social Care. Personal Social Services Research Unit; 2007.*

(81) *Newcastle upon Tyne Hospital Trusts Diagnostic Service Tariff. Newcastle upon Tyne Hospital Trusts Diagnostic Service 2008 [cited 2008 Apr 1];Available from: URL: http://www.newcastle-hospitals.org.uk/directorates/finance/diagnostic-service-tariffs*

(82) *NHS. NHS Reference Costs. http://www dh gov uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_082571 2007 [cited 2008 Apr 1];*

(83) *Grieve R, Porsdal V, Hutton J, Wolfe C. A comparison of the cost-effectiveness of stroke care provided in London and Copenhagen. Int J Tech Assess Health Care 16[2], 684-695. 2000.*
Ref Type: Journal (Full)

(84) *British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax 58[6], 470-483. 2003.*
Ref Type: Journal (Full)

(85) *MacDougall DA, Feliu AL, Boccuzzi SJ, Lin J. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. Am J Health Syst Pharm 63[20 suppl 6], S5-S15. 2006.*
Ref Type: Journal (Full)

(86) *Muntz J, Scott DA, Lloyd A, Egger M. Major bleeding rates after prophylaxis against venous thromboembolism: systematic review, meta-analysis, and cost implications. Int J Tech Assess Health Care 20[4], 405-414. 2004.*
Ref Type: Journal (Full)

(87) *Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. Arch Intern Med 160[14], 2208-2215. 2000.*
Ref Type: Journal (Full)

(88) *Harrison J, Warwick DJ, Coast J. Economics of thromboprophylaxis in total hip replacement surgery. Pharmacoeconomics 12[1], 30-41. 1997.*
Ref Type: Journal (Full)

(89) *Drummond M, Aristides M, Davies L, Forbes C. Economic evaluation of standard heparin and enoxaparin for prophylaxis against deep vein thrombosis in elective hip surgery. Br J Surg 81[12], 1742-1746. 1994.*
Ref Type: Journal (Full)

(90) *Menzin J, Richner RE, Huse D, Colditz GA, Oster G. Prevention of deep-vein thrombosis following total hip replacement surgery with enoxaparin versus unfractionated heparin: a pharmacoeconomic evaluation. Ann Pharmacother. Ann Pharmacother 28[2], 271-275. 1994.*
Ref Type: Journal (Full)

(91) *Menzin J, Colditz GA, Regan MM, Richner RE, Oster G. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. Arch Intern Med 155[7], 757-764. 1995.*
Ref Type: Journal (Full)

(92) *Bergqvist D, Lindgren B, Matzsch T. Comparison of the cost of preventing postoperative deep vein thrombosis with either unfractionated or low molecular weight heparin. Br J Surg 83[11], 1548-1552. 1996.*
Ref Type: Journal (Full)

(93) *Hawkins DW, Langley PC, Krueger KP. A pharmacoeconomic assessment of enoxaparin and warfarin as prophylaxis for deep vein thrombosis in patients undergoing knee replacement surgery. Clin Ther 20[1], 182-195. 1998.*
Ref Type: Journal (Full)

(94) *Bergqvist D, Jendteg S, Johansen L, Persson U, Odegaard K. Cost of long-term complications of deep venous thrombosis of the lower extremities: an analysis of a defined patient population in Sweden. Ann Intern Med. 1997 Mar 15;126(6):454-7. Ann Intern Med 126[6], 454-457. 1997.*
Ref Type: Journal (Full)

(95) *Caprini JA, Botteman MF, Stephens JM, Nadipelli V, Ewing MM, Brandt S. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States Value Health 2003;6(1):59-74. Value Health 6[1], 59-74. 2003.*
Ref Type: Journal (Full)

(96) *Douketis JD, Eikelboom JW, Quinian DJ, Willan AR, Crowther MA. Short-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes. Arch Intern Med 2002; 162: 1465-71. Arch Intern Med 162, 1465-1471. 2002.*
Ref Type: Journal (Full)

(97) *Nuijten MJ, Villar FA, Kosa J, Nadipelli V, Rubio-Terres C, Suarez C. Cost-effectiveness of enoxaparin as thromboprophylaxis in acutely ill medical patients in Spain. Value Health 6[2], 126-136. 2003.*
Ref Type: Journal (Full)

(98) *Office for National Statistics. 2006 Based Population Projections. Office for National Statistics 2006 [cited 2008 Sep 1];Available from: URL: http://www.statistics.gov.uk/downloads/theme_population/NPP-2006/wew065y.xls*

10 Appendices

See document: Xarelto VTE Prevention_STA form_Appendices_confidential.doc