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Apixaban for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery

Produced by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University

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

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Contributions of authors
Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Manuela Joore acted as health economic project lead, critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Janneke Grutters acted as health economist on this assessment, critiqued the manufacturer's economic evaluation and contributed to the writing of the report. Nigel Armstrong acted as health economist on this assessment, critiqued the manufacturer's submission and contributed to the writing of the report. Kate Misso and Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Doreen Allen Tushabe and Sohan Deshpande acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Johan L. Severens critiqued the manufacturer's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the health economic sections of the report. Jos Kleijnen critiqued the manufacturer's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AAOS	American Academy of Orthopedic Surgeons
ACC	American College of Cardiology
ACCP	American College of Chest Physicians
AE	Adverse Events
AIDS	Acquired Immune Deficiency Syndrome
ASH	American Society of Hematology
bd/b.i.d	Twice Daily
BOA	British Orthopaedic Association
BSH	British Society of Haematology
CC	Complications and Co-morbidities
CE	Cost Effectiveness
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness Acceptability Curve
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
CRNM	Clinically Relevant non Major
CTPA	Computerised Tomography Pulmonary Angiograph
DBG	Dabigatran Etexilate
DVT	Deep Vein Thrombosis
EFFORT	European Federation of National Associations of Orthopedics and Traumatology
EHS	European Hematology Society
EMEA	European Medicines Agency
EORS	European Orthopedic Research Society
ERG	Evidence Review Group
EUR	Erasmus University Rotterdam
FID	Foot Impulse Device
GCS	Graduated Elastic Compression Stockings
HIT	Heparin-induced Thrombocytopenia
HRG	Health Resource Group
HRQL	Health-related Quality of Life
HTA	Health Technology Assessment
IC	Indirect Comparison
ICER	Incremental Cost-effectiveness Ratio
ICH	Intracranial haemorrhage
ICMJE	International Committee of Medical Journal Editors
ICT	International Congress on Thrombosis
iHEA	International Health Economics Association
IPCD	Intermittent Pneumatic Compression Device
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention to Treat
KSR	Kleijnen Systematic Reviews
LMWHs	Low Molecular Weight Heparins
LYS	Life Year Saved
mg	Milligram
MS	Manufacturer's Submission
MTC	Mixed Treatment Comparison
NCC-AC	National Collaborating Centre for Acute Care
NHS	National Health Services
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NOAC	New Oral Anticoagulant
NR	Not Reported
od	Once Daily

OR	Odds Ratio
PBR	Payment by Results
PCT	Primary Care Trust
PE	Pulmonary Embolism
po	Orally/by mouth
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PTS	Post Thrombotic Syndrome
QALY(s)	Quality-adjusted Life Year(s)
RCT	Randomised Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Events
sc	Subcutaneous
ScHARR	School of Health and Related Research
STA	Single Technology Appraisal
THR	Total Hip Replacement
TKR	Total Knee Replacement
UFH	Unfractionated Heparin
UMC	University Medical Centre
VTE	Venous Thromboembolic Events

1. SUMMARY

1.1 Scope of the manufacturer submission

The Manufacturer's Submission (MS) generally reflects the scope of the appraisal issued by NICE, and is appropriate to the NHS. The MS reports on the use of apixaban in adults who have elective total hip replacement (THR) or elective total knee replacement (TKR) surgery. The intervention is defined as apixaban (Eliquis®) for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective THR or TKR surgery. The MS considered enoxaparin, a low molecular-weight heparin (LMWH), as the most relevant comparator, as reflected in the scope. Indirect comparisons as well as mixed treatment comparisons with alternative standard care (including other LMWHs, as well as the other stated comparators, rivaroxaban, dabigatran and fondaparinux) were undertaken. The outcome measures identified in the scope were all relevant and the majority of these efficacy outcomes (mortality, incidence of symptomatic and asymptomatic deep vein thrombosis (DVT), and pulmonary embolism (PE)), and safety outcomes (bleeding events), were reported. However, outcomes relating to post DVT complications, length of hospital stay, joint outcomes and health related quality of life, although identified in the scope, were not reported.

The ERG would like to comment on the quantity of the MS. The MS contains 217 pages, this is much longer than the 70-100 pages recommended by NICE. In addition, separate documents with appendices with a total of 630 pages were submitted by the manufacturer. The length of the MS make the review by the ERG more difficult than it should have been. The main document contained direct evidence and the main conclusions from the indirect comparisons. Details of the indirect comparisons were presented in appendix 15 and the mixed treatment comparisons were presented in appendix 16. Appendices 15 and 16 were two large documents produced by organisations independent to the manufacturers (384 pages in total). This information should have been contained within the main document of the MS.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The MS appears to contain an unbiased estimate of the treatment effect of apixaban in relation to the relevant outcomes and the comparator, enoxaparin. Overall the evidence from the three ADVANCE trials in the MS indicates that apixaban 2.5mg bd is significantly superior to the comparator enoxaparin (40mg od) in terms of [redacted], any DVT, [redacted]. [redacted] These results were the same for THR and TKR.

The results of the indirect comparisons showed that apixaban:

- **when compared to rivaroxaban** showed no significant differences in terms of [redacted] any DVT. [redacted]
- **when compared to dabigatran** was significantly superior in terms of [redacted] any DVT; [redacted]. These results were the same for THR and TKR.

- **when compared to fondaparinux** in THR showed no significant differences in terms of any DVT, [redacted]. Other main outcomes (Total VTE and all-cause mortality, Major VTE, and Any bleeding) were not reported using indirect comparisons; although, for the total VTE and all-cause mortality the MTC showed no significant differences. For TKR an indirect comparison with enoxaparin, 40mg od was not possible.

1.3 Summary of cost effectiveness submitted evidence by the manufacturer

Due to insufficient information from published cost-effectiveness studies as demonstrated by the literature review in the MS, the manufacturer conducted a de-novo economic analysis. In this analysis the costs and health outcomes of apixaban, rivaroxaban, dabigatran and enoxaparin (representing al LMWHs) for the prevention of VTE in adult patients who have undergone elective THR or TKR were compared. Upon request of the ERG fondaparinux was also included in the analyses.

The manufacturer adopted a two-stage modelling approach. A decision tree was used to model treatment in the acute phase (surgery to 90 days post surgery) and a Markov model was used to model the long-term events (35 years). Efficacy and safety of the treatments was modelled in line with the endpoints in the trials: 'total VTEs and all deaths' and 'total bleeds'. The model did not account for differences in types of VTEs or types of bleeds between the treatments. Upon request of the ERG, the manufacturer provided analyses that did take differences in types of VTEs and/or bleeds into account. The remaining probabilities in the model were assumed to be treatment independent. As a result, the major model parameters that caused differences between the treatments were the probabilities of 'total VTEs and all deaths' and 'total bleeds' in the acute phase.

The probabilities of 'total VTEs and all deaths' and 'total bleeds' were based on an indirect comparison with enoxaparin as reference treatment. The results of a MTC were used in a sensitivity analysis. The values for health related quality of life were based on several studies. These studies used a large variety of instruments, perspectives and populations. Healthcare resource group 4.0 procedure codes were used to determine the costs of health states and events.

The manufacturer conducted a full incremental deterministic analysis of the treatment options. However, for the PSA only selected options were compared, by that deviating from the requested full incremental analysis. The manufacturer adjusted the PSA in order to allow for a full incremental analysis after request by the ERG. In THR rivaroxaban was the most effective annd most costly treatment, followed by apixaban. The ICER of rivaroxaban versus apixaban amounted to 21,661 per QALY gained. In TKR rivaroxaban was the most effective and least costly treatment option, and therefore dominated all other treatments. These results were robust.

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

1.4.1 Strengths

Search methods were clearly presented and reported. The manufacturer searched the required databases. The MS provided sufficient detail for the ERG to appraise the searches. Additional searches of conference abstracts were undertaken for the clinical effectiveness and cost effectiveness sections. The ERG noted that several of the errors identified were not consequential, due to the comprehensiveness of the rest of the strategies. For the most part, these inconsequential errors would not have impacted the recall of searching.

The three identified trials, which represent the main clinical efficacy evidence were of reasonable methodological quality and measured a range of outcomes that were appropriate and clinically relevant. Processes and validation of study screening and data extraction appear to be appropriate. Statistical methods were explicitly described for the meta-analyses and indirect comparisons and all relevant analyses were performed.

The economic part of the submission presented a thorough and well-performed analysis. The analysis provided an overview and synthesis of all available evidence. Some errors were identified in the economic model and in the report. The errors were however all relatively minor and did not substantially impact the results or conclusions. The ERG requested some adaptations to the model and model inputs, which were all provided in the clarification phase.

1.4.2 Weaknesses and areas of uncertainty

In general the searches were constructed in a systematic fashion, however there was some redundant usage of explode and search headings. There was one significant typographical error relating the comparator drug fondaparinux. There were disparities between the search strategies in the way hip/knee replacement was searched for. Particularly there was limited use of synonyms, truncation and controlled vocabulary.

The submission was not concise and lacked transparency. Therefore, the ERG cannot guarantee that no errors are still undiscovered.

The effectiveness and safety of apixaban, and therefore its cost-effectiveness, are based on a single trial that included a population that is not entirely representative for the population in the NHS.

1.5 Summary of additional work undertaken by the ERG

The ERG reran the clinical effectiveness searches but was not able to screen search results due to time constraints, and therefore can only show the numerical differences in the numbers of references retrieved between manufacturer and ERG searches without a definitive indication that relevant studies were missed (See Appendix 1A). ERG search results checked by the manufacturer did not produce any new evidence (see Response to Clarification Letter).

The ERG checked to see if results reported in the full paper of RE-NOVATE II (dabigatran versus enoxaparin in THR) as opposed to the abstract included in the MS had any impact on the overall results and concluded that they produced very small changes and slightly smaller confidence intervals. These changes are unlikely to cause significant changes to the analyses in the MS.

The ERG conducted additional economic analyses with corrected (higher) costs of fondaparinux and with the results reported in the full paper of RE-NOVATE II. Both additional analyses did not alter the conclusions.

2 BACKGROUND

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

Does the ERG believe that the manufacturer's description of the underlying health problem is appropriate and relevant to the decision problem under consideration?

The ERG largely agrees with the description of the underlying health problem. It is not clear whether the incidence, prevalence, mortality and costing are directly linked to THR or TKR, or VTE in general. Additionally, it is unclear if the VTE described is caused by either THR or TKR, or as a result of other factors, or in combination. The ERG provides a detailed overview on VTE (DVT and PE), THR and TKR.

Venous Thromboembolism is a collective term for two conditions namely deep vein thrombosis (DVT) which is the most common type of VTE, and pulmonary embolism (PE). DVT occurs when there is a formation of a blood clot in the veins of the legs whereas PE occurs when a blood clot forms in one of the blood vessels in the lungs.[1] In the United Kingdom, VTE affects 1 in 1000 people, and around one in 10 persons with untreated DVT develop PE.[2] The risk of developing VTE is dependent on the patients' health, surgical procedure to be undertaken, and other predisposing factors such as age, genetics, medical conditions, obesity and pregnancy. Persons undergoing orthopaedic surgery including knee and hip replacement have an increased risk, and the majority of affected patients develop DVT and PE while in hospital.[3] The typical symptoms of DVT include swelling, tenderness to the leg muscles and skin discoloration (reddish or bluish) whereas PE symptoms include mild fever, sudden shortness of breath, rapid heart rate and sometimes patients may present with DVT symptoms such as swelling to the legs. Nonetheless, in some cases such symptoms may not be present, which is suggestive of why VTE is at times called a "silent killer".[4] The incidence and prevalence rates of VTE outside the hospital environment are unknown.[3] The diagnosis is often assessed by prevailing symptoms in combination with a relevant test such as D-dimer test, ultrasound scan, venogram and a Doppler study for DVT, while the PE diagnosis is based on use of a computerised tomography pulmonary angiograph (CTPA), ventilation (perfusion) scan or D-dimer test. PE is the primary cause of death in 10% of all hospitalised patients, with related annual mortality figures of 25,000 and 32,000 for DVT and PE respectively.[2] The mortality figures for VTE exceed the pooled total deaths from acquired immune deficiency syndrome (AIDS), breast cancer and traffic accidents.[2] However, the figures are often used as a guide rather than the definite number of deaths. This is because the deaths are usually not followed by a post-mortem or are either recorded as those caused by a heart attack or acute respiratory failure.[3] The majority of deaths are thought to be preventable by appropriate reference to the NICE guideline[3] on prevention of VTE in hospitalised persons (use of thromboprophylaxis during hospital and after discharge). The direct and indirect cost of currently managing VTE is projected at £640 million annually.[2, 5]

The THR and TKR surgery is grouped in to three main types of operations. These include primary procedures, revision procedures, and re-operation other than revision procedures. Primary surgery represents the majority of TKR and TKR operations. There has been a gradual increase in the number of TKR procedures compared to THR. In 2005/06 TKR represented a 2.1% and 5.5% in 2009/10 increase in primary procedures over THR.[6]

Table 2.1. Summary of Annual TKR and THR Statistics (England and Wales)

National Health Service (NHS)		Independent
	2010	**2010**
Hip Replacements	55,882	24,226
Knee Replacements	59,950	25,333

Source: National Joint Registry: 7th annual Report, 2010

According to the 2003-2009 implant survivorships on TKR and THR, overall mortality after primary hip replacement was 0.6% at 90 days, and 9.9% at five years. The mean length of stay in hospital was 6.9 days. In comparison, TKR mortality was estimated at 0.4% at 90 days and 9.4% at 5 years. The mean length of hospital stay was 6.6 days.[6]

2.2 Critique of manufacturer's overview of current service provision

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

The MS description of current service provision is adequate and is based on the NICE guideline CG92.[3] The guideline recommends use of mechanical VTE prophylaxis pre-operatively and pharmacological VTE prophylaxis post-operatively. The pharmacological interventions recommended for use in elective knee or hip replacement surgery include, low molecular weight heparin, fondaparinux, rivaroxaban and dabigatran etexilate. Additionally, the guideline recommends that a risk assessment of VTE be carried out on admission to hospital, patients should be re-assessed 24 hours after admission, and whenever there is a clinical change in patients' health. The MS comments that there are considerable variations between current practice and NICE guidance on VTE with regards to LMWH and VTE prophylaxis postoperative after knee or hip surgery. However, the statements presented do not have a firm evidence base and their justification is not indicated too. Such statements include:

- MS Page 24 "The UK NICE clinical guideline recommends starting LMWH 6-12hr after surgery. However, LMWH is often started post-operatively, with anecdotal evidence suggesting considerable variation in clinical practice"
- MS page 24 "In the previous NICE Guidelines,[5] and the current ones,[3] NICE (and others) recommend VTE prophylaxis for up to 35 days following total hip replacement (THR) and up to 14 days post total knee replacement (TKR), and these regimens were investigated in the apixaban trials. However, this regimen is rarely followed in the UK"
- MS page 25 "Aspirin is generally not recommended in any UK or international guide"

3 Critique of manufacturer's definition of decision problem

The ERG has no major concerns with the manufacturer's definition of the decision problem.

3.1 Population

To what extent does the clinical evidence submitted by the manufacturer match the patient population described in the final scope? Where there is a mismatch, provide further details. Does the clinical evidence submitted by the manufacturer reflect the characteristics of the patient population in England and Wales eligible for treatment? If not, provide further comment.

The manufacturer's statement of the decision problem appropriately defines the population as adults undergoing elective total hip replacement (THR) or total knee replacement (TKR) surgery.

3.2 Intervention

Does the intervention described in the MS match the intervention described in the final scope? What is the technology and what is its relevant or proposed marketing authorisation/ CE mark?

Apixaban (Eliquis®, Bristol Myers Squibb and Pfizer) is a direct oral factor Xa inhibitor which prevents the formation of thrombin and fibrin; the key components in blood clot formation.

Apixaban, is marketed as an intervention for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. The recommended dose is one 2.5 mg tablet taken twice daily, with a duration of 5 weeks for patients undergoing THR and for 2 weeks in patients undergoing TKR. It is anticipated that apixaban will be prescribed and initiated whilst the patient is in hospital (12–24 hours after surgery) and the course of treatment will be completed post discharge. No dose adjustments are required in patients with mild or moderate renal impairment.

3.3 Comparators

Do the comparators described in the MS match the comparators described in the final scope? If not, provide further details. Where evidence is limited or not available for relevant comparators has the manufacturer asked an unbiased clinical panel, or carried out its own survey, and do the views elicited agree with what the clinical advisors to the ERG advocate?

The chosen comparators are enoxaparin, which is taken to be indicative of low molecular weight heparin; dabigatran a direct inhibitor of the enzyme thrombin that has been recommended for use in patients undergoing THR or TKR (http://www.nice.org.uk/nicemedia/pdf/DabigatranFAD.pdf); rivaroxaban an oral, direct factor Xa inhibitor, that has also been recommended for use in patients undergoing THR or TKR (http://www.nice.org.uk/nicemedia/pdf/RivaroxabanFAD.pdf); and fondaparinux which is a synthetic pentasaccharide Factor Xa inhibitor, that in contrast to heparin, does not inhibit thrombin. Fondaparinux, according to the MS (page 13) is used in less than one percent of patients undergoing TKR or THR and it is given by injection, and requires similar administration resources as the LMWHs.

The NICE clinical guideline on reducing the risk of VTE in patients admitted to hospital (CG92) recommends that dabigatran etexilate (starting 1 to 4 hours after surgery), fondaparinux sodium (starting 6 hours after surgical closure provided haemostasis has been established), low molecular weight heparin (LMWH) (starting 6–12 hours after surgery), rivaroxaban (starting 6–10 hours after surgery), or unfractionated heparin for patients with renal failure (starting 6–12 hours after surgery) should be offered in combination with mechanical and pharmacological methods for patients undergoing elective knee and hip replacement surgery.

The ERG has no concerns with these choices of comparators.

3.4 Outcomes

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

The majority of the key clinical outcomes are considered within the model both in the short term and in the long term. These are VTEs, PTS, mortality and bleeds.

3.5 Other relevant factors

For example: Does the MS include a section on equity considerations? Is there an ongoing Patient Access Scheme application?

The ERG considers that the time horizon of the model of 35 years is appropriate for this decision problem given the mean age of the population of 65 or 68 (depending on sex and whether THR or TKR); this makes the final age at least 100 years, which approximates a lifetime.

The ERG has listed all concerns in the previous and in the following sections.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods used by the manufacturer to systematically review clinical effectiveness evidence

4.1.1 State objective of systematic review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

List databases and other sources of information including unpublished sources, describe any restrictions.

An evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), developed by McGowan et al. was adapted to inform this critique. The submission was checked against the Single Technology Appraisal (STA) specification for manufacturer/sponsor submission of evidence.[7, 8] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1B. To highlight any remaining shortcomings in the manufacturer's searching after response to the Clarification Letter, the ERG ran a search combining all of the manufacturer's corrections and compared them with their own search created to maximise results. Both search strategies are presented in Appendix 1A. The ERG was not able to screen search results due to time constraints, and therefore can only show the numerical differences in the numbers of references retrieved between manufacturer and ERG searches without a definitive indication that relevant studies were missed.

Clinical effectiveness

Searches were carried out on all databases required by NICE. The search dates were reported for all searches but the date span was not accurately reported for Medline or which issue of the Cochrane Library was searched. The research question was stated as "the clinical and cost effectiveness of Apixaban, within its licensed indication, for the prevention of venous thromboembolism in people undergoing elective knee and hip replacement surgery".[9] The manufacturer translated the research question into appropriate search strategies and the ERG considered these searches to be adequate. The ERG questioned the use of the term Arthroscopy rather than Arthroplasty in the searches undertaken for Clinical Effectiveness and mixed treatment comparisons on Medline, Cochrane and Cinahl databases. Whilst this was addressed adequately in the manufacturer's response (Response to Clarification Letter, A10, page 26),[10] the ERG noted a few remaining weaknesses (Appendix 1B)

The manufacturer reported that additional searches were undertaken for relevant material in conference proceedings of the American Society of Hematology (ASH), the British Society of Haematology (BSH), the British Orthopaedic Association (BOA), the International Congress on Thrombosis (ICT), the International Society on Thrombosis and Haemostasis (ISTH), the American College of Chest Physicians (ACCP), the American College of Cardiology (ACC), the American Academy of Orthopedic Surgeons (AAOS), European Orthopedic Research Society (EORS), European Federation of National Associations of orthopedics and Traumatology (EFORT), European Hematology Society (EHS) and the British Society of Haematology.[11] The MS did not include details of the search terms used to search these additional resources, therefore the ERG was unable to comment on these searches.

Indirect and mixed treatment comparisons

Searches were carried out on all NICE required databases and used the same strategies as 9.2.[11] The ERG noted a typographical error for Fondaparinux in the original submission which was subsequently addressed in the manufacturer's response (Response to Clarification Letter, A4, page 18) (see Appendix 1A). The ERG noted that not all low molecular weight heparins were searched for as free text and queried this omission with the manufacturers. The manufacturers responded that *"At the initial citation screening stage (on the basis of title and abstract), all LMWH RCTs which met the inclusion criteria for the review were included. However, as stated in appendix 16 of the submission, it was decided a priori that meta-analysis was restricted to licensed doses of LMWHs, since the NICE appraisal is primarily focused on UK licensed doses of apixaban and its relevant comparison treatments* (Response to Clarification Letter, A6, page 19) In the original submission the ERG also queried the omission of the abbreviation "LMWH" from the search strategy, this was addressed satisfactorily in the manufacturer's response (Response to Clarification Letter, A5, page 18).

Adverse events

The Manufacturer stated that searches created for sections 5.1 and 9.2 of the Industry submission, were also designed to identify eligible studies for adverse events associated with Apixaban.[11] CRD guidance recommends that if searches have been limited by an RCT filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed.[12] The ERG considered it was possible that some relevant evidence might not have been identified as a consequence of the RCT limit.

Non-RCT Evidence (Apixaban)

Adequate searches were carried out on all NICE required databases, plus additional hand searches of the bibliographies of relevant articles and unpublished data from the manufacturer's own clinical trials database.[11] The ERG noted the same limitations in the facets for hip/knee replacement as in earlier searches (see Appendix 1B)

Cost effectiveness

Searches were carried out on all NICE required databases. The search date was reported for all searches but no Issue date was reported for the Cochrane search. The searches were well reported and reproducible. The ERG did notice a recurring typographical error on the word analysis in the Medline and Embase search of the original submission, which the manufacturer addressed in their response (Response to Clarification Letter, B7, page 56).

Embase

The ERG queried why a Medline cost filter was applied to the Embase search, the use of Medline mesh such as "exp cost/" in Embase would also pick up unwanted terms such as Energy cost/. The Manufacturer addressed this in their response (Response to Clarification Letter, B8, page 56). The ERG reran the manufacturers search with all corrections (n=348) but noted some remaining weaknesses and addressed this by conducting an additional search (n=485) (See Appendix 1A)

The manufacturer reported that additional searches were undertaken for relevant material by hand searching reference lists of previous trials and systematic reviews and by searching conference

proceedings of the American Society of Hematology (ASH), the British Society of Haematology (BSH), the British Orthopaedic Association (BOA), the International Congress on Thrombosis (ICT), the International Society on Thrombosis and Haemostasis (ISTH), the American College of Chest Physicians (ACCP), the American College of Cardiology (ACC), the American Academy of Orthopedic Surgeons(AAOS), European Orthopedic Research Society (EORS), European Federation of National Associations of orthopedics and Traumatology (EFORT), European Hematology Society (EHS), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Health Economics Association (iHEA).[11] The MS did not include details of the search terms used to search these additional resources, therefore the ERG was unable to comment on these searches.

Measurement and valuation of health effects

Searches were carried out on all NICE required databases. Searches were adequate and easily reproducible. The ERG noted the same typographical error for Fondaparinux as with previous searches. The search was not rerun with the corrected spelling, but the rerun search for clinical effectiveness suggests that it would have had little impact on the recall of searching. The search date was reported for all searches but the ERG noted a disparity between dates listed for Embase in sections 9.12.1 and 9.12.4 of the Industry submission.[11] This was addressed by the manufacturers in their response (Response to Clarification Letter, B19, page 76), no issue date was reported for Cochrane.

Resource identification, measurement and valuation

The Manufacturer reported that searches created for cost effectiveness (9.10.4 of the Industry submission) were also used for Resource Identification.[11] Therefore the same ERG comments about typographical errors, missing issue date for Cochrane and inappropriate inclusion of economics filter terms for cost-effectiveness searches, applied to this section.

Summary of searching

The searches documented in the initial manufacturer's submission contained several areas of weakness which were queried by the ERG.[13] The manufacturer addressed all the points of concern raised by the ERG in their response to clarification.[10] Despite remaining weaknesses in the Embase filter used for cost effectiveness and the limited use of synonyms and subject headings for Hip/Knee replacements, the ERG concluded that searching was carried out to an adequate standard and accurately reflected the research questions.

4.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Details of the inclusion and exclusion criteria, as reported in the MS, are reproduced in Table 4.1. (MS, Chapter 5.2.1, Table 4, p.32).

Table 4.1: Eligibility criteria used in search strategy for RCT evidence

	Description
Inclusion criteria	
Population	Adult patients (≥ 18 years) undergoing elective knee or hip replacement surgery
Interventions	• Apixaban • Low molecular weight heparins (to include enoxaparin) • Fondaparinux • Rivaroxaban • Dabigatran

Outcomes	• Mortality (VTE-related, all cause)
	• Incidence of VTE
	• Post DVT complications including post thrombotic syndrome (PTS)
	• Length of hospital stay
	• Joint outcomes, including joint infection
	• Adverse events including bleeding events
	  o Intracranial bleeding
	  o Major bleeding
	  o Clinically relevant, non-major bleeding
	• Health-related quality of life

Study design	Prospective, randomised controlled trials, phase II-IV
Language restrictions	Only abstracts in English were included
Exclusion criteria	
Population	Patients: • undergoing emergency hip or knee surgery • undergoing surgery for hip fracture repair • undergoing other types of surgery • treated under non-surgical indications; e.g. to prevent VTE in acute medical illness • treated only once a VTE event has occurred (i.e. active treatment of VTE event)
Interventions	Mechanical • graduated elastic compression stockings • intermittent pneumatic compression devices • vena cava filters Nursing care/physiotherapy

The inclusion/exclusion criteria appear to be appropriate, they include appropriate detail and the justification for the inclusion and exclusion criteria, provided in a separate column, is that they are in line with the final scope.

4.1.3 What studies were included in the clinical effectiveness review and what were excluded? Provide a table of identified studies. Please identify the most important clinical effectiveness studies.

The MS identifies four direct head-to-head, phase III, randomised, blinded, trials of apixaban versus enoxaparin (ADVANCE-1,[14, 15] ADVANCE-2,[16, 17] ADVANCE-3[18, 19] and APROPOS[20]). ADVANCE-3 was conducted in patients undergoing THR, whilst ADVANCE-1, ADVANCE-2 and APROPOS were conducted in patients undergoing TKR. ADVANCE-2 and ADVANCE-3 used the U.K dosing of the comparator enoxaparin (40mg once daily), whilst ADVANCE-1 and APROPOS used the U.S dosing of enoxaparin (30mg twice daily).

ADVANCE-2 and ADVANCE-3 are used in the main analyses and the base-case of the economic model. This is justified as these two trials used the U.K dosing of the comparator enoxaparin (40mg once daily). In addition, APROPOS was correctly excluded as it was a phase II, dose-ranging study. All four trials are included in a sensitivity MTC analysis. Details of the study design and patient characteristics of the apixaban trials are summarised in Table 4.2 (see also MS, Table 7, page 38).

Table 4.2. Design and Patient Characteristics of the Apixaban trials.

Study	Design	Participants	Interventions and comparators (n=randomised)	Outcomes	Duration (planned)
ADVANCE-1[14, 15]	Phase 3, randomised, active controlled, parallel group study	• Male and female subjects, ≥ 18 years scheduled to undergo either elective unilateral or same-day bilateral TKR or a revision of at least one component of a TKR • Subjects had to be willing and able to undergo bilateral ascending contrast venography	• Apixaban 2.5 mg bd po + placebo injection (n = 1599) • Enoxaparin 30 mg bd sc + placebo tablets (n = 1596) First oral dose of apixaban or matching placebo 12-24 hours after skin wound closure; twice daily schedule for 12 days. First sc dose of enoxaparin or matching placebo 12-24 hours after skin wound closure; 12 hourly dose schedule for 12 days	Primary outcomes: The primary efficacy endpoint was the composite of adjudicated asymptomatic and symptomatic DVT, non-fatal PE, and all-cause death following 12±2 days of double-blind treatment. Secondary outcomes: The key secondary efficacy endpoint was the composite of adjudicated proximal DVT, non-fatal PE and all-cause death during the intended treatment period.	• Screening period 30 days prior to surgery to 24 hours after surgery • Treatment period of 12 (±2) days starting on the day of surgery or the next day • Follow-up period for 60 (±3) days after the last dose of study drug
ADVANCE-2,[16, 17]	Phase 3, randomised, active controlled, parallel group study	• Male and female subjects, ≥ 18 years scheduled to undergo either elective unilateral or same-day bilateral TKR or a revision of at least one component of a TKR • Subjects had to be willing and able to undergo bilateral ascending contrast venography	• Apixaban 2.5 mg bd po + enoxaparin-placebo injection (n = 1528) • Enoxaparin 40 mg od sc + apixaban-placebo tablets (n = 1529) First oral dose of apixaban or matching placebo 12-24 hours after skin wound closure; bd dosing through 11 days after surgery day. Initial dose of enoxaparin or placebo injected 12±3 hours prior to surgery. Next dose injected after skin wound closure; od dosing through 11 days after surgery day.	Primary outcomes: The primary efficacy endpoint was the composite of all adjudicated VTE (PE, symptomatic DVT, and asymptomatic DVT) and all-cause death during the intended treatment period. Secondary outcomes: The key secondary efficacy endpoint was the composite of adjudicated asymptomatic and symptomatic proximal DVT, non-fatal PE, and VTE-related death during the intended treatment period.	• Screening period up to 14 days prior to randomisation • Randomisation period 1-4 days prior to surgery • Treatment period, starting with first dose of sc study drug 12 (±3) hours prior to surgery and extending 10-14 days after surgery • Follow-up period for 60 (±5) days after last dose of study drug
ADVANCE-3[18, 19]	Phase 3, randomised, active controlled parallel group study	• Male and female subjects, ≥ 18 years scheduled to undergo elective unilateral total hip replacement or revision of at least one component of a previously inserted hip prosthesis	• Apixaban 2.5 mg bd po + enoxaparin-placebo injection (n = 2708) • Enoxaparin 40 mg od sc + apixaban-placebo tablets (n = 2699) First oral dose of apixaban or placebo was given 12-24 hours after wound closure; bd dosing for 32-38 days. First sc dose of enoxaparin or placebo was started 12±3 hours before surgery and	Primary outcomes: The primary efficacy outcome was the composite of adjudicated asymptomatic or symptomatic DVT, non-fatal PE and all-cause death during the intended treatment period (32-38 days or within 2 days of the last dose of study drug). Secondary outcomes: The key secondary efficacy endpoint was the composite of adjudicated asymptomatic and symptomatic	• Screening period up to 14 days prior to randomisation • Treatment period, starting with first dose of sc study drug 12 (±3) hours prior to surgery. Study medications were continued for 32-38 days • Follow-up period for 60 (±5) days

			resumed after surgery according to investigator's standard of care; od dosing for 32-38 days	proximal DVT, non-fatal PE, and VTE-related death during the intended treatment period.	
APROPOS[20]	Phase II, randomised, eight-arm, parallel group study	Males and females aged 18–90 years scheduled to undergo total knee replacement.	Oral apixban 2.5 mg (n= 153) Subcutaneous enoxaparin 30 mg bd (n= 152)	The primary efficacy outcome was a composite of adjudicated VTE events (asymptomatic and symptomatic DVT, symptomatic non-fatal PE) and death from any cause. The primary safety outcome was major bleeding.	12±2 days, when mandatory venography was performed

For the purposes of the indirect comparison analyses four trials comparing dabigatran at two different doses (150mg od, 220mg od) with enoxaparin were included in the MS. The 220mg od dose was used for the indirect comparisons. These trials were, RE-NOVATE,[21] and RE-NOVATE II[22] which were conducted in a population undergoing THR and RE-MODEL[23] and RE-MOBILIZE[24] which were conducted in patients undergoing TKR.

Four trials comparing rivaroxaban (10mg od) with enoxaparin were included in the MS. These trials were, RECORD-1,[25] and RECORD-2[26]which were conducted in a population undergoing THR and RECORD-3[27] and RECORD-4[28] which were conducted in patients undergoing TKR. RECORD-1, RECORD-2 and RECORD-3 used the U.K dosing of the comparator enoxaparin (40mg once daily), whilst RECORD-4 used the U.S dosing of enoxaparin (30mg twice daily).

Three trials comparing fondaparinux (2.5mg od) with enoxaparin were included in the MS. These trials were, Lassen et al. 2002[29] and Turpie et al. 2002[30] which were conducted in a population undergoing THR and Bauer et al. 2001[31] which was conducted in patients undergoing TKR. Lassen et al. 2002 used the U.K dosing of the comparator enoxaparin (40mg once daily), whilst Turpie et al. 2002 and Bauer et al. 2001used the U.S dosing of enoxaparin (30mg twice daily).

The ERG does not believe that the in- and exclusion criteria for the trials using the U.K dosing of the comparator enoxaparin are sufficiently different to prohibit comparison.

The MS also provided a mixed treatment comparison (MTC) in which 43 trials were included, using both the U.K dosing of the comparator enoxaparin and the U.S dosing. However, the MS concluded that the "adjusted indirect comparison is regarded as the most appropriate analysis for informing the clinical efficacy and safety of apixaban versus relevant treatment comparators in this submission, since the MTC results were inconsistent with some of the head-to-head RCT data." (MS, page 85). In the response to the clarification letter the manufacturer explained these inconsistencies as follows:

> "The juxtaposition of results from the head-to-head comparisons and the MTC below indicates there were no inconsistencies between the direct and MTC evidence for dabigatran 220 mg od. For the comparisons of apixaban and rivaroxaban vs. enoxaparin 40 mg od respectively, there was inconsistency in the direct and MTC evidence on the VTE composite outcome across both THR and TKR populations, and inconsistency between the direct evidence and the MTC on the any DVT outcome in the TKR population only. In addition, for apixaban, the direct and MTC evidence was inconsistent for the asymptomatic DVT outcome across both TKR and THR populations (see Table 8 below, the inconsistencies are highlighted in red). For all other outcomes, the respective direct head-to-head and MTC apixaban and rivaroxaban evidence was consistent." (Response to Clarification Letter, A7, page 20).

"For all inconsistent outcomes, the MTC displayed wider credibility intervals (i.e. increased uncertainty) which resulted in no statistically significant between-treatment differences. In contrast the head-to head comparisons for apixaban and rivaroxaban displayed narrower confidence intervals on the outcomes affected, which resulted in statistically significant differences favouring apixaban and rivaroxaban respectively vs. enoxaparin 40 mg od." (Response to Clarification Letter, A7, page 20).

"The explanation for this inconsistency between the direct head-to-head comparisons and the MTC has already been outlined in section 5.7.9 of the submission document, viz. that the wider credibility intervals in the MTC may be due to the large number of trials contributing to the enoxaparin 40mg od node within the MTC network in addition to the trial sub-set reporting head-to-head comparisons of treatments that all fall within the NICE scope for apixaban. The former tended to 1) be older (...), 2) have fewer study quality criteria reported (...), 3) have fewer participants (mean study arm size N=184, ...), and 4) compare enoxaparin 40mg od against treatments not within the NICE STA scope for apixaban (...), compared to the within-scope head-to-head comparison trial sub-set. These factors could have contributed to a lack of precision and an increase in uncertainty (i.e. wider credibility intervals) in the relative treatment effects for enoxaparin 40 mg od observed in the MTC results, despite the apparent increase in power (i.e. more eligible studies) afforded by the MTC study inclusion criteria." (Response to Clarification Letter, A7, page 21-22).

4.1.4 Provide details of any relevant studies not discussed in the submission? Why were these studies excluded and how were these studies identified by the ERG?

The searches performed by the manufacturer were examined by the ERG and found to be satisfactory.

The ERG is not aware of any relevant studies that were not included in the MS. The ERG did find a full publication for the RENOVATE-II trial,[22] for which the MS used an abstract only.[32] Data from the full paper have been included in the ERG analyses.

The MS reported that "there is no additional evidence concerning the indication being appraised for this submission anticipated to be available in the next 12 months". However, it is not clear whether this statement relates to apixaban trials only, or comparator trials as well.

4.2 Summary and critique of submitted clinical effectiveness evidence

If there is more than one RCT described in the MS, it may be appropriate to discuss each trial individually using the headings described.

4.2.1 Summary of submitted clinical evidence for each relevant trial.

The MS identified four trials of apixaban versus enoxaparin (ADVANCE-1,[14, 15] ADVANCE-2,[16, 17] ADVANCE-3[18, 19] and APROPOS[20]) Results of the ADVANCE-1, -2 & -3 trials are described in section 5.5 and 5.9 of the MS (MS, pages 55-68, 103-116). According to the manufacturer "APROPOS is a phase II dose finding study and as such is not presented in full in this submission. However, a brief overview is provided in Appendix 14" (MS, page 38). The inclusion criteria clearly state that phase II-IV trials are included and no reference is made to dose-finding studies being excluded. Therefore it is unclear why this study is treated differently. However, as ADVANCE-1 and APROPOS used enoxaparin 30mg b.d. as the comparator, the ERG agrees that these trials are not included in the main analyses.

In this section we will summarise all evidence from the four apixaban trials relating to the outcomes in the scope:
- ADVANCE-2: Apixaban vs Enoxaparin 40 mg o.d. in TKR;
- ADVANCE-3: Apixaban vs Enoxaparin 40 mg o.d. in THR;
- ADVANCE-1 and APROPOS: Apixaban vs Enoxaparin 30 mg b.d. in TKR.

None of the trials reported results for joint outcomes including infections, or health related quality of life. Pulmonary embolism was reported by three trials as the main post-DVT complication but results for thrombotic syndrome are not presented in any trial.

ADVANCE-2 is the only trial comparing apixaban with enoxaparin 40 mg o.d. in patients with total knee replacement. Apixaban was statistically superior to enoxaparin in terms of the primary composite endpoint of all VTE and all cause death, as well as in terms of major VTE and all DVT. The available evidence for each outcome mentioned in the NICE scope is summarised in Table 4.3. The 60 days follow-up period was completed by 1458 (95%) apixaban patients and 1469 (96%) enoxaparin patients.

Table 4.3: Results for Apixaban versus Enoxaparin 40 mg od in TKR (ADVANCE-2)

Outcome\population	**ADVANCE-2**		
	Apixaban* (Responders/ Patients analysed) N=1528	**Enoxaparin (Responders/ patients analysed) N=1529**	**Effect size (95% CI)**
- VTE/All-cause death	147/976	243/997	RR= 0.62 (0.51 to 0.74)
- Death	2/1528	0/1529	RR= 5.0 (0.24 to 104.13)
- Major VTE	13/1195	26/1199	RR= 0.5 (0.26 to 0.97)
- All DVT	142/971	243/997	RR= 0.6 (0.50 to 0.72)
Post DVT complications:			
- Pulmonary Embolism (fatal or non-fatal)	4/1528	0/1529	RR= 9.01 (0.49 to 167.13)
- Post-Thrombotic syndrome	NR	NR	

Duration of hospital stay in days	NR	NR	
Joint outcomes including joint infection	NR	NR	
Adverse events:			
- All adverse events n(%)	786/1501 (52%)	836/1508 (55%)	RR= 0.94 (0.88 to 1.01)
- Serious AEs n(%)	72/1501 (5%)	88/1508 (6%)	RR= 0.82 (0.61 to 1.11)
- Major bleeding events	9/1501 (0.6%)	14/1508 (0.9%)	RR= 0.65 (0.28 to 1.49)
- All bleeding events n(%)	104/1501 (6.9%)	126/1508 (8.4%)	RR= 0.83 (0.65 to 1.06)
Health related quality of life	NR	NR	

VTE=Venous thromboembolism; DVT=Deep-vein thrombosis; NR- Not-reported

ADVANCE-3 is the only trial comparing apixaban with enoxaparin 40 mg o.d. in patients with total hip replacement. Apixaban was statistically superior to enoxaparin in terms of the primary composite endpoint of all VTE and all cause death, as well as in terms of major VTE and all DVT. Follow-up for 60 days after the last dose of study medication was completed by 2598 (96%) apixaban patients and 2577 (95%) enoxaparin patients. The available evidence for each outcome mentioned in the NICE scope is summarised in Table 4.4.

Table 4.4: Results for Apixaban versus Enoxaparin 40 mg od in THR (ADVANCE-3)

Outcome\population	**ADVANCE-3**		
	Apixaban* (Responders/ Patients analysed) N= 2708	**Enoxaparin (Responders/ patients analysed) N= 2699**	**Effect size (95% CI)**
- VTE/All-cause death	27/1949	74/1917	RR= 0.36 (0.23 to 0.56)
- Death	3/2708	1/2699	RR= 2.99 (0.31 to 28.73)
- Major VTE	10/2199	25/2195	RR= 0.40 (0.19 to 0.83)
- All DVT	22/1944	68/1911	RR= 0.32 (0.20 to 0.51)
Post DVT complications:			
- Pulmonary Embolism (fatal or non-fatal)	3/2708	5/2699	RR= 0.60 (0.14 to 2.50)
- Post-Thrombotic syndrome	NR	NR	
Duration of hospital stay in days	NR	NR	
Joint outcomes including joint infection	NR	NR	
Adverse events:			
- All adverse events n(%)	NR	NR	
- Serious AEs n(%)	NR	NR	
- Major bleeding events	22/2673 (0.8%)	18/2659 (0.7%)	RR= 1.22 (0.65 to 2.26)
- All bleeding events n(%)	313/2673 (11.7%)	334/2659 (12.6%)	RR= 0.93 (0.81 to 1.08)
Health related quality of life	NR	NR	

VTE=Venous thromboembolism; DVT=Deep-vein thrombosis; NR- Not-reported

The ADVANCE-1 and the APROPOS studies employed the American dosing regimen for enoxaparin (30 mg bid), and both trials were in patients with total knee replacement. Both trials reported no significant differences for nearly all of the outcomes reported. Follow-up for 60 days after the last dose of study medication was completed in 1562/1599 (97.7%) patients assigned to apixaban and in 1554/1596 (97.4%) assigned to enoxaparin.

Table 4.5: Results for Apixaban versus Enoxaparin 30 mg bd in TKR (ADVANCE-1 & APROPOS)

Outcome\population	ADVANCE-1			APROPOS		
	Apixaban* (Responders/ Patients analysed) N= 1599	**Enoxaparin (Responders/ patients analysed) N= 1596**	**Effect size (95% CI)**	**Apixaban* (Responders/ Patients analysed) N= 111**	**Enoxaparin (Responders/ patients analysed) N= 109**	**Effect size (95% CI)**
- VTE/All-cause death	104/1157	100/1130	RR= 1.02 (0.78 to 1.32)	10/111	17/109	RR= 0.58 (0.28 to 1.20)
- Death	3/1599	3/1596	RR= 1.00 (0.20 to 4.94)	1/111	0/109	RR= 2.95 (0.12 to 71.55)
- Major VTE/All-cause death	26/1269	20/1216	RR= 1.25 (0.7 to 2.22)	2/111	5/109	RR= 0.39 (0.08 to 1.98)
- All DVT	89/1142	92/1122	RR= 0.95 (0.72 to 1.26)	10/111	15/109	RR= 0.65 (0.31 to 1.39)
Post DVT complications:						
- Pulmonary Embolism (fatal or non-fatal)	16/1599	7/1596	RR= 2.28 (0.94 to 5.53)	0/111	2/109	RR= 0.20 (0.01 to 4.05)
- Post-Thrombotic syndrome	NR	NR		NR	NR	
Duration of hospital stay in days	NR	NR		NR	NR	
Joint outcomes including joint infection	NR	NR		NR	NR	
Adverse events:						
- All adverse events n (%)	NR	NR		134/154 (87%)	129/149 (86.6%)	RR= 1.01 (0.92 to 1.10)
- Serious AEs n (%)	135/1596 (8.5%)	136/1588 (8.6)	RR= 0.99 (0.79 to 1.24)	12/154 (7.8%)	10/149 (6.7%)	RR= 1.16 (0.52 to 2.61)
- Major bleeding events n(%)	11/1596 (0.7%)	22/1588 (1.4%)	RR= 0.50 (0.24 to 1.02)	0/154	0/149	RR= not estimable
- All bleeding events n (%)	85/1596 (5.3%)	108/1588 (6.8%)	RR= 0.78 (0.59 to 1.03)	6/154 (3.9%)	8//149 (5.4%)	RR= 0.73 (0.26 to 2.04)
Health related quality of life	NR	NR		NR	NR	

VTE=Venous thromboembolism; DVT=Deep-vein thrombosis; NR- Not-reported

The incidence of reported adverse events and severe adverse events was similar between two groups. The available evidence from both trials for each outcome mentioned in the NICE scope is summarised in Table 4.5.

4.2.2 Describe and critique the manufacturer's approach to validity assessment for each relevant trial.

Formal appraisals of the validity of the trials ADVANCE 1, 2 & 3 were clearly presented in the MS (MS, table 12, page 54; appendix 3, page 36-38). All the criteria listed under Section 5.4.1 (MS page 54 – as specified in the NICE STA Specification for manufacturer/sponsor submission of evidence) were addressed in the quality assessment findings. These findings are reproduced in table 4.6 alongside a validity assessment provided by the ERG for the APROPOS trial. The APROPOS was reported to be a dose finding study and subsequently excluded in the main submission. However, as it fulfils all inclusion criteria, the ERG group thinks that this study should be included alongside the ADVANCE 1, 2 & 3 studies for validity assessment.

The ERG checked the quality assessment findings against the provided trial data and original study publications and any additional points are discussed within this section. Overall the ERG was in agreement with the MS quality assessment findings. It was not clear if any of the procedures for searching, screening, assessing validity, extraction and synthesis were undertaken by a single reviewer and independently checked by a second reviewer or using a consensus of multiple reviewers.

Table 4.6: Quality assessment results for RCTs

Trial no. (acronym)	ADVANCE 1	ADVANCE 2	ADVANCE 3	*APROPOS**
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No

Trial no. (acronym)	ADVANCE 1	ADVANCE 2	ADVANCE 3	*APROPOS**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary efficacy analysis dataset included all randomised subjects who had; an adjudicated and evaluable bilateral venogram; or had an adjudicated VTE; or died due to any cause. The key secondary efficacy analysis data sets included all randomised subjects if asymptomatic events were not part of the endpoint or all randomised subjects with either an adjudicated event that was part of the endpoint or an adjudicated evaluable bilateral venogram (MS, Table 11, page 48). This was deemed clinically appropriate since asymptomatic DVT can only be detected with an evaluable venogram. The ITT analysis assumes that no readable venogram represents no event, therefore potentially underestimating the number of VTE events occurring within the ITT population. The remaining efficacy and safety outcome analyses were conducted on the ITT population.			

There is debate around the use of venographically confirmed VTE as the primary endpoint. It can be argued that symptomatic VTE and VTE-related mortality is a more clinically relevant outcome. However the problems associated with the use of this endpoint are well documented (i.e. the rarity of the event) and the primary endpoint adheres with the EMEA guideline for study development in this therapeutic area (reference 72 in the main submission.[33] In addition, two previous STAs on rivaroxaban[34] and dabigatran[35] also used this outcome and described it as appropriate.

Nevertheless, the large amount of missing data is problematic. The most appropriate way to assess whether missing data are likely to have an effect on the results is by performing a sensitive analysis in which all missing data are treated as negative events. However, with one-third of respondents having missing data there is no possibility to do any kind of sensitivity analysis.

4.2.3 Describe and critique the statistical approach used within each relevant trial.

The statistical analysis in the ADVANCE 1, 2& 3 trials are described in the MS on pages 48-50 and in table 11 (MS, page 48) and copied into Table 4.7 below. The analyses for the APROPOS trial were copied from the trial data. The statistical analyses in the trials seemed appropriate.

Table 4.7: Summary of statistical analyses in apixaban RCTs

Trial no. (acronym)	Statistical analysis	Data management, patient withdrawals
ADVANCE 1	Point estimates and 95% CIs for the risk ratio and risk difference between apixaban and enoxaparin were calculated for primary and key secondary outcomes using knee replacement surgery type as stratification factor. Non-inferiority for apixaban on the primary efficacy endpoint would be demonstrated if both of the following conditions were met: • Upper bound of the two-sided 95% CI for relative risk <1.25, and • Upper-bound of the two-sided 95% CI for risk difference <5.6% Test for superiority was planned if apixaban met the pre-specified criteria for non-inferiority	Analysis populations for ADVANCE 1 and 2 were: • **Randomised subjects data set**: all randomised subjects • **Primary efficacy data set**: all randomised subjects who during the intended treatment period had; an adjudicated and evaluable bilateral venogram; or had an adjudicated VTE; or died due to any cause. • **Secondary efficacy data sets**: the data sets used to perform the analyses of the secondary efficacy endpoints were o all randomised subjects if asymptomatic events were not part of the endpoint o all randomised subjects with either an adjudicated event that was part of the endpoint or an adjudicated evaluable bilateral venogram to detect presence or absence of the asymptomatic event of interest (proximal DVT, distal DVT, or both depending on the endpoint). • **Treated subjects' dataset**: all subjects who received at least 1 dose of study drug during the treatment period. • **Per Protocol analysis data set**: primary efficacy data set excluding subjects with significant protocol deviations expected to affect the primary efficacy endpoint (per-protocol efficacy analysis set).
ADVANCE 2	Non-inferiority of apixaban versus enoxaparin for the primary efficacy endpoint was tested first at a 1-sided $\alpha = 0.025$ level. If non-inferiority was demonstrated, superiority for the primary efficacy outcome was tested. If superiority was demonstrated, non-inferiority was then tested on the key secondary efficacy endpoint and if demonstrated, superiority for the key secondary efficacy endpoint was tested. Non-inferiority for apixaban on the primary efficacy endpoint would be demonstrated if both conditions below were met: • Upper bound of the two-sided 95% CI for relative risk <1.25, and • Upper-bound of the two-sided 95% CI for risk difference <5.6% Non-inferiority for apixaban on the key secondary efficacy endpoint would be demonstrated if the upper bound of the 2-sided 95% CI for RR <1.5. Superiority for an efficacy outcome would be demonstrated if the upper bound of the 2-sided 95% CI for relative risk was <1.	
ADVANCE 3	Non-inferiority for apixaban on the primary efficacy endpoint would be demonstrated if the upper limit of the 95% CI for RR <1.25. If non-inferiority was established for the primary outcome, the secondary efficacy outcome would be tested for non-inferiority. Non-inferiority for apixaban on the key secondary efficacy endpoint would be demonstrated if the upper bound of the CI for RR <1.5. If apixaban met the pre-specified criteria for non-inferiority on both the primary and secondary efficacy outcomes, superiority would be tested using Pearson's Chi-square test. This sequential testing procedure maintained the 1-sided alpha level of 0.025.*Differences in bleeding rates were analysed with the use of the Mantel-Haenszel test.	• **Primary efficacy data set**: all randomised subjects who during the intended treatment period had; an adjudicated and evaluable bilateral venogram; or had an adjudicated VTE; or died due to any cause. • **Secondary efficacy data set**: as for primary efficacy data set, however venograms with evaluable proximal venous segments were accepted regardless of whether distal segments were adequately visualised. • **Safety population**: all randomised patients who received at least one dose of study medication. • **Per Protocol analysis data set ***: efficacy data set excluding patients with relevant protocol violations.
APROPOS	Point estimates with Clopper-Pearson Exact 95% CI were calculated for the primary efficacy outcome rate observed during the evaluation period in each of the treatment group using the primary efficacy data set.	• **Primary efficacy data set**: all randomised patients who had an adjudicated and evaluable bilateral venogram performed at any time during the evaluation period or an event of interest that was confirmed by adjudication or died due to any cause. • **Safety population**: all randomised patients who received at least one dose study medication.

4.2.4 Describe and critique the manufacturer's approach to outcome selection within each relevant trial.

According to NICE scope the outcomes required were:

- mortality
- incidence of VTE (symptomatic and asymptomatic)
- post DVT complications including thrombotic syndrome
- length of hospital stay
- joint outcomes (medium and long term), including joint infection
- adverse effects of treatment including bleeding events
- health-related quality of life

All of the outcomes listed above were reported in the inclusion criteria in Table 4 in MS, page 32-33. Table 4.8 below compares the outcomes identified in the scope with those reported in the relevant trials.

Table 4.8: Outcomes mentioned in the NICE scope and reported in relevant trials

Trial	Mortality	Incidence of VTE (symptomatic and asymptomatic)	**Post DVT complications**		Length of hospital stay	Joint outcomes including joint infection	AEs of treatment including bleeding events	Health related quality of life
			Pulmonary Embolism	Thrombotic syndrome				
ADVANCE-1	✔	✔	✔	X	✔	X	✔	X
ADVANCE-2	✔	✔	✔	X	✔	X	✔	X
ADVANCE-3	✔	✔	✔	X	✔	X	✔	X
APROPOS	✔	✔	✔	X	X	X	✔	X

AE=Adverse events

None of the trials reported results for length of hospital stay, joint outcomes, or health related quality of life. Pulmonary embolism was reported by three trials as the main post-DVT complication but results for thrombotic syndrome are not presented in any trial.

4.2.5 To what extent does each relevant trial include the patient population(s), intervention(s), comparator(s) and outcomes as defined in the final scope?

Population

One trial included patients with total hip replacement (ADVANCE-3), and three trials included patients with total knee replacement (ADVANCE-1 and 2, and APROPOS).

Intervention

The three ADVANCE trials used the same intervention: oral apixaban, 2.5 mg bd. The APROPOS trial used 6 different doses of apixaban: oral apixaban 5mg, 10mg, 20mg, od and bd.

Comparators

All apixaban trials directly compare apixaban with enoxaparin, which is included amongst the appropriate comparators stated in the decision problem. ADVANCE-2 and ADVANCE-3 compare

apixaban with the UK licensed dose of enoxaparin (40 mg od). In APROPOS and ADVANCE-1 the dosing of enoxaparin is according to U.S. licensed dose (30 mg bd).

Outcomes
All trials reported data on mortality, incidence of VTE, and adverse events. None of the trials reported results for length of hospital stay, joint outcomes, or health related quality of life. Pulmonary embolism was reported by three trials as the main post-DVT complication but results for thrombotic syndrome are not presented in any trial.

4.2.6 Where appropriate, describe and critique any meta-analysis, indirect comparisons and/ or mixed treatment analysis carried out by the manufacturer.

This section should include a summary of the manufacturer's methods and results as described in the MS. The ERG should critique the methods used and interpret the results in light of the methods used by the manufacturer and generalisability to patients in England and Wales.

The NICE scope mentions several comparators: LMWHs, fondaparinux, rivaroxaban and dabigatran etexilate. Apixaban has only been compared directly with enoxaparin, a LWMH. All other comparators have also been compared directly with enoxaparin. Therefore, the relative effectiveness of apixaban compared with all comparators can be assessed using indirect comparisons.

The MS does not seem to make any attempt to assess the relative effectiveness of apixaban compared with other LMWHs. And is not clear how enoxaparin compares to other LMWHs. According to the MS (MS, page 25): "Enoxaparin is the most widely used LMWH in the UK (13), and is the most widely studied. Enoxaparin was used as the comparator in the apixaban registrational trials." And in chapter 5.6 describing the meta-analysis (MS, page 70): "Enoxaparin was the only LMWH considered for inclusion, as it is the most widely used LMWH VTE prophylaxis option in the UK (13) for the THR and TKR populations." Unfortunately, reference 13 is an internal company document, which was not part of the manufacturer submission. Therefore the source could not be checked by the ERG.

Regarding the comparators, "only dabigatran 220mg od (standard UK dose) was included in the submission analyses, since it is inappropriate to compare the 150mg od dabigatran dose indicated for elderly patients with the apixaban 2.5mg bd, rivaroxaban 10mg od, and fondaparinux 2.5mg od doses indicated for general population use." (MS, page 70). Therefore, the following doses were used in the main MS analyses: apixaban 2.5mg bd, rivaroxaban 10mg od, fondaparinux 2.5mg od, dabigatran 220mg od, and enoxaparin 40 mg od.

The MS describes two strategies for the indirect comparisons:

1. An indirect comparison using Bucher's method.
2. A full mixed treatment comparison.

The main indirect comparison, using the UK dose of enoxaparin, is reported in the main report. In appendix 15 two additional sets of indirect comparisons are reported: 1) using the US dose of enoxaparin, and 2) using the pooled UK and US doses for enoxaparin. In appendix 16 two different types of MTC are reported: 1) using only the UK dose of enoxaparin, and 2) using the pooled UK and US doses for enoxaparin.

Table 4.9: Results from indirect comparisons and MTC relative to apixaban in Total Hip Replacement (THR)

	VTE Comp OR (95% CI/CrI)	Any DVT OR (95% CI)	Major VTE OR (95% CI)	PE OR (95% CI)	Any Bleeding OR (95% CI)	Major Bleeding OR (95% CI)
Apix vs Enox						
- IC1	[redacted]	0.31 (0.191, 0.504)	[redacted]	[redacted]	[redacted]	[redacted]
- IC2	NR	NR	NR	NR	NR	NR
- IC3	NR	NR	NR	NR	NR	NR
- MTC1	[redacted]	0.317 (0.09883, 0.991)	NR	NR	[redacted]	[redacted]
- MTC2		0.315 (0.0898, 1.108)	NR	NR		
Riva vs Apix						
- IC1	[redacted]	0.709 (0.304, 1.652)	[redacted]	[redacted]	[redacted]	[redacted]
- IC2	NR	NR	NR	NR	NR	NR
- IC3	NR	NR	NR	NR	NR	NR
- MTC1	[redacted]	0.698 (0.133, 3.698)	NR	NR	[redacted]	[redacted]
- MTC2		0.622 (0.131, 2.924)	NR	NR		
Dabi vs Apix						
- IC1	[redacted]	2.63 (1.402, 4.931)	[redacted]	[redacted]	[redacted]	[redacted]
- IC2	NR	NR	NR	NR	NR	NR
- IC3	NR	NR	NR	NR	NR	NR
- MTC1	[redacted]	2.601 (0.5151, 13.1)	NR	NR	[redacted]	[redacted]
- MTC2		2.6 (0.45, 14.65)	NR	NR		
Fond vs Apix						
- IC1	NR	1.339 (0.713, 2.514)	NR	[redacted]	NR	[redacted]
- IC2	NR	NR	NR	NR	NR	NR
- IC3	NR	1.643 (0.838, 3.222)	NR	3.524 (0.413, 30.063)	NR	1.295 (0.618-2.716)
- MTC1	[redacted]	0.631 (0.043, 7.752)	NR	NR	NR	[redacted]
- MTC2		1.668 (0.366, 7.491)	NR	NR	NR	

Apix=Apixaban , Enox= Enoxaparin, Riva= Rivaroxaban, Dabi= Dabigatran , Fond= Fondaparinux, VTE Comp= Venous Thromboembolic Events Composite outcome, DVT= Deep Vein Thrombosis, OR= Odds Ratio, CI= Confidence Interval, PE=Pulmonary Embolism.

IC1= Indirect comparison using Enox 40 mg od; IC2= IC using Enox 30 mg bd; IC3= IC using Enox 40 mg od and 30 mg bd;

MTC1= mixed treatment comparison using Enox 40 mg od; MTC2= MTC using Enox 40 mg od and 30 mg bd;

OR < 1: favours first treatment over second.

IC1 results are taken from the main report; IC2 and IC3 results are taken from Appendix 15; and MTC results are taken from Appendix 16 (IC1 results in appendix 15 are different from the results reported in the main report).

Notes: RECORD-2 excluded because Enox 40mg od arm had short duration (see p.70, MS)**;** BISTRO-2 excluded, 220 mg od is standard UK dose for Dabi (see p.70, MS); ODIXa excluded, treatment duration only 5-9 days for both arms (see p.79, MS); For apixaban, one dose was used: 2.5mg bd. For enoxaparin, the European dose (40 mg od) and the US dose (30 mg bd) were used. For the other comparators the following doses were used: rivaroxaban 10mg od, fondaparinux 2.5mg od, and dabigatran 220mg od; For all the results the UK indication doses were considered and any doses for specific populations have not been included; For the outcome "Any bleed", MTC base model has included 'Enoxaparin 40 mg (UK indication)+Ext > 1 week' (instead of only UK indication); For outcomes 'VTE composite, 'Any DVT' and 'Major VTE' results from primary efficacy population were reported. Whereas, for outcomes 'PE', 'Any Bleeding' and 'Major Bleeding' results from ITT population were reported.

Table 4.10: Results from indirect comparisons and MTC relative to apixaban in Total Knee Replacement (TKR)

	VTE Comp OR (95% CI/CrI)	Any DVT OR (95% CI)	Major VTE OR (95% CI)	PE OR (95% CI)	Any Bleeding OR (95% CI)	Major Bleeding OR (95% CI)
Apix vs Enox						
- IC1	[redacted]	0.531 (0.423, 0.668)	[redacted]	[redacted]	[redacted]	[redacted]
- IC2	0.894 (0.571, 1.401)	0.902 (0.678, 1.201)	0.93 (0.28, 3.086)	1.043 (0.108, 10.071)	0.77 (0.58, 1.02)	0.5 (0.24, 1.03)
- IC3	0.71 (0.437, 1.154)	0.686 (0.435, 1.08)	0.735 (0.313, 1.726)	1.885 (0.393, 9.044)	0.79 (0.65, 0.96)	0.55 (0.32, 0.96)
- MTC1	[redacted]	0.872 (0.4, 1.865)	NR	NR	[redacted]	[redacted]
- MTC2		0.681 (0.267, 1.697)	NR	NR		
Riva vs Apix						
- IC1	[redacted]	0.895 (0.621, 1.294)	[redacted]	[redacted]	[redacted]	[redacted]
- IC2	0.742 (0.426, 1.29)	0.759 (0.487, 1.185)	0.625 (0.156, 2.496)	0.591 (0.047, 7.402)	1.468 (1.013, 2.126)	4.96 (1.26, 19.518)
- IC3	0.768 (0.417, 1.412)	0.82 (0.46, 1.47)	0.652 (0.24, 1.767)	0.238 (0.03, 1.861)	1.38 (1.05, 1.814)	3.055 (1.169, 7.981)
- MTC1	[redacted]	0.857 (0.319, 2.773)	NR	NR	[redacted]	[redacted]
- MTC2		0.832 (0.205, 3.609)	NR	NR		
Dabi vs Apix						
- IC1	[redacted]	1.772 (1.258, 2.498)	[redacted]	[redacted]	[redacted]	[redacted]
- IC2	1.489 (0.892, 2.485)	1.458 (0.997, 2.131)	1.646 (0.416, 6.515)	1.171 (0.09, 15.167)	1.117 (0.616, 2.024)	0.84 (0.237, 2.975)
- IC3	1.577 (0.874, 2.847)	1.618 (0.923, 2.836)	1.456 (0.47, 4.508)	0.552 (0.08, 3.785)	1.177 (0.863, 1.607)	1.291 (0.426, 3.91)
- MTC1	[redacted]	1.83 (0.513, 9.639)	NR	NR	[redacted]	[redacted]
- MTC2		1.406 (0.24, 8.438)	NR	NR		
Fond vs Apix						
- IC1	NR	NR	NR	NR	NR	NR
- IC2	NR	0.42 (0.26, 0.68)	NR	0.24 (0.01, 5.34)	NR	22.3 (2.52, 197.47)
- IC3	NR	0.55 (0.31, 1.00)	NR	0.13 (0.01, 1.85)	NR	20.27 (2.42, 169.57)
- MTC1	[redacted]	0.44 (0.11, 1.798)	NR	NR	[redacted]	[redacted]
- MTC2		0.561 (0.085, 3.442)	NR	NR		

Apix=Apixaban , Enox= Enoxaparin, Riva= Rivaroxaban, Dabi= Dabigatran , Fond= Fondaparinux, VTE Comp= Venous Thromboembolic Events Composite outcome, DVT= Deep Vein Thrombosis, OR= Odds Ratio, CI= Confidence Interval, PE=Pulmonary Embolism.

IC1= Indirect comparison using Enox 40 mg od; IC2= IC using Enox 30 mg bd; IC3= IC using Enox 40 mg od and 30 mg bd;

MTC1= mixed treatment comparison using Enox 40 mg od; MTC2= MTC using Enox 40 mg od and 30 mg bd;

OR < 1: favours first treatment over second.

IC1 results are taken from the main report; IC2 and IC3 results are taken from Appendix 15; and MTC results are taken from Appendix 16 (IC1 results in appendix 15 are different from the results reported in the main report).

Results for the main outcomes from each of these analyses are reported in tables 4.9 and 4.10. The Response to the Clarification Letter has a similar overview of results of different analyses with explanations for differences between results (Response to Clarification Letter: A3, Table 3, page 9 and A7, Table 8, page 21).

In the Response to the Clarification Letter the manufacturer explains that "For all inconsistent outcomes, the MTC displayed wider credibility intervals (i.e. increased uncertainty) which resulted in no statistically significant between-treatment differences." (Response to Clarification Letter: A7, page 20) – See also section 4.1.3.

COMMENT

The ERG agrees with the chosen doses for each treatment included in the analyses. In addition the conclusion that the MTC is less reliable because the MTC results were inconsistent with some of the head-to-head RCT data (MS, page 85 and 100) seems reasonable.

4.2.7 Additional clinical work conducted by the ERG

Provide details of any additional work conducted by the ERG in relation to clinical effectiveness. If the results of any of the additional work affect the size of the ICER, refer the reader to the summary table in Section 6.

In the MS an abstract was used for the RE-NOVATE-II study.[32] The full paper for this study was published after completion of the MS.[22] Five outcomes were reported in the full paper, that were not reported in the abstract: Any DVT, Symptomatic DVT, Any bleeding, CRNM bleeding and Minor bleeding. All other outcomes were the same in the full paper as in the abstract. The original ORs and RRs have been reproduced in the table below together with the ORs and RRs including the results from the full paper of RE-NOVATE-II.

Table 4.11: Results with and without the full paper for RE-NOVATE-II (Comparison: Dabigatran etexilate 220 mg od vs. Enoxaparin 40 mg od in THR)

Outcomes:	Based on RE-NOVATE alone	Based on RE-NOVATE and Eriksson 2011 (RE-NOVATE II)[22]
Any DVT event (PE analysis)	OR = 0.82 (0.55, 1.22) RR = 0.83 (0.57, 1.20)	OR = 0.85 (0.65, 1.11) RR = 0.86 (0.67, 1.10)
Symptomatic DVT (ITT analysis)	OR = 6.05 (0.73, 50.35) RR = 6.03 (0.73, 49.97)	OR = 5.01 (1.10, 22.89) RR = 4.99 (1.10, 22.74)
Any bleeding (ITT analysis)	OR = [redacted] RR = [redacted]	OR = 1.13 (0.93, 1.37) RR = 1.11 (0.93, 1.32)
CRNM bleeding (ITT analysis)	OR = [redacted] RR = [redacted]	OR = 1.19 (0.84, 1.69) RR = 1.18 (0.84, 1.66)
Minor bleeding (ITT analysis)	OR = 0.95 (0.68-1.33) RR = 0.95 (0.69-1.30)	OR = 1.02 (0.80, 1.32) RR = 1.02 (0.81, 1.29)

Adding the results reported in the full paper for RE-NOVATE II to those from RE-NOVATE alone produces very small changes and slightly smaller confidence intervals. These changes are unlikely to cause significant changes to the analyses in the MS.

4.3 Conclusions

Describe the completeness of the MS with regard to relevant clinical studies and relevant data within those studies. Does the submission contain an unbiased estimate of the technology's (relative and absolute) treatment effects in relation to relevant populations, interventions, comparators and outcomes? Are there any remaining uncertainties about the reliability of the clinical effectiveness evidence? Reference should also be made concerning the extent to which the submitted evidence reflects the decision problem defined in the final scope.

The manufacturer's search strategy was adequately reported and the submission appears to contain all of the relevant head-to-head RCTs. The outcomes selected were relevant and appropriate, although post DVT complications, length of hospital stay, joint outcomes and health related quality of life, included in the final scope issued by NICE, were not available from the clinical trials for apixaban.

Processes and validation of study screening and data extraction appear to be appropriate. Statistical methods were explicitly described for the meta-analyses and indirect comparisons and all relevant analyses were performed.

The MS appears to contain an unbiased estimate of the treatment effect of apixaban in relation to the relevant outcomes and the comparator, enoxaparin. Overall the evidence from the three ADVANCE trials in the MS indicates that apixaban 2.5mg bd is significantly superior to the comparator enoxaparin (40mg od) in terms of [redacted] any DVT, [redacted] These results were the same for THR and TKR.

The results of the indirect comparisons showed that apixaban:

- **when compared to rivaroxaban** showed no significant differences in terms of [redacted] any DVT, [redacted]

- **when compared to dabigatran** was significantly superior in terms of [redacted] any DVT; [redacted]. These results were the same for THR and TKR.

- **when compared to fondaparinux** in THR showed no significant differences in terms of any DVT [redacted]. Other main outcomes (Total VTE and all-cause mortality, Major VTE, and Any bleeding) were not reported using indirect comparisons; although, for the total VTE and all-cause mortality the MTC showed no significant differences. For TKR an indirect comparison with enoxaparin, 40mg od was not possible.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 State objective of cost effectiveness review. Provide description of manufacturers search strategy and comment on whether the search strategy was appropriate. If the manufacturer did not perform a systematic review, was this appropriate?

The objective was to perform a systematic review of economic evaluations for interventions for the prophylaxis of venous thromboembolism (VTE) in patients undergoing elective total knee and hip replacement.

5.1.2 State the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The inclusion criteria for the literature review were:

- Patients undergoing hip and/or knee replacement or, in a mixed population, where information was reported specifically for the hip and/or knee replacement patient population.
- Graduated elastic compression stockings / anti-embolism stockings (GCS)
- Intermittent pneumatic compression (IPCD) devices
- Foot pumps or foot impulse devices (FID)
- Vena cava filters
- Aspirin or antiplatelet therapy
- Low-dose unfractionated heparin administered subcutaneously (UFH)
- Low molecular weight heparin (LMWH)
- The synthetic pentasaccharide, Fondaparinux
- Vitamin K Antagonists (For example, warfarin, coumarin)
- Early mobilisation
- Foot elevation
- Hydration
- New oral anticoagulants licensed during the guideline development period (rivaroxaban and dabigatran)

Papers not meeting the inclusion criteria above or published in a language other than English were excluded.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the most important cost effectiveness studies.

Based on the search and the inclusion and exclusion criteria, the cost effectiveness review included 96 studies.In total 14 UK studies were included:

- eight publications (Davies et al,[36] Davies and Saltzman,[37] Drummond et al,[38] Gordois et al,[39] McCullagh et al[40], Nicolaides and Bosanquet,[41] Wolowacz et al,[42] Wolowacz et al[43]).
- three abstracts (Diamantopoulos,[44] Diamantopoulos,[45]Ryttberg[46])
- three UK HTA documents (Dabigatran STA [47, 48] Rivaroxaban STA,[34, 49] NICE guidelines 2010[3]).

Of the 14 included studies the manufacturer found the two studies by Wolowacs[42, 43] the STA reports,[34, 47-49] and the NICE guideline [3] to be most relevant. According to the manufacturer the remaining studies were either not relevant because of publication date (too old), jurisdiction (Ireland), or not reporting QALYs. The main findings of the relevant studies, excluding the NICE guideline are listed in Table 5.1.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

Both Davies and Saltzman (TKR only)[37] and the NICE VTE clinical guideline[3] concluded that prophylaxis was superior to no prophylaxis in TKR and THR. In terms of injectable prophylaxis Drummond et al. [38] found the LMWH enoxaparin to be cost effective on a per patient cost compared to unfractionated heparin (THR patients). Davies et al.[36] found that extended enoxaparin (21 days post discharge) was cost effective compared with enoxaparin for the hospital admission period only, with a cost per incremental QALY of £5,732 in THR patients. Gordois et al.[39] found fondaparinux to be cost effective compared to enoxaparin in THR and TKR with less VTE events and a lower per person cost; this result was sensitive to the difference in the price of the drugs and the rate of late DVT assumed. Nicolaides and Bosanquet[41] found desirudin to be more cost effective than enoxaparin with a cost per life year saved of £2,566. The new oral anticoagulant dabigatran was found to dominate enoxaparin in TKR and THR at a dose of 220mg od.[42, 43, 47, 48] 150mg od of dabigatran dominated enoxaparin in THR and the reverse was found in TKR.[47, 48] Fondaparinux was cost effective compared to dabigatran 220mg od and 150mg od in THR and TKR with ICERs below £12,000 per QALY.[47, 48] Rivaroxaban was found to dominate both enoxaparin and dabigatran in TKR and THR.[40, 44-46, 49]

Comment
The ERG agrees with the conclusions of the cost-effectiveness review.

Table 5.1 Main findings of studies included in the cost-effectiveness review

References	Yr. of costs	Patients	QALY	Costs	ICER
Wolowacz et al.[42]	2008	TKR 70 yrs THR 68 yrs	dabigatran: THR 8.432; TKR 7.647 enoxaparin: THR 8.426; TKR 7.639	dabigatran: TKR; £589/pt.;THR £392/pt. enoxaparin: TKR £606/pt.;THR £493/pt.	Cost/QALY dominant, Cost/VTE avoided dominant Cost /LYS dominant
Wolowacz et al.[43]	2010	Indication: THR, TKR Age: over 75 yrs.	dabigatran: THR 6.088; TKR 6.016 enoxaparin: THR 6.076; TKR 5.992	dabigatran: THR £410 /pt; TKR £475 /pt enoxaparin: THR £565 /pt; TKR £572 /pt	Cost/QALY dominant, Cost /LYS dominant Cost /VTE avoided dominant
Dabigatran STA[47, 48]	2006-2009	Indication: THR, TKR Age: 68yrs (THR) 70yrs (TKR)	dabigatran: (220mg/150mg) THR; 8.432/ 8.423 TKR; 7.647/ 7.634 enoxaparin: THR; 8.422 TKR; 7.636 dabigatran: (220mg/150mg) THR; 8.422/ 8.412 TKR; 7.734/ 7.731 Fondaparinux: THR; 8.440 TKR; 7.750	dabigatran: (220mg/ 150mg) THR; £6,426/ £6,442 TKR; £6,976/ £7,013 enoxaparin: THR; £6,525 TKR; £6,993 dabigatran: (220mg/ 150mg) THR; £6,489/ £6,497 TKR; £6,706/ £6,714 Fondaparinux: THR; £6,689 TKR; £6,690	THR: dabigatran (220mg and 150mg) dominated enoxaparin TKR; dabigatran 220mg dominated enoxaparin, dabigatran 150mg was dominated by enoxaparin, neither dose dominant vs. fondaparinux
Rivaroxaban STA[34, 49]	2009	Indication:THR, TKR Age: n/a	rivaroxaban: RECORD 1 (THR); 13.79901 RECORD 2 (THR); 13.79861 RECORD 3 (TKR); 13.67062 Enoxaparin: RECORD 1 (THR); 13.79724 RECORD 2 (THR); 13.79075 RECORD 3 (TKR); 13.66498 Indirect comparisons versus dabigatran Intervention RECORD 1 (THR); 13.79901 RECORD 2 (THR); 13.79861 RECORD 3 (TKR); 13.67062 Dabigatran RECORD 1 (THR); 13.79400 RECORD 2 (THR); 13.78483 RECORD 3 (TKR); 13.66934	rivaroxaban: RECORD 1 (THR); £224.87 RECORD 2 (THR); £248.72 RECORD 3 (TKR); £222.98 Enoxaparin: RECORD 1 (THR); £357.45 RECORD 2 (THR); £476.19 RECORD 3 (TKR); £473.54 Indirect comparisons versus dabigatran rivaroxaban RECORD 1 (THR); £224.86 RECORD 2 (THR); £248.72 RECORD 3 (TKR); £222.96 Dabigatran RECORD 1 (THR); £396.22 RECORD 2 (THR); £749.36 RECORD 3 (TKR); £259.59	Rivaroxaban dominated both enoxaparin and dabigatran

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

Summarise and critique the cost effectiveness evidence submitted by the manufacturer (headings 5.2.1 to 5.2.11 are suggested headings). It is noted that the ERGs may prefer NOT to combine the summary and critique of the submitted economic evidence and instead report summary and critique sections separately.

Summarise and critique the cost effectiveness evidence submitted by the manufacturer (headings 5.2.1 to 5.2.11 are suggested headings). It is noted that the ERGs may prefer NOT to combine the summary and critique of the submitted economic evidence and instead report summary and critique sections separately.

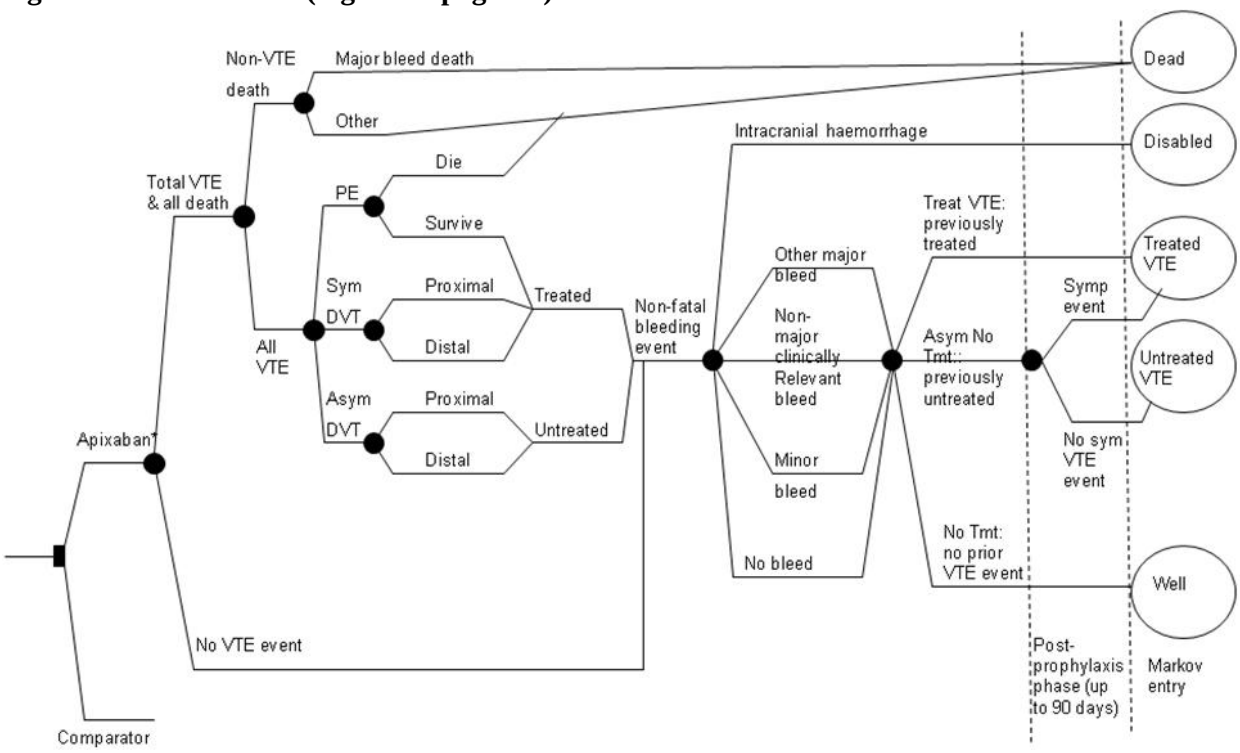
5.2.1 NICE reference case checklist (TABLE ONLY)

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	Comparison with fondaparinux was deemed not possible by manufacturer because data were lacking. Upon request by the ERG, fondaparinux was included as a comparator in the analysis of THR. Also, upon request a full incremental cost-effectiveness analysis on both TKR and THR was provided
Type of economic evaluation	Cost-effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	No significant PSS costs were identified
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	At a maximum 60 years, at which moment 99.99% of the population has died
Synthesis of evidence on outcomes	Systematic review	Yes	
Measure of health effects	QALYs	Yes	
Source of data for measurement of HRQL	Reported directly by patients and/or carers	Yes	HRQoL was reported by patients, but from different populations
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Yes / No	Some health states were valued by a representative sample of the public, others were valued by patients
Discount rate	Annual rate of 3.5% on both costs and health effects	Yes	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Not for all parameters but only those not included in the one way sensitivity analysis

5.2.2 Model structure

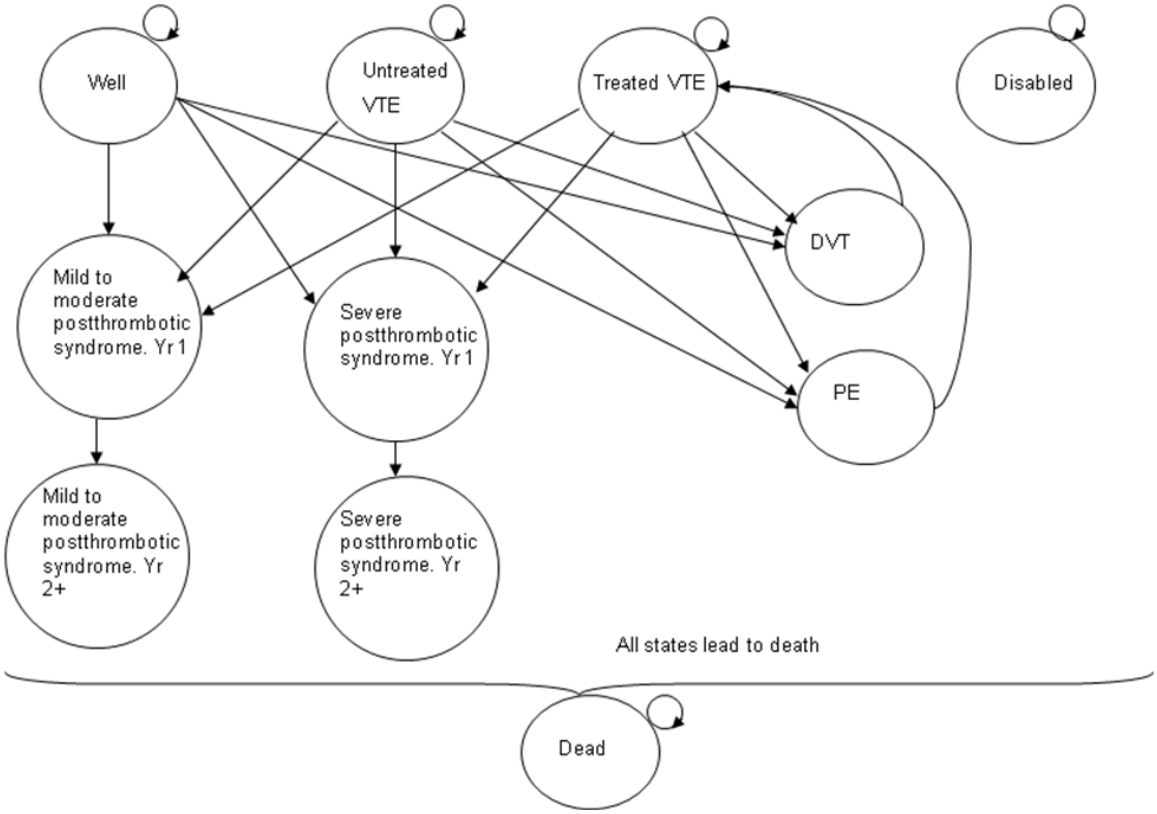
The manufacturer submitted a model in Microsoft Excel. A two stage modelling approach was adopted. A decision tree was used to model treatment in the acute phase (surgery to 90 days post surgery) and a Markov process model was used to model the long-term events (90 days post surgery and beyond). The differential effects of treatment are only realised in the acute phase of the model. The decision tree and long-term Markov model are depicted in Figures 5.1 and 5.2 respectively.

Figure 5.1 Decision tree (Fig 8 MS-page128)



Note: Other deaths refer to non-VTE and non-treatment-related deaths.
Abbreviations: THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; Sym/Symp, symptomatic, Asym, asymptomatic; Tmt, treatment

Figure 5.2 Long-term Markov model (Fig 9 MS-page 129)



Abbreviations: VTE; venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; Yr1, Year one; Yr2, Year two and beyond

In the model, a patient can experience no event or an event (total VTE or all cause death). In case of an event which is not a VTE, the patient dies from a major bleed or other cause. Other cause deaths refer to non-VTE and non-treatment-related deaths occurring during the prophylactic phase. A VTE event can be PE, symptomatic DVT or asymptomatic DVT (both either distal or proximal). Patients with a PE can die or survive. Surviving PE patients and all symptomatic DVT patients receive treatment and progress to the non-fatal bleeding events state of the model. Asymptomatic DVT patients progress to the non-fatal bleeding events state without treatment. Patients without events directly progress to this state. Probabilities of bleeding are independent of what happened earlier in the model. Patients experiencing an intracranial haemorrhage proceed immediately to the disabled health state and remain there for the duration of the model or until they die. Alternatively patients can experience no bleeding, minor bleeding, a non-major clinically relevant bleed or a major bleed (other than an intracranial haemorrhage).

In the period between the end of prophylaxis and 90 days post surgery asymptomatic patients can become symptomatic. Asymptomatic DVTs which convert to symptomatic DVT during the post-prophylaxis period are assumed to be of the same type (i.e., distal to distal, proximal to proximal). At 90 days post surgery patients leave the decision tree model and enter the long term Markov model. Patients that have not experienced a VTE event enter the Markov model in the well state whereas patients that are asymptomatic enter the Markov model in the untreated VTE state. Patients that have had a PE or a DVT or have transitioned from asymptomatic to symptomatic (had a DVT) enter the Markov in the treated VTE state. Patients that have had an intracranial haemorrhage enter in the disabled state. Patients that

died in the decision tree enter the Markov in the dead state. In the long term Markov patients can remain well, die, have a PE, have a DVT, have mild to moderate post thrombic syndrome (segregated into year one and subsequent years) or a severe post thrombic syndrome (segregated into year one and subsequent years). The same transitions are possible for treated and untreated patients. Once a patient has a PE or DVT they transition to the treated VTE state. There is no differential treatment effect in this long term phase of the model.

The Markov model has a cycle length of 1 year and a maximum time horizon of 60 years (base case 35 years). Half-cycle correction was not applied in the Markov model.

The following assumptions regarding model structure were made:

- During the prophylactic phase, other and PE deaths are assumed to occur at 35 days for THR and 14 days for TKR for each treatment arm.
- During the post-prophylactic phase, PE deaths are assumed to occur at 63 days for THR and 52 days for TKR, which are the mid points of the post-prophylactic phase for each indication.
- Major bleeds deaths are assumed to occur at 35 days for THR and 14 days for TKR, regardless of whether the bleeding rates are based on the prophylactic duration or 90 days.

Comment

- This modelling approach appears to be reasonable and has followed the lead from previous models, including a previous submission to NICE.[48, 49] The health states used are considered appropriate for the required analysis. The treatment effect is only reflected in the acute phase, which was considered to be reasonable according to the clinical experts.

- The model does not allow movement from mild to moderate PTS to severe PTS, does not have bleeding events in the long term Markov model, and does not account for HIT. Although the ERG considers this a limitation, it is not expected to strongly affect the cost-effectiveness results. Incorporation of HIT would be a disadvantage only to enoxaparin, as the other comparators do not cause HIT.

- The original model as provided by the manufacturer did not allow a full incremental analysis, but only allowed for a comparison of two comparators at the time. The ERG asked the manufacturer to adapt the model in order to perform an incremental analysis and probabilistic sensitivity analysis for all comparators simultaneously. An adapted model was provided by the manufacturer.

- The original model did not distinguish between types of bleed and types of VTE for each comparator individually, but assumed they were all the same. However, as an example, apixaban has fewer total bleeds, but more major bleeds compared with enoxaparin in THR.[18] Since this assumption may favour apixaban, the ERG asked for an adjusted model that allowed for differences in type of bleed and type of VTE. This adapted model was provided by the manufacturer.

5.2.3 Population

The patient groups included in the economic evaluation are patients aged 18 years and over who have undergone elective total hip or knee replacement surgery. Patients who have undergone hip (THR) and knee (TKR) surgery are modelled separately to reflect the differences in VTE risk, treatment duration, patient characteristics and to reflect the appraisal scope. The populations used in the model are slightly younger and for TKR less often male (Table 5.2).

Table 5.2: Comparison of age and gender of TKR and THR patients in apixaban trials versus clinical practice (National Joint Registry) (based on Table 55 MS-page 127)

	THR		TKR	
	Advance 3	Clinical practice	Advance 2	Clinical practice
Males	46.2–47.6%[§]	44%	26–30%[§]	43%
Age at initial surgery for males		65.89[#]		68.26[#]
Age at initial surgery for females		68.51[#]		68.14[#]
Age at initial surgery all	60.0–60.9*		65.1–66.0*	

*Mean age in each arm of the trial; #Mean age; §% in each arm of the trial.

Comment

- According to the ERG the population is in line with the scope.

- The fact that a younger population was included in the apixaban trials compared to clinical practice may impact the relative risks in the model. Sensitivity analyses were performed on age, but in these analyses relative risks were not changed. The ERG feels that the efficacy of apixaban compared to enoxaparin may have been overestimated, because earlier studies showed that oral anticoagulants are potentially more effective in younger patients.[21, 23, 24, 48] However, this also holds for rivaroxaban and dabigatran compared to enoxaparin, and will therefore probably not affect the efficacy of apixaban compared to the other new oral anticoagulants.

- The fact that the TKR population consisted of fewer males than is seen in clinical practice may also influence the cost-effectiveness results. No sensitivity analyses were performed in the manufacturer's submission. In the clarification letter the ERG asked the manufacturer to describe whether sex and age are predictors of bleeding and VTE. If so, the manufacturer was asked to adjust baseline risks and relative risks in the model. The manufacturer responded that statistically significant predictors such as age and sex were not assessed because a small number of studies were available.

5.2.4 Interventions and comparators

The indication considered in the economic evaluation is the prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery.

Administration of apixaban is oral, a film-coated tablet. Dosing is 2.5mg tablet to be taken twice a day. The initial dose should be administered 12 to 24 hours post surgery. Average length of treatment is 32-38 days for THR and 10-14 days for TKR. Dose adjustments are not required. Apixaban can be used with caution in patients with a creatinine clearance 15-29 ml/min.

In the base case analysis a comparison is made between apixaban, enoxaparin (40mg once daily, representing all LMWHs), dabigatran and rivaroxaban. Duration of treatment is based upon mean trial length, and in the absence of these data it is based on the median trial length. A comparison with fondaparinux could not be undertaken because of insufficient data on the primary endpoint to allow an indirect comparison. Although 40 mg od is the licensed dose for enoxaparin in Europe, sensitivity analyses were undertaken including evidence for enoxaparin 30mg bd. Also, sensitivity analyses were undertaken using a weighted cost of LMWHs but clinical data for tinzaparin and dalteparin are not explicitly incorporated into the model.

It is assumed that mechanical prophylaxis, such as graduated elasticated compression stockings, intermittent pneumatic foot compression or foot impulse devices, is used equally in all patients regardless of pharmacological intervention, and is not considered as a comparator in the economic evaluation.

Comment

- The intervention and comparators are implemented as per their marketing authorisations/CE marking and doses.
- For enoxaparin the base case analysis was restricted to 40 mg od, which is the licensed dose in Europe. Sensitivity analyses were undertaken including the US dose of 30 mg bd. The ERG agrees with this approach.
- Fondaparinux was included in the scope, but excluded from the comparison because according to the manufacturer any VTE and death were reported separately in the relevant trials and therefore could not be combined. The ERG requested that for THR a pragmatic approach be taken and suggested that combining these outcomes was reasonable. This was because the overlap between any VTE and death was likely to be small and the ERG showed that assuming no overlap or complete overlap would make little difference to the odds ratio or relative risk. In reaction, the manufacturer provided additional analyses including fondaparinux for THR.
- Enoxaparin was used as a representative for LMWHs. Since all comparative trials include enoxaparin as the comparator, and enoxaparin was used as a representative in previous STAs,[47, 49] the ERG believes that the use of enoxaparin representing LMWHs is reasonable.

5.2.5 Perspective, time horizon and discounting

The manufacturer's model allows for a maximum time horizon of 60 years (plus 90 days in the acute phase), with a 35 year time horizon adopted in the base case analysis. The cycle length of the Markov model was 1 year. In the sensitivity analyses the time horizon was shortened. The discount rate applied was 3.5% for utilities and costs (0% and 6% in the sensitivity analyses). Costs were considered from an NHS perspective, since no Personal Social Services costs were identified in the clinical pathway.

Comment

- The discount rates and perspective are in line with the NICE reference case.

- Since patients are 65 to 68 years of age when they enter the model, a 35 year time horizon seems to reflect lifetime. After 35 years 98% of the cohort had died.

5.2.6 Treatment effectiveness

Efficacy and safety of the treatments is modelled in line with the corresponding endpoints in the ADVANCE,[16, 18] RECORD,[25, 27] RE-MODEL and RE-NOVATE[21, 23] trials:

- 'total VTEs and all deaths' (all adjudicated VTE and all cause death and adjudicated, symptomatic or asymptomatic DVT, non-fatal PE and death from any cause)
- 'total bleeds' (bleeding at the surgical site, non-surgical bleeding events, clinically relevant non-major bleeding and minor bleeding events).

It should be noted that this approach to model the efficacy and safety of the comparators does not allow for differences between *types of bleed* (major, minor) and *types of VTE* (symptomatic, asymptomatic) for each comparator individually.

Enoxaparin was the reference treatment in the model. In the MS it was stated that both the reference treatment rates and the apixaban relative risk were taken from the ADVANCE-2[16] for TKR patients, and from the ADVANCE-3[18] for THR. In the absence of head to head RCT evidence for apixaban 2.5 mg bd versus rivaroxaban 10 mg od, and dabigatran 220 mg od, an adjusted indirect comparison approach was adopted. It was stated that because data for an indirect comparison with fondaparinux 2.5 mg od was not available, apixaban could not be compared with fondaparinux in the model. A primary efficacy population was used for 'total VTEs and all deaths', as the asymptomatic DVT outcome can only be detected via an evaluable venogram.

Table 5.3 Composite VTE and bleed rates (indirect comparison Group 1) (Table 58 MS-page 133)

	THR: All VTE & All cause death (95% CI)	**TKR: All VTE & All cause death (95% CI)**	**THR: Any bleeding (95% CI)**	**TKR: Any bleeding (95% CI)**
	Primary efficacy population analysis		**ITT analysis**	
Baseline risk (Enoxaparin 40mg OD)	4.58%	26.29%	9.39%	8.75%
Apixaban RR	0.359 (0.232–0.555)	0.618 (0.514–0.743)	0.93 (0.81–1.08)	0.83 (0.64–1.06)
Rivaroxaban RR	0.3 (0.18–0.51)	0.507 (0.395–0.651)	1.02 (0.81–1.29)	1.02 (0.72–1.44)
Dabigatran RR	0.887 (0.696–1.131)	0.965 (0.822–1.133)	1.07 (0.86–1.34)	0.96 (0.76–1.22)

A mixed treatment comparison (MTC) was also undertaken of relevant trial data, the results are assessed in a scenario analysis.

Table 5.4 Composite VTE and bleed rates (mixed treatment comparison Group 1) – taken from model worksheets 'efficacyrev' and 'efficacydata'

	THR: All VTE & All cause death	TKR: All VTE & All cause death	THR: Any bleeding	TKR: Any bleeding
	Primary efficacy population analysis		ITT analysis	
Baseline risk	5,4%	19.4%	9.4%	7.0%
Apixaban	0.357	0.895	0.927	0.809
Enoxaparin 30 mg bd	0.925	1.000	0.825	1.000
Enoxaparin 40 mg	0.638	1.410	0.821	1.037
Rivaroxaban	0.302	0.731	1.009	1.094
Dabigatran	0.893	1.354	1.074	1.003
Fondaparinux	0.306	0.582		0.888

Comment

- The ERG agrees with the use of indirect comparison Group 1 in the base case analysis.

- The model does not distinguish between types of bleed and types of VTE for each comparator individually. However, as an example, apixaban has fewer total bleeds, but more major bleeds compared with enoxaparin in THR. This assumption may favour apixaban. Therefore in the clarification phase the manufacturer was asked to adjust the model to allow for differences in type of bleed and type of VTE. As requested, the model was adapted so that types of VTE and bleed could vary across the comparators. Absolute risks for the reference treatment (enoxaparin 40mg od) were generated from the indirect comparison so that they were comparable to each of the NOACs so that relative risks for each comparator could then be applied. Indirect comparisons could not be undertaken to generate relative risks for each drug on the probabilities of All VTE and non-VTE death, and so the model continues to use blended NOAC and Advance trial data. In addition, indirect comparisons for all types of VTE (PE, asymptomatic and symptomatic DVT) and bleed (CRNM, major and minor) could not be undertaken for neither fondaparinux nor rivaroxaban, as these data were not available from the trials. The results of this adapted analysis are presented in paragraph 5.2.9.

- The manufacturer was asked to clarify why, for THR, fondaparinux 2.5 mg od was not included in the indirect comparison, as used in the CEA model, and to re-run the indirect comparison and include fondaparinux 2.5 mg od. As requested, data from Lassen et al.[29] has been included in the analysis. In the indirect comparison group 1, the relative risk of fondaparinux 2.5 mg od versus Enoxaparin 40mg od was found to be 0.430 (95% CI 0.30- 0.62), assuming no overlap between the outcomes any VTE and death. The results of this adapted analysis are also presented in paragraph 5.2.9.

Post event treatment independent probabilities

The remaining clinical probabilities in the decision tree element of the model were assumed to be treatment independent and assumed to not differ between apixaban, enoxaparin, dabigatran and rivaroxaban. As stated by the manufacturer, this approach was taken as the trials for apixaban, rivaroxaban and dabigatran are only powered to detect differences in the composite primary efficacy and safety endpoints. Where possible the probabilities for the post event treatment independent probabilities were obtained from a synthesis of all trials on new oral anticoagulants (all NOAC trials; RECORD RE-MODEL and RE-NOVATE).To synthesise the data, the sum of events was taken across the trials and event types thus providing a numerator yielding a total count for each event type. The denominator was obtained by summing all event counts within an endpoint (VTE or any death, Bleeds). If the event was not reported in one or more of the trials, data was extracted from both arms (apixaban and enoxaparin) of the ADVANCE-2 and 3 trials. As stated, this approach was chosen as the number of events recorded was small and it was likely that using apixaban results alone would introduce chance findings and potentially bias the results for all the interventions evaluated.

Table 5.5 Conditional Post-Event Distributions for All VTE and all-cause death and bleeding events (based on Table 59-60 MS-page 136-137)

	THR		**TKR**	
	Probability	**Source**	**Probability**	**Source**
All VTE Events	96.5%	All NOAC trials	96.5%	All NOAC trials
PE	3.6%	All NOAC trials	3.6%	All NOAC trials
Die (CFR)	12.5%	ADVANCE-3	25.0%	ADVANCE-2
Survive	87.5%	ADVANCE-3	75.0%	ADVANCE-2
Sym DVT	2.6%	All NOAC trials	4.5%	All NOAC trials
Distal	16.7%	ADVANCE-3	80.0%	ADVANCE-2
Proximal	83.3%	ADVANCE-3	20.0%	ADVANCE-2
Asym DVT	93.8%	All NOAC trials	91.9%	All NOAC trials
Distal	73.8%	ADVANCE-3	91.2%	ADVANCE-2
Proximal	26.2%	ADVANCE-3	8.8%	ADVANCE-2
% ofAsym ->Sym (60 days)	0.0%	ADVANCE-3	0.5%	ADVANCE-2
Distal	0.0%	ADVANCE-3	58.0%	ADVANCE-2
Proximal	100.0%	ADVANCE-3	42.0%	ADVANCE-2
Non-VTE Death	3.5%	All NOAC trials	3.5%	All NOAC trials
Due to Major Bleed	0.0%	ADVANCE-3	0.0%	ADVANCE-2
Other Cause	100.0%	ADVANCE-3	100.0%	ADVANCE-2
Intracranial haemorrhage	0.0%	All NOAC trials	0.0%	All NOAC trials
% Disabled	0.0%		0.0%	
Major Bleed - Other	7.5%		7.5%	
Non major clinically relevant bleed	34.1%		34.1%	
Minor	58.3%		58.3%	

NOAC: new oral anticoagulant

Comment

The ERG considers this an appropriate approach.

Long term recurrent risks of VTE and PTS – drug treatment independent

A literature review was carried out to identify parameter estimates for the long term risk of recurrent VTE and/or the development of PTS in TKR and THR patients who suffered a VTE event.[50]

DVT

Rates of recurrent DVT fro treated and untreated patients were based on Prandoni[51] and Imperiale and Speroff .[52] The unadjusted pooled risk of 0.42 for all types of DVT in control arm patients reported in Imperiale was assumed to be a life-time risk, rather than an annual risk (no time-specifics are given by Imperiale and Speroff). This rate was adjusted by assuming the rate would decrease to 0 in seven years, in a manner similar to that seen in treated patients as reported by Prandoni et al.[51]

Table 5.6 Time Dependent Rates of Recurrent DVT by Treatment Status – drug treatment independent (Table 61 MS-page 139)

	Treated VTE to DVT				Untreated VTE to DVT		
	Rate Estimate	Range for Sensitivity			Rate Estimate	Range for Sensitivity	
		Lower	Upper			Lower	Upper
year 1	0.054760	0.022320	0.108320		0.214495	0.182549	0.241877
year 2	0.022820	0.012280	0.041000		0.089386	0.076073	0.100797
year 3	0.014120	0.008460	0.026740		0.055308	0.047071	0.062369
year 4	0.009300	0.006020	0.019540		0.036428	0.031003	0.041078
year 5	0.009060	0.004240	0.014630		0.035488	0.030203	0.040018
year 6	0.005190	0.004200	0.015210		0.020329	0.017301	0.022924
year 7+	0.004740	0.001950	0.008890		0.018567	0.015801	0.020937

Pulmonary embolism (PE)

PE rates were not provided in any of the articles identified in the review. As a result, the risk of pulmonary embolism reported in the meta-analysis article on THR by Imperiale and Speroff (1994) were used. For the 7-year rate of PE among patients untreated for VTE, the unadjusted pooled risk of pulmonary embolism of 2.4% is used. The average of risk estimates for the treatment groups (1.15%) is used as the estimate for the 7-year rate of PE among treated patients. The overall rates were annualized assuming an annual risk decrease similar to that reported by Prandoni et al (1996) for DVT.

Table 5.7 Time Dependent Rates of PE by Treatment Status – drug treatment independent (Table 62 MS-page 139)

	Treated VTE to PE				Untreated VTE to PE		
	Rate Estimate	Range for Sensitivity			Rate Estimate	Range for Sensitivity	
		Lower	Upper			Lower	Upper
year 1	0.005248	0.009242	0.00194		0.010953	0.005933	0.000383
year 2	0.002187	0.003851	0.000808		0.004564	0.002472	0.000160
year 3	0.001353	0.002383	0.0005		0.002824	0.001530	0.000099
year 4	0.000891	0.00157	0.000329		0.001860	0.001008	0.000065
year 5	0.000868	0.001529	0.000321		0.001812	0.000982	0.000063

year 6	0.000497	0.000876	0.000184		0.001038	0.000562	0.000036
year 7+	0.000454	0.0008	0.000168		0.000948	0.000514	0.000033

Post Thrombotic Syndrome (PTS)

The literature search yielded five useful sources of data on PTS in hip and knee replacement surgery patients, however according to the manufacturer wide variation made a formal meta-analysis impossible. The rate estimates for severe PTS in treated patients at years 1 through 8 were made using the digitized values from the Prandoni et al.[51] rate curves for 'Severe PTS' that were then adjusted using the 0.36 surgery group hazard ratio.

Table 5.8 Time Dependent Rates of PTS by Treatment Status – drug treatment independent (Table 63-64 MS-page 139-140)

Mild/ moderate PTS	Treated VTE				Untreated VTE		
	Rate Estimate	Range for Sensitivity			Rate Estimate	Range for Sensitivity	
		Lower	Upper			Lower	Upper
year 1	0.063240	0.031980	0.118970		0.180693	0.063960	0.297425
year 2	0.008290	0.003630	0.015420		0.022905	0.007260	0.038550
year 3	0.009920	0.003510	0.017550		0.025448	0.007020	0.043875
year 4	0.006370	0.005810	0.013250		0.022373	0.011620	0.033125
year 5+	0.002410	0.001000	0.003120		0.004900	0.002000	0.007800
Severe PTS							
year 1	0.011210	0.002080	0.030740		0.040505	0.004160	0.076850
year 2	0.006290	0.006180	0.030100		0.043805	0.012360	0.075250
year 3	0.013460	0.004350	0.013710		0.021488	0.008700	0.034275
year 4	0.006590	0.001250	0.009140		0.012675	0.002500	0.022850
year 5+	0.006770	0.000100	0.000820		0.001125	0.000200	0.002050

Estimates of severe PTS among untreated patients were assumed to be 2 to 2.5 times higher without treatment (based on Prandoni, 1996).[51] The rate estimates for mild/moderate PTS at years 1 through 8 were made by first estimating the overall PTS risk. This was done because Prandoni et al.[51] reports a set of rate curves for 'All PTS', but not for mild/moderate PTS specifically. Once the risks of 'All PTS were found, the difference between these risks and the risks for 'Severe PTS' were found and used as the risk of mild/moderate PTS.

Comment

– The ERG considers this a reasonable approach given the available data.

5.2.7 Health related quality of life

A systematic literature review was conducted to identify utility inputs for use in the model. Each year 0.00029 was subtracted from a patient's health state utility value before the QALYs for that year are calculated.[53] This age decrement was based on the EQ-5D US tariff. Below the utility values and decrements used in the model are listed per health state.

Well or treated VTE

To represent the quality of life of a fully recovered well patient following surgery, the model uses a value of 0.78 per year for the health state of well derived from EQ-5D UK population norms by Kind et al.[54] The model uses a utility decrement of -0.01 for one month to represent the drop in quality of life of a patient experiencing a VTE event but receiving treatment for it (the treated VTE state in the model). This utility estimate came from Gage et al.[55] and was based on a sample of 70 patients with atrial fibrillation using the time trade-off method.

PE and DVT

The model uses utility decrements for PE and DVT (symptomatic proximal and distal) of -0.08 from Ingelgard et al.[56] This utility value is based on data obtained from 121 Swedish outpatients with DVT using EQ-5D (tariff used unknown).

Post Thrombotic Syndrome (PTS)

The model uses utility decrement of -0.02 for mild to moderate PTS and -0.07 for severe PTS from Lenert and Soetikno.[57] These values were obtained from a sample of 30 healthy women using the standard gamble method.

Major bleed and disability following intracranial haemorrhage

A utility decrement of -0.03 is used for major bleed and was the median taken from a study by Robinson et al.[58] of 54 patients with atrial fibrillation in which the standard gamble method was used. A utility decrement of -0.49 is used to represent the drop in quality of life for patients who become disabled following an intracranial bleed. This decrement is based on an average of 109 published stroke utility decrements reported in the studies by Wolowacz[42, 43] and BoehringerIngleheim.[47]

Table 5.9 Utility input (Table 69&71-74 MS)

State	Utility value or decrement	Confidence interval or Std Error	Reference	Duration		Reference
				THR	TKR	
General male population	0.78	0.018543	Kind[54]	N/A	N/A	
General female population	0.78	0.015504	Kind[54]	N/A	N/A	
Death	0	N/A	Assumption			
Hospitalization Period				**Days**	**Days**	
PE	–0.08	0.004082*	Ingelgard[56]	5.63	7.49	Assumption
Symptomatic Distal DVT	–0.08			0.949	1.73	
Symptomatic Proximal DVT	–0.08			0.949	1.73	
Asymptomatic DVT	0.0	N/A		N/A	N/A	
Intracranial haemorrhage	–0.49	0.03*	Boehringer[47]	90	90	
Major Bleed – other	–0.03	0.001531*	Robinson[58]	5.63	7.49	

State	Utility value or decrement	Confidence interval or Std Error	Reference	Duration		Reference
				THR	TKR	
NMCR Bleed	0	-	Assumption	0.949	1.73	
Minor Bleed	0	-		0.949	1.73	
Post-Discharge Period				**Days**	**Days**	
PE	0	-		30	30	Assumption
Symptomatic Distal DVT	−0.08	0.004082*	Ingelgard[56]	30	30	
Symptomatic Proximal DVT	−0.08			30	30	
ICH Disabled	−0.49	0.03*	Boehringer[47]	90	90	
Long-term Markov phase				**Months**	**Months**	
Aging (annual impact)	−0.00029	−0.000015*	Sullivan[53]	12	12	Sullivan[53]
Treated VTE	−0.01	0.000510*	Gage[55]	1	1	Assumption
ICH Disabled State	−0.49	−0.025000*	Boehringer[47]	12	12	NCC for Acute Care[59]
PE	−0.08	−0.004082*	Ingelgard[56]	1	1	
DVT	−0.08	−0.004082*		1	1	
Mild/Moderate PTS (yr 1)	−0.02	−0.001020*	Lenert[57]	12	12	Lenert[57]
Mild/Moderate PTS (yr 2+)	−0.02	−0.001020*		12	12	
Severe PTS (yr 1)	−0.07	0.003571*		12	12	
Severe PTS (yr 2+)	−0.07	0.003571*		12	12	

* 95% confidence interval assumed to be ±10%.

Comment

- The ERG identified a possible typographical error was identified for the word analy* in line #74 of the Medline search for cost-effectiveness, where it appears as anlay*. The error appeared to have been repeated in all subsequent strategies using this filter. Also, Medline Mesh terms were used to search Embase in lines #76-97 of the Embase cost-effectiveness strategy, and the appropriate Emtree translations were not used. In the clarification phase, the Manufacturer has updated the searches taking the above issues into account. This resulted in the identification of additional citations. However, as stated in the response on the clarification requests the manufacturer stated that on review of the title and abstract, none of the references met the inclusion criteria for the review.

- The standard errors for the utilities and the utility decrements were all set to 10%. The ERG considered that it would have been more appropriate to use estimates based on empirical evidence. In the response on the clarification issue, the manufacturer reported standard errors from the literature, if available.

- For some of the utility inputs (PTS, impact of age, intracranial haemorrhage, symptomatic DVT) the method used to derive utilities was not mentioned. The ERG requested and received this additional information in the clarification phase. Based on the information provided by the manufacturer, it was clear that a variety of instruments (standard gamble, time trade off, several tariffs of EQ-5D), perspectives (patients / general public), and populations (UK / Sweden / US / various countries) were used to derive utility input. Therefore, the utility values and decrements are considered to be prone to some bias. In addition, the duration for which utility decrements are applied was predominantly based

on assumptions, and not further justified. However, it is likely that the best available sources of information have been used.

5.2.8 Resources and costs

Only the costs that differ by intervention were considered. Healthcare Resource Group (HRG) 4.0 procedure codes were used to determine the costs of health states and events in the economic model. All costs are presented in 2008/09 pounds. In the base case analysis 2008/09 NHS reference costs[60] were used.

Intervention and comparators' costs

In order to maintain the link between efficacy and drug dosage in the Phase III DBG trials the MS has based the cost of prophylaxis on the number of administrations in the trials. Only enoxaparin had testing costs that are not common to all the interventions considered. The costs comprise of 4 blood counts at a total cost of £40.44. Patients on LMWH need a blood count at baseline and every 4 days (4 counts)[49]. Unit cost were taken from the rivaroxaban STA submission[49] and were updated to 2008/9 costs using the Hospital and Community Health Services Pay and Price Index.[61] Post discharge drug administration costs were applicable for enoxaparin as it is administered subcutaneously. Only 87% of patients are able to self inject or have a carer/relative that can inject them.[62] Home visits to administer injections were assumed to be undertaken by a community nurse (£27) and training to self inject (for those that could) was assumed to comprise of 30 minutes of nurse time (24 hour ward nurse) (£50 per hour) (Curtis, 2008).[61] Post discharge treatment was assumed to be duration of treatment minus hospital inpatient stay. Inpatient stay was assumed to be 5 days, based on 2010 national reference cost data (THR: HB12C Major Hip Procedures for non Trauma Category 1 without CC; TKR: HB23C Intermediate Knee Procedures for non Trauma.[60]

Table 5.10 Drug costs (Table 77 MS-page 167)

Drug	Dose	Per pack		Per day		Days of treatment		Costs per course	
		Pack	Pills	Pills	Cost	TKR	THR	TKR	THR
Enoxaparin	40mg#	£40.36 MIMS, 2010	10	1	£4.04	12 ADVANCE	34	£48.48	£137.36
Rivaroxaban	10mg#	£441.45 MIMS, 2010	100	1	£4.41	12 RECORD	33	£52.97	£145.68
Dabigatran*	220mg#	£126.00 MIMS, 2010	60	2	£4.20	8 RE-MODEL	32	£33.60	£134.40
Apixaban	2.5¥	£102.90 (Pfizer/BMS)	60	2	£3.43	12 ADVANCE	34	£41.16	£116.62

#OD/ once a day; ¥BID/ twice a day

Table 5.11 Administration costs Enoxaparin (Table 71 MS-page 167)

Number of blood counts	Cost of blood count @	Cost of nurse training for 30 minutes *	Home visits from a community nurse to inject prophylaxis	Number of days where home visit is required ¥		Community nurse #	Total	
				TKR	THR		TKR	THR
4	£10.11	£25.00 (87% of patients)	13% of patients	7	29	£27.00	£86.76	£163.98

@unit cost taken from the rivaroxaban STA submission to NICE[49] and updated to 2008/9 costs using the Hospital and Community Health Service Pay and Price Index[61] (See Appendix 19 MS); *(24-hour ward [costs including qualifications])[61] ¥Treatment duration minus inpatient stay. #(includes district nursing sister, district nurse) - home visit (including wages/salary, salary oncosts, qualifications, overheads, capital overheads and travel)[61]

Health state costs and costs of events

The PE cost comprises of the cost of treating PE that occurs during TKR or THR surgery and following discharge weighted by the proportion experiencing each event.[63] All Patients experiencing PE following discharge were assumed to be re-hospitalised.

Distal DVT costs comprised of the cost of treating Distal DVT that occurs during TKR or THR surgery weighted by the proportion of patients experiencing this event[63] as an inpatient, plus the cost of treating the cost of distal DVT as an outpatient and readmission weighted by the proportion of patients experiencing each form of treatment.[42, 63]

Proximal DVT costs comprised of the cost of treating Distal DVT that occurs during TKR or THR surgery weighted by the proportion of patients experiencing this event[63] as an inpatient, plus the cost of treating the cost of proximal DVT as an outpatient and readmission weighted by the proportion of patients experiencing each form of treatment.[42, 63]

The long term costs, costs applied in the long term Markov model, for PE, DVT, mild to moderate PTS (year 1/first instance and subsequent years) and severe PTS (year 1/first instance and subsequent years) were taken from Cohen et al. 2001[64] and inflated to 2008/09 costs using the Hospital and Community Health Services Pay and Price Index.[61] The cost of caring for and treating disabled patients was taken from Youman et al.[65] and inflated to 2008/09 using the Hospital and Community Health Services Pay and Price Index.[61]

Table 5.12 Costs for health states and event in the model (Table 75 MS-page 160)

Item	THR	TKR	HRG Codes/Other Sources
PE	£1929.42	£1929.42	Inpatients (68.9%;[63]): index surgery for PE Non inpatients (31.1%;[63]): inpatient stay for PE
Index surgery for PE	£1,831.52	£1,831.52	Weighted average of NHS codes (2008/09£) NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): DZ09A Pulmonary Embolus with Major CC; DZ09B Pulmonary Embolus with CC; DZ09C Pulmonary Embolus without CC
Inpatient stay for PE	£2,146.22	£2,146.22	Weighted cost of NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): Z09A Pulmonary Embolus with Major CC, DZ09B Pulmonary Embolus with CC, and DZ09C Pulmonary Embolus without CC £1831.52 + Ambulance £263 (Curtis)[66] inflate to 08/09 (Curtis)[61] £274.84 *5% using ambulance) £13.74 + Diagnosis cost £288 from Wolowacz et al.[42] inflate to 08/09 using Curtis[61] £300.96
Distal DVT	£1306.54	£1306.54	= Inpatient Ratio (68.9%;[63]) * index surgery for distal DVT (£1,344) + non inpatient ratio (31.1%) * [rehospitalisation for distal DVT ratio (62%;[36, 42] * Inpatient stay Distal DVT (£1,580.29) + Non-rehospitalisation ratio for DVT (38%)* Outpatient treatment DVT (£641.63)
Distal DVT	£1,344	£1,344	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): EB11Z Deep Vein Thrombosis
Inpatient stay Distal DVT	£1,580.29	£1,580.29	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): EB11Z Deep Vein Thrombosis £1344 + ambulance £263 (120) inflate to 08/09 £274.84 (121) * 5% using ambulance) £13.74 + diagnosis £213 (121) [Inflate to 08/09[61]] £222.59
Outpatient treatment Distal DVT	£641.63	£641.63	Wolowacz used an outpatient cost of Outpatient £401 + diagnosis £213 (derived from NHS reference costs and the NCC for Acute Care analysis for the VTE prevention clinical guideline)[42]. Inflate to 08/09[61]. £419.05 + £222.59
Proximal DVT	£1314.20	£1314.20	= Inpatient Ratio (68.9%; Pei et al, 2010[63]) * index surgery for proximal DVT (£1,344) + non inpatient ratio (31.1%) * [rehospitalisation ratio for proximal DVT (62%; Davis 2000; Wolowacz, 2009[36, 42]) * Inpatient stay Proximal DVT (£1580.29) + Non-rehospitalisation ratio for DVT (38%) * Outpatient treatment proximal DVT (£706.42)]
Proximal DVT	£1,344	£1,344	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): EB11Z Deep Vein Thrombosis
Inpatient stay Proximal DVT	£1,580.29	£1,580.29	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): EB11Z Deep Vein Thrombosis £1344 + ambulance £263[66] inflate to 08/09 £274.84[61] * 5% using ambulance) £13.74 + diagnosis £213 [Inflate to 08/09[61]] £222.59
Outpatient treatment proximal DVT	£706.42	£706.42	Wolowacz[42] used an outpatient cost of £463 and diagnosis of £213, (derived from NHS reference costs and the NCC for Acute Care analysis for the VTE prevention clinical guideline). Inflate to 08/09[61] £483.84 + £222.59
Long Term Events	**TKR and THR**		**Unit**
PE	£4338.56		£ per event	PE £3046 taken from a conference abstract by Cohen et al.[64] Inflate to 08/09.[61]
DVT	£2788.87		£ per event	Mild/moderate PTS Y1 £1958 from Cohen et al.[64] Inflate to 08/09.[61]
Mild/moderate PTS Y1	£47.00		£ per event	£33 Cohen et al.[64]. Inflate to 08/09[61]
Mild/moderate PTS Y2+	£41.31		£ per event	Mild/moderate PTS Y2+ £29 from Cohen et al.[64] Inflate to 08/09[61]
Severe PTS Y1	£4424.02		£ per event	Severe PTS Y1 £3106 from Cohen et al.[64] Inflate to 08/09[61]
Severe PTS Y2+	£2028.27		£ per event	Severe PTS Y2+£1424 from Cohen et al.[64] Inflate to 08/09[61]
Caring for and treating disabled patients	£7648.86		£ per year	Cost of a stroke including informal care over a 5 year period £29405/5 from Youman et al.[65] Inflate to 08/09[61]

Adverse event costs

Intracranial bleed costs comprised of Short term acute care plus long term follow-up care costs (5 year costs £11,043.91 = £2,867 + £8,176.91; see Table below). Major, non major clinically relevant and minor bleeds comprised of the weighted mean costs of the codes identified in Table 76, £1,250.16, £1,000.00 and £274 respectively.

Table 5.13 Costs of adverse events (Table 76 MS-page 163)

Averse event and associated costs in the economic model	Value (2008/09 £)		HRG Codes/Other Sources
Intracranial bleed	£11,043.91	5 year	Short term acute care + Long term follow-up care (5 years). £2,867 + (£1,635.38*5). Please see derivation below.
Bleed - Short term acute care	£2,867	event	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): AA23Z Haemorrhagic Cerebrovascular Disorders
Bleed - Long term follow-up care	£1,635.38	annual	£6287 (£15306 5 year cost of stroke - £9019 acute hospital cost) from the UK study by Youman.[65] Refers to follow-up cost for all patients with intracranial bleed after discharge per year. Inflate to 08/09.[61] £8176.91/5.
Major bleed	£1250.16	event	Weighted average of NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): FZ38D Gastrointestinal Bleed with length of stay 1 day or more with Major CC £1544 (weight 10906); FZ38E Gastrointestinal Bleed with length of stay 1 day or more without Major CC £1012 (weight 13465)
Non Major Clinically relevant bleed	£1000.00	event	NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (2010): FZ38F Gastrointestinal Bleed with length of stay 0 days
Minor bleed	£274.00	event	NHS Trusts and PCTs combined Regular Day / Night Admissions data (2010): FZ38F Gastrointestinal Bleed with length of stay 0 days

Comment

- Costs are (slightly) different than costs used in the STA of rivaroxaban and dabigatran. Possibly, this is due time differences in the cost calculations, and differences in assumptions. It is however unlikely that the differences in cost inputs between the STAs will have impact on the conclusions. In general, the ERG agrees with the adopted approach to estimate costs of the interventions, health states and events.

- The ERG requested scenario analyses with fondaparinux. Drug and administration costs of fondaparinux were not reported in the report of the manufacturer submission. These costs were however listed in the economic model (worksheet <treatment>), and amount to £43.96. However, the total costs of fondaparinux did not include the post-discharge administration costs (£28.77). The ERG corrected this, and presents the results in an additional analysis (paragraph 5.3). The total costs of fondaparinux amount to £72.73.

Table 5.14 Drug and administration costs of fondaparinux (based on the economic model)

Drug	Dose	Per day	Days of treatment		Costs per course	
		Cost	TKR	THR	TKR	THR
Fondaparinux	2.5	£6.28	7	7	£43.96	£43.96

Cost of nurse training for 30 minutes *	Home visits from a community nurse to inject prophylaxis	Number of days where home visit is required ¥		Community nurse #	Total	
		TKR	THR		TKR	THR
£25.00 (87% of patients)	13% of patients	2	2	£27.00	£28.77	£28.77

*(24-hour ward [costs including qualifications])[61] ¥Treatment duration minus inpatient stay. #(includes district nursing sister, district nurse) - home visit (including wages/salary, salary oncosts, qualifications, overheads, capital overheads and travel)[61]

5.2.9 Cost effectiveness results

In the base case analyses, a comparison was made between enoxaparin, apixaban, dabigatran and rivaroxaban. For both THR and TKR apixaban, dabigatran and rivaroxaban were less expensive than enoxaparin. In general, QALY differences were very small between the comparators.

Total Hip Replacement

For THR, the original base case results are listed in Table 5.15. In the deterministic base case analysis, apixaban, rivaroxaban and dabigatran all dominated enoxaparin. Apixaban was the least expensive technology, while rivaroxaban was the most effective comparator. Both apixaban and rivaroxaban were more effective and less costly, and thus dominant, compared to dabigatran and enoxaparin. Rivaroxaban was £29.47 more expensive, and yielded 0.001 more QALYs than apixaban, resulting in an ICER of £21,661 per QALY gained.

Total Knee Replacement

For TKR, the base case results are listed in Table 5.16. Apixaban was less expensive than dabigtran and enoxaparin, but more expensive than rivaroxaban. Apixaban was also more effective than dabigatran and enoxaparin, but less effective than rivaroxaban. Both apixaban and rivaroxaban dominated dabigatran and enoxaparin in TKR. Rivaroxaban dominated apixaban.

Table 5.15 Base case results in THR (adapted from Table 95, MS-page 186)

Technologies	Total costs (£)	Total QALYs	Comparison with conventional treatment (Enoxaparin)			Full incremental analysis			
			Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/ (QALY)
Apixaban	196.81	9.535	-238.98	0.015	Dominant				
Rivaroxaban	226.28	9.536	-209.51	0.016	Dominant	Apixaban	29.47	0.001	21,661
Dabigatran	263.89	9.523	-171.90	0.003	Dominant	Rivaroxaban	37.61	-0.013	Dominated
Enoxaparin	435.79	9.520				Rivaroxaban	209.51	-0.016	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 5.16 Base case results in TKR (adapted from Table 96, MS-page 186)

Technologies	Total costs (£)	Total QALYs	Comparison with conventional treatment (Enoxaparin)			Full incremental analysis			
			Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/ (QALY)
Rivaroxaban	332.66	9.090	-301.51	0.068	Dominant				
Apixaban	360.54	9.075	-273.63	0.052	Dominant	Rivaroxaban	27.88	-0.015	Dominated
Dabigatran	514.80	9.028	-119.36	0.005	Dominant	Rivaroxaban	182.15	-0.063	Dominated
Enoxaparin	634.17	9.023				Rivaroxaban	301.51	-0.068	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Comment

- The ERG restructured the Tables to present the base case cost-effectiveness results more clearly. Apixaban dominates both enoxaparin and dabigatran. However, rivaroxaban is either cost-effective (THR) or dominant (TKR) compared to apixaban.

- The MS did not include fondaparinux as a comparator. In the clarification phase, the ERG asked to include fondaparinux in THR. This resulted in additional analyses provided by the manufacturer (Table 5.17). Fondaparinux was the least expensive comparator in THR, being £36.90 less expensive than apixaban. Apixaban was both more expensive and more effective (0.002 QALYs) than fondaparinux, and was extended dominated by rivaroxaban.

Table 5.17 Base case results in THR including fondaparinux (based on manufacturer's response to clarification letter, Table 22)

Technologies	Total costs (£)	Total QALYs	Comparison with conventional treatment (Enoxaparin)			Full incremental analysis			
			Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/ (QALY)
Fondaparinux	159.91	9.533	-275.88	0.012	Dominant				
Apixaban	196.81	9.535	-238.98	0.015	Dominant	Fondaparinux	36.90	0.002	Extended dominated
Rivaroxaban	226.28	9.536	-209.51	0.016	Dominant	Fondaparinux	66.37	0.003	22,123
Dabigatran	263.89	9.523	-171.90	0.003	Dominant	Rivaroxaban	37.61	-0.013	Dominated
Enoxaparin	435.79	9.520				Rivaroxaban	209.51	-0.016	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

5.2.10 Sensitivity analyses

Methods

One way sensitivity analyses were performed for a number of parameters (Table 5.18).

Table 5.18 Input for one-way sensitivity analyses (adapted from Table 80, MS-page 168)

Variable	Base case	One-way sensitivity analysis
Discount rate	3.5%	0% and 6%
Health care unit costs	Listed in MS-Table 80	+/-10% & PBR tariff costs[67]
Duration of short-term utility decrement	Listed in MS-Table 80	+/-10%
Utility treated VTE	-0.01	= -0.095
Weighted mean of LMWH costs	£4.04	£3.76 (weighted mean) / £2.82 (lowest)
Dabigatran cost	£4.20	-50%
Wastage cost apixaban	12 days for TKR / 34 for THR	15 days of apixaban for TKR / 45 for THR
Treatment duration	Apixaban TKR 12 / THR 34, Enoxaparin TKR 12 / THR 34, Rivaroxaban TKR 12 / THR 33, Dabigatran TKR 8 / THR 32	Reduce TKR to 10 days and THR to 28 days for all except dabigatran / increased TKR to 14 days and THR to 38 days for apixaban.
Time horizon	35 years	1, 5, 10, 20 years
Age at surgery	THR males 65.89, females 68.51; TKR males 68.26, females 68.14	40, 50, 80
Length of stay of index hospitalisation	5 days	+/- 10%, +/- 20%
Total VTE and all-cause death apixaban	Listed in MS-Table 80	Upper 95% confidence interval / +10%
Total VTE and all-cause death comparator	Listed in MS-Table 80	Upper 95% confidence interval / +10%
Bleeding events apixaban	Listed in MS-Table 80	Upper 95% confidence interval / +10%
Bleeding events comparator	Listed in MS-Table 80	Upper 95% confidence interval/ +10%

In addition, scenario analyses were undertaken. In these scenario analyses, the sources of data were changed. First, in the indirect comparison the data on 30mg enoxaparin were included ('indirect comparison group 2'). Second, a mixed treatment comparison was used, both for the base case group excluding 30mg enoxaparin ('MTC group 1') and while including 30mg enoxaparin ('MTC group 2'). The scenario analysis using the Group 2- indirect comparison was performed for TKR only.

Finally, probabilistic sensitivity analyses (PSA) were undertaken. The MS stated that the PSA included only parameters that were not varied in the one-way sensitivity analyses. Normal distributions were used for treatment duration. Lognormal distributions were used for relative risks. Beta distributions were used for long term probabilities and utility scores. Gamma distributions were used for costs and utility decrements.

Results: Total hip replacement

For THR, apixaban remained dominant compared to enoxaparin and dabigatran for all changes in the one-way sensitivity analysis. Apixaban saved more than £30,000 per QALY lost, and was thus cost-effective, as opposed to rivaroxaban, only for a time horizon of 10 years or lower, when age at surgery was 80 years, when the 'total VTE and all-cause death parameter for rivaroxaban was set at +10% or at its upper 95% confidence interval, and when the upper 95% confidence interval was used for the 'bleeding events' parameter for rivaroxaban.

In all scenario analyses apixaban dominated enoxaparin and dabigatran. The ICER of apixaban compared to rivaroxaban was similar or lower in all scenario analyses. Since the ICER represents costs saved per QALY lost for apixaban versus rivaroxaban, this indicates that the results of the scenario analyses were all in favour of rivaroxaban. Table 5.19 shows the results of those sensitivity or scenario analyses that impacted the conclusions for THR.

Table 5.19 Results of one-way sensitivity and scenario analysis in THR that change the conclusions of the deterministic analysis (based on MS-Table 98 and MS-Table 101)

	Apixaban vs. rivaroxaban		
Results	**Incremental costs**	**Incremental QALYs**	**ICER**
Base case	*-£29.47*	*-0.0014*	*£21,661*
Time Horizon 1 year	–£31.98	–0.0001	£269,744
Time Horizon 5 year	–£30.33	–0.0005	£63,311
Time Horizon 10 year	–£29.93	–0.0008	£35,527
Age at surgery 80 years	–£30.27	–0.0007	£41,990
Comparator worse composite 'Total VTE and all-cause death' +10%	–£31.83	–0.0007	£47,603
Comparator worse composite 'Total VTE and all-cause death' - upper 95% CI	–£45.97	0.0035	Apixaban dominant
Comparator worse 'bleeding events' - upper 95% CI	–£44.56	–0.0014	£32,775

The results of the PSA showed that at a threshold of £20,000 per QALY, apixaban had 100% probability of being cost-effective compared to enoxaparin (Figure 5.3), a 100% probability of being cost-effective compared to dabigatran (Figure 5.4) and a 55% probability of being cost-effective compared to rivaroxaban (Figure 5.5). At a threshold of £30,000 per QALY, these probabilities were 100%, 100% and 36%, respectively.

Figure 5.3 Cost-effectiveness acceptability curve for apixaban versus enoxaparin in THR (Fig 3 MS-Appendix 23)

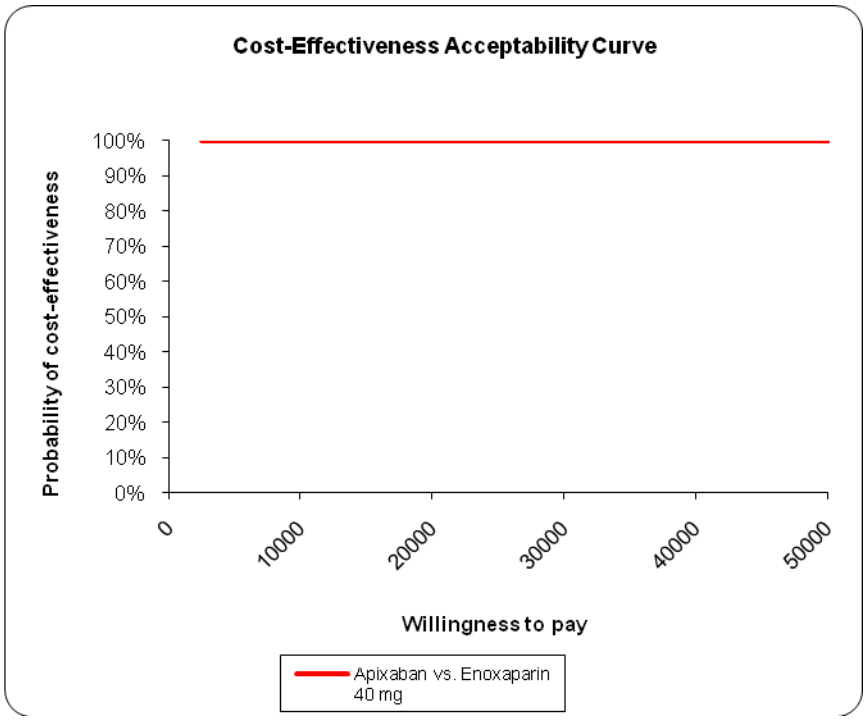


Figure 5.4 Cost-effectiveness acceptability curve for apixaban versus dabigatran in THR (Fig 5 MS-Appendix 23)

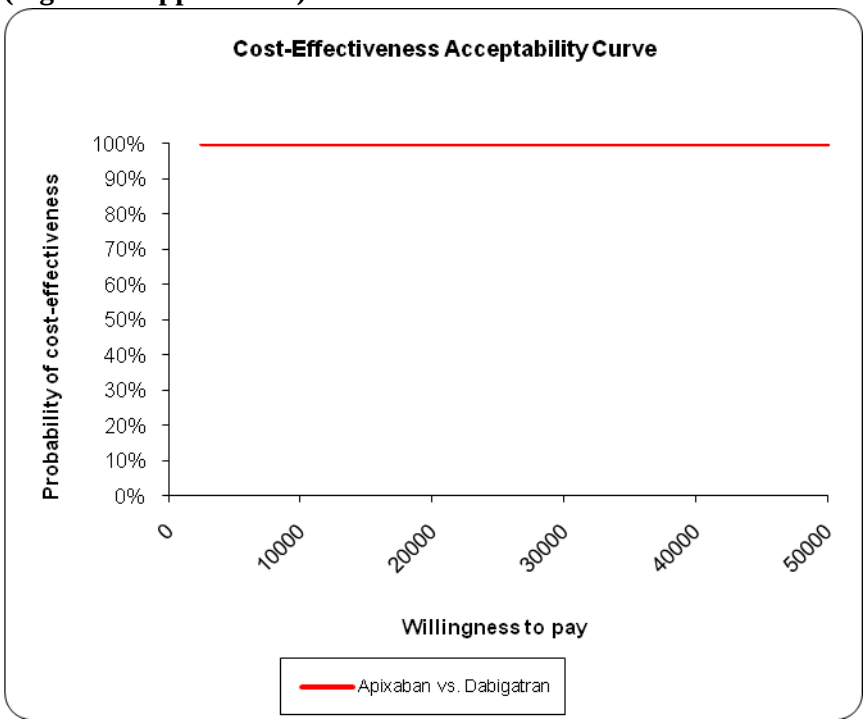
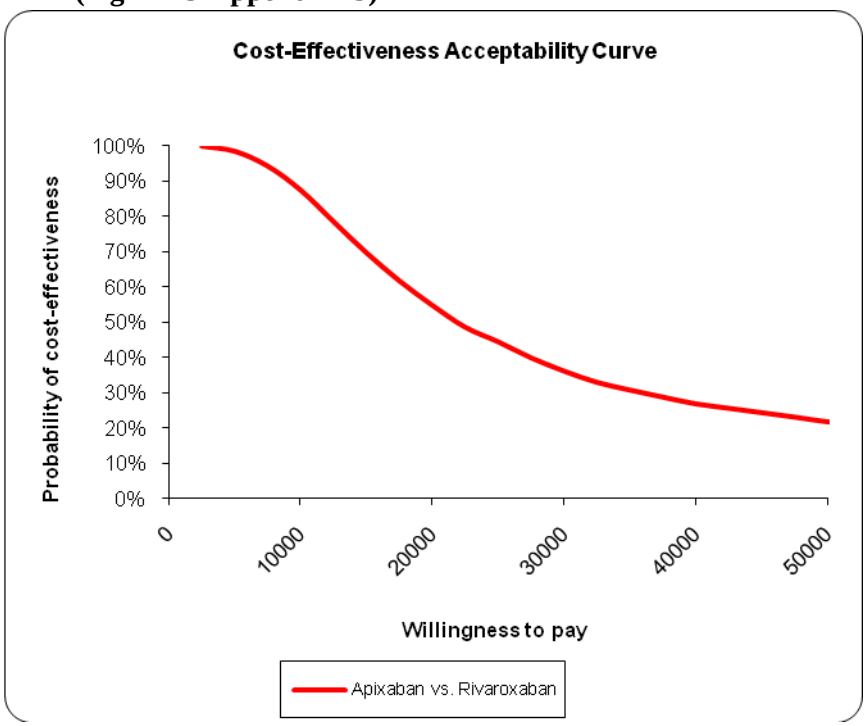


Figure 5.5 Cost-effectiveness acceptability curve for apixaban versus rivaroxaban in THR (Fig 7 MS-Appendix 23)



Results: Total knee replacement

For TKR, the results were highly robust. Apixaban remained dominant compared to enoxaparin and dabigatran for all changes in the one-way sensitivity analysis. Similarly, rivaroxaban dominated apixaban for all changes.

The scenario analyses did not show any changes in the base case results. Apixaban dominated enoxaparin and dabigatran, and was dominated by rivaroxaban, for all scenario analyses.

The results of the PSA showed that at a threshold of £20,000 as well as £30,000 per QALY, apixaban had 100% probability of being cost-effective compared to enoxaparin (Figure 5.6), a 100% probability of being cost-effective compared to dabigatran (Figure 5.7) and a 2% probability of being cost-effective compared to rivaroxaban (Figure 5.8).

Figure 5.6 Cost-effectiveness acceptability curve for apixaban versus enoxaparin in TKR (Fig 9 MS-Appendix 23)

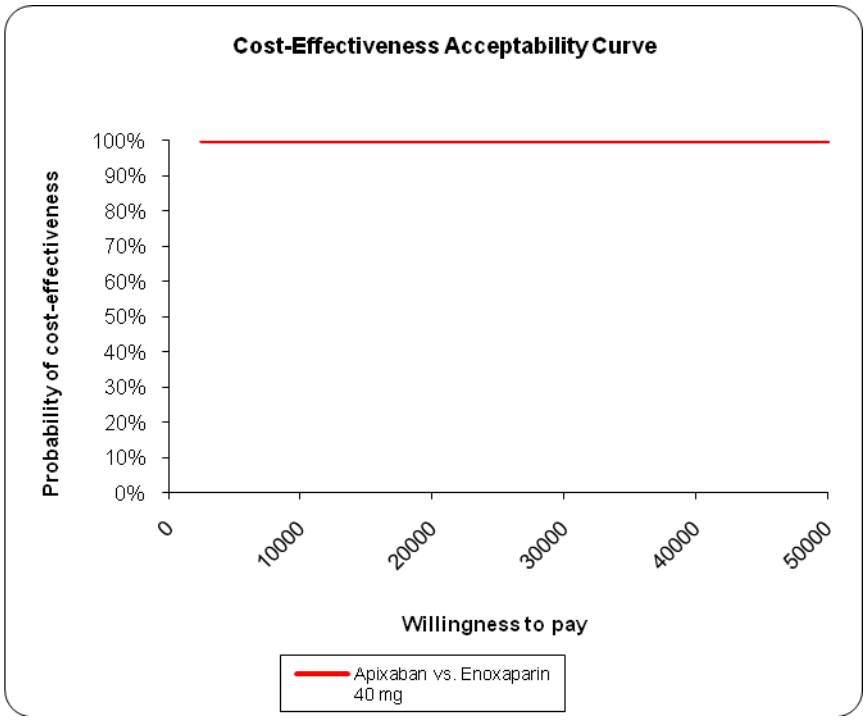


Figure 5.7 Cost-effectiveness acceptability curve for apixaban versus dabigatran in TKR (Fig 11 MS-Appendix 23)

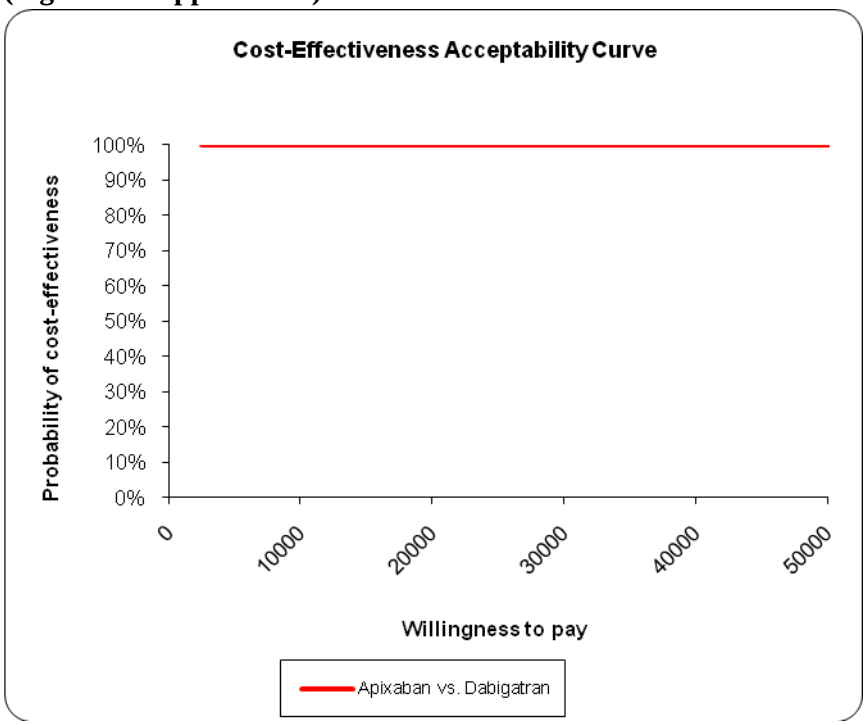
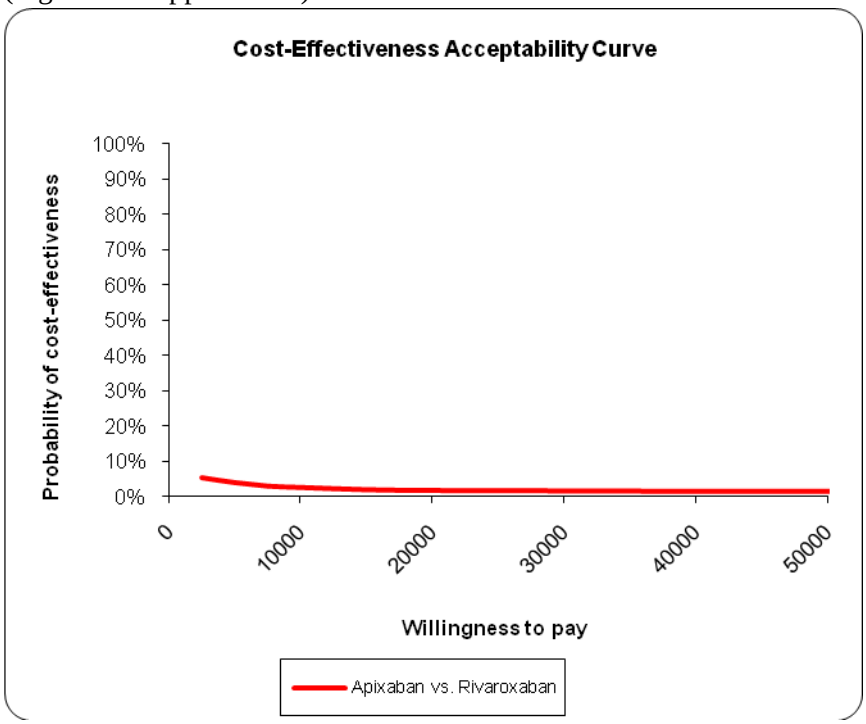


Figure 5.8 Cost-effectiveness acceptability curve for apixaban versus rivaroxaban in TKR (Fig 13 MS-Appendix 23)



Comment

- In the original model only two treatments could be compared at once. This means that a probabilistic sensitivity analysis for all four comparators was not possible. The ERG requested a full incremental analysis in the clarification letter, which was then provided. The adapted PSA showed that in THR, apixaban had a 53% probability of being the most cost-effective drug at a threshold of £20,000 per QALY (Figure 5.9). Rivaroxaban had a probability of 47%. At a threshold of £30,000 these probabilities were 47% and 53%, respectively. For TKR, a threshold of £20,000 apixaban had a 11% probability of being the most cost-effective drug. For rivaroxaban this probability was 89%. At a threshold of £30,000 these probabilities were 10% and 90%, respectively. The cost-effectiveness acceptability curves including all four comparators are presented in Figure 5.9 (THR) and 5.10 (TKR).

Figure 5.9 Cost-effectiveness acceptability curve for apixaban, enoxaparin, dabigatran and rivaroxaban in THR (manufacturer's response to clarification letter, Figure 3)

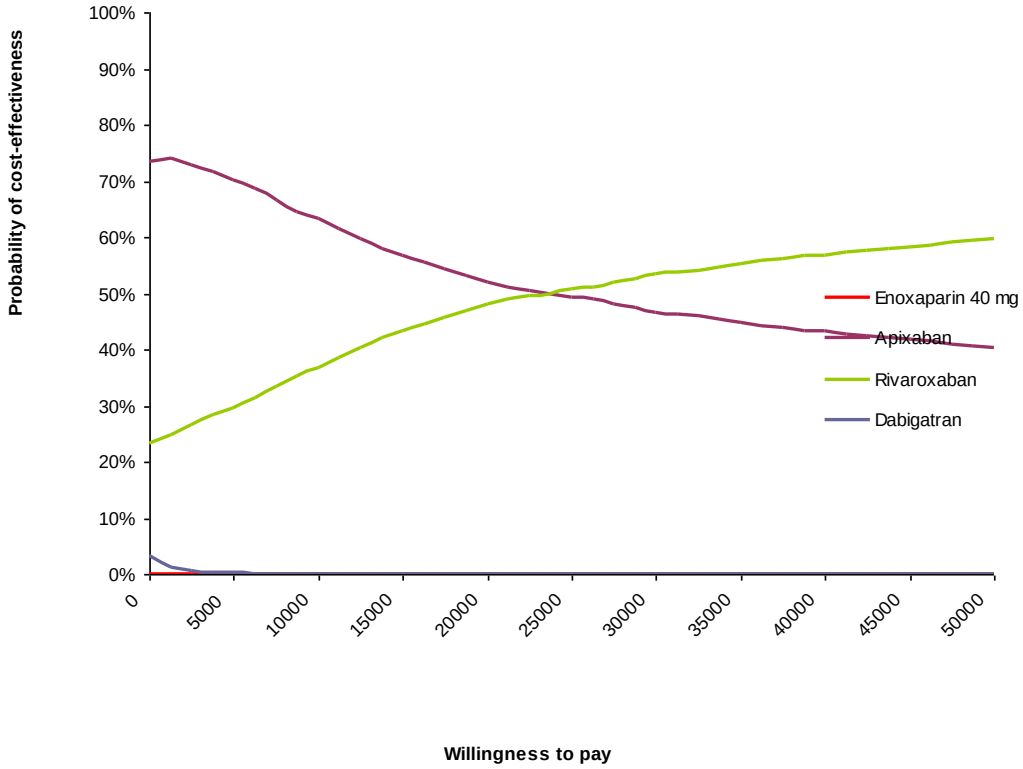
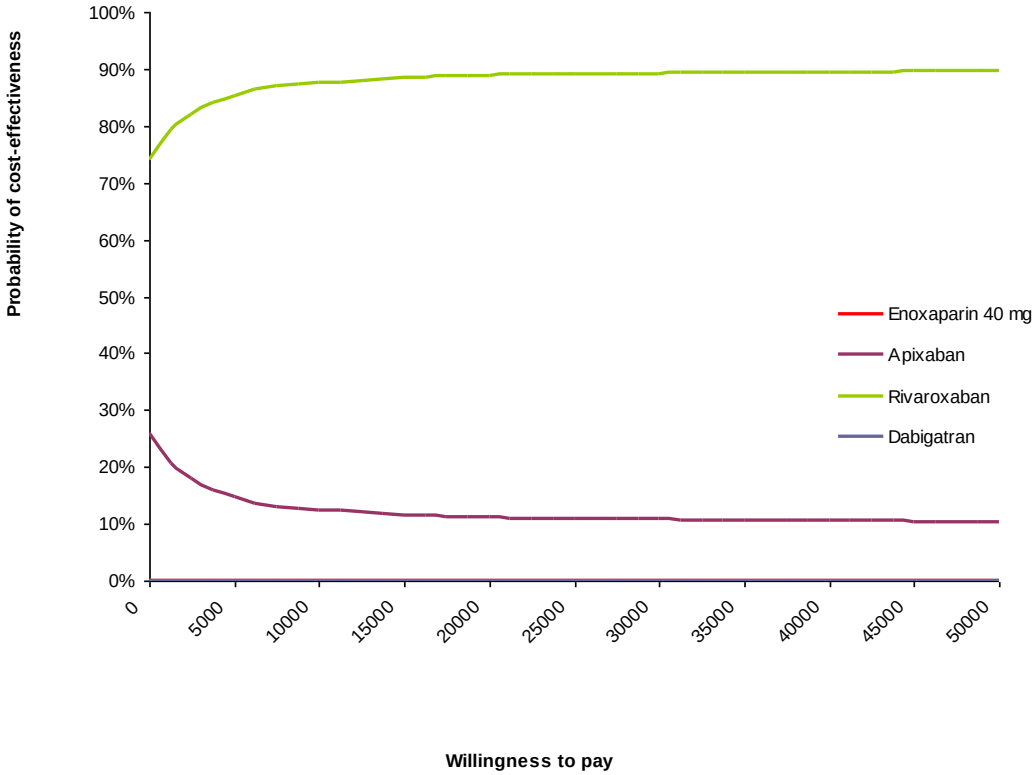


Figure 5.10 Cost-effectiveness acceptability curve for apixaban, enoxaparin, dabigatran and rivaroxaban in TKR (manufacturer's response to clarification letter, Figure 4)

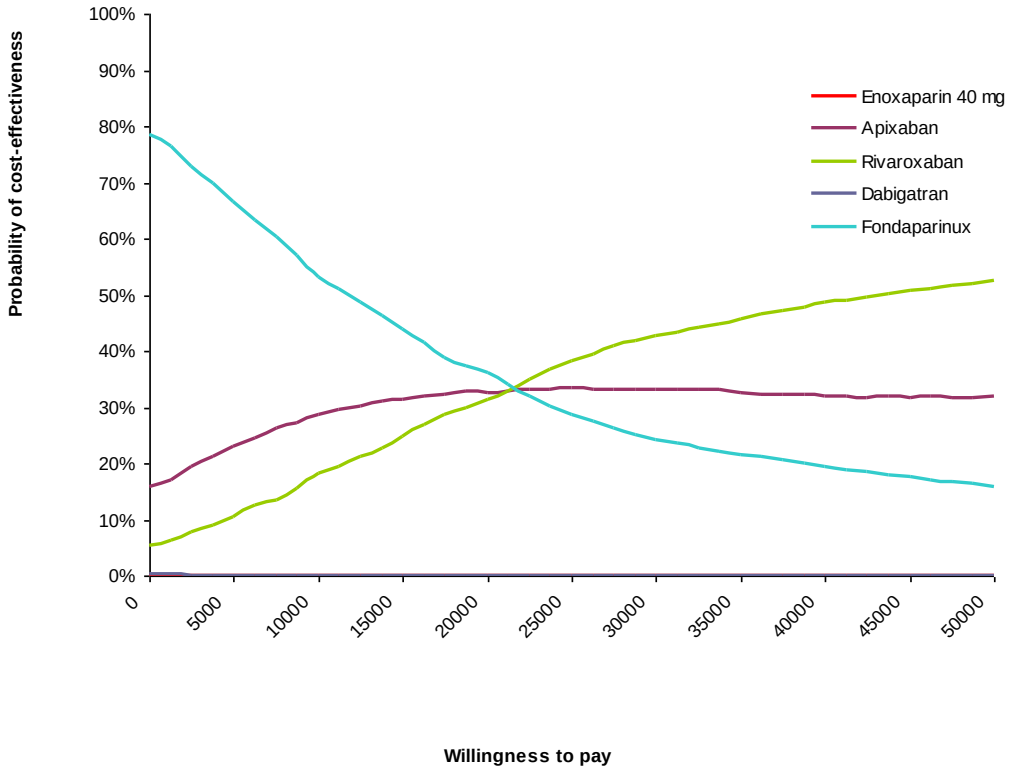


- In the requested analyses including fondaparinux, apixaban was cost-effective in comparison to fondaparinux (based on a maximum threshold of £30,000) unless the treatment duration for apixaban was extended to 38 days, the time horizon was 10 years or less, age at surgery was 80 years or unless the 'total VTE and all-cause death' for apixaban was increased by 10% or set at the upper 95% confidence interval. Scenario analyses showed that fondaparinux dominated apixaban in THR when data from the MTC were used (both group 1 and 2) instead of data from the indirect comparison. However, these analyses only compare apixaban and fondaparinux, and do not acknowledge that in the full incremental base case analysis, apixaban was extended dominated by rivaroxaban. The results of the one-way sensitivity and scenario analyses that changed the conclusion of the deterministic analysis of apixaban versus fondaparinux are presented in Table 5.20. The results of the PSA including all comparators showed that, at a threshold of £20,000 per QALY, fondaparinux had the highest probability of being cost-effective (36%), followed by apixaban (33%) and rivaroxaban (31%). At £30,000 these probabilities were 26%, 33% and 41%, respectively. Cost-effectiveness acceptability curves are presented in Figure 5.11. It should be noted that these results are all based on the requested analysis provided by the manufacturer, with incomplete costs for fondaparinux.

Table 5.20 Results of one-way sensitivity and scenario analysis in THR that change the conclusions of the deterministic analysis of apixaban versus fondaparinux (based on manufacturer's response to clarification letter, Table 23 and Table 25)

	Apixaban vs. Fondaparinux		
Results	**Incremental costs**	**Incremental QALYs**	**ICER**
Base Case	*£36.90*	*0.001639425*	*£22,506.41*
Treatment Duration extended to maximum recommended of 38 days for apixaban	£50.62	0.002	£30,875.20
Time Horizon 1 year	£39.92	0.000144812	£275,674.69
Time Horizon 5 year	£37.93	0.000578568	£65,553.35
Time Horizon 10 year	£37.45	0.00101583	£36,862.76
Age at surgery 80 years	£37.85	0.000869529	£43,534.02
Apixaban worse composite 'Total VTE and all-cause death' +10%	£39.72	0.000811371	£48,951.09
Apixaban worse composite 'Total VTE and all-cause death' - upper 95% CI	£52.29	-0.002881427	Apixaban dominated
MTC Group 1	£128.98	-0.00138998	Apixaban dominated
MTC Group 2	£118.99	-0.001221221	Apixaban dominated

Figure 5.11 Cost-effectiveness acceptability curve for apixaban, enoxaparin, dabigatran, rivaroxaban and fondaparinux in THR (manufacturer's response to clarification letter, Figure 5)



- Upon request by the ERG, the model was adapted so that types of VTE and bleed could vary across the comparators. Additional analyses were undertaken by the MS based on this adapted model. Because of a lack of data, rivaroxaban and fondaparinux were not included in these scenario analyses. The results of these scenario analyses were comparable to the base case analyses. In both THR and TKR, apixaban dominated enoxaparin and dabigatran. Although rivaroxaban and fondaparinux could not be included, these additional analyses suggest that varying types of VTE and bleed across comparators does not have a significant impact on the results.

- It is unclear to the ERG why not all parameter uncertainty is reflected in the probabilistic sensitivity analyses. The MS states that the PSA included only parameters that were not varied in the one-way sensitivity analyses. However, treatment duration was included in both. The fact that not all uncertainty was included in the PSA likely underestimates the total uncertainty.

- There is little comment on interpreting cost per QALY ratios calculated from points in the south-west quadrant of the cost-effectiveness plane. In this quadrant 'standard' criteria regarding meeting cost-effectiveness thresholds are reversed and the intervention must have a value greater than the threshold to be considered cost-effective. The MS fails to note that in the sensitivity analyses of apixaban versus rivaroxaban, a lower ICER actually is in favour of rivaroxaban instead of apixaban.

5.2.11 Model validation

The MS stated that "quality assurance was assessed by modellers that were not involved in producing the model. Two primary criteria were used in quality assessment, internal (verification) and external consistency (validation). Verification was assessed using the techniques of extreme value analysis (substituting minimum and maximum values for appropriate parameter values), using parallel inputs for all interventions for efficacy, costs and utilities. These techniques help reveal inappropriate algorithms in a model and identify any irregularities between the programming of treatment arms. External consistency was assessed by assessing the results of the model against published results." (MS-section 6.8)

Comment

- The results were comparable to earlier evaluations (described in section 5.1.4) in that dabigatran was found to dominate enoxaparin and that rivaroxaban was found to dominate both dabigatran and enoxaparin. Clinical experts were not used to validate the model structure or input values. However, clinical experts called in by the ERG confirmed that in general the assumptions that were made were deemed valid.

- The ERG noted some internal errors within the model which were disclosed to the manufacturer. These included the distributions for relative risk not properly reflecting the uncertainty as found in the original papers and incorrect use of standard errors instead of standard deviations in informing distributions. These errors were fixed to the satisfaction of the ERG.

5.3 Additional work undertaken by the ERG

Provide details of any additional work conducted by the ERG in relation to cost effectiveness. If the results of any of the additional work affect the size of the ICER, refer the reader to the summary table in Section 6.

The ERG found that in the inclusion of fondaparinux as a comparator, the extra post-discharge costs were not included, while these were included for the other injections (enoxaparin). Therefore, the ERG performed additional analyses including post-discharge costs. After including post discharge costs, fondaparinux was still the least expensive comparator in THR. However, as the difference in costs between fondaparinux and apixaban was smaller, the ICER decreased to £4,958 (Table 5.21). The corresponding CEACs showed that at a threshold of £20,000 per QALY, fondaparinux no longer had the highest probability of being cost-effective (Figure 5.12). This was now apixaban with 43%, followed by rivaroxaban (39%) and fondaparinux (19%). At a threshold of £30,000 per QALY these probabilities were 40%, 46% and 14%, respectively.

Additionally, the ERG analysed the cost-effectiveness including evidence from the recently published RE-NOVATE-II study for the dabigatran relative risk of bleeding[22] (see paragraph 4.2.7). A comparison was made between all comparators, including the total costs of fondaparinux as described above. The updated RR resulted in total costs of dabigatran of £266.12, which was £2.23 higher than in the previous analysis. The update did not affect the

number of QALYs gained by dabigatran, and did not impact any of the ICERs presented in Table 5.21.

Figure 5.12 Cost-effectiveness acceptability curve for apixaban, enoxaparin, dabigatran, rivaroxaban and fondaparinux including post discharge costs in THR

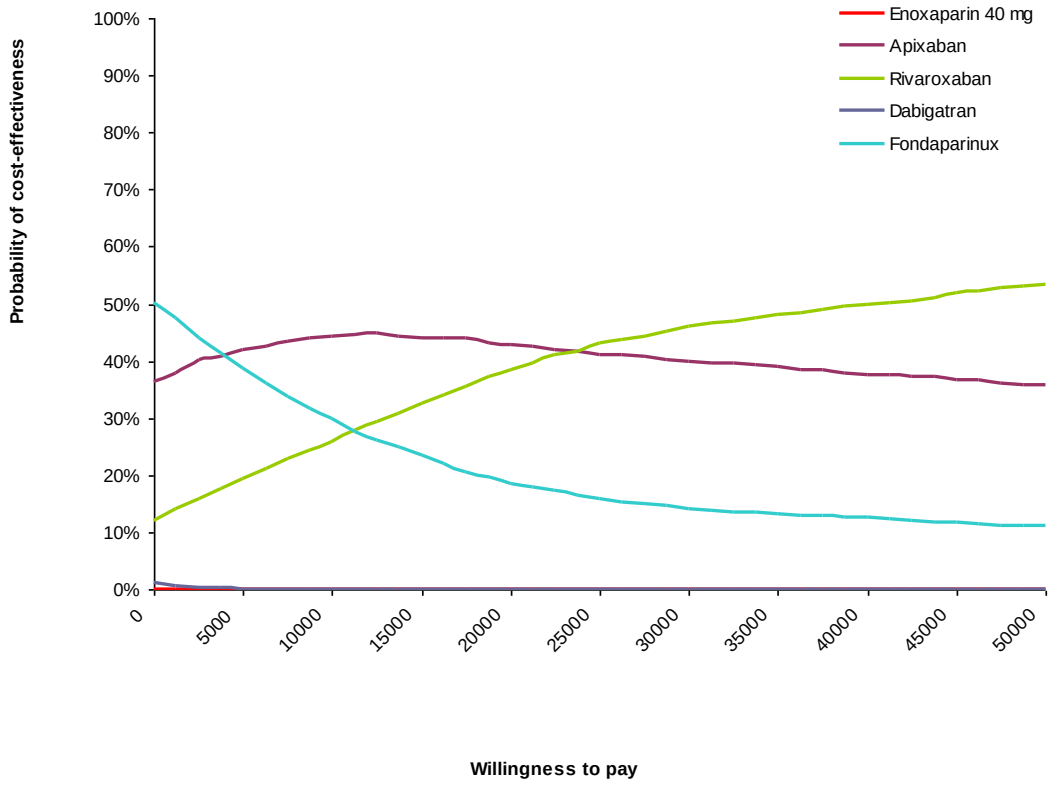


Table 5.21 Base case results in THR, including post discharge costs for fondaparinux

Technologies	Total costs (£)	Total QALYs	Comparison with conventional treatment (Enoxaparin)			Full incremental analysis			
			Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)	Comparator	Incremental costs (£)	Incremental QALYs	ICER (£/ (QALY)
Fondaparinux	188.68	9.533	-247.11	0.012	Dominant				
Apixaban	196.81	9.535	-238.98	0.015	Dominant	Fondaparinux	8.13	0.002	4,958
Rivaroxaban	226.28	9.536	-209.51	0.016	Dominant	Apixaban	29.47	0.001	21,661
Dabigatran	263.89	9.523	-171.90	0.003	Dominant	Rivaroxaban	37.61	-0.013	Dominated
Enoxaparin	435.79	9.520				Rivaroxaban	209.51	-0.016	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

5.4 Conclusions

Describe the completeness of the MS with regard to relevant cost effectiveness studies and data described in any de novo economic evaluations. Does the submission contain an unbiased estimate of the technology's ICERs in relation to relevant populations, interventions comparators and outcomes? Are there any remaining uncertainties about the reliability of the cost effectiveness evidence? Reference should also be made concerning the extent to which the submitted evidence reflects the decision problem defined in the final scope.

The ERG believes that the MS represents an unbiased attempt to assess the cost-effectiveness of apixaban for the prevention of VTE in people undergoing THR or TKR.

The ERG comment that the absolute incremental differences between apixaban and the comparators are small, and based on only one or two trials per comparator. New evidence from future trials may therefore impact the current cost-effectiveness results. Also, were health providers to negotiate prices for interventions that were markedly different to those assumed within the analyses, then conclusions on the intervention that is most likely to be cost-effective may change.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Where appropriate, this section should include a table which shows (i) the effect of any major clinical or cost parameter change or structural change on the size of the base-case ICER and (ii) the effect of making all changes simultaneously on the size of the base-case ICER.

The additional analysis undertaken by the ERG resulted in a lower ICER for apixaban as opposed to fondaparinux. This however does not change the conclusion that, based on the deterministic results, apixaban is deemed cost-effective as opposed to fondaparinux.

7 End of life

Where appropriate, this section should summarise the manufacturer's case for using the NICE end of life treatment criteria and discuss to what extent the manufacturer's argument is valid.

Not applicable.

8 Conclusions

The section should focus on any difference(s) of opinion between the manufacturer and the ERG that might influence the size of the ICER. Priority should be focussed on discussing information that will be useful to the Appraisal Committee including strengths, weaknesses and remaining uncertainties. Further summary of evidence is not required in this section.

The MS appears to contain an unbiased estimate of the treatment effect of apixaban in relation to the relevant outcomes and the comparator, enoxaparin. Overall the evidence from the three ADVANCE trials in the MS indicates that apixaban 2.5mg bd is significantly superior to the comparator enoxaparin (40mg od) in terms of [redacted], any DVT, [redacted]

[redacted]. These results were the same for THR and TKR.

The results of the indirect comparisons showed that apixaban:

- **when compared to rivaroxaban** showed no significant differences in terms of [redacted] any DVT, [redacted].

- **when compared to dabigatran** was significantly superior in terms of [redacted] any DVT; [redacted]. These results were the same for THR and TKR.

- **when compared to fondaparinux** in THR showed no significant differences in terms of any DVT, [redacted]. Other main outcomes (Total VTE and all-cause mortality, Major VTE, and Any bleeding) were not reported using indirect comparisons; although, for the total VTE and all-cause mortality the MTC showed no significant differences. For TKR an indirect comparison with enoxaparin, 40mg od was not possible.

There are no differences of opinion between the manufacturer and the ERG that might influence the size of the ICER in a way that it would alter general conclusions. The full incremental analyses indicate that in THR the ICER of rivaroxaban versus apixaban amounts to £21,661/QALY. In TKR apixaban is dominated by rivaroxaban. These results are robust.

The strengths of the submission are:

- In general, the submission appeared to present a thorough and well performed analysis.
- The submission includes an overview of all available evidence.
- Errors identified in the economic model and report by the ERG were all relatively minor, and did not substantially impact the results and conclusions.

Weaknesses are:

- The submission was not concise and lacked transparency. Therefore, the ERG cannot guarantee that no errors are still undiscovered.
- The effectiveness and safety of apixaban, and therefore its cost-effectiveness, are based on a single trial that included a population that is not entirely representative for the NHS.

8.1 Implications for research

Further trials of apixaban compared to other LMWHs in both THR and TKR would serve to lessen the uncertainty surrounding the effectiveness and cost-effectiveness of these treatments. Head to head trials of apixaban versus rivaroxaban, dabigatran and fondaparinux would strengthen the evidence base for these comparisons.

The key parameters that drive cost-effectiveness are the relative risks for 'total VTE and all-cause death' and 'bleeding events'. These were derived from single trials. Additional trials that support these results could be valuable.

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Appendix 1A: ERG Search Strategies

Clinical effectiveness search from Industry Submission rerun by ERG to include all changes in Manufacturers response to points of clarification
MEDLINE (OvidSP): 1948 to 2011 August Week 5
Rerun 12.9.11

(Changes made by the manufacturer in their response are in bold)

1 exp Thromboembolism/ (38477)
2 exp Pulmonary Embolism/ (28526)
3 exp Venous Thrombosis/ (40656)
4 exp Thrombophlebitis/ (20592)
5 ((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp. (39706)
6 (dvt or vte).mp. (7706)
7 ((pulmonary or lung) adj6 (embolism or emboli)).mp. (35756)
8 thrombophlebitis.mp. (22277)
9 (fonadaparin* or ***fondaparinux*** or arixtra or ic851589 or org31540 or quixidar or sr90107*).mp. (999)
10 (rivaroxaban or bay597939).mp. (336)
11 (dabigatran or rendix or pradaxa or bibr1048).mp. (390)
12 (apixaban or bms562247).mp. (149)
13 exp Heparin/ or exp Heparin, Low-Molecular-Weight/ or (***LMWH or low molecular weight heparin***).mp. (54413)
14 exp Dalteparin/ (683)
15 (dalteparin or fragmin* or k2165).mp. (1119)
16 exp Enoxaparin/ (2177)
17 (enoxaparin or clexane or klexane or lovenox or pk10169).mp. (2981)
18 exp Nadroparin/ (397)
19 (nadroparin or fraxiparin* or fraxodi or seleparine or tedegliparin or cv216).mp. (616)
20 (ardeparin or normiflo or wy90493).mp. (34)
21 (tinzaparin or innohep or logiparin of lhn1).mp. (288)
22 (certoparin or sandoparin or embolex or monoembolex).mp. (98)
23 (parnaparin or fluxum or lohepa or minidalton or parvoparin or op2123).mp. (48)
24 (reviparin or cilvarin* or lomorin or lu47311).mp. (116)
25 (tedelparin or ***tafoxiparin or livaraparin or idrabiotaparinux or rd-11885 or rd11885 or idraparinux or semuloparin or deligoparin or cy-222 or cy222 or antixarin).mp. (183)***
26 (calciparine or monoparin or bemiparin or hibor or phivor).mp. (80)
27 Randomized controlled trials as Topic/ (76360)
28 Randomized controlled trial/ (316345)
29 Random allocation/ (72797)
30 Double blind method/ (112708)
31 Single blind method/ (15498)
32 Clinical trial/ (467920)
33 exp Clinical Trials as Topic/ (248910)
34 or/27-33 (796979)
35 (clinic$ adj trial$1).tw. (160987)
36 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (110101)

37 Placebos/ (30156)
38 Placebo$.tw. (132592)
39 Randomly allocated.tw. (12904)
40 (allocated adj2 random).tw. (670)
41 or/35-40 (334839)
42 34 or 41 (898482)
43 Case report.tw. (163123)
44 Letter/ (725669)
45 Historical article/ (279830)
46 Review of reported cases.pt. (0)
47 Review, multicase.pt. (0)
48 or/43-47 (1158609)
49 42 not 48 (872894)
50 Meta-Analysis as Topic/ (11769)
51 meta analy$.tw. (35509)
52 metaanaly$.tw. (1039)
53 Meta-Analysis/ (30619)
54 (systematic adj (review$1 or overview$1)).tw. (27764)
55 exp Review Literature as Topic/ (5843)
56 or/50-55 (74197)
57 cochrane.ab. (17451)
58 embase.ab. (14834)
59 (psychlit or psyclit).ab. (830)
60 (psychinfo or psycinfo).ab. (5105)
61 (cinahl or cinhal).ab. (5779)
62 science citation index.ab. (1356)
63 bids.ab. (292)
64 cancerlit.ab. (503)
65 or/57-64 (27532)
66 reference list$.ab. (6383)
67 bibliograph$.ab. (9092)
68 hand-search$.ab. (2741)
69 relevant journals.ab. (470)
70 manual search$.ab. (1526)
71 or/66-70 (18122)
72 selection criteria.ab. (14712)
73 data extraction.ab. (6682)
74 72 or 73 (20232)
75 Review/ (1676497)
76 74 and 75 (14054)
77 Comment/ (451657)
78 Letter/ (725669)
79 Editorial/ (283470)
80 animal/ (4874456)
81 human/ (12075385)
82 80 not (80 and 81) (3584947)
83 or/77-79,82 (4630168)
84 56 or 65 or 71 or 76 (95459)

85 84 not 83 (88613)
86 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (111798)
87 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (55538)
88 49 or 85 (928407)
89 exp Orthopedics/ (14334)
90 exp Arthroscopy/ (13899)
91 ((hip or knee) and (replacement* ***or arthroplast**** or arthroscop*)).mp. (47604)
92 89 or 90 or 91 (68412)
93 86 and 87 and 88 and 92 (532)

Clinical effectiveness search reworked by ERG to maximise results
MEDLINE (OvidSP): 1948 to August Week 5 2011
Rerun 12.9.11

(Changes made by the ERG in addition to those made by the manufacturer in their response are in bold)

1 exp Thromboembolism/ (38477)
2 exp Pulmonary Embolism/ (28526)
3 exp Venous Thrombosis/ (40656)
4 ((venous or vein) adj (thrombosis ***or thromboses*** or thrombus or thromboembolism)).mp. (40407)
5 (dvt or vte).mp. (7706)
6 ((pulmonary or lung) adj6 (embolism or emboli)).mp. (35756)
7 thrombophlebitis.mp. (22277)
8 or/1-7 (112135)
9 (fondaparin* or arixtra or ic851589 or org31540 or quixidar or sr90107*).mp. (1000)
10 (rivaroxaban or bay597939).mp. (336)
11 (dabigatran or rendix or pradaxa or bibr1048).mp. (390)
12 (apixaban ***or eliquis*** or bms562247).mp. (149)
13 exp Heparin/ or exp Heparin, Low-Molecular-Weight/ or (LMWH or low molecular weight heparin).mp. (54413)
14 (dalteparin or fragmin* or k2165).mp. (1119)
15 (enoxaparin or clexane or klexane or lovenox or pk10169).mp. (2981)
16 (nadroparin or fraxiparin* or fraxodi or seleparine or tedegliparin or cv216).mp. (616)
17 (ardeparin or normiflo or wy90493).mp. (34)
18 (tinzaparin or innohep or logiparin of lhn1).mp. (288)
19 (certoparin or sandoparin or embolex or monoembolex).mp. (98)
20 (parnaparin or fluxum or lohepa or minidalton or parvoparin or op2123).mp. (48)
21 (reviparin or cilvarin* or lomorin or lu47311).mp. (116)
22 tedelparin.mp. (6)
23 (calciparine or monoparin or bemiparin or hibor or phivor).mp. (80)
24 (livaraparin-calcium or tafoxiparin or idrabiotaparinux or rd-11885 or idraparinux or semuloparin or cy-222 or deligoparin or antixarin).mp. (164)
25 or/9-24 (55538)
26 Randomized controlled trials as Topic/ (76360)
27 Randomized controlled trial/ (316345)

28 Random allocation/ (72797)
29 Double blind method/ (112708)
30 Single blind method/ (15498)
31 Clinical trial/ (467920)
32 exp Clinical Trials as Topic/ (248910)
33 or/26-32 (796979)
34 (clinic$ adj trial$1).tw. (160987)
35 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (110101)
36 Placebos/ (30156)
37 Placebo$.tw. (132592)
38 Randomly allocated.tw. (12904)
39 (allocated adj2 random).tw. (670)
40 or/34-39 (334839)
41 33 or 40 (898482)
42 Case report.tw. (163123)
43 Letter/ (725669)
44 Historical article/ (279830)
45 Review of reported cases.pt. (0)
46 Review, multicase.pt. (0)
47 or/42-46 (1158609)
48 41 not 47 (872894)
49 Meta-Analysis as Topic/ (11769)
50 meta analy$.tw. (35509)
51 metaanaly$.tw. (1039)
52 Meta-Analysis/ (30619)
53 (systematic adj (review$1 or overview$1)).tw. (27764)
54 exp Review Literature as Topic/ (5843)
55 or/49-54 (74197)
56 cochrane.ab. (17451)
57 embase.ab. (14834)
58 (psychlit or psyclit).ab. (830)
59 (psychinfo or psycinfo).ab. (5105)
60 (cinahl or cinhal).ab. (5779)
61 science citation index.ab. (1356)
62 bids.ab. (292)
63 cancerlit.ab. (503)
64 or/56-63 (27532)
65 reference list$.ab. (6383)
66 bibliograph$.ab. (9092)
67 hand-search$.ab. (2741)
68 relevant journals.ab. (470)
69 manual search$.ab. (1526)
70 or/65-69 (18122)
71 selection criteria.ab. (14712)
72 data extraction.ab. (6682)
73 71 or 72 (20232)
74 Review/ (1676497)
75 73 and 74 (14054)

76 Comment/ (451657)
77 Letter/ (725669)
78 Editorial/ (283470)
79 animal/ (4874456)
80 human/ (12075385)
81 79 not (79 and 80) (3584947)
82 or/76-78,81 (4630168)
83 55 or 64 or 70 or 75 (95459)
84 83 not 82 (88613)
85 48 or 84 (928407)
86 Orthopedics/ (14334)
87 arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ (20253)
88 ((hip or knee or ***femoral head***) and ***(replac$ or*** arthroplast$ ***or prosthe$ or surgery or surgical or implant$***)).mp. (72084)
89 or/86-88 (85377)
90 8 and 25 and 85 and 89 (628)

Cost Effectiveness searches from Industry Submission rerun by ERG to include all changes in Manufacturers response to points of clarification
Embase (OvidSP):1980 to 2011 Week 36
Searched: 12.9.11

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1 exp venous thromboembolism/ or exp thromboembolism/ (262048)
2 exp lung embolism/ (46099)
3 exp thrombophlebitis/ (15469)
4 ((venous or vein) adj (thrombosis or thrombus or thromboembolism)).mp. (73099)
5 (dvt or vte or thrombophlebitis).mp. (27549)
6 ((pulmonary or lung) adj3 (embolism or emboli)).mp. (51223)
7 exp anticoagulant agent/ (386660)
8 exp fibrinolytic agent/ (85675)
9 exp antithrombocytic agent/ (211486)
10 exp thrombin inhibitor/ (26785)
11 (anticoagulan* or (anti adj coagula*) or antithromb* or (anti adj thrombin) or antiemboli* or (anti adj embolism) or (anti adj embolic) or antiplatelet or (anti adj platelet) or (thrombin adj (inhibitor or inhibition)) or (direct adj thrombin)).mp. (141494)
12 exp heparin derivative/ (115106)
13 exp hirudoid/ (80)
14 exp suleparoide/ (13)
15 exp warfarin/ (47778)
16 exp coumarin anticoagulant/ or exp coumarin/ or exp coumarin derivative/ (70923)
17 exp brodifacoum/ (189)
18 exp bromadiolone/ (133)
19 (acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin).mp. (71192)
20 exp hirudin/ (3730)

21 exp lepirudin/ (2121)
22 exp ximelagatran/ (1822)
23 exp pentasaccharide/ (1058)
24 pentasaccharide*.mp. (2192)
25 exp dextran 40/ or exp dextran/ or exp dextran 60/ or exp dextran 70/ (21493)
26 dextran*.mp. (40157)
27 exp acetylsalicylic acid/ (127051)
28 (aspirin or (acetylsalicylic adj acid)).mp. (133688)
29 exp clopidogrel/ (24848)
30 exp dipyridamole/ (18673)
31 (clopidogrel or dipyridamole).mp. (42948)
32 (fonadaparin* or arixtra or ic851589 or org31540 or quixidar or sr90107*).mp. (670)
33 exp rivaroxaban/ (1230)
34 (rivaroxaban or bay597939).mp. (1259)
35 exp dabigatran/ (953)
36 (dabigatran or rendix or pradaxa or bibr1048).mp. (1469)
37 exp apixaban/ (622)
38 (apixaban or bms562247).mp. (640)
39 exp heparin/ (97190)
40 exp low molecular weight heparin/ (31824)
41 exp dalteparin/ (5217)
42 (dalteparin or fragmin* or k2165).mp. (5373)
43 exp enoxaparin/ (12215)
44 (enoxaparin or clexane or klexane or lovenox or pk10169).mp. (12455)
45 exp nadroparin/ (3396)
46 (nadroparin or fraxiparin* or fraxodi or seleparine or tedegliparin or cv216).mp. (3490)
47 exp ardeparin/ (313)
48 (ardeparin or normiflo or wy90493).mp. (320)
49 exp tinzaparin/ (2065)
50 (tinzaparin or innohep or logiparin of lhn1).mp. (2093)
51 exp certoparin/ (554)
52 (certoparin or sandoparin or embolex or monoembolex).mp. (709)
53 exp parnaparin/ (244)
54 (parnaparin or fluxum or lohepa or minidalton or parvoparin or op2123).mp. (250)
55 exp reviparin/ (805)
56 (reviparin or cilvarin* or lomorin or lu47311).mp. (813)
57 exp tedelparin/ (43)
58 exp bemiparin/ (231)
59 exp heparin calcium/ (1216)
60 (calciparine or monoparin or bemiparin or hibor or phivor).mp. (488)
61 exp Bandages/ (9224)
62 mechanical.mp. (197790)
63 Intermittent Pneumatic Compression Devices/ (372)
64 (stocking or stockings or hose).mp. (4281)
65 (((calf or elastic or graded or limb or leg or pneumatic or plantar or foot) adj compression) or (compression adj device)).mp. (4405)
66 (((foot adj pump) or foot) adj pumps).mp. (38)
67 flowtron.mp. (36)

68 Motion Therapy, Continuous Passive/ (1039)
69 Early Ambulation/ (12231)
70 (mobilisation or mobilization or physiotherapy or ambulation or kinetic therapy or ((continuous or lateral) adj rotation) or ((therapeutic or specialised or specialized) adj bed) or air loss mattress or bedrest or bed rest or immobili$ or leg exercises).mp. (207645)
71 Hindlimb Suspension/ (25973)
72 ((foot or feet or limb or leg or legs) adj3 (elevat$ or raise$ or suspend$)).mp. (1401)
73 Fluid Therapy/ (12639)
74 Rehydration Solutions/ (2000)
75 (hydrat$ or rehydrat$).mp. (55406)
76 exp "Costs and Cost Analysis"/ (208263)
77 Economics/ (186154)
78 Economics, Nursing/ or Economics, Medical/ or Economics, Hospital/ or Economics, Pharmaceutical/ (34400)
79 exp "Fees and Charges"/ (29950)
80 Budgets/ (15895)
81 budget$.tw. (18660)
82 cost$.ti. (80256)
83 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (81015)
84 (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti. (33203)
85 (price$ or pricing$).tw. (24648)
86 (financial or finance or finances or financed).tw. (51414)
87 (fee or fees).tw. (11829)
88 (value adj2 (money or monetary)).tw. (1263)
89 exp Models, Economic/ (73446)
90 models, theoretical/ or models, organizational/ (87910)
91 economic model$.tw. (1675)
92 markov chains/ (46380)
93 markov$.tw. (10606)
94 Monte Carlo Method/ (14767)
95 monte carlo.tw. (20172)
96 exp Decision Theory/ (1355)
97 (decision$ adj2 (tree$ or ***analy$*** or model$)).tw. (11819)
98 1 or 2 or 3 or 4 or 5 or 6 (270000)
99 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 (759661)
100 ((knee or hip) adj2 (surgery or replacement)).mp. (29824)
101 hip arthroplasty/ or total hip prosthesis/ (24737)
102 total knee replacement/ or knee arthroplasty/ (17089)
103 (arthroplasty adj2 (knee or hip)).mp. (29842)
104 total hip replacement.mp. (6316)
105 total knee replacement.mp. (11086)
106 100 or 101 or 102 or 103 or 104 or 105 (52097)
107 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 (975046)

108 98 and 99 and 106 and 107 (340)
109 exp "cost benefit analysis"/ (55747)
110 Economics/ (186154)
111 Health economics/ or Pharmacoeconomics/ (34400)
112 exp fee/ or exp medical fee/ (29950)
113 budget/ (15895)
114 exp statistical model/ (73446)
115 theoretical model/ or nonbiological model/ (87910)
116 probability/ (46380)
117 Monte Carlo method/ (14767)
118 exp decision theory/ (1355)
119 or/109-118 (483081)
120 99 or 119 (776569)
121 98 and 106 and 107 and 120 (348)

Cost Effectiveness Embase search reworked by ERG to translate Economics filter and maximise results
Embase (OvidSP): 1980 to 2011 Week 36
Searched 12.8.11

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1 exp venous thromboembolism/ or exp thromboembolism/ (262048)
2 ((venous or vein) adj (thrombosis ***or thromboses*** or thrombus or thromboembolism)).mp. (73550)
3 (dvt or vte or thrombophlebitis).mp. (27549)
4 ((pulmonary or lung) adj3 (embolism or emboli)).mp. (51223)
5 or/1-4 (270134)
6 exp anticoagulant agent/ (386660)
7 exp fibrinolytic agent/ (85675)
8 exp antithrombocytic agent/ (211486)
9 exp thrombin inhibitor/ (26785)
10 (anticoagulan* or (anti adj coagula*) or antithromb* or (anti adj thrombin) or antiemboli* or (anti adj embolism) or (anti adj embolic) or antiplatelet or (anti adj platelet) or (thrombin adj (inhibitor or inhibition)) or (direct adj thrombin)).mp. (141494)
11 exp heparin derivative/ (115106)
12 exp hirudoid/ (80)
13 exp suleparoide/ (13)
14 exp warfarin/ (47778)
15 exp coumarin anticoagulant/ or exp coumarin/ or exp coumarin derivative/ (70923)
16 exp brodifacoum/ (189)
17 exp bromadiolone/ (133)
18 (acenocoumarol or brodifacoum or bromadiolone or cloricromen or coumafos or coumadin or coumarin or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or nicoumalone or phenindione or phenprocoumon or phepromaron or tioclomarol or sinthrone or warfarin).mp. (71192)
19 exp hirudin/ (3730)
20 exp lepirudin/ (2121)
21 exp ximelagatran/ (1822)
22 exp pentasaccharide/ (1058)

23 pentasaccharide*.mp. (2192)
24 exp dextran 40/ or exp dextran/ or exp dextran 60/ or exp dextran 70/ (21493)
25 dextran*.mp. (40157)
26 exp acetylsalicylic acid/ (127051)
27 (aspirin or (acetylsalicylic adj acid)).mp. (133688)
28 exp clopidogrel/ (24848)
29 exp dipyridamole/ (18673)
30 (clopidogrel or dipyridamole).mp. (42948)
31 (***fondaparin**** or arixtra or ic851589 or org31540 or quixidar or sr90107*).mp. (3641)
32 exp rivaroxaban/ (1230)
33 (rivaroxaban or bay597939).mp. (1259)
34 exp dabigatran/ (953)
35 (dabigatran or rendix or pradaxa or bibr1048).mp. (1469)
36 exp apixaban/ (622)
37 (apixaban ***or eliquis*** or bms562247).mp. (640)
38 exp heparin/ (97190)
39 exp low molecular weight heparin/ (31824)
40 (LMWH or low molecular weight heparin or tedelparin or livaraparin-calcium or tafoxiparin or idrabiotaparinux or rd-11885 or danaparoid or idraparinux or semuloparin or cy-222 or deligoparin or antixarin).mp. (24637)
41 (dalteparin or fragmin* or k2165).mp. (5373)
42 (enoxaparin or clexane or klexane or lovenox or pk10169).mp. (12455)
43 (nadroparin or fraxiparin* or fraxodi or seleparine or tedegliparin or cv216).mp. (3490)
44 (ardeparin or normiflo or wy90493).mp. (320)
45 (tinzaparin or innohep or logiparin of lhn1).mp. (2093)
46 (certoparin or sandoparin or embolex or monoembolex).mp. (709)
47 (parnaparin or fluxum or lohepa or minidalton or parvoparin or op2123).mp. (250)
48 (reviparin or cilvarin* or lomorin or lu47311).mp. (813)
49 exp heparin calcium/ (1216)
50 (calciparine or monoparin or bemiparin or hibor or phivor).mp. (488)
51 exp Bandages/ (9224)
52 mechanical.mp. (197790)
53 Intermittent Pneumatic Compression Devices/ (372)
54 (stocking or stockings or hose).mp. (4281)
55 (((calf or elastic or graded or limb or leg or pneumatic or plantar or foot) adj compression) or (compression adj device)).mp. (4405)
56 (((foot adj pump) or foot) adj pumps).mp. (38)
57 flowtron.mp. (36)
58 Motion Therapy, Continuous Passive/ (1039)
59 Early Ambulation/ (12231)
60 (mobilisation or mobilization or physiotherapy or ambulation or kinetic therapy or ((continuous or lateral) adj rotation) or ((therapeutic or specialised or specialized) adj bed) or air loss mattress or bedrest or bed rest or immobili$ or leg exercises).mp. (207645)
61 Hindlimb Suspension/ (25973)
62 ((foot or feet or limb or leg or legs or ***limbs or hindlimb$***) adj3 (elevat$ or ***rais$*** or ***suspen$***)).mp. (2851)
63 Fluid Therapy/ (12639)
64 Rehydration Solutions/ (2000)

65 (hydrat$ or rehydrat$).mp. (55406)
66 or/6-64 (928362)
67 cost/ or exp health-care-cost/ (206886)
68 Economics/ (186154)
69 exp health economics/ (506060)
70 budget/ (15895)
71 budget$.tw. (18660)
72 cost$.ti. (80256)
73 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (81015)
74 (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti. (33203)
75 (price$ or pricing$).tw. (24648)
76 (financial or finance or finances or financed).tw. (51414)
77 (fee or fees).tw. (11829)
78 (value adj2 (money or monetary)).tw. (1263)
79 statistical model/ (73446)
80 model, theoretical/ or nonbiological model/ (87910)
81 economic model$.tw. (1675)
82 probability/ (46380)
83 markov$.tw. (10606)
84 Monte Carlo Method/ (14767)
85 monte carlo.tw. (20172)
86 Decision Theory/ (1355)
87 (decision$ adj2 (tree$ or analy$ or model$)).tw. (11819)
88 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 (946789)
89 hip arthroplasty/ or total hip prosthesis/ (24737)
90 total knee replacement/ or knee arthroplasty/ (17089)
91 (arthroplasty adj2 (knee or hip)).mp. (29842)
92 total hip replacement.mp. (6316)
93 total knee replacement.mp. (11086)
94 ((hip or knee or ***femoral head***) and (***replac$ or prosthe$*** or surgery or ***surgical or implant$***)).mp. (89078)
95 89 or 90 or 91 or 92 or 93 or 94 (92227)
96 5 and 66 and 88 and 95 (485)

Appendix 1B: Review of search strategies for Apixaban studies

Clinical effectiveness

Limitations

- The ERG questioned the use of the term Arthroscopy rather than Arthroplasty in the searches Medline, Cochrane and Cinahl databases. The Manufacturer reran these searches with the additional term, but the ERG noted a few remaining weaknesses with this facet, including missing truncation and synonyms such as replac$ or arthroplast$ or prosthe$ or surgery or surgical or implant$ (see Appendix 1A).
  The manufacturer stated in their response that the term arthroscopy was the relevant Mesh term to use for those databases. Medline and Cochrane do contain the Mesh terms "Arthroplasty, replacement, knee" and "Arthroplasty, replacement, hip" and the ERG notes that these were used by the manufacturer in the Cost Effectiveness searches.[11]
- Neither the Apixaban synonym "Eliquis" nor the CAS registry number were searched, although an additional search by the ERG showed that this made no change to the results (Appendix 1A).
- Limited use of truncation. Examples:
  i. Line #91 from Medline search, should use replac* rather than replacement to pick up replac**e**, replac**ed**, replac**ing**, replac**ement** and replac**ements**.
- There were a number of redundant terms in the strategies. Examples:
  i. Line #4 from the Medline search, "exp Thrombophlebitis/" is redundant due to the previous line #3, "exp Venous Thrombosis/".
- Although start dates and search dates were reported there was no Issue given for the Cochrane search.

Indirect and mixed treatment comparisons

Searches were carried out on all NICE required databases and used the same strategies as 9.2 of the Industry submission. As well as the previous limitations the ERG also noted:

- There were a number of redundant terms in the strategies. Examples:
  ii. Line #4 from the Medline search, "exp Thrombophlebitis/" is redundant due to the previous line #3, "exp Venous Thrombosis/".
  iii. Line #18 from the Embase search, "exp Dalteparin/" is redundant due to line #17, "exp low molecular weight heparin/".

Adverse events (comparators)

- In utilizing the same searches as with Clinical Effectiveness and Mixed Treatment Comparators the search strategies in this section carried the same problems as the previous sections. Given the CRD advice on not using RCT filters in these cases,[12] the ERG would recommend removing the RCT filter on Lines #27-86 (Medline Search 9.2.4 of the Industry submission) and replace them with a suitable adverse events filter, a number of which can be found in the ISSG Search Filters Resource. [68]

Non-RCT Evidence (Apixaban)

Adequate searches were carried out on all NICE required databases. ERG noted the same limitations in the facets for hip/knee replacement as in earlier searches (see Clinical Effectiveness)

Cost effectiveness

Further limitations

- There were some missed opportunities to use truncation. Examples:
    i. Line #78 Medline strategy "(surgery or replac*) rather than replacement to pick up replac**e**, replac**ed**, replac**ing**, replac**ement** and replace**ments**.
    ii. Line #49 Medline strategy raise$ would be better as rais$, suspend$ would be better as suspen$
- There are cases where broader MeSH terms make the use of narrower ones redundant:
    i. Line #24 Medline exp Heparin, Low-Molecular-Weight/" makes line #27, "exp Nedroparin/" redundant.
- There were a variety of synonyms and variants that were not used for hip/knee replacement. Those missed include prosthe$ or surgical or implant$ (see Appendix 1A).
- Although start dates and search dates were reported there was no Issue given for the Cochrane search.
- The ERG queried why a Medline cost filter (lines #76-97) was applied to the Embase search, the use of Medline mesh such as "exp cost/" in Embase will also pick up unwanted terms such as Energy cost/. The Manufacturer addressed this in their response by adding additional terms. The ERG reran the manufacturer's search with all corrections (n=348) but noted some remaining weaknesses so conducted an additional search (n=485) (See Appendix 1A)

Measurement and valuation of health effects

Limitations

- There were some missed opportunities to use truncation. Examples within the Cochrane search:
- Line #77 use replac* rather than replacement to pick up replac**e**, replac**ed**, replac**ing**, replac**ement** and replace**ments**
- There are cases where broader terms make the use of narrower ones redundant:
    i. Line #25 Medline is redundant due to line #24 exp Heparin, Low-Molecular-Weight/
- There were a variety of synonyms and variants that were not used for hip/knee replacement. Those missed include prosthe$ or surgical or implant$ (see Appendix 1A).

Resource identification, measurement and valuation

See cost effectiveness

Appendix 2: Phillips et al. Checklist

Question(s)	Response (Y, N, or NS)	Comments
Is there a clear statement of the decision problem?	Y	
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Y	
Is the primary decision-maker specified?	Y	
Is the perspective of the model stated clearly?	Y	
Are the model inputs consistent with the stated perspective?	Y	
Has the scope of the model been stated and justified?	Y	
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y/N	Partly. Transition from mild/moderate to severe PTS is not possible. Also, no difference in type of VTE and type of bleeding between the comparators. Both issues are in the clarification letter. The first issue was due to lack of data. The second issue has been resolved.
Are the sources of data used to develop the structure of the model specified?	N	But the process of validating the modelling approach and model structuring is
Are the causal relationships described by the model structure justified appropriately?	Y	
Are the structural assumptions transparent and justified?	Y/N	Not all justified. See earlier comment.
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	
Is there a clear definition of the options under evaluation?	Y	
Have all feasible and practical options been evaluated?	N	Not all options could be included in each analysis due to lack of data.
Is there justification for the exclusion of feasible options?	Y	Lack of data.
Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Y	
Is the time horizon of the model sufficient to reflect all important differences between options?	Y	
Are the time horizon of the model, the duration of treatment and the duration of treatment effect	Y	

described and justified?		
Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y/N	Not for PTS (see earlier comment)
Is the cycle length defined and justified in terms of the natural history of disease?	Y	
Are the data identification methods transparent and appropriate given the objectives of the model?	Y	
Where choices have been made between data sources, are these justified appropriately?	Y	
Has particular attention been paid to identifying data for the important parameters in the model?	Y	
Has the quality of the data been assessed appropriately?	Y	
Where expert opinion has been used, are the methods described and justified?	N.A.	
Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Y	
Is the choice of baseline data described and justified?	Y	
Are transition probabilities calculated appropriately?	Y	
Has a half-cycle correction been applied to both cost and outcome?	N	
If not, has this omission been justified?	Y	
If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Y	
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	Costs and clinical outcomes are extrapolated beyond the end of the trial. Patients who experience an event are at risk of recurrence of a VTE event or complication over a longer timeframe. These risks are not assumed to be treatment dependent.
Have alternative extrapolation assumptions been explored through sensitivity analysis?	Y	
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Y	
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	Y	
Are the costs incorporated into the model justified?	Y	

Has the source for all costs been described?	Y	
Have discount rates been described and justified given the target decision-maker?	Y	
Are the utilities incorporated into the model appropriate?	Y/N	Utilities incorporated in the model are based on a wide variety of methods.
Is the source for the utility weights referenced?	Y	
Are the methods of derivation for the utility weights justified?	Y/N	Due to lack of data some utility inputs were not reference case (for instance no preference data from the public). This was further justified in the clarification phase.
Have all data incorporated into the model been described and referenced in sufficient detail?	Y	
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Y	
Is the process of data incorporation transparent?	Y/N	Inclusion of trials in the indirect comparison and MTC for efficacy not safety was not clear. However, this was resolved in the clarification phase.
If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	Y	
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Y	
Have the four principal types of uncertainty been addressed?	Y	
If not, has the omission of particular forms of uncertainty been justified?	N.A.	
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Y	
Has heterogeneity been dealt with by running the model separately for different subgroups?	Y	
Are the methods of assessment of parameter uncertainty appropriate?	Y/N	It was stated that only parameters not included in the deterministic sensitivity analyses were included in the PSA. Although some parameters were included in both, this indicates that not all parameter uncertainty was reflected in the PSA. …
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y	
Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Y	

Are any counterintuitive results from the model explained and justified?	N.A.	
If the model has been calibrated against independent data, have any differences been explained and justified?	N.A.	
Have the results of the model been compared with those of previous models and any differences in results explained?	Y	