NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE

Contents

Instructions for manufacturers and sponsors

This specification for submission of evidence to the National Institute of Health and Clinical Excellence (NICE, or the Institute) as part of the single technology appraisal (STA) process is designed to indicate to manufacturers and sponsors the information required by the Institute and the format in which it should be presented. Use of the specification and completion of Appendices 9.1 to 9.3 are mandatory, and the format should be adhered to wherever possible. Reasons for not adhering to this format must be clearly stated. Sections that are not considered to be relevant should be marked 'N/A' and a justification given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise the Institute immediately of any variation between the preliminary and final approval.

A submission should be as succinct and informative as possible. It is expected that the main body of the submission will not usually exceed 75 pages. The submission should be sent to the Institute electronically in Word or a compatible format, and not as a PDF file. A list of all references must be provided, together with paper or electronic copies.

For model-based economic evaluations, a transparent and fully executable electronic copy of the model should be submitted. The Evidence Review Group should have full access to the programming code, and running of the model should be unhindered. Please ensure that the submitted versions of the model program and the content of the submission match. The model should be constructed using standard software, such as Excel or DATA. If non-standard software is required for the construction of the model, please discuss this with the Institute at the earliest opportunity in advance of submission.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but which is considered to be relevant to the submission. Any additional appendices should be clearly referenced in the body of the submission and should not be used to present core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the efficacy section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID rather than relying on numerical referencing alone (for example, 'Trial 123/Jones et al. [126] found ABC' rather than 'One trial [126] found ABC').

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to the Institute at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by the Institute.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to the Institute with all confidential information highlighted and underlined
- a fully executable electronic copy of the economic model has been submitted
- all key references have been made available (electronic or hard copy versions as appropriate)
- the checklist of confidential information has been completed and submitted.

Disclosure of information

To ensure that the appraisal process is as transparent as possible, the Institute considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. The Institute recognises, however, that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the Final Appraisal Determination (FAD) or Appraisal Consultation Document (ACD) to consultees and commentators, all the evidence seen by the Committee should ideally be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). As a minimum, a structured abstract will need to be made available for public disclosure, using a recognised format such as that provided by the CONSORT statement (www.consort-statement.org).

Where data are commercial in confidence or academic in confidence, it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The NICE checklist of confidential information should be completed. If no checklist of confidential information is provided, the Institute will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor will be requested to supply a second 'stripped' version of the submission from which any information that is to remain confidential has been removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear how much data have been removed and where they have been removed from.

The Institute will request the stripped version of the submission at least 2 weeks before the anticipated date of issue of the FAD or ACD to consultees and commentators. The stripped version will be issued to consultees and commentators along with the ACD or FAD, and made available on the Institute's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the stripped version of the submission does not contain any confidential information. **No further amendments or corrections may be made to the submission at this stage.** The NICE checklist of confidential information should be updated and submitted at the same time. The Institute will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for the Institute to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Appraisal Committee. Confidential information may be distributed to consultees with the permission of the manufacturer or sponsor. The Institute will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by the Institute that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges the Institute to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to the Institute. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed as commercial in confidence before making any decision on disclosure.

For further information, please see the NICE website (www.nice.org.uk).

Glossary of commonly used acronyms

ALT	alanine aminotransferase
BILI	bilirubin
CRBE	clinically relevant bleeding event
DBG	dabigatran etexilate
DVT	deep vein thrombosis
HIT	heparin-induced thrombocytopenia
LMWH	low molecular weight heparin
MBE	major bleeding event
NCC-AC	National Collaborating Centre for Acute Care
PE	pulmonary embolism
PTS	post-thrombotic syndrome
THR	total hip replacement
TKR	total knee replacement
ULN	upper limit of normal
VTE	venous thromboembolism

Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process' – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

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

Dabigatran etexilate (Pradaxa®) is an oral direct thrombin inhibitor, a type of anticoagulant.

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

Positive opinion from the CHMP for dabigatran etexilate (DBG) was received on January 24th 2008 for the indication detailed in this submission. Marketing authorisation is expected approximately 90 days from this date. Regulatory approval was sought through the EMEA centralised procedure. The EPAR is included with the submission as Appendix 9.4.

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

DBG will initially be indicated for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. This is the indication considered in this submission.

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

DBG is not currently available. The UK launch of DBG is planned to coincide with the confirmation of full marketing authorisation (see question 1.2).

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

No. DBG will gain regulatory approval throughout the European Union as detailed above in question 1.2. To date, dossiers have also been filed in the following other countries:

[redacted]

- Canada[redacted]

[redacted]

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

Yes, DBG in this indication was submitted to the Scottish Medicines Consortium on February 4th 2008, to be considered at their committee meeting on May 6th 2008.

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

DBG will be available in capsules, in the following dosages and pack sizes:

PRADAXA 75 mg, hard capsules:
- Pack of 10 capsules.
- Pack of 60 capsules.

PRADAXA 110 mg, hard capsules:
- Pack of 10 capsules.
- Pack of 60 capsules.

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

The proposed course of treatment varies between elective total hip replacement (THR) and elective total knee replacement (TKR).

THR:

The recommended dose of DBG is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

TKR:

The recommended dose of DBG is 220 mg once daily taken as 2 capsules of 110 mg. Treatment should be initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

Special patient populations:

Renal impairment: Treatment in patients with severe renal impairment (creatinine clearance < 30 ml/min) is contraindicated. In patients with moderate renal impairment (creatinine clearance 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg.

Elderly: In elderly patients (> 75 years) there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg.

Hepatic impairment: Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials. Therefore the use of DBGis not recommended in this population.

Children and adolescents: There is no experience in children and adolescents. DBG is not recommended for use in patients below 18 years due to lack of data on safety and efficacy.

Concomitant use of DBG with Amiodarone: Dosing should be reduced to 150 mg DBG daily in patients who receive DBG and amiodarone concomitantly.

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

The NHS list prices for DBG are as follows:

PRADAXA 75 mg, hard capsules:

- Pack of 10 capsules: £21.00
- Pack of 60 capsules. £126.00

PRADAXA 110 mg, hard capsules:

- Pack of 10 capsules: £21.00
- Pack of 60 capsules. £126.00

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

In this indication, DBG will be exclusively dispensed in secondary care. As patients will be required to complete a course of therapy that extends beyond the typical length of stay (either 10 days of therapy (TKR) or 28-35 days (THR)), any medication to be taken at home will be dispensed to the patient prior to discharge from hospital.

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

Other than the precautions listed in question 1.8, treatment with DBG does not necessitate further monitoring, tests or investigations of any kind. As with other types of chemical thromboprophylaxis in this indication, DBG may be used concomitantly with one of the various types of mechanical prophylaxis (e.g. graduated elasticated compression stockings, intermittent pneumatic compression etc.).

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults undergoing elective hip or knee replacement surgery	As defined in the final scope.
Intervention	Dabigatran etexilate	Recommended standard dose of 220mg o.d (half dose on day 1) as administered in the RE-NOVATE trial for total hip replacement and the RE-MODEL trial for total knee replacement, and in line with the product SPC. The reduced dose of 150mg is reserved for special populations and will be presented in a subgroup analysis.
Comparator(s)	• low-molecular-weight heparin (LMWH) • fondaparinux	Both comparisons will be presented in the submission. The comparison with LMWH will be a direct comparison based on the pivotal clinical trials. The comparison with fondaparinux will be an indirect comparison based on a mixed treatment comparison meta-analysis.
Outcomes	• mortality • incidence of DVT • incidence of PE • post DVT complications including post thrombotic syndrome • length of hospital stay • health-related quality of life. • adverse effects of treatment including bleeding events (minor and major) • joint outcomes (medium and long-term), including joint infection.	All outcomes as defined in the final scope will be presented, with the exception of joint outcomes (medium and long-term), including joint infection. The pivotal clinical trials did not routinely report this particular outcome. It will be investigated if these values can be obtained. The economic evaluation will not consider medium to long-term joint outcomes as an outcome in its own right. This is not expected to bias the results in any way and will be justified in the final submission. Medium and long-term outcomes considered will include post-thrombotic syndrome and recurrent VTE. It will be assumed that all bleeding complications are resolved (either fatal or non-fatal) within the acute phase, with the exception of intracranial haemorrhage which will have long-term impact on costs and quality of life.
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed	The economic evaluation will present a cost-utility analysis with cost effectiveness expressed in terms of

	in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation should be appropriate for the nature of the condition. Costs will be considered from an NHS and Personal Social Services perspective.	incremental cost per quality-adjusted life year. Given the potential chronic nature of some complications from VTE, the model time horizon will be lifetime. Costs will be considered as defined in the final scope.
Special considerations and other issues	The duration of treatment with dabigatran etexilate is different for patients undergoing elective hip or knee surgery. Therefore the analysis of cost effectiveness will have to be done separately for the two conditions. There may also be subgroups of patients who can be identified as being at higher or lower risk of DVT, for example as a result of co-morbidities.	Separate analyses will be presented for total hip replacement and total knee replacement. The base case of the economic evaluation will focus on the entire population defined by the proposed licensed indication. However, efficacy data for patient subgroups will be presented and, should these results justify it, scenario analysis of the economic evaluation can be performed.

Section B

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- ***The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.***
- ***The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.***
- ***The indication(s) and any restriction(s).***
- ***The recommended course of treatment.***
- ***The main comparator(s).***
- ***Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.***
- ***The main clinical results of the randomised trials and any relevant non RCTs.***
- ***In relation to the economic evaluation, details of:***
  - ***the type of economic evaluation and justification for the approach used***
  - ***the pivotal assumptions underlying the model/analysis***
  - ***the incremental ratios from the evaluation.***

Product specifics (Section 1)

Dabigatran etexilate (Pradaxa®) is an oral direct thrombin inhibitor, a type of anticoagulant. Positive opinion from the CHMP for dabigatran etexilate (DBG) was received on January 24th 2008 for the indication detailed in this submission. Marketing authorisation is expected approximately 90 days from this date.

DBG will be available in capsules, in the following dosages and pack sizes and at the noted NHS list prices:

PRADAXA 75 mg, hard capsules:
- Pack of 10 capsules, list price = £21.00
- Pack of 60 capsules, list price = £126.00

PRADAXA 110 mg, hard capsules:
- Pack of 10 capsules, list price = £21.00
- Pack of 60 capsules, list price = £126.00

Indication and dosing regimen (Section 1)

DBG will initially be indicated for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. This is the indication considered in this submission.

The proposed course of treatment varies in terms of duration between elective total hip replacement (THR) and elective total knee replacement (TKR) in line with national [1] and international clinical guidelines [2].

THR: 220 mg once daily, initiated within 1–4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

TKR: 220 mg once daily, initiated orally within 1–4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

Special patient populations:

Patients with severe renal impairment (creatinine clearance < 30 ml/min) are contraindicated. Treatment in children and adolescents (les than 18 years) is not recommended.

Patients with moderate renal impairment (creatinine clearance 30-50 ml/min), elderly patients over 75 years and those receiving concomitant amiodarone should receive a reduced dose of 150mg once daily.

Comparsions and evidence base

The economic evaluation compares DBG with the two most appropriate alternatives for the NHS in England and Wales: low molecular weight heparin (LMWH) and fondaparinux (Section 6.2.3).

Pharmacological alternatives can be used in addition to mechanical methods of thromboprophylaxis and need not affect their usage. Therefore it would be incorrect to compare DBG directly to mechanical thromboprophylaxis in this economic evaluation. Approximately 60% of all THR and TKR patients receive LMWH therapy, which is recommended by the consensus of international clinical guidelines (see Section 4.6). Therefore it is clear that LMWH is an appropriate comparison.

Moreover, the recent NICE clinical guidelines [1] recommend the use of fondaparinux in this indication as a potential alternative to LMWH. The SMC have also approved fondaparinux for use in this indication in Scotland. Therefore this comparison should also be presented. Nevertheless, it is extremely important to note that that the use of fondaparinux in this indication is negligible (approximately 1% of total pharmacological thromboprophylaxis). Therefore the relevance of this comparison to decision makers (based on current practice) may be questioned.

Despite accounting for approximately 25% of current practice, aspirin is now explicitly not recommended by clinical guidelines, including those recently published by NICE [1], (see Section 4.6) on the grounds of inferior efficacy. Aspirin is an outdated modality in this indication and therefore this comparison will not be presented.

No other pharmacological agents are recommended by clinical guidelines in this indication, nor is there any evidence that any other pharmacological alternative has a significant proportion of use in current practice. Therefore no further comparisons with other pharmacological agents will be presented in the economic evaluation.

The comparison with LMWH is based on the evidence from the two pivotal head-to-head DBG phase-III clinical trials (RE-NOVATE in THR and RE-MODEL in TKR). As discussed in Section 6.2.7.6 and throughout the submission, the specific differences in trial design, dosing and treatment duration make the supporting RE-MOBILIZE study inappropriate for inclusion in this economic evlautaion.

There are no head-to-head trials comparing DBG with fondaparinux. Therefore this comparison is based on the relative efficacy and safety as derived from a mixed treatment comparison meta-analysis (detailed in Section 5.6).

Clinical evidence (Section 5.4)

In the pivotal RE-NOVATE and RE-MODEL trials versus enoxaparin 40 mg o.d., both DBG doses demonstrated non-inferiority to enoxaparin in terms of the primary endpoint (total VTE and all-cause mortality), with confidence intervals falling within pre-defined non-inferiority margins (**Table 1**). In the supporting 'North American' RE-MOBILIZE trial, the rate of VTE and all-cause mortality in the enoxaparin group was uncharacteristically low, resulting in mean outcomes favouring the comparator. In this trial different enoxaparin dosage, timing of first dose (30mg enoxaparin b.i.d initiated post-operatively and DBG initiated 6-12 hours post-operatively) and duration of prophylaxis were studied compared to RE-NOVATE and RE-MODEL.

Table 1 Summary of the primary endpoint results

	DBG 220mg	DBG 150mg	Enoxaparin
RE-NOVATE			
Total VTE and all-cause mortality (%)	6.0	8.6	6.7
Risk difference *versus* enoxaparin	0.9	1.28	
95% CI (%)	(0.63, 1.29)	(0.93, 1.78)	
RE-MODEL			
Total VTE and all-cause mortality (%)	36.4	40.5	37.7
Risk difference *versus* enoxaparin	0.97	1.07	
95% CI (%)	(0.82, 1.13)	(0.92, 1.25)	
RE-MOBILIZE			
Total VTE and all-cause mortality (%)	31.1	33.7	25.3
Risk difference *versus* enoxaparin	1.23	1.33	
95% CI (%)	(1.03, 1.47)	(1.12, 1.58)	

CI, confidence interval; DBG, dabigatran etexilate; VTE, venous thromboembolism.

Analysis of the individual VTE components showed that asymptomatic DVT accounted for the vast majority of the primary efficacy endpoint in all three trials. Symptomatic DVT rates were low in all three trials (less than 2% in all treatment groups).

The rates of major bleeding, and of major and clinically relevant bleeding combined, were comparable between the treatment groups in all three trials (**Table 2**). The majority of major bleeding events in the three trials occurred at the surgical site.

Table 2 Summary of bleeding endpoint results

	DBG 220mg	DBG 150mg	Enoxaparin
RE-NOVATE			
Major bleeding	2.0%	1.3%	1.6%
Major bleeding plus clinically-relevant bleeding	6.2%	6.0%	5.0%
Absolute difference *versus* enoxaparin (%)	1.2	1.0	
95% CI	(-0.7, 3.1)	(-0.9, 2.9)	
RE-MODEL			
Major bleeding	1.5%	1.3%	1.3%
Major bleeding plus clinically-relevant bleeding	7.4%	8.1%	6.6%
Absolute difference *versus* enoxaparin (%)	0.7	1.5	
95% CI	(-2.0, 3.4)	(-1.3, 4.2)	
RE-MOBILIZE			
Major bleeding	0.6%	0.6%	1.4%
Major bleeding plus clinically-relevant bleeding	3.3%	3.1%	3.8%
Absolute difference *versus* enoxaparin (%)	-0.5	-0.7	
95% CI	(-2.3, 1.2)	(-2.4, 1.0)	

CI, confidence interval; DBG, dabigatran etexilate.

In all three trials, the incidence of hepatotoxicity in the DBG groups is similar to that seen with enoxaparin. There were no cases that met the criteria for severe hepatotoxicity that did

not have a clear cause. Liver Function Test (LFT) monitoring during DBG treatment is not necessary.

Economic evaluation (Section 6)

The economic evaluation is a cost-utility analysis that compares DBG with both LMWH and fondaparinux. A distinct two-stage approach to modelling this clinical pathway is adopted, with a combination of a decision tree and a Markov model. Events in the peri-operative acute phase (where the patient is at greatest risk of VTE and adverse events) were modelled within the decision tree. The health status of patients as they exit the decision tree is then used to inform the longer term (chronic phase) events within the Markov model. From this point, a Markov model is most appropriate to track the (less frequent) potential changes in health status over patients' remaining lifetime.

As described in Section 6.1, a systematic review of published economic evaluations included compilation and critical appraisal of previous modelling approaches in this indication. From the reviews presented, the model reported by Botteman [3] stands out as the most comprehensive model structure with a life-time analysis horizon. With one or two exceptions, as described in Section 6.2.6, it was determined that the model for this economic evaluation should be based on the same principles.

Key assumptions of the economic evaluation:

- All LMWHs are bioequivalent (enoxaparin is representative of the class)
- In the indirect comparison, the calculation of relative risks assumes that treatment effect is independent of surgery type
- The probability of recurrent VTE and PTS is the same for patients with treated and untreated VTE events
- Patients who suffer an intracranial haemorrhage and survive are permanently disabled
- Patients unable or unwilling to self-administer LMWH or fondaparinux at home require daily community nurse visits to ensure compliance
- Patients able and willing to self-administer LMWH or fondaparinux at home require training in the correct method of self-administration
- The length of stay of the primary hospitalisation is not affected by the choice of pharmacological prophylaxis irrespective of differences in the time of first dose (i.e. enoxaparin is initiated pre-operatively thereby requiring patients to be admitted on the day prior to surgery; DBG is initiated post-operatively)

In the direct comparison, the economic evaluation estimates that on average DBG is associated with lower costs and greater health benefits over the lifetime of patients compared to LMWH in both THR and TKR. Therefore DBG dominates LMWH in all analyses. Results of the probabilistic sensitivity analysis (PSA) indicate that DBG has a 99% and 82% probability of cost-effectiveness in THR and TKR respectively.

In the indirect comparison, the results are more complex and require careful interpretation. In THR, DBG 220mg is estimated to be associated with lower costs and lower health benefits compared to fondaparinux. In TKR, the economic evaluation estimates that fondaparinux dominates DBG. The PSA indicates that DBG has a 40% and 0% probability of cost-effectiveness in THR and TKR respectively. In both cases, the results of the analysis are extremely sensitive to the relative risk of VTE for fondaparinux compared to nil (Section 6.3.3), which in the case of THR is almost certainly artificially low when the source of the estimate is critically appraised (Section 6.2.7.1).

These are the important facts to note:

- DBG and LMWH have similar efficacy and safety profiles
- The acquisition costs of DBG and LMWH are the same, fondaparinux has a price premium of 59%
- Inpatient administration and the training of patients in self-administration of LMWH and fondaparinux consumes resources that can be eliminated with DBG treatment
- Some LMWH and fondaparinux patients will be unwilling or unable to self-administer their medication at home and require expensive, daily assistance to ensure compliance
- An oral medication is likely to be preferred to subcutaneous injection by the vast majority of patients, resulting in improved compliance
- The introduction of an oral medication with proven efficacy may encourage some clinicians to prescribe extended thromboprophylaxis who may otherwise have been reticent due to issues with LMWH and fondaparinux administration
- LMWH and fondaparinux can be associated with other costs not considered in the economic evaluation, e.g. platelet monitoring, needlestick injuries, sharps disposal. These costs are eliminated with DBG treatment
- Fondaparinux accounts for only approximately 1% of thromboprophylaxis in this indication in England and Wales, therefore the relevance of this comparison may be questioned

- Despite consistent demonstration of cost-effectiveness versus LMWH, fondaparinux is not advocated as the treatment of choice by any clinical guideline (including NICE) indicating considerable uncertainty, particularly regarding safety (i.e. bleeding)

DBG can be confidently regarded as an innovation in this indication and cost-effective when compared to the standard of care in England and Wales.

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

VTE disease characteristics

Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is characterised by the formation of blood clots (thrombi) or emboli (broken off clots or other material such as fat or air) that block the blood vessels preventing blood flow, which may have serious consequences depending on the vessel involved and how extensive the blockage is.

In cases of DVT, the veins of the legs are blocked by thrombi, often causing pain and swelling of the affected leg. DVT is often described according to the location of the thrombus formation:

- distal – furthest away from the heart i.e. below the knee (in the calf veins)
- proximal – closer to the heart i.e. above the knee (in the femoral veins of the thigh)

The thrombi that form in the legs can grow. Fragments may break off and travel to the pulmonary artery in the lungs and cause PE with symptoms such as shortness of breath and oedema. The risk of PE is greater with DVT in the large proximal veins than with distal DVT.

Total hip or knee replacement surgery is a strong risk factor for VTE, with about half of patients developing asymptomatic or symptomatic VTE without prophylaxis. For this reason patients are generally encouraged to become mobile as early as possible following surgery to reduce the risk of VTE.

Post-thrombotic syndrome (PTS) is a severe complication associated with VTE. PTS typically occurs following DVT and can be associated with symptoms that limit patients'

mobility and reduce quality of life. The most serious sign of PTS is the development of venous ulceration, which is slow to heal and painful for patients.

Recurrence of DVT is another common complication of VTE. The frequency of recurrent DVT has been evaluated in several studies lasting up to 15 years after the initial episode (**Table 3**). They show that in a heterogeneous population of patients who have experienced an acute DVT, up to 30% will experience one or more recurrences over 10–15 years.

Table 3 Rates of recurrent DVT

Reference	Country	Population	Rate of recurrent VTE	Duration of follow up
Bergqvist 1997 [4]	Sweden	257 patients with DVT and matched controls	74 episodes in 257 patients	15 years
Janssen 1997 [5]	The Netherlands	81 patients with acute DVT of the leg	11.1% recurrent DVT (9/81 patients)	7–13 years
Schulman 2006 [6]	Sweden	897 patients with previous DVT treated with warfarin for 6 weeks or 6 months	29.1% recurrence	10 years

Mortality due to VTE is significant. It is estimated that the number of deaths from VTE in the UK is five times greater than the combined total number of deaths from breast cancer, AIDS and road traffic accidents [7].

Few controlled studies have been identified that study the long-term mortality rates of patients who have experienced an episode of VTE. Long-term follow up of patients who have experienced an episode of VTE (usually acute DVT) have shown that there is a high mortality rate over the subsequent 10–15 years (**Table 4**).

PE has a high mortality rate with 13% proving fatal in elderly patients 1 month after onset [8] and 17.5% within 3 months [9].

Table 4 Comparison of mortality rates for patients with DVT and the general population

Reference	Country	Population	Survival rate	Duration of follow up
Eichlisberger 1994 [10]	Switzerland	223 consecutive patients with DVT	Stage I 18% and stage 4 33%	13 years
Murray 1996 [11]	UK (systematic review)	Data on 93,000 patients in 181 papers	Fatal PE after THR 0.12% without prophylaxis	Not specified
Bergqvist 1997 [4]	Sweden	257 patients with DVT and matched controls	35% survival vs 57% for controls	15 years
Schulman 2006 [6]	Sweden	897 patients treated with previous DVT treated with warfarin for 6 weeks or 6 months	28.5% patients died	10 years

Several studies have shown that patients with VTE have impaired health-related quality of life (QoL) compared with population norms [12-15]. The QoL of VTE patients is reduced on all components of the SF-36 scale compared with population norms [15]. Likewise, physical component score QoL in patients with DVT at baseline and 1 month is lower than for patients with chronic disease such as chronic lung disease and arthritis and similar to patients with angina [13].

Thromboprophylaxis in major orthopaedic surgery

Prevention of VTE (thromboprophylaxis) in orthopaedic surgery may be achieved using both mechanical and pharmacological methods, either alone or in combination.

Mechanical methods work by maintaining blood flow, and include graduated compression stockings (GCS), intermittent pneumatic compression (IPC) and venous foot pumps (VFP).

A number of medications are used for pharmacological prophylaxis of VTE in major orthopaedic surgery, and may be grouped according to class:

- unfractionated heparin (UFH)
- low-molecular-weight heparins (LMWH)
- vitamin K antagonists such as warfarin (VKAs)
- fondaparinux
- aspirin and other forms of chemical prophylaxis

Thromboprophylaxis is typically administered during the hospitalisation for the index surgery and may be initiated either pre or post-operatively depending on the modality employed. Patients may also continue with thromboprophylaxis post-discharge up to 5 weeks post-surgery.

4.2 What was the rationale for the development of the new technology?

In this indication, there is a clear unmet need for a thromboprophylactic option that is at least as efficacious and safe as current gold standard options, has no requirement for monitoring and has a convenient formulation and dosing regimen suitable thereby making it suitable for extended prophylaxis after discharge from hospital. Dabigatran etexilate has been developed to meet this unmet need.

4.3 What is the principal mechanism of action of the technology?

Dabigatran etexilate is an oral pro-drug of the active direct thrombin inhibitor dabigatran. Dabigatran is a low molecular weight, reversible thrombin inhibitor, which binds to thrombin with a high affinity and specificity. The pro-drug has no anticoagulant activity. In-vivo and ex-vivo animal studies have demonstrated antithrombotic efficacy and anticoagulant activity in numerous models. An ex-vivo anticoagulant effect of both dabigatran after intravenous administration and dabigatran etexilate after oral administration has been shown by a dose- and time-related prolongation of activated partial thromboplastin time (aPTT). The antithrombotic efficacy of dabigatran and dabigatran etexilate were investigated in different in-vivo models of venous and arterial thrombosis. The compound effectively inhibited clot formation in two models of venous thrombosis.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Dabigatran etexilate can directly replace the other methods of pharmacological prophylaxis currently used in this indication. It has proven efficacy and safety, and unlike current alternatives requires no anticoagulation monitoring, can be taken by the patient without training or assistance from a healthcare professional and facilitates the extended prophylaxis as recommended by NICE [1] and international clinical guidelines [2].

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

This is considerable disparity between the current consensus from international clinical guidelines (see next subsection) and how thromboprophylaxis is currently practiced in England and Wales. The trade-off between efficacy (preventing VTE) and safety (avoiding bleeding complications) is a source of much debate amongst clinicians, leading to patients receiving sub-optimal prophylaxis in many cases.

Data reported in the latest annual report from the National Joint Registry [16] illustrates this trend (**Table 5**).

Table 5 Pharmacological thromboprophylaxis uptake (2006/7)

Medication	Proportion usage in THR	Proportion usage in TKR
Aspirin	25%	26%
Low dose heparin	2%	2%
Low molecular weight heparin	60%	57%
Pentasaccharide	1%	1%
Warfarin	2%	1%
Other chemical	2%	1%

Source: Adapted from the National Joint Registry 4th Annual Report [16]

The persistent and significant use of an inferior treatment option (aspirin) as the sole thromboprophylactic agent in patients at such high risk of VTE clearly demonstrates the controversy.

Moreover, the data above do not account for duration of prophylaxis. The NICE Clinical Guideline [1], for example, recommended that the vast majority of THR patients should receive LMWH or fondaparinux for 4 weeks post-surgery. Of the approximately 60% of THR patients receiving optimal therapy (LMWH or fondaparinux), it is likely that many are not prescribed the extended regimen. All the LMWH alternatives and fondaparinux are administered by subcutaneous injection and any extended regimen is reliant on the patient being able and willing to self-administer, or, assistance with administration. Where patients are unable or unwilling to self-administer, it is plausible that clinicians, many of whom are sceptical of the importance of VTE prevention, will simply decide against the extended regimen and the expensive daily community nurse visits that will be required to ensure compliance.

4.6 Provide details of any relevant guidelines or protocols.

Table 6 summarises the recommendations of the relevant current clinical guidelines relating to prevention of VTE in major orthopaedic surgery.

With the exception of SIGN (which has proposed a review of its guideline), all the various guidelines and consensus statements recommend the use of LMWH or fondaparinux as preferred methods of thromboprophylaxis, with aspirin specifically not recommended.

Table 6 Recommendations from national and international guidelines

Guideline	Recommendation	Grade of recommendation
Scottish Intercollegiate Guidelines Network (SIGN). Prophylaxis of venous thromboembolism: a national clinical guideline (2002) [17]	*Total hip or knee replacement* – the following can be considered: • Mechanical prophylaxis (GCS±IPC or foot pumps) • Aspirin • UFH or LMWH for 7 to 15 days after surgery, extended to 4 to 5 weeks in very high-risk patients • Warfarin (INR target, 2.0 to 3.0)	 A A A A
SIGN proposed review 2005 [18]	*Based on the review of new evidence, the following revisions were recommended:* • More emphasis on LMWH and discussion of role of fondaparinux; aspirin should not be recommended • Orthopaedics needs revision due to ximelagatran and fondaparinux	
Prevention of venous thromboembolism: The seventh ACCP conference on antithrombotic and thrombolytic therapy (2004) [2]	*Total hip replacement* – one of the following: • LMWH (at the usual high-risk dose, started 12 h before surgery (US practice) or 12 to 24 h after surgery (EU practice), or 4 to 6 h after surgery at half the usual high-risk dose, increased to the usual high-risk dose the following day) • Fondaparinux (2.5mg started 6 to 8 h after surgery) • Dose-adjusted VKA started preoperatively or the evening after surgery (INR target, 2.5; INR range, 2.0 to 3.0) *Total knee replacement* – one of the following: • LMWH (at the usual high-risk dose) • Fondaparinux • Dose-adjusted VKA (INR target, 2.5; INR range, 2.0 to 3.0) • The optimal use of IPC is an alternative to anticoagulant prophylaxis	 1A 1A 1A 1A 1A 1A 1B
Prevention of venous thromboembolism: international consensus statement (2006) [19]	*Total hip replacement* – one of the following: • LMWH or fondaparinux (preferred methods) • Oral anticoagulant therapy • IPC or FIT combined with GCS (equivalent alternative to LMWH where there is concern about bleeding) *Total knee replacement:* • LMWH; or warfarin (although the latter is less effective) • Fondaparinux • IPC or FIT plus GCS (alternative options, but more studies needed)	 A A A A B B

Guideline	Recommendation	Grade of recommendation
National Institute for Health and Clinical Excellence (NICE). Reducing the risk of VTE in inpatients undergoing surgery (2007) [1]	• All inpatients having surgery should be offered thigh-length graduated compression/anti-embolism stockings from the time of admission to hospital unless contraindicated • Intermittent pneumatic compression or foot impulse devices may be used as alternatives or in addition to graduated compression/antiembolism stockings while surgical patients are in hospital • Patients having elective orthopaedic surgery should be offered mechanical prophylaxis and either LMWH or fondaparinux • Patients having hip replacement surgery with one or more risk factors for VTE should have their LMWH or fondaparinux therapy continued for 4 weeks after surgery	Not specified
British Orthopaedic Association [20] [21]	*Total hip replacement (Guide to Good Practice, 1999 revised 2006)* • Acknowledges strong evidence for the effectiveness of low dose heparin, LMWH or warfarin • Advises that the most effective thromboprophylaxis should be used • This may mean a combination of mechanical and chemical methods for several weeks after surgery. *Total knee replacement (Guide to Good Practice 1999)* • Prefers mechanical methods and early mobilisation over chemical thromboprophylaxis	Not specified
British Committee for Standards in Haematology guidelines on the use and monitoring of heparin (2006) [22]	• Patients undergoing major elective orthopaedic surgery should be considered for LMWH or fondaparinux at recommended prophylactic dose for at least 7-10 days • Considers the use of aspirin to be suboptimal therapy. Comments that the use of aspirin is based on the PEP study, and that this has been criticised, with strong recommendations made against the use of aspirin	A

LMWH = low-molecular-weight heparin; VKA = vitamin K antagonist; INR = international normalised ratio; IPC = intermittent pneumatic compression; FIT = foot impulse technology; GCS = graduated elastic compression stockings; UFH = unfractionated heparin; ACCP = American College of Chest Physicians

SIGN grades of recommendation:

- Grade A = based on at least one meta-analysis, systematic review of RCTs or body of evidence consisting of high-quality studies and demonstrating consistency of results

ACCP grades of recommendation:

- Grade 1 = strong recommendation, indicating that benefits do, or do not, outweigh risks, burden and costs
- Grade A = based on randomised clinical trials (RCTs) with consistent results
- Grade B = based on RCTs with inconsistent results, or with major methodological weaknesses

ICS grades of recommendation:

- Grade A = based on Level 1 evidence from randomised controlled trials with consistent results (e.g. in systematic reviews), which are directly applicable to the target population
- Grade B = based on Level 1 evidence from a single high-quality randomised controlled trial, or trials with less consistent results, limited power or other methodological problems

5 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUORUM statement checklist (www.consort-statement.org/QUOROM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. Where no head–to-head RCTs are available, consideration will be given to indirect comparisons, subject to careful and fully described analysis and interpretation.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data.

5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Literature searches were conducted in a range of commercial databases and in the internal company database. The search strategy was designed to identify documents providing relevant clinical data on the use of dabigatran etexilate (DBG), at the dose proposed for use in the UK, for the prevention of venous thromboembolism in patients undergoing total hip or knee replacement, compared to other treatments. It was designed to identify not only RCTs but also any other potentially useful studies of various designs.

Two reviewers screened all titles and abstracts. Full copies of any papers or abstracts that were considered potentially relevant by either reviewer were obtained. The relevance of each study was assessed according to the inclusion and exclusion criteria as given below (section 5.2.2).

The results of the searches were combined, and duplicates removed. This gave a total of 19 studies. The abstracts or papers were screened to remove those which did not contribute information potentially relevant to the decision problem.

From those 19 studies, a further 15 were removed for the following reasons:

- Comment letters/editorials/reviews with no original data (3)
- Non-RCTs with clinical data potentially relevant to the decision problem (0)
- Non-RCTs without clinical data (e.g. pharmacokinetic or dose-ranging studies) (5)
- Abstracts of conference presentations of trial results subsequently published in full (7)

This left 4 RCTs, as listed in section 5.2.

5.2 Study selection

5.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The four RCTs identified were as follows:

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, Niek van Dijk C, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Bueller HR, RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 370 (9591), 949 - 956 (2007) [23]

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, Dijk CN van, Frostick SP, Kalebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Buller HR, RE-MODEL Study Group. Oral Dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 5 (11), 2178 - 2185 (2007) [24]

Friedman RJ, Caprini JA, Comp PC, Davidson BL, Francis CW, Ginsberg J, Huo M, Lieberman J, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee J. Dabigatran etexilate versus enoxaparin in preventing venous thromboembolism following total knee arthroplasty. 21st Cong of the International Society on Thrombosis and Haemostasis (ISTH), Geneva, 6 - 12 Jul 2007. *J Thromb Haemost* 5 (Suppl 2),, Abstr O-W-051 (2007) [25]

Eriksson BI, Dahl OE, Buller HR, Hettiarachchi R, Rosencher N, Bravo ML, Ahnfelt L, Piovella F, Stangier J, Kalebo P, Reilly P, BISTRO II Study Group. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost*. 3(1):103-11, 2005 Jan [26]

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Inclusion criteria:

- Randomised controlled trials (RCTs) evaluating DBG in the prevention of thromboembolic events after total hip or knee replacement
- Observational studies evaluating DBG in the prevention of thromboembolic events after total hip or knee replacement

Exclusion:

- Reviews
- Comments letters/editorials containing no original data
- Abstracts presenting results of studies subsequently published in full
- Studies not using the dose of DBG proposed for use in the UK for this indication
- Studies which did not have clinical efficacy/ safety as the primary objective

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Of the four identified RCTs, one was excluded based on the above criteria as irrelevant to the decision problem. The BISTRO II trial [26] was a phase-II clinical trial with the primary objective of examining dose-response, and did not examine the final dosing regimens for DBG that will be used in the UK. For information, the results of BISTRO II are presented in Appendix 9.5.

The remaining three studies met all inclusion and exclusion criteria, and are therefore included as relevant RCTs for this submission.

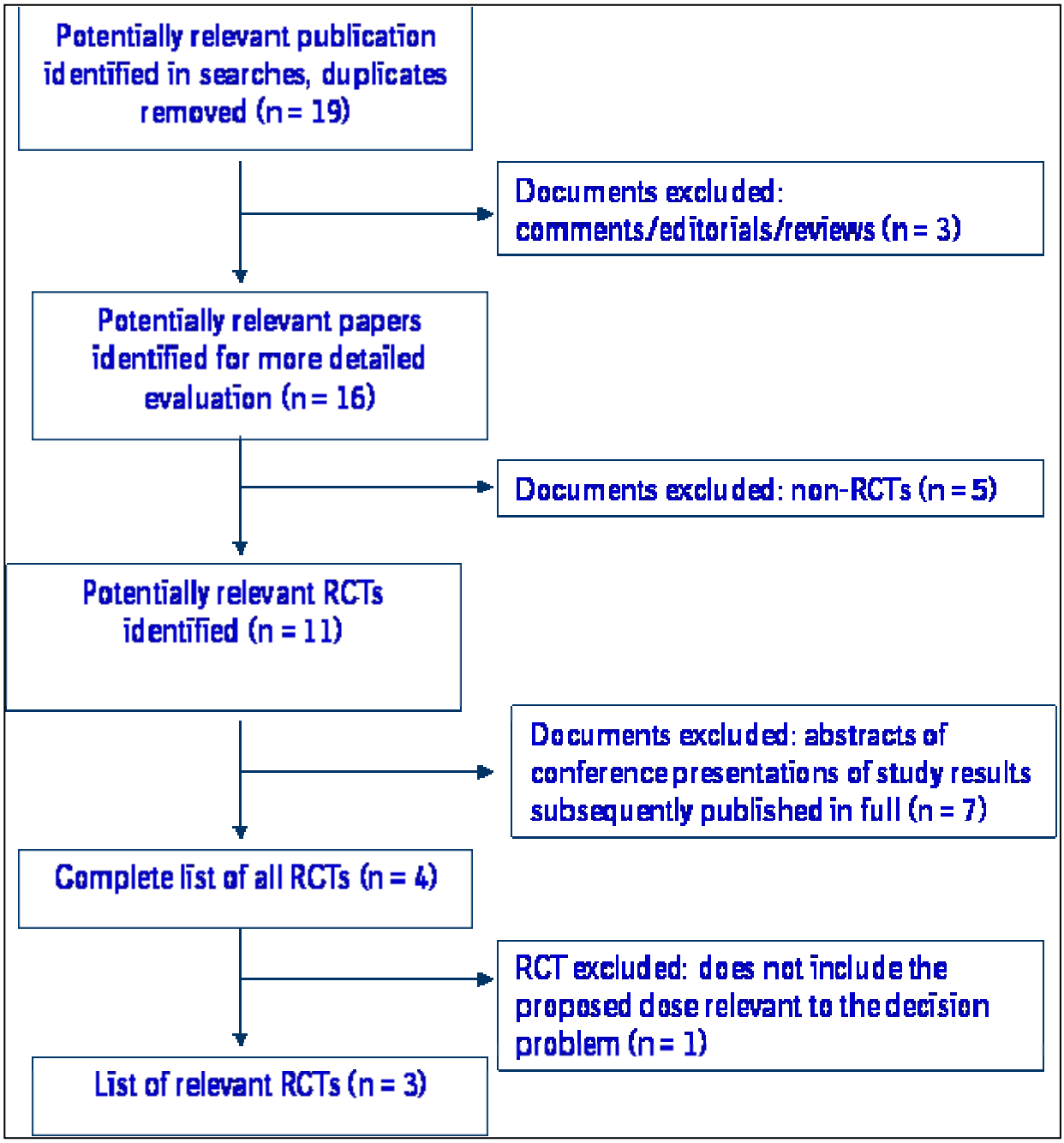
Eriksson BI, Dahl OE, Rosencher N, Kurth AA, Niek van Dijk C, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Bueller HR, RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 370 (9591), 949 - 956 (2007) [23]

Eriksson BI, Dahl OE, Rosencher N, Kurth AA, Dijk CN van, Frostick SP, Kalebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Buller HR, RE-MODEL Study Group. Oral Dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 5 (11), 2178 - 2185 (2007) [24]

Friedman RJ, Caprini JA, Comp PC, Davidson BL, Francis CW, Ginsberg J, Huo M, Lieberman J, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee J. Dabigatran etexilate versus enoxaparin in preventing venous thromboembolism following total knee arthroplasty. 21st Cong of the International Society on Thrombosis and Haemostasis (ISTH), Geneva, 6 - 12 Jul 2007. *J Thromb Haemost* 5 (Suppl 2),, Abstr O-W-051 (2007) [25]

A full QUORUM flow diagram of all search results, exclusions and reasons for exclusion is presented in **Figure 1**.

Figure 1 QUORUM flow diagram



5.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

None were identified.

5.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

RECENTLY COMPLETED STUDY (1160.50) [27]

A further trial, not included in the regulatory submission to the EMEA, has recently been completed with the specific primary objective of fulfilling the requirements for registration in Japan. At the time of writing, the results of this trial are preliminary, therefore the details of this study are presented here separate from the main evidence submission. Whilst the patient population is dissimilar to that in England and Wales (in terms of ethnicity), there is data to suggest that there is no clinically relevant difference in pharmacokinetics and pharmacodynamics after administration of DBG in Japanese and Caucasian patients [28].

Trial 1160.50 is a parallel group, double-blind randomised phase-II trial, comparing DBG to placebo in the prevention of VTE in total knee placement patients, which provides additional evidence on the efficacy and safety of DBG in this indication.

It must be clearly pointed out that the results of this study are preliminary and all details are provided strictly commercial-in-confidence.

There were four study groups:

1. DBG 110mg o.d
2. DBG 150mg o.d
3. DBG 220mg o.d
4. Placebo

Study inclusion criteria:

- Patients scheduled to undergo a primary, unilateral elective total knee replacement
- Male or female 20 years of age or older
- Weight at least 40kg
- Written informed consent

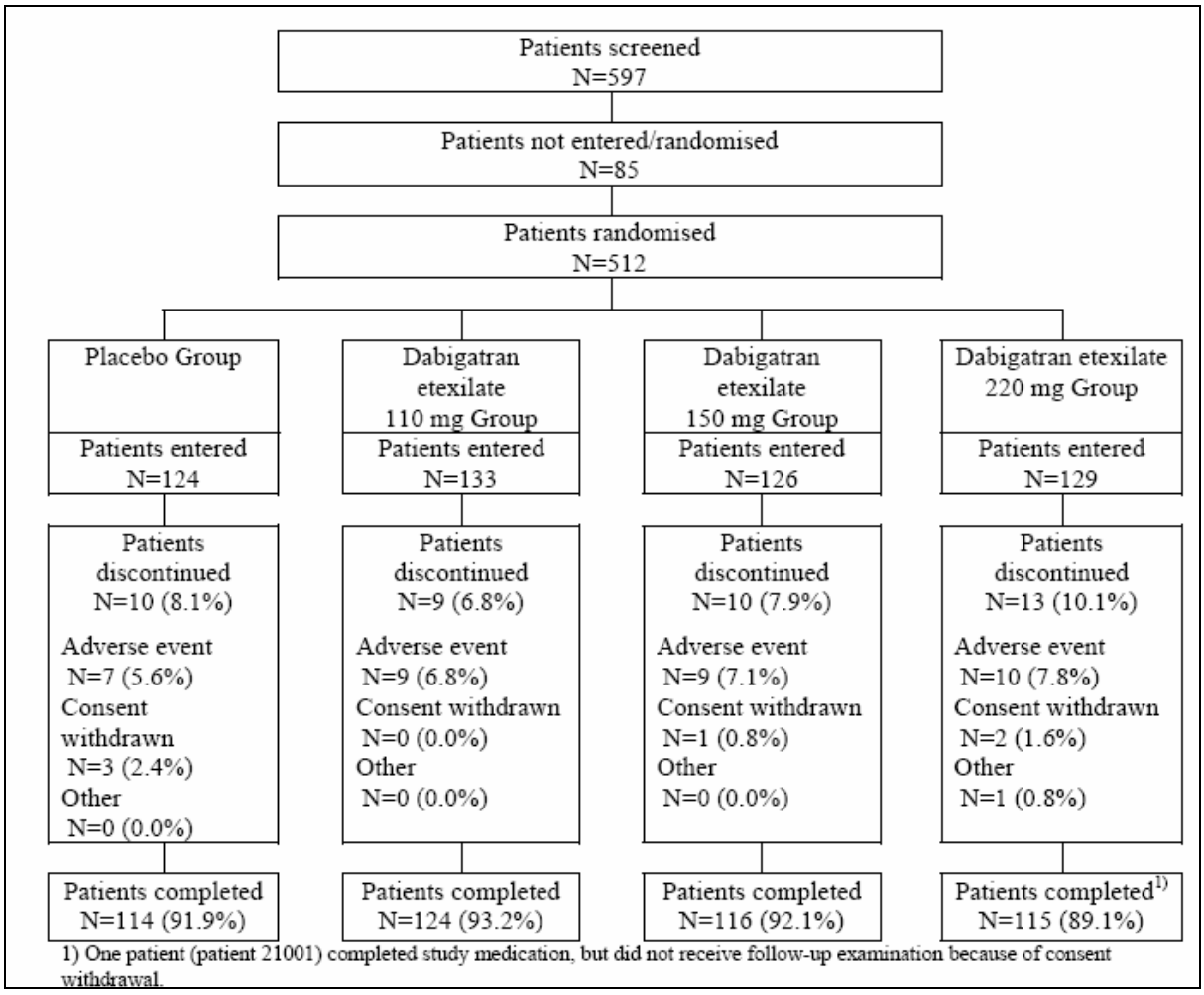
Exclusion criteria:

- History of bleeding diathesis
- Constitutional or acquired coagulation disorders that in the investigator's judgement puts the patient at excessive risk for bleeding
- Major surgery or trauma (e.g. hip fracture) within the last 3 months
- Recent unstable cardiovascular disease, such as uncontrolled hypertensive at time of enrolment (investigator's judgement) or history of myocardial infarction within last 3 months
- Any history of haemorrhagic stroke or any of the following intracranial pathologies: bleeding, neoplasm, AV malformation or aneurysm

- Clinically relevant bleeding (i.e. gastrointestinal, pulmonary, intraocular or urogenital bleeding) within last 6 months
- Gastric or duodenal ulcer within last 6 months
- History of VTE or pre-existing condition requiring anti coagulation therapy
- Elevated AST, ALT, >2x upper limit of normal range based on central lab results or any history of clinically relevant liver disease, such as hepatitis or cirrhosis
- Patients with a history of clinically significant renal diseases or with a creatinine value exceeding upper limit of normal range based on central lab results

The goal of this study was to evaluate the comparative efficacy and safety of three different doses of DBG, compared to placebo, and to evaluate dose response. Treatment duration was 11-14 days and 512 patients were randomised. Unlike the phase-III trials described above, the first dose of DBG was as full dose and was administered as early as possible on the day *after* surgery. Similar efficacy endpoints to the trials outlined in the previous sub-section were recorded, with the primary endpoint remaining total VTE and all-cause mortality. A hypothesis of superiority to placebo was tested.

Figure 2 Disposition of patients (study 1160.50)



The final analysis set (FAS) comprised 79.5% of all patients randomised, treated, and operated (**Figure 2**). In all the treatment groups, the proportions of patients included in the FAS were similar: 79.7% in the DBG 110 mg group, 82.5% in the DBG 150 mg group, 74.4% in the DBG 220 mg group, and 81.5% in the placebo group. The primary reason for exclusion from the FAS was the lack of an evaluable venogram. In the calculation of the sample size, the expected rate for the rate of exclusion from FAS because of non-evaluable venograms or no objective testing was 20%. Hence, the observed rate (20.3%) was very similar to the expected rate.

The demographic characteristics were similar in all the treatment groups (**Table 7**). The median age was 73.0 years and the proportion of female patients was 83.0%.

Table 7 Baseline characteristics (study 1160.50)

	Placebo	DBG		
		110mg	150mg	220mg
Treated	124	133	126	129
Mean age	71.3	71.3	70.9	72.7
Male (%)	15.3	20.3	16.7	15.5

DBG, dabigatran etexilate

All the DBG groups showed a significantly lower incidence in total VTE and all-cause mortality than the placebo group (**Table 8**). There was a linear relationship between the incidence of the primary endpoint (total VTE and all-cause mortality), and DBG doses and placebo (p<0.0001: Cochran-Armitage test).

Table 8 Primary endpoint (study 1160.50)

	Placebo	DBG		
		110mg	150mg	220mg
FAS	101	106	104	96
Incidence (%)	57 (56.4)	42 (39.6)	34 (32.7)	23 (24.0)
95% CI	46.8-66.1	30.3 - 48.9	23.7 - 41.7	15.4 - 32.5
Risk difference versus placebo	-	-16.8	-23.7	-32.5
95% CI	-	-30.2 - -3.4	-37-0 – -10.5	-45.4 - -19.6
p-value	-	0.0155	0.0006	<0.0001

CI, confidence interval; DBG, dabigatran etexilate; FAS, full analysis set

For the primary efficacy endpoint of a composite total VTE and all-cause mortality, asymptomatic DVTs, which were detected by venography, were most frequently observed. Symptomatic DVTs were experienced by only 6 patients in total (**Table 9**).

Table 9 Individual components of the primary endpoint (study 1160.50)

	Placebo	DBG		
		110mg	150mg	220mg
FAS	101	106	104	96
Incidence (%)	57 (100)	42 (100)	34 (100)	23 (100)
Asymptomatic DVT	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic DVT	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal PE	0	0	0	0
Death (VTE cannot be ruled out)	0	0	0	0
Death not associated with VTE	0	0	0	0
Location of DVT (%)				
Distal	[redacted]	[redacted]	[redacted]	[redacted]
Proximal	[redacted]	[redacted]	[redacted]	[redacted]

DBG, dabigatran etexilate; DVT, deep vein thrombosis; FAS, full analysis set; PE, pulmonary embolism; VTE, venous thromboembolism

It was demonstrated that all three doses of DBG were superior to placebo in preventing VTE with comparable rates of bleeding (see Section 4). DBG 220 mg was shown to be superior to placebo for preventing major VTE and VTE-related mortality as well as proximal DVTs. A dose response relationship was demonstrated as the incidence of VTE decreased linearly with increasing doses of DBG.

The total number of patients in the safety analysis was 512 (i.e. all those randomised). The median exposure was 13 days for all treatment groups and the mean exposure days were similar in all treatment groups ranging from 11.8 to 12.1 days.

Table 10 Treatment exposure (study 1160.50)

	Placebo	DBG		
		110mg	150mg	220mg
Treated	124	133	126	129
Mean exposure (SD) [days]	12.1 (2.7)	12.0 (2.5)	12.0 (2.4)	11.8 (2.9)

DBG, dabigatran etexilate; SD, standard deviation

Table 11 presents a summary of bleeding events reported in the trial. Major bleeding events were experienced by 5 patients during the treatment period: 1 patient in the DBG 110 mg group (at the surgical site), none in the DBG 150 mg group, 3 in the DBG 220 mg group (including 1 event at the surgical site), and 1 in the placebo group. Neither fatal bleeding nor bleeding into a critical organ was reported during this study.

In total, 11 patients experienced major bleeding or clinically-relevant bleeding during the treatment period: 1 patient in the DBG 110 mg group, 1 in the DBG 150 mg group, 5 in the DBG 220 mg group, and 4 in the placebo group. Any bleeding events including minor bleeding events were reported by 13 (9.8%) patients in the DBG 110 mg group, 13 (10.3%) in the DBG 150 mg group, 14 (10.9%) in the DBG 220 mg group, and 10 (8.1%) in the placebo group. No statistically significant differences were noted between each of the DBG groups and the placebo group.

All patients recovered from the major bleeding events and no patient experienced worsening of the symptoms. No deaths were reported in this trial.

Table 11 Summary of bleeding events (study 1160.50)

	Placebo	DBG		
		110mg	150mg	220mg
Treated	124	133	126	129
Patients with MBE (%)	1 (0.8)	1 (0.8)	0	3 (2.3%)
95% CI	0.0 - 4.4	0.0 – 4.1	-	0.5 – 6.6
p-value	-	1.0000	0.4960	0.6223
Patients with MBE or CBE (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]	[redacted]
Patients with MBE or CBE (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	[redacted]	[redacted]
p-value		[redacted]	[redacted]	[redacted]

CI, confidence interval; CBE, clinically-relevant bleeding event; DBG, dabigatran etexilate; FAS, full analysis set; MBE, major bleeding event

During the treatment period, ALT increase of more than 2.0 times the upper limit of normal range was observed in 1 patient in the DBG 110 mg group, 1 in the DBG 150 mg group, none in the DBG 220 mg group, and 2 in the placebo group. AST increase more than 2.0 times the upper limit of normal range was observed in 2 patients in the DBG 110 mg group, none in the DBG 150 mg group, none in the DBG 220 mg group, and 2 in the placebo group. Total bilirubin increase more than 1.5 times the upper limit of normal range was observed in 1 patient in the DBG 110 mg group, none in the DBG 150 mg group, 1 in the DBG 220 mg group, and 1 in the placebo group.

No differences were noted between the treatment groups in the number of patients who experienced ALT or AST increase 2.0 times the upper limit of normal range. No patients experienced abnormal increases of both liver enzyme and total bilirubin. All the safety results are comparable to those in RE-NOVATE, RE-MODEL AND RE-MOBILIZE:

5.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

5.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

Trial design

The three phase-III trials identified above were conducted to support the regulatory submissions for DBG. In the European regulatory submission, RE-NOVATE [23] and RE-

MODEL [24] were presented as pivotal trials; RE-MOBILIZE [25] was positioned as a supporting study as it was undertaken in North America and included elements that reflect clinical practice specific to this region.

These three trials were designed to be as similar as possible to each other, and the dose-finding study BISTRO II [26], in order to enable pooling of results. However, the designs could not be identical due to the different treatment duration for patients following THR than following TKR. Consistent with this, the treatment duration in the RE-NOVATE study in THR was 28 to 35 days, while the RE-MODEL and RE-MOBILIZE knee studies had treatment durations of 6–10 days and 12-15 days, respectively.

Furthermore, standard treatment protocols in the North American setting are somewhat different to those in Europe and the rest of the world. In Europe, dosing of enoxaparin 40 mg o.d. starts in the evening of the day before the surgery, while in North America the protocol is for enoxaparin 30 mg b.i.d., starting 12–24 hours after surgery and only after adequate haemostasis has been established. It has been argued that these differences in dosing (i.e. total daily dose and time to first dose) reflect different perceptions of the risk/benefit ratio, which in Europe is weighted more towards optimising clinical benefit (VTE prevention), and in North America is weighted more towards minimising risk (bleeding). The current American College of Chest Physician (ACCP) guidelines [2] explicitly state that a relatively low value is placed on the prevention of venographic thrombosis and a relatively high value on minimising bleeding complications.

Accordingly, the first dose of DBG was administered 1–4 hours after surgery in Europe/Rest of World (RE-MODEL and RE-NOVATE) and 6–12 hours after surgery in North America (RE-MOBILIZE). The dose of enoxaparin was also adjusted to reflect local treatment practices. **Table 12** summarises key design similarities and differences across the three trials.

Table 12 Overview of the phase-III trials

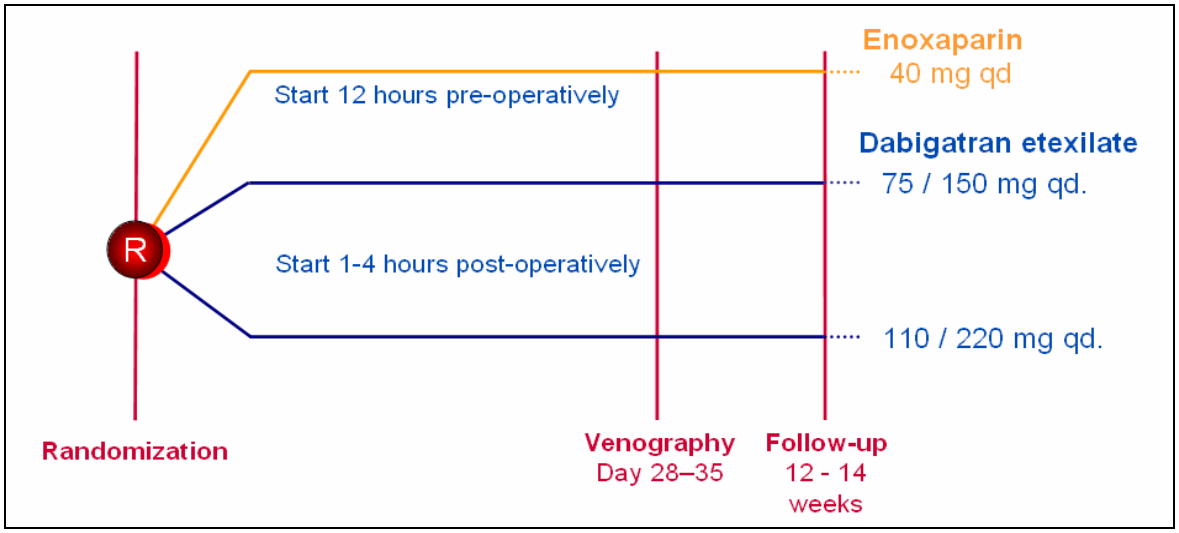
Study	RE-MOBILIZE	RE-MODEL	RE-NOVATE
Indication	VTE prophylaxis		
Target population	knee replacement patients		hip replacement patients
Test therapies	dabigatran etexilate 75mg o.d. day 1; 150 mg o.d. day 2 and on dabigatran etexilate 110mg o.d. day 1; 220 mg o.d. day 2 and on		
1st dosing time/ test therapy	6 to 12 hours post-op	1 to 4 hours post-op	
Reference therapy	Enoxaparin		
Dose regimen/ reference therapy	30mg b.i.d. starting 12-24 hour post-op	40mg o.d. starting the evening of the day before the surgery	
Study location	North America	Europe/Australia/South Africa	
Treatment duration	12-15 days	6-10 days	28-35 days
Primary endpoint	Incidence of Total VTE (proximal & distal DVT based on venogram, objectively confirmed symptomatic DVT & PE) and all-cause mortality		
Objective	To show non-inferiority of dabigatran etexilate to enoxaparin		
Non-inferiority margin	Derived to demonstrate preservation of at least 2/3 the effect of enoxaparin over placebo based on the indirect confidence interval approach		

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

All three trials compared each of two DBG dose regimens, 220mg o.d. and 150mg o.d. with a half dose on day one, to enoxaparin.

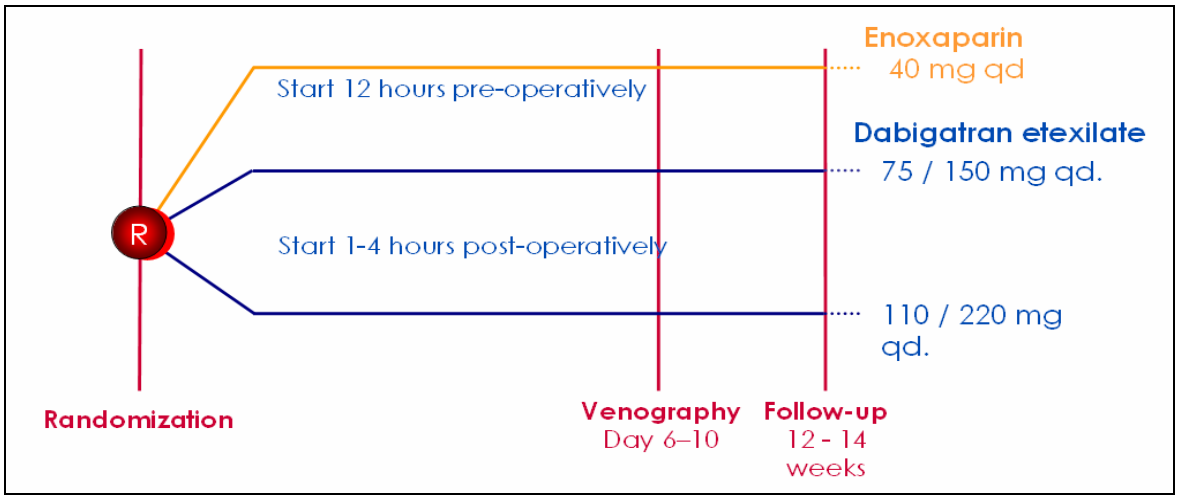
Figure 3 through **Figure 5** summarise the design of each trial individually.

Figure 3 RE-NOVATE study design



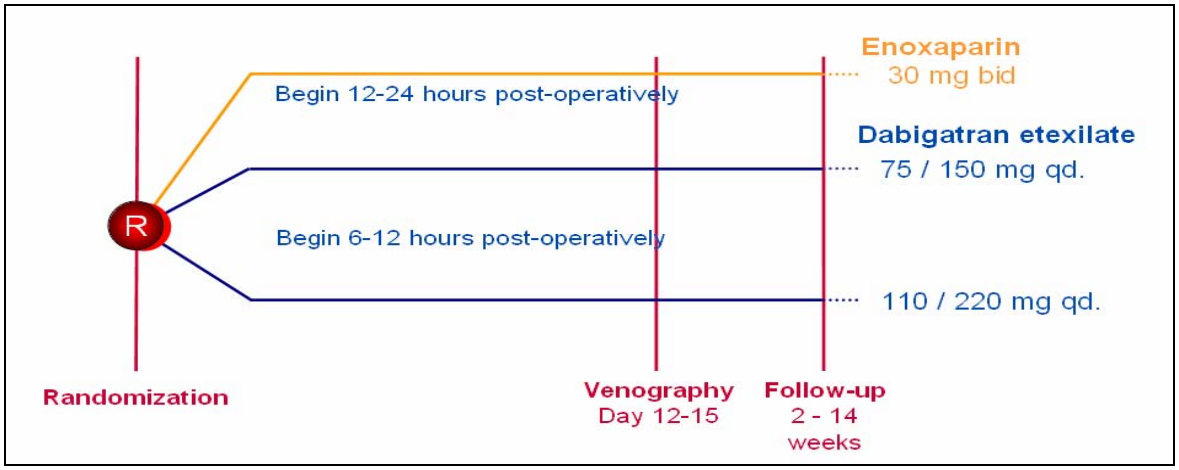
qd, once daily dosing

Figure 4 RE-MODEL study design



qd, once daily dosing

Figure 5 RE-MOBILIZE study design



qd, once daily dosing

Blinding and randomisation

Each phase-III trial had a double blind, double dummy design. Patients were randomly assigned to treatment groups with equal probability of assignment to each treatment. Randomisation was stratified by study centre and performed in blocks to prevent unequal treatment allocation. The randomisation schedule was generated using validated software and verified by an internal statistician not involved in the planning or analysis of the trials.

Randomisation was blinded to both investigators and patients. In rare cases it can not be excluded that an investigator decoded the treatment allocation of a patient based on the occurrence of injection site haematomas and mild local irritations known to occur with enoxaparin treatment. However, the investigator had no means to confirm his suspicion and this presumed knowledge would not have impacted on the study conduct. Since the

primary endpoint assessments were performed by an independent committee that was unaware of the treatment allocation, the integrity of the data was not compromised.

The definition of the primary and secondary endpoints was based on the guidance provided by the EMEA for the development of anticoagulants [29]. In accordance with these guidelines, all observations related to key efficacy and safety parameters were adjudicated by independent, external adjudication committees. The method to determine the primary efficacy parameter, i.e. bilateral venography, was chosen in agreement with the EMEA guidance and represented the best available assessment. The bilateral venography was to be performed within 24 hours after the last oral administration of study drug (12 hours in RE-MOBILIZE). Since the terminal elimination half-life of DBG is 14 to 17 hours after multiple dosing, the limitation to a period of 24 hours ensured that patients had maintained an adequate DBG blood concentration. Similarly, for enoxaparin, anti-factor Xa activity can still be demonstrated 24 hours after administration according to the SPC of enoxaparin [30]. Since each study was primarily designed to show non-inferiority of DBG versus enoxaparin, and the DBG doses were chosen based on substantial experience in the relevant indications, there was no perceivable opportunity for an investigator to decode the treatments based on clinical parameters such as bleeding or frequency of thromboembolic events.

All patients received double-blind clinical supplies with double-dummy matching placebo to ensure complete blinding during the conduct of the trial. Each patient received one capsule on the day of surgery, and two capsules on each day of treatment thereafter (i.e., DBG or matching placebo). Each patient also received twice daily subcutaneous injections (i.e., enoxaparin or matching placebo).

All members of the Clinical Project Team remained blinded to the randomisation schedule until after the final database was locked. The randomisation schedule was examined only if required by an emergency. An unblinding mechanism was provided to the investigator for use only in an emergency situation, when the identity of the study drug had to be known in order to provide appropriate medical treatment. The details of unblinded patients are as follows:

- RE-NOVATE: 5 patients in the DBG 220 mg group, 3 patients in the DBG 150 mg group and 2 patients in the enoxaparin group
- RE-MODEL: 2 patient in the DBG 220 mg group, 4 patients in the DBG 150 mg group and 3 patients in the enoxaparin group

- RE-MOBILIZE: 1 patient in the DBG 220 mg group, 2 patients in the DBG 150 mg group and 4 patients in the enoxaparin group

The independent VTE endpoint adjudication committees that were responsible for the central adjudication of all suspected PEs, DVTs, and deaths, and that assessed all venograms, ultrasound images and all other objective tests for suspected VTEs, performed their work blinded to randomised treatment assignments, as did the independent Bleeding Adjudication Committee, which was responsible for adjudicating all bleeding events. The same was true for the activities of the Hepatology Panel, which was charged with reviewing and evaluating all hepatic adverse events and laboratory abnormalities and the Cardiac Safety Panel, which reviewed all cases involving cardiac events to determine an ischaemic cardiac aetiology.

Prior to database lock, procedures were in place to ensure that individuals associated with the conduct of the study remained blinded to the PK/PD data to preserve blinding of individual patient treatment assignments. The results of the independent analysis of the PK/PD data were not made available until after database lock. The results were not released to the trial team nor were they entered into the trial database until after database lock.

5.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

The inclusion and exclusion criteria for each phase-III trial are listed below.

Inclusion criteria

Patients were included if the following criteria were fulfilled:

1. Patients were scheduled to undergo primary, unilateral elective total knee (RE-MODEL or RE-MOBILIZE) or total hip (RE-NOVATE) replacement surgery.
2. Male or female patients of 18 years or older.
3. Patients weighing at least 40 kg.
4. Patient provided written informed consent for study participation.

Exclusion criteria

If any of the following criteria applied, the patient was excluded from entering the study:

1. History of bleeding diathesis.
2. Constitutional or acquired coagulation disorders that in the investigator's judgement would have put the patient at excessive risk of bleeding.
3. Major surgery or trauma (e.g. hip fracture) within the last 3 months.
4. Recent unstable cardiovascular disease, such as uncontrolled hypertension at the time of enrolment (investigator's judgement) or history of myocardial infarction within the last 3 months.
5. Spinal or epidural anaesthesia, for which more than 3 attempts at placement were made (sticks), or the placement was traumatic. Subsequent to protocol amendment 1 (dated 1 Dec

2004) this exclusion criterion was deleted because this information was not available at the screening visit. Instead a stopping rule with the same content and to the same effect was formulated in the study protocol.

6. Any history of haemorrhagic stroke or any intracranial pathology such as bleeding, neoplasm, AV-malformation, or aneurysm.
7. History of VTE or pre-existing condition requiring anticoagulant therapy.
8. Clinically-relevant bleeding e.g. gastrointestinal, pulmonary, intraocular, or urogenital bleeding within the last 6 months.
9. Gastric- or duodenal ulcer within the last 6 months.
10. Liver disease which was expected to have a potential impact on survival e.g. hepatitis B or C, cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery.
11. Elevated AST or ALT >2x upper limit of normal based on central lab results or local lab results within 1 month before enrolment.
12. Severe renal insufficiency (CrCl < 30 mL/min). However, creatinine clearance (CrCl) needed only be calculated if serum creatinine was elevated or renal insufficiency was suspected.
13. Elevated creatinine, which in the investigator's opinion contraindicated venography.
14. Treatment with anticoagulants, clopidogrel, ticlopidine, abciximab, aspirin >160mg/day or NSAID with t½ >12 hours within 7 days prior to knee or hip replacement surgery or had an anticipated need for these medications during the study treatment period (COX-2 selective inhibitors were allowed).
15. Anticipated requirement for use of intermittent pneumatic compression and electric stimulation of lower limb.
16. Pre-menopausal women (last menstruation ≤1 year prior to signing informed consent) who:
    a) were pregnant
    b) were nursing
    c) were of child-bearing potential and were not practising acceptable methods of contraception, or did not plan to continue practising an acceptable method throughout the study. Acceptable methods of contraception included Intra Uterine Device (IUD), oral, implantable, or injectable contraceptives, and surgical sterility.
17. Known allergy to radio-opaque contrast media or iodine.
18. History of thrombocytopenia (incl. heparin-induced thrombocytopenia) or a platelet count <100,000 cells/microliter at Visit 1.
19. Allergy to heparins or to DBG.
20. Active malignant disease or currently received cytostatic treatment.
21. Participation in a clinical trial during the last 30 days.
22. Leg amputee.
23. Known alcohol or drug abuse which would interfere with completion of the study.
24. Contraindications to enoxaparin.
25. Patient had previously participated in RE-NOVATE, RE-MOBILIZE or RE-MODEL.

The demographic and baseline characteristics for each trial are shown in **Table 13**.

Table 13 Demographic and baseline characteristics of treated patients

	RE-MOBILIZE	RE-MODEL	RE-NOVATE
Treated	2596 (100%)	2076 (100%)	3463 (100%)
Age (years)			
Mean (SD)	66.1 (9.5)	67.7 (8.9)	63.9 (10.8)
Median	67.0	68.0	65.0
Age categories (years)			
<65	1048 (40.4)	707 (34.1)	1686 (48.7)
65-75	1093 (42.1)	953 (45.9)	1310 (37.8)
>75	455 (17.5)	416 (20.0)	467 (13.5)
<70	1580 (60.9)	1115 (53.7)	2332 (67.3)
≥70	1016 (39.1)	961 (46.3)	1131 (32.7)
Gender			
Male	1099 (42.3)	706 (34.0)	1509 (43.6)
Female	1497 (57.7)	1370 (66.0)	1954 (56.4)
Race			
White	2242 (86.4)	2050 (98.7)	3441 (99.4)
Black	100 (3.9)	17 (0.8)	14 (0.4)
Asian	254 (9.8)	9 (0.4)	8 (0.2)
Height			
Mean (SD), cm	167.1 (10.7)	166 (9.6)	168 (9)
Median	166.5	165.0	168.0
Weight			
Mean (SD), kg	88.0 (19.4)	82.6 (15.0)	78.5 (15.1)
Median	86.0	81.0	78.0
Body mass index			
Mean (SD), kg/m^2	31.5 (6.1)	29.9 (4.9)	27.7 (4.5)
Median	30.5	29.4	27.3
CrCl at screening (mL/min)			
Missing	37 (1.4)	69 (3.3)	84 (2.4)
<30	16 (0.6)	4 (0.2)	11 (0.3)
30-50	266 (10.2)	130 (6.3)	207 (6.0)
50-80	1050 (40.4)	725 (34.9)	1181 (34.1)
≥80	1227 (47.3)	1148 (55.3)	1980 (57.2)
Mean (SD)	82.9 (29.9)	88.4 (28.4)	89.3 (29.9)
Median	78.3	85.1	85.9

CrCl, Creatinine clearance; SD, standard deviation

In the phase-III trials, the demographic characteristics were similar in all three treatment groups. The treatment groups were also well balanced in terms of surgical characteristics (including type of anaesthesia, time to first dose relative to surgery, duration of surgery and drainage volume until the first oral dose) medical history and concomitant use of anticoagulant medication, cardiac therapy and serum-lipid reducing agents.

In all three trials, similar proportions of treated patients in the three arms were included in the final analysis set (FAS) (**Table 14**). The majority of patients who were excluded from the FAS did not have an evaluable venogram.

Table 14 Patients (%) in the full analysis set

	DBG 220 mg	DBG 150 mg	Enoxaparin	Total
RE-NOVATE	880 (77.4)	874 (75.6)	897 (78.5)	2651 (77.2)
RE-MODEL	503 (74.5)	526 (75.6)	512 (74.7)	1541 (75.0)
RE-MOBILIZE	604 (70.5)	649 (74.5)	643 (74.1)	1896 (73.0)

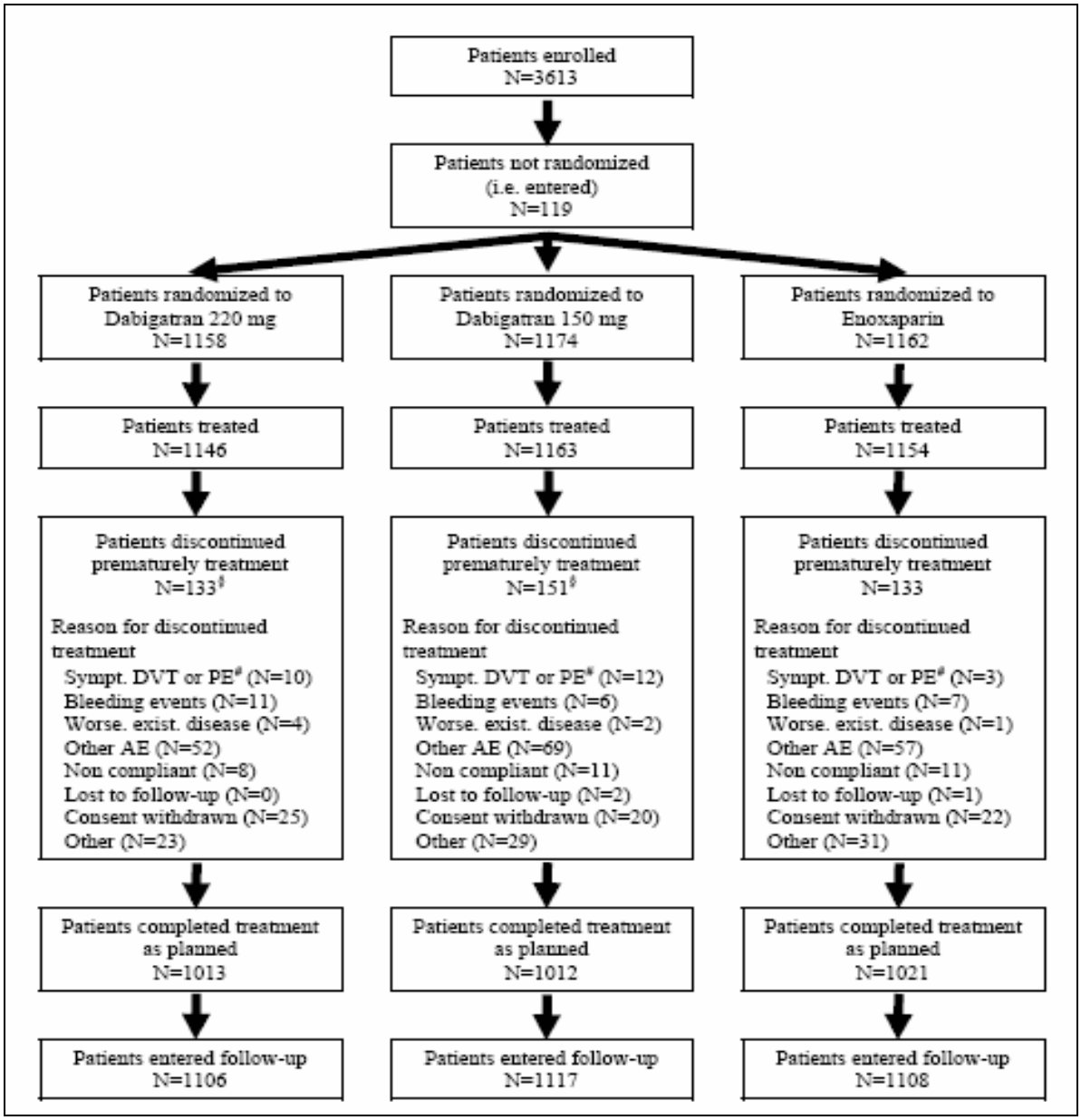
DBG, dabigatran etexilate

5.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 6 through **Figure 8** present the CONSORT flow diagrams for RE-NOVATE, RE-MODEL and RE-MOBILIZE respectively.

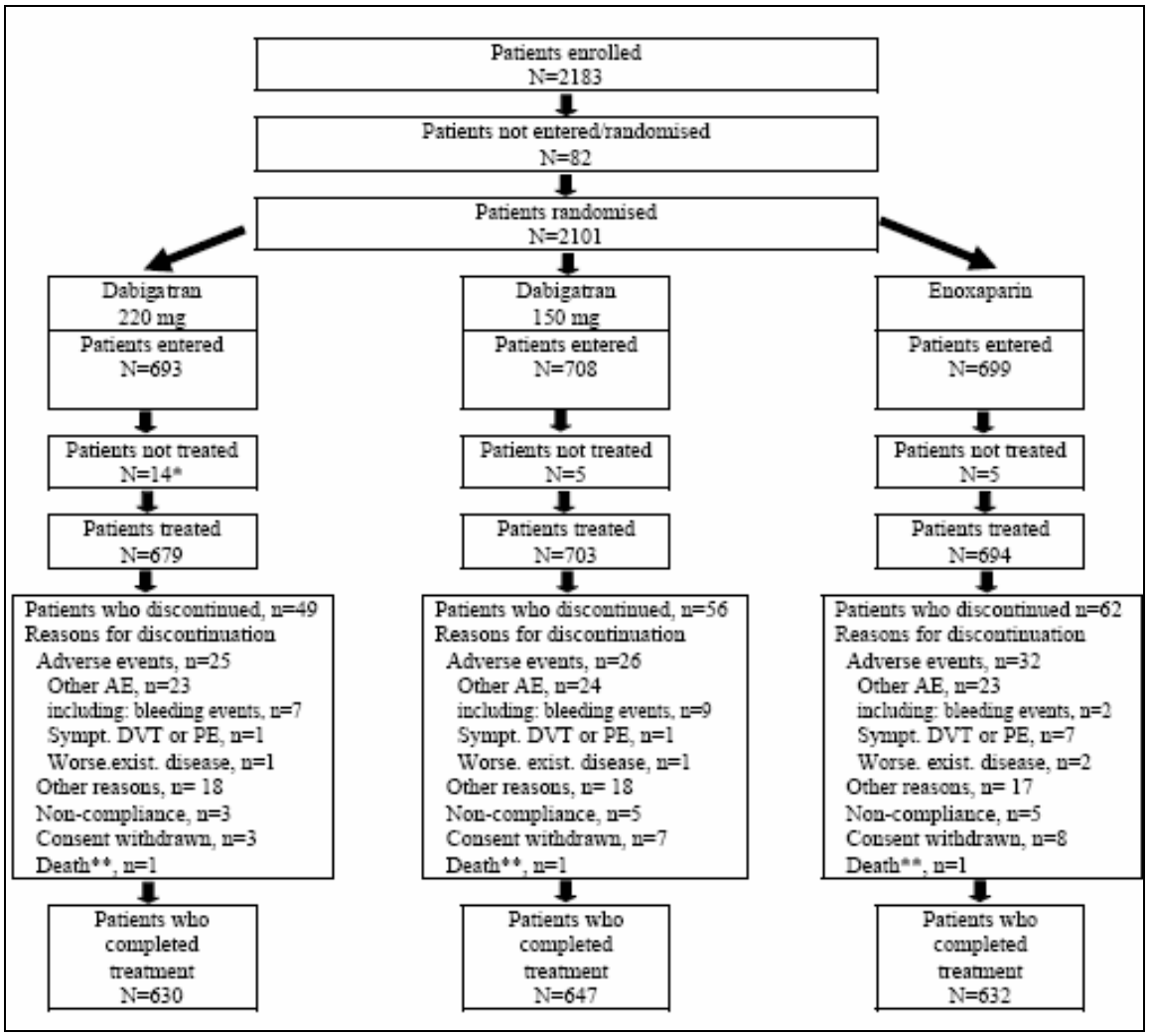
Figure 6 CONSORT flow chart (RE-NOVATE)



during treatment period
§ During the treatment period, three patients died in each dabigatran group including one fatal PE in the dabigatran 150 mg group.

The 119 patients that were not randomised failed to meet some inclusion or exclusion criteria, withdrew informed consent, or experienced an adverse event prior to randomisation.

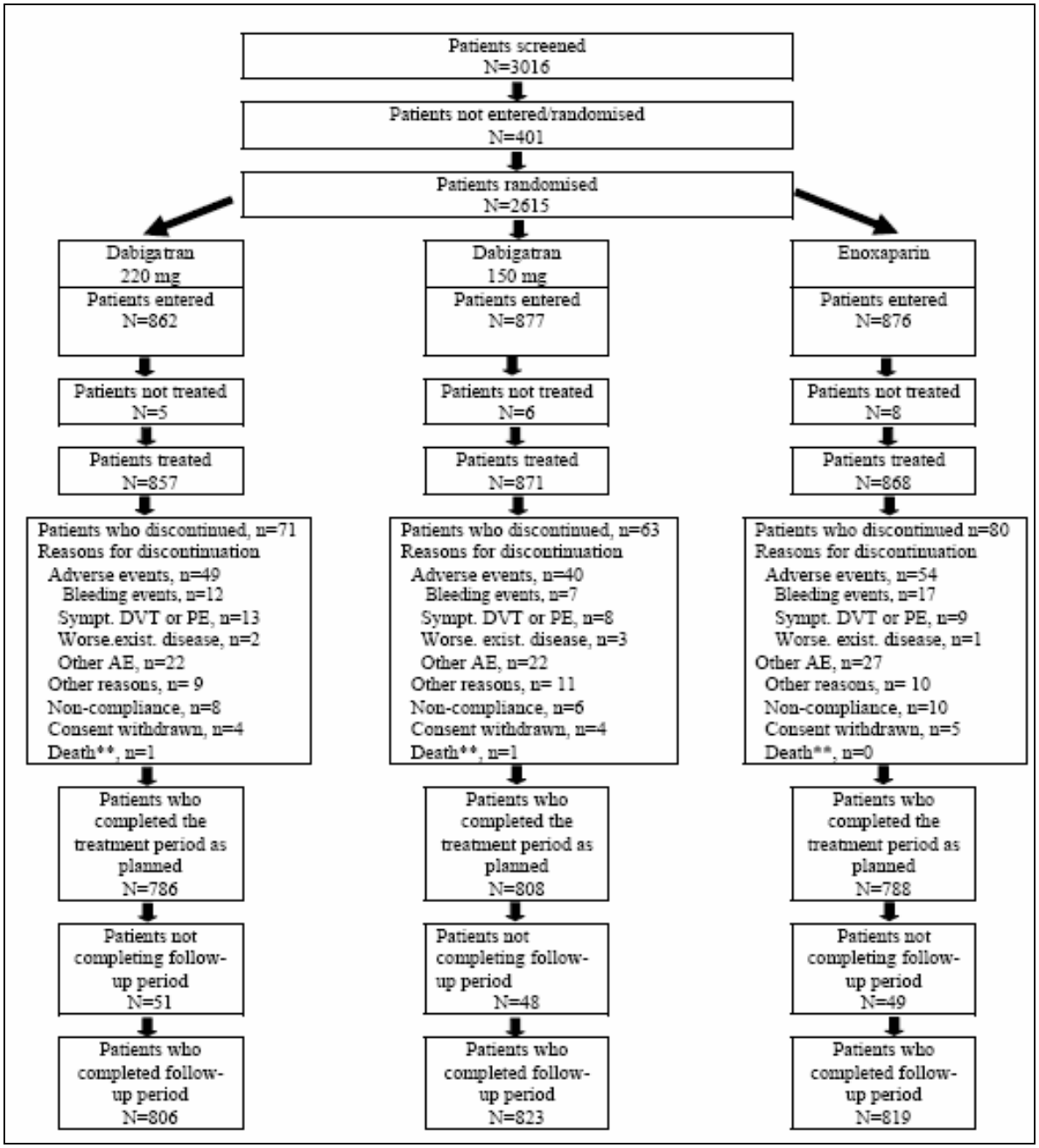
Figure 7 CONSORT flow chart (RE-MODEL)



* Patient 3693 was randomised to Dabigatran 220mg (kit no 1915) but never received any treatment. The investigator reassigned the kit to patient 3689. Therefore, this patient is counted in the total column but not in the Dabigatran 220mg column.
** during treatment period

The 82 patients enrolled but not randomised to treatment did not meet the inclusion or exclusion criteria.

Figure 8 CONSORT flow chart (RE-MOBILIZE)



** During treatment period

The 401 patients that were screened but not randomised to treatment did not meet the inclusion or exclusion criteria.

5.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

Efficacy

Both the definition of the primary endpoint and of the secondary endpoints followed the guidance provided by the EMEA for the development of antithrombotic drugs [29]. The study endpoints used in the pivotal studies RE-NOVATE and RE-MODEL, and the supporting study RE-MOBILIZE, were consistent across all three trials (**Table 15**).

Table 15 Dabigatran etexilate phase-III study efficacy endpoints

Primary endpoint	A composite endpoint consisting of total venous thromboembolic events* (VTEs) and all-cause mortality during the treatment period
Secondary endpoints	**During the treatment period**
	Composite of major VTE (defined as proximal DVT and PE) and VTE-related mortality Proximal DVT Total DVT Symptomatic DVT Pulmonary Embolism (PE) Death
	During the follow-up period
	Composite of total VTE and all-cause mortality

*** Including deep vein thrombosis** (proximal or distal) as detected by routine venography s**ymptomatic DVT** confirmed by venous duplex ultrasound, venography or by autopsy and p**ulmonary embolism** confirmed by pulmonary ventilation-perfusion (V-Q) scintigraphy and chest X-ray, pulmonary angiography, spiral CT or during autopsy.

An external and independent adjudication committee centrally assessed all venograms, ultrasound images, and all other objective tests for suspected VTE.

The studies used a composite endpoint combining clinical elements with asymptomatic venographic DVT. Appropriate endpoints to show clinically relevant benefits for studies of thromboprophylaxis are a subject of much debate. One school of thought is that studies should aim to detect all VTE events using contrast venography. Another is that assessment of efficacy should be based on reduction of all-cause mortality.

Screening venography has the advantage of being sensitive and yielding a high incidence of VTE, giving statistical power to relatively small trials. On the other hand, it has been argued that most of the thrombi detected using screening venography are small and of little

clinical importance; many are confined to the calf, are clinically silent, and remain so without any obvious adverse consequences. Whilst this is true, it is also known that approximately 10-20% of calf thrombi propagate to the proximal veins and, particularly in patients undergoing major surgery involving the hip, isolated femoral vein DVT is common. Also, a strong association between asymptomatic DVT and the subsequent development of symptomatic VTE has been reported in several studies, as has strong concordance between the 'surrogate' outcome of asymptomatic DVT and clinically important VTE. With few exceptions, interventions that reduce asymptomatic DVT also show similar reductions in symptomatic VTE, suggesting that asymptomatic events provide a reliable surrogate endpoint. Venographically-detected asymptomatic VTE is often used in clinical trials as a surrogate measure for the clinical outcomes of symptomatic VTE and PE, and is recognised as a valid surrogate when comparing antithrombotic regimens in the same population. [2]

Although some may argue that reduction in all-cause mortality or fatal PE is the most clinically important outcome, this has practical difficulties. Due to the rarity of these events such studies would need to be very large (tens of thousands of patients) to show a statistically significant result. Moreover, it is increasingly difficult to obtain autopsy confirmation of VTE as the cause of death. To concentrate clinical trials on these outcomes would ignore the significant burden of illness due to (non-fatal) symptomatic thromboembolic events as well as the risks of consequent anticoagulation therapy and the demands on healthcare resources when these events occur.

The use of a composite endpoint combining clinical events with asymptomatic venographic VTE is advocated by several guidelines (ACCP [2], EMEA [29], NICE [1], SIGN [17]).

Thus it can be stated with some confidence that the outcomes used in the DBG phase-III studies to show clinical benefit are appropriate and in line with those used in other published studies in this therapeutic area.

Safety

Safety outcomes measure in the phase-III trials were focused on bleeding events, as is common in clinical trials of anticoagulants.

Given recent experience with ximelagatran (Exanta, AstraZeneca), a previous direct thrombin inhibitor withdrawn from the market due to hepatic safety concerns, special attention was also paid to hepatic toxicity events. In addition, due to some acute coronary events with ximelagatran believed to be caused by a rebound effect on thrombin

production, coronary events were also specifically monitored. Crucially, all safety outcomes were recorded over an extended period of follow-up (91 days post-surgery).

Bleeding

The following bleeding endpoints were analysed in the three trials:

1. Incidence of bleeding events
   a. Major Bleeding Events (MBE)
   b. MBE and clinically-relevant bleeding events
   c. Any bleeding events (major, clinically-relevant, and minor)
2. Volume of blood loss
3. Number and type of blood transfusions
4. Incidence of adverse events
5. Incidence of discontinuations due to adverse events
6. Laboratory measures, especially changes in liver function tests
7. Results of physical examinations

Major bleeding events were defined according to modified McMaster criteria [31] and similar to the recommendations of the EMEA [29]. The criteria for major bleeding events were as follows:

- fatal bleeding
- clinically overt bleeding in excess of what was expected and associated with ≥ 2 g/dL (corresponds to 1.24 mmol/L) fall in haemoglobin in excess of what was expected
- clinically overt bleeding in excess of what was expected and leading to transfusion of ≥ 2 units packed cells or whole blood in excess of what was expected
- symptomatic retroperitoneal, intracranial, intraocular, or intraspinal bleeding
- bleeding requiring treatment cessation
- bleeding leading to re-operation

Objective testing was required for a retroperitoneal bleed (ultrasound or CT scan) and for an intracranial and intraspinal bleed (CT scan or MRI).

Clinically-relevant bleeding events were defined as:

- spontaneous skin haematoma ≥ 25 cm^2
- wound haematomas ≥ 100 cm^2
- spontaneous nose bleed >5 minutes
- macroscopic haematuria (a) spontaneous or (b) lasting more than 24 hours if associated with an intervention
- spontaneous rectal bleeding (more than spot on toilet paper)
- gingival bleeding >5 minutes
- any other bleeding event considered as clinically relevant by the investigator

Minor bleeding events were defined as all other bleeding events that did not fulfil the criteria of MBE or clinically-relevant bleeding events.

All bleeding events, including injection-site haematoma, gastro-intestinal, nasal, or urethral bleeding during the treatment periods, were regarded as adverse events and were recorded.

Serious, significant, and other significant adverse events

A serious adverse event was defined as any adverse event which resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalisation, was a congenital anomaly/birth defect, or was deemed serious for any other reason representing a significant hazard comparable to the aforementioned criteria.

For this study, no 'significant' adverse events were defined for DBG or enoxaparin. 'Other significant adverse events' were defined as adverse events leading to dose reduction or withdrawal of the patient. In contrast to the ICH E3 guideline, marked haematological changes and laboratory abnormalities were not included into this category for this study. The reason for omitting these events was that marked haematological changes were to be expected in a population undergoing total hip and knee replacement surgery and their inclusion would have artificially inflated the frequency of 'other significant adverse events'. Marked laboratory changes such as elevations of liver function enzymes were closely monitored in this study.

A particular focus was on liver function using the following algorithm:

- If a patient developed liver enzymes abnormality exceeding two times the upper limit of normal (> 2x ULN), the patient had to be followed-up with repeat liver function tests (LFTs) until liver enzymes reached normal limits or returned to the patient's baseline (if this was not within normal limits). Repeat LFTs were to be obtained weekly for patients who met both of the following criteria:

1. They were still in the treatment period and
2. Liver enzymes had not improved to < 1.8 x ULN

- If LFT was above 3x ULN or the total bilirubin was > 1.5 x ULN, the patient had to be monitored with weekly LFT determinations until liver enzymes and total bilirubin reached normal limits or returned to the patient's baseline (if this was not within normal limits).
  In addition these patients were to be evaluated for liver disease. This included review of patient's history regarding alcohol intake and any concomitant medications that had been added to the patient's regimen within 3 months of start of the study. In addition the following laboratory evaluations were to be done centrally: 1) serology for HBsAg (if positive then HBV DNA by PCR), and HCV (if positive then HCV-RNA by PCR); 2) a metabolic screen (glucose, cholesterol, triglycerides, and TSH); 3) screening for auto antibodies (ANA, AMA, anti-LKM1, and ASM); 4) transferrin saturation and 5) amylase, lipase, ceruloplasmin and α1 anti-trypsin.

Additional evaluations including, for example, right upper quadrant ultrasound had to be performed if clinically indicated.

- If LFT was > 5x ULN, or > 3x ULN in association with a total bilirubin elevation of > 2x ULN the patient needed to be discontinued from the medication immediately (if the patient was still receiving treatment), and the sponsor had to be alerted. If such an observation was made as the patient's first abnormal LFT value, the tests were to be repeated for verification.

All laboratory samples for LFT monitoring had to be evaluated by the central laboratory. Patients who had liver enzymes exceeding 3x ULN or total bilirubin exceeding 1.5x ULN had to be encouraged to obtain appropriate follow-up by central laboratory evaluation.

In addition, if a patient developed jaundice or other signs or symptoms that in the clinical investigator's judgement were attributable to hepatic insufficiency, the study medication was to be terminated, and the sponsor needed to be notified immediately.

Any patient who had to be discontinued from study medication was to receive appropriate DVT prophylaxis to the investigator's discretion.

If, for any patient who was followed-up by weekly monitoring, the LFTs neither stabilised nor improved but remained above ULN after several weeks of monitoring or if the cause of the LFT abnormality was diagnosed (non-drug related) the monitoring frequency could be decreased or stopped, based on agreement of the investigator and the sponsor.

5.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

Hypotheses

The three phase-III trials aimed to demonstrate therapeutic equivalence (non-inferiority) of DBG compared with enoxaparin by showing that the rate of total VTE plus all-cause mortality in DBG-treated patients did not exceed the rate in patients receiving enoxaparin treatment by more than a pre-defined non-inferiority margin (delta).

The corresponding null hypotheses of interest were that the difference in rates of total VTE plus all-cause mortality with DBG treatment versus enoxaparin was greater than delta. Delta was based on the 'minimum important difference' (MID), which preserved 2/3 of the

difference between enoxaparin and placebo as observed in previous clinical studies. The basis for this MID criterion is summarised and discussed below.

After achieving non-inferiority, the trials also aimed to establish superiority (by means of hierarchical tests) of DBG over enoxaparin by showing that the rates of total VTE plus all-cause mortality in each of the two DBG dose regimens was smaller than the rates of total VTE plus all-cause mortality with enoxaparin treatment.

Let π_H and π_L denote the percentage rate of total VTE and all-cause mortality in the high-dose and low-dose DBG groups respectively, and π_E denote the corresponding rate in the enoxaparin group. The non-inferiority/superiority of DBG was established by testing these null hypotheses of interest in the following conditional and pre-specified manner (an *a priori* ordering of the null hypotheses of interest) for the primary efficacy endpoint;

a. Test for the non-inferiority of high dose of DBG compared with enoxaparin using the null hypothesis that the difference in rates of total VTE plus all-cause mortality in the high- dose group of DBG versus enoxaparin exceeded delta. This hypothesis test was expressed in mathematical terms as

H_0: $\pi_H - \pi_E >$ delta versus H_1: $\pi_H - \pi_E \leq$ delta

b. Test for the non-inferiority of low-dose of DBG compared with enoxaparin using the null hypothesis that the difference in rates of total VTE plus all-cause mortality in the low-dose group of DBG versus enoxaparin exceeded delta. This hypothesis test was expressed in mathematical terms as

H_0: $\pi_L - \pi_E >$ delta versus H_1: $\pi_L - \pi_E \leq$ delta

c. Test for the superiority of high-dose of DBG to enoxaparin using the null hypothesis that the rate of total VTE plus all-cause mortality in the high-dose group of DBG was the same as the rate of total VTE plus all-cause mortality in the enoxaparin group. This hypothesis test was expressed in mathematical terms as:

H_0: $\pi_H \geq \pi_E$ versus H_1: $\pi_H < \pi_E$

d. Test for the superiority of low-dose of DBG to enoxaparin using the null hypothesis that the rate of total VTE plus all-cause mortality in the low-dose group of DBG was the same as the rate of total VTE plus all-cause mortality in the enoxaparin group. This hypothesis test was expressed in mathematical terms as:

H_0: $\pi_L \geq \pi_E$ versus H_1: $\pi_L < \pi_E$

Inference that DBG is non-inferior/superior to enoxaparin was to be based on this strategy and was only extended through the sequence of rejected null hypotheses, thus preserving the overall significance level. All comparisons were effectively one-sided with a significance level of 0.025. However, *p*-values testing no difference were reported as two-sided resulting in a significance level of 0.05 following the convention. Confidence Intervals (CI) were also two-sided with a level of 95%.

Missing data were not imputed in any of the efficacy or safety analyses.

Primary endpoint analyses

The primary analysis was based on the Full Analysis Set (FAS) that comprised those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, underwent surgery, and had had confirmed VTE data (i.e. evaluable venogram or confirmed symptomatic DVT, PE, or death during treatment period).

The primary analysis was to be repeated using the per-protocol set (PPS) if this population fell below 90% of the primary efficacy analysis population. The PPS comprised those patients in the FAS without any major protocol violations. To be included in the PPS, patients had to receive at least:

- RE-NOVATE: 24 daily subcutaneous injections or 23 oral doses in total during the treatment period
- RE-MODEL: 6 daily subcutaneous injections or 6 oral doses in total during the treatment period
- RE-MOBILIZE: 10 days of subcutaneous injections of enoxaparin twice a day or 10 oral doses of DBG during the treatment period

However, if an endpoint was reached before this minimum planned treatment period, such a patient was also included in the PPS, if the endpoint was confirmed by the appropriate independent adjudication committee.

The primary comparisons were the pair-wise comparisons between each of the DBG treatments versus enoxaparin treatment in a pre-defined order as described above.

Point estimates for the rates of total VTE plus all-cause mortality and their two-sided 95% confidence intervals were to be calculated by treatment group. The rate difference between each DBG treatment versus enoxaparin, its two-sided 95% CI, and corresponding *p*-value for no difference in proportions based on the large sample Z-test for two proportions was also presented. These calculations were to be based on the normal approximation of

independent binomial distributions without any stratification. In the calculation, centres were not included to avoid over-stratification of a binomial endpoint that had limited information of 0 or 1. For the non-inferiority claim, the two-sided 95% CI for the rate difference was to be compared to the pre-defined margin of delta. For the superiority claim, the same *p*-value that was obtained for rate differences was to be used for consistency across non-inferiority and superiority claims.

For the primary endpoint, the relative risk reduction of each of the DBG treatments over enoxaparin and its 95% CI was also to be presented. For the CI calculation of the relative risk, a log-transformation method was to be utilised without continuity correction.

In addition, the primary endpoint (the composite of total VTE and all-cause mortality) was to be summarised according to important subgroup criteria including, but not limited to, country, age (< 70, ≥ 70 years), gender, BMI, time from surgery to first oral dose, and type of anaesthesia. Logistic regression models were to be employed to sequentially test the interaction between treatment and subgroup factor and the main effect of the subgroup factor.

Secondary endpoint analyses

The analysis sets for the secondary efficacy endpoints were based on the availability of observed data in regard to the specific endpoint. **Table 16** presents the definition of the analysis sets as specified in the trial protocols.

Table 16 Definition of analysis set for the secondary efficacy endpoints

Endpoint	Definition of analysis set
Composite of Major VTE and VTE-related mortality	FAS without patients whose death was not related to VTE
Proximal DVT	Patients, who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had evaluable venograms, or confirmed symptomatic DVT.
Total DVT	Patients, who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had evaluable venograms, or confirmed symptomatic DVT.
Symptomatic DVT	Patients, who were randomised, received at least one subcutaneous injection or one oral dose of study medication and went through surgery.
Pulmonary Embolism	Patients, who were randomised, received at least one subcutaneous injection or one oral dose of study medication and went through surgery.
Death	Patients, who were randomised, received at least one subcutaneous injection or one oral dose of study medication and went through surgery.

DVT, deep vein thrombosis; FAS, full analysis set; VTE, venous thromboembolism.

The same analyses that are used for the primary endpoint were to be presented for venographic findings (proximal DVT, total DVT) and the composite of major VTE and VTE related mortality. For symptomatic events (symptomatic DVT, PE, and death) that were expected to have rates below 2%, only the incidence, and when appropriate its 95% CI, by treatment were to be calculated. For pair-wise comparisons, Fisher's exact test was to be utilised when appropriate. This test was chosen due to the expected low event rate for these endpoints.

Safety endpoints

Safety endpoints that pertained to surgery (blood transfusion, blood loss, and volume of drainage) were analysed based on the treated patients who went through surgery. Other safety endpoints were summarised and analysed based on the treated patients who had received at least one subcutaneous injection or one oral dose of study medication.

For MBE, the incidence and its 95% CI when appropriate were presented by treatment using the same method as for the primary endpoint. For treatment comparisons Fisher's exact test was used. This test was chosen due to the expected low event rate for these endpoints. Other bleeding events (incidence of MBE or clinically-significant bleeding events; and incidence of any bleeding events) were summarised and analysed using the same method as for the primary analysis.

In addition, the Cochran-Mantel-Haenszel test compared ordered categories of worst bleeding between treatments with the following two categorisations: (1) major bleeding, clinically relevant bleeding, and all others and (2) major bleeding, clinically-relevant bleeding, minor bleeding, and no bleeding.

Volume of blood loss during surgery and transfusion volume were descriptively summarised by treatment.

The adverse events were coded using MedDRA dictionary and summarised as overall, by body system, by preferred term, and by onset time. Adverse events that occurred between the first study drug administration and 3 days following the last administration of study drug were considered as treatment-emergent. Additionally adverse events were summarised by severity and relationship to study drug. Serious adverse events, bleeding events, and patient discontinuation due to adverse events was also summarised and analysed descriptively; laboratory tests and physical exam were analysed similarly.

The planned analysis for MBE was to be repeated for the full analysis set in order to present the major safety assessment for the same analysis set as used for the primary efficacy analysis.

Sample size

RE-NOVATE

Depending on the assumed incidences, sample sizes were to be calculated to achieve 95% power to declare non-inferiority with a margin of 7.7% difference for total VTE and all-cause mortality. The calculations were based on one-sided tests with $\alpha = 0.025$ and explored the range of 14 to 20% in rates assuming equal rates of total DVT plus all-cause mortality for the two treatments (**Table 17**). The rates of 14% to 20% were consistent with the published rates in overall LMWH [32-35] as well as rates in more recent active-controlled trials [26,36-37].

A sample size of 2160 evaluable patients (720 per treatment group) was determined to have sufficient power (≥ 95%) to demonstrate non-inferiority of DBG to the enoxaparin group for enoxaparin event rate as high as 20%. Assuming a rate of 35% for non-evaluable patients due to inadequate venogram, a total of 3330 patients were needed for randomisation.

Table 17 Calculation of sample size (RE-NOVATE)

Non-inferiority margin	Power	Equal VTE rate	N (evaluable per treatment group),
7.7% difference in proportions	95%	14%	550
		16%	620
		18%	670
		20%	720

N, number of patients.

RE-MODEL

Depending on the assumed incidence rates, sample sizes were calculated to achieve 90% power to state non-inferiority with a margin of 9.2% in the difference of incidences in the primary endpoint based on one-sided tests with α = 0.025. Taking the result from the DBG phase-II trial BISTRO II [26] into consideration, the calculation assumed that the incidence of the primary endpoint (the composite endpoint of total VTE and all-cause mortality) was 1% smaller for DBG treatment than for enoxaparin treatment (**Table 18**). The explored rates in the control arm ranged from 30% to 48% based on the published rates of LMWH [32,38-39] and the enoxaparin rates from more recent active-controlled trials [26,36-37].

A sample size of 1500 evaluable patients (500 per treatment group) was determined to have sufficient power (≥ 90%) to demonstrate non-inferiority of DBG to the enoxaparin for enoxaparin event rates as high as 48%. Assuming that 25% of the venograms were inadequate, a total of 2010 patients needed to be randomised.

Table 18 Calculation of sample size (RE-MODEL)

Non-inferiority margin	Power	Enoxaparin rate	Dabigatran rate	N (evaluable per treatment group),
9.2% difference in proportions	90%	20%	19%	320
		30%	29%	420
		33%	32%	450
		36%	35%	470
		39%	38%	480
		42%	41%	490
		45%	44%	495
		48v	47%	500

N, number of patients.

RE-MOBILIZE

Sample sizes were calculated to achieve 90% of power to declare non-inferiority with the margin of 9.2% in difference in proportions. The calculation was based on one-sided tests with α = 0.025, and assumed equal rates for the composite endpoint of total VTE and all-cause mortality between DBG and enoxaparin (**Table 19**). The assumed rates ranged from

30% to 48% based on the published rates of LMWH [32,38-39] and enoxaparin rates from more recent active-controlled trials including DBG phase-II trial results [26,36-37].

A sample size of 1950 evaluable patients (650 per treatment group) was determined to have sufficient power (≥ 90%) to demonstrate non-inferiority of DBG to the enoxaparin group for event rates as high as 48%. Assuming a rate of 25% for inadequate venogram, a total of 2610 patients was needed for randomisation.

Table 19 Calculation of sample size (RE-MOBILIZE)

Non-inferiority margin	Power	Equal VTE rate	N (evaluable per treatment group),
9.2% difference in proportions	90%	20%	400
		30%	530
		33%	560
		36%	600
		39%	600
		42%	610
		45%	620
		48%	650

N, number of patients.

5.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- ***How was allocation concealed?***
- ***What randomisation technique was used?***
- ***Was a justification of the sample size provided?***
- ***Was follow-up adequate?***
- ***Were the individuals undertaking the outcomes assessment aware of allocation?***
- ***Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.***
- ***Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?***
- ***How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.***
- ***For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?***
- ***Were the study groups comparable?***
- ***Were the statistical analyses used appropriate?***
- ***Was an intention-to-treat analysis undertaken?***
- ***Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?***

Much of the information for critical appraisal of the clinical trials has been presented in the preceding sections. A detailed description of the following has been presented previously and will not be restated here:

- Randomisation and blinding (Section 5.3.1)
- Justification of sample size (Section 5.3.5)
- Statistical analyses (section 5.3.5)
- Interpretation of results and confounders (5.9.1 and 5.9.2)

Table 20 presents a critical appraisal of the remaining elements of the clinical trials.

Table 20 Critical appraisal of the phase-III clinical trials

Trial aspect	RE-NOVATE	RE-MODEL	RE-MOBILIZE
Was follow-up adequate?	Yes. Follow up to 3 months. Mean duration of study 94 days. Haematology & clinical chemistry tests at 2 & 3months.	Yes. Follow up for 3 months. Haematology & clinical chemistry tests at 3months.	Yes. Patients were followed up for 12-14 weeks
Was the design parallel-group or crossover?	Parallel group.		
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	A multinational trial with no UK centres. European, Australian & S African populations. Design very similar to UK practice.		No, this trial was conducted in North America. Dose regimens of enoxaparin differ from those used in UK, and timing of the DBG dose differ from that proposed in the UK. See below for detail Higher proportion of general (rather than localised) anaesthesia
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	Trial: 99.4% caucasian, 0.4 % black, 0.2% asian, Average age 63.9 years. 43.6% male. (refer to Section 5.9.2 and **Table 48**) NJR[16]: Average age 68 years. 40% male.	Trial: 98.7% caucasian, 0.8 % black, 0.4% asian, Average age 67.7 years. 34.0% male. (refer to Section 5.9.2 and **Table 48**) NJR[16]: Average age 70 years. 43% male.	Trial: 86.4% caucasian, 3.9 % black, 9.8% asian, Average age 66.1 years. 42.3% male. (refer to Section 5.9.2 and **Table 48**) NJR[16]: Average age 70 years. 43% male.
What dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	DBG: 220mg or 150mg o.d., starting with a half dose 1-4 hours after surgery Enoxaparin: 40mg o.d., starting the day before surgery. Both are as in the UK SPCs for the products.	DBG:220mg or 150mg o.d., starting with a half dose 1-4 hours after surgery Enoxaparin: 40mg o.d., starting the day before surgery Both are as in the UK SPCs for the products.	DBG: 220mg or 150 mg o.d., starting 6-12 hours after surgery. This is the same dose as the UK SPC, but treatment in started later. Enoxaparin: 30mg b.d., starting 12-24 hours after surgery. This is a higher dose and started later than the UK SPC (but complies with the American label)
Were the study groups comparable?	Yes. Demographic and surgical characteristics were similar for the treatment groups within each study.		
Was an intention-to-treat analysis undertaken?	Patients with inadequate or missing mandatory bilateral venography who neither died nor experienced venous thromboembolic events were excluded from efficacy analysis (i.e. efficacy analyses were done by a modified intention to treat basis). This is common practice for studies of this type.		

b.id., twice-daily dosing; DBG, dabigatran etexilate; o.d. once daily dosing.

5.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- ***The unit of measurement.***
- ***The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.***
- ***A 95% confidence interval.***
- ***The number of patients included in the analysis.***
- ***The median follow-up time of analysis***
- ***State whether intention-to-treat was used for the analysis and how data were imputed if necessary.***
- ***Discuss and justify definitions of any clinically important differences.***
- ***Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.***
- ***If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.***
- ***Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.***

Primary endpoint

Key points
• In the RE-MODEL and RE-NOVATE trials versus enoxaparin 40 mg o.d., both DBG doses demonstrated non-inferiority to enoxaparin in terms of the primary endpoint, with confidence intervals falling within pre-defined non-inferiority margins
• In RE-MOBILIZE, the rate of VTE and all-cause mortality in the enoxaparin 30mg b.i.d. group was surprisingly low, resulting in mean outcomes favouring the comparator

Results reported for the primary efficacy endpoint are for the full analysis set as presented in **Table 14**.

RE-NOVATE

The result of the primary efficacy outcome from RE-NOVATE is presented in **Table 21**. The rate of total VTE and all-cause mortality was substantially lower than expected for all treatment arms. The confidence intervals were well within the pre-specified non-inferiority margin of 7.7%.

Table 21 RE-NOVATE primary efficacy outcome

	DBG 220mg	DBG 150mg	Enoxaparin
FAS (n)	880	874	897
Total VTE and all-cause mortality (%)	6.0	8.6	6.7
Risk difference *versus* enoxaparin	-0.7	1.9	
95% CI (%)	(-2.9, 1.6)*	(-0.6, 4.4)*	
p-value	0.5648	0.1339	
Relative risk over enoxaparin	0.9	1.28	
95% CI	(0.63, 1.29)	(0.93, 1.78)	

CI = confidence interval; DBG, dabigatran etexilate; FAS = full analysis set, i.e. mITT (modified intention to treat) analysis
*Within the pre-defined non-inferiority margin of 7.7%

The treatment-blinded review of protocol deviations resulted in only 7.5% of the FAS patients being excluded from the per protocol set, therefore the PPS analysis was not required.

Subgroup analyses were performed for the primary endpoint in an exploratory manner (**Table 22**). The analysis of subgroups was supported by univariate and multivariate logistic regression analyses.

Table 22 Subgroup analyses of the primary endpoint (RE-NOVATE)

Subgroup	DBG 220mg			DBG 150mg			Enoxaparin		
	N	Incidence	%	N	Incidence	%	N	Incidence	%
FAS	880	53	6.0	874	75	8.6	897	60	6.7
Age (years)									
<65	423	17	4.0	448	40	8.9	463	27	5.8
65-75	346	28	8.1	313	29	9.3	320	15	4.7
>75	111	8	7.2	113	6	5.3	114	18	15.8
Age (years)									
<70	611	35	5.7	588	52	8.8	625	35	5.6
≥ 70	269	18	6.7	286	23	8.0	222	25	9.2
Gender									
Male	417	27	6.5	389	37	9.5	400	21	5.3
Female	463	26	5.6	485	38	7.8	497	39	7.8
Weight (kg)									
<50	10	0	0.0	6	0	0.0	10	0	0.0
50-90	700	43	6.1	698	58	8.3	728	54	7.4
>90	170	10	5.9	170	17	10.0	159	6	3.8
BMI (kg/m^2)									
Missing	0	0	0.0	0	0	0.0	1	0	0.0
<25	255	13	5.1	255	17	6.7	263	18	6.8
25-30	387	27	7.0	384	34	8.9	388	27	7.0
30-35	180	9	5.0	169	16	9.5	208	13	6.3
>35	58	4	6.9	66	8	12.1	37	2	5.4
Creatinine clearance (mL/min)									
Missing	16	0	0.0	23	3	13.0	21	2	9.5
<30	3	0	0.0	0	0	0.0	4	0	0.0
30-50	52	2	3.8	41	4	9.8	52	10	19.2
50-80	284	17	6.0	299	19	6.4	297	18	6.1
≥ 80	525	34	6.5	511	49	9.6	523	30	5.7

BMI, body mass index; DBG, dabigatran etexilate; FAS, full analysis set; N, number of patients; VTE, venous thromboembolism.

The analysis of total VTE and all-cause mortality by age category indicated a trend towards higher incidences of total VTE and all-cause mortality in older patients in the DBG 220 mg group and enoxaparin group while this was not apparent in the DBG 150 mg group. This observation was supported by a p-value of 0.0027 for the age effect and a *p*-value of 0.0415 for the age by treatment interaction in the logistic regression using age as a continuous variable.

For gender, weight and BMI no consistent trend was apparent in the DBG groups and the enoxaparin group. The proportion of patients with moderate renal impairment (creatinine clearance < 50 mL/min) was small in the study population. There was no indication of higher incidences of total VTE and all-cause mortality for patients with impaired kidney function. However, there was a trend towards reduced rates of total VTE and all-cause

mortality for patients with a low creatinine clearance for the DBG 220 mg group. In the DBG 150 mg group, this trend was only observed for the categories of patients with mild renal impaired (CrCl 50 to 80 mL/min) and for patients with normal kidney function (CrCL > 80mL/min). Such a trend was not observed for the enoxaparin group. The univariate logistic regression using continuous, i.e., not categorised, creatinine clearance values showed a *p*-value of 0.0068 for the 'creatinine by treatment' interaction but a p-value of 0.3191 for the main effect.

RE-MODEL

The results of RE-MODEL with respect to the primary endpoint (total VTE and all-cause mortality) are presented in **Table 23**. Since the 95% confidence intervals for the risk difference *versus* enoxaparin were within the non-inferiority margin of 9.2% specified in the hypothesis, both DBG doses demonstrated non-inferiority to enoxaparin.

Table 23 RE-MODEL primary efficacy outcome

	DBG 220mg	**DBG 150mg**	**Enoxaparin**
FAS (n)	503	526	512
Total VTE and all-cause mortality (%)	36.4	40.5	37.7
Risk difference *versus* enoxaparin	-1.3	2.8	
95% CI (%)	(-7.3, 4.6)*	(-3.1, 8.7)*	
p-value	0.6648	0.3553	
Relative risk over enoxaparin	0.97	1.07	
95% CI	(0.82, 1.13)	(0.92, 1.25)	

CI = confidence interval; DBG, dabigatran etexilate; FAS = full analysis set, i.e. mITT (modified intention to treat) analysis.
*Within the pre-defined non-inferiority margin of 9.2%

The treatment-blinded review of protocol deviations resulted in only 6.6% of the FAS patients being excluded from the per protocol set, therefore the PPS analysis was not required.

Subgroup analyses were performed for the primary endpoint in an exploratory manner (**Table 24**). The analysis of subgroups was supported by univariate and multivariate logistic regression analyses.

Table 24 Subgroup analyses of the primary endpoint (RE-MODEL)

Subgroup	DBG 220mg			DBG 150mg			Enoxaparin		
	N	Incidence	%	N	Incidence	%	N	Incidence	%
FAS	503	183	36.4	526	213	40.5	512	193	37.7
Age (years)									
<65	172	57	33.1	183	70	38.3	152	42	27.6
65-75	230	90	39.1	239	100	41.8	261	111	42.5
>75	101	36	35.6	104	43	41.3	99	40	40.4
Age (years)									
<70	267	89	33.3	285	110	38.6	272	95	34.9
≥ 70	236	94	39.8	241	103	42.7	240	98	40.8
Gender									
Male	183	57	31.1	194	75	38.7	162	50	30.9
Female	320	126	39.4	332	138	41.6	350	143	40.9
Weight (kg)									
Missing	0	0	0.0	0	0	0.0	1	1	100.00
<50	3	1	33.3	0	0	0.0	5	0	0.0
50-110	483	173	35.8	504	207	41.1	482	183	38.0
>110	17	9	52.9	22	6	27.3	24	9	37.5
BMI (kg/m^2)									
Missing	2	2	100.00	1	0	0.0	1	1	100.0
<25	76	19	25.0	78	25	32.1	86	24	27.9
25-30	201	78	38.8	199	80	40.2	189	76	40.2
30-35	154	64	41.6	155	77	49.7	158	59	37.3
>35	70	20	28.6	93	31	33.3	78	33	42.3
Creatinine clearance (mL/min)									
Missing	19	10	52.6	18	8	44.4	11	5	45.5
<30	0	0	0.0	1	0	0.0	1	0	0.0
30-50	27	12	44.4	27	12	44.4	38	15	39.5
50-80	174	61	35.1	185	73	39.5	190	74	38.9
≥ 80	283	100	35.3	295	120	40.7	272	99	36.4

BMI, body mass index; DBG, dabigatran etexilate; FAS, full analysis set; N, number of patients; VTE, venous thromboembolism.

For the different subgroups, some trends seemed apparent. The incidence of total VTE and all-cause mortality appeared to be lower in patients below 70 years of age than in patients of 70 years of age and above in all treatment groups. Patients with a lean BMI of <25 kg/m^2 appeared to have lower total VTE rates than obese patients (BMI 30 to 35 kg/m^2).

With regard to renal function, patients with moderate impairment (CrCl for 30 to 50 mL/min) appeared to have somewhat higher incidences of total VTE than patients with normal creatinine clearance (CrCl ≥ 80 mL/min). This effect was more pronounced in the DBG 220 mg group and was of comparable magnitude in the DBG 150 mg group and the enoxaparin group.

The incidence of the primary endpoint was lower in male patients than in female patients independent of the treatment.

RE-MOBILIZE

The results of the RE-MOBILIZE trial were surprising in that the rate of VTE and all-cause mortality in the enoxaparin group was substantially lower than expected (**Table 25**). VTE rates for both DBG doses were also lower than those observed in RE-MODEL.

Table 25 RE-MOBILIZE primary efficacy outcome

	DBG 220mg	**DBG 150mg**	**Enoxaparin**
FAS (n)	604	649	643
Total VTE and all-cause mortality (%)	31.1	33.7	25.3
Risk difference *versus* enoxaparin	5.8	8.4	
95% CI (%)	(0.8, 10.8)	(3.4, 13.3)	
p-value	0.0234	0.0009	
Relative risk over enoxaparin	1.23	1.33	
95% CI	(1.03, 1.47)	(1.12, 1.58)	

CI = confidence interval; DBG, dabigatran etexilate; FAS = full analysis set, i.e. mITT (modified intention to treat) analysis

The treatment-blinded review of protocol deviations resulted in only 4.5% of the FAS patients being excluded from the per protocol set, therefore the PPS analysis was not required.

Subgroup analyses were performed for the primary endpoint in an exploratory manner (**Table 26**). The analysis of subgroups was supported by univariate and multivariate logistic regression analyses.

Table 26 Subgroup analyses of the primary endpoint (RE-MOBILIZE)

Subgroup	DBG 220mg			DBG 150mg			Enoxaparin		
	N	Incidence	%	N	Incidence	%	N	Incidence	%
FAS	604	188	31.1	649	219	33.7	643	163	25.3
Age (years)									
<65	257	72	28.0	266	89	33.5	254	51	20.1
65-75	255	82	32.2	278	89	32.0	282	80	28.4
>75	92	34	37.0	105	41	39.0	107	32	29.9
Age (years)									
<70	376	115	30.6	400	133	33.3	392	92	23.5
≥ 70	228	73	32.0	249	86	34.5	251	71	28.3
Gender									
Male	272	83	30.5	279	94	33.7	278	73	26.3
Female	332	105	31.6	370	125	33.8	365	90	24.7
Weight (kg)									
<50	2	0	0.0	5	1	20.0	4	0	0.0
50-110	527	171	32.4	568	197	34.7	560	132	23.6
>110	75	17	22.7	76	21	27.6	79	31	39.2
BMI (kg/m^2)									
<25	70	18	25.7	77	21	27.3	71	10	14.1
25-30	205	71	34.6	243	88	36.2	222	55	24.8
30-35	182	56	30.8	196	73	37.2	199	45	22.6
>35	147	43	29.3	133	37	27.8	151	53	35.1
Creatinine clearance (mL/min)									
Missing	8	1	12.5	8	1	12.5	7	1	14.3
<30	3	1	33.3	4	1	25.0	3	0	0.0
30-50	52	9	17.3	65	21	32.3	64	13	20.3
50-80	229	82	35.8	288	102	35.4	259	67	25.9
≥ 80	312	95	30.4	284	94	33.1	310	82	26.5

BMI, body mass index; DBG, dabigatran etexilate; FAS, full analysis set; N, number of patients; VTE, venous thromboembolism.

The lowest event rates were generally observed in the enoxaparin group, followed by the DBG 220 mg group, and with slightly higher incidences in the DBG 150 mg group for most subgroups.

The incidence of total VTE and all-cause mortality appeared to be slightly lower in patients below 65 years of age than in patients over 75 years of age in all treatment groups. Patients with a lean BMI of <25 kg/m^2 appeared to have lower total VTE rates than patients with BMI 35 kg/m2 or higher, but the event rates were too infrequent to allow clinically meaningful comparisons.

Secondary endpoints

Key point
• As was to be expected, analysis of the individual VTE components showed that asymptomatic DVT was the main component of the primary efficacy endpoint

Results reported for the secondary efficacy endpoints are for the patient sets as defined in **Table 16**.

RE-NOVATE

In the RE-NOVATE study, the primary efficacy endpoint was mainly composed of asymptomatic DVTs (**Table 27**). Symptomatic event rates were low and the only fatal PE occurred in the DBG 150mg group.

Table 27 RE-NOVATE - individual components of the primary efficacy outcome

	DBG 220mg	DBG 150mg	Enoxaparin
FAS	880	874	897
Total VTE and all-cause mortality, *N* (%)	53 (6.0%)	75 (8.6%)	60 (6.7%)
Asymptomatic DVT	40 (4.5%)	63 (7.2%)	56 (6.2%)
Symptomatic DVT	5 (0.6%)	9 (1.0%)	1 (0.1%)
Nonfatal PE	5 (0.6%)	0	3 (0.3%)
Death, VTE cannot be ruled out	1 (0.1%)	3 (0.3%)	0
Death not associated with VTE	2 (0.2%)	0	0

DBG, dabigatran etexilate; FAS = full analysis set, i.e. mITT (modified intention to treat) analysis

RE-MODEL

The individual components of the primary efficacy outcome (**Table 28**) demonstrated that asymptomatic DVT was the main component of the efficacy endpoint. Symptomatic event rates were low: in the 220mg DBG group, the 150mg DBG group and the enoxaparin group, the numbers of patients with symptomatic DVT were 1, 3 and 8, respectively; for PE, the numbers were 0, 1 and 1; one death occurred in each treatment arm.

Table 28 RE-MODEL - individual components of the primary efficacy outcome

	DBG 220mg	DBG 150mg	Enoxaparin
FAS (n)	503	526	512
Total VTE and all-cause mortality, *N* (%)	183 (36.4)	213 (40.5)	193 (37.7)
Asymptomatic DVT	181 (36.0)	208 (39.5)	184 (35.9)
Symptomatic DVT	1 (0.2)	3 (0.6)	8 (1.6)
Nonfatal PE	0	1 (0.2)	0
Death, VTE cannot be ruled out	0	1 (0.2)	1 (0.2)
Death not associated with VTE	1 (0.2)	0	0

DBG, dabigatran etexilate; FAS = full analysis set, i.e. mITT (modified intention to treat) analysis

RE-MOBILIZE

As in the pivotal trials, the primary efficacy endpoint in RE-MOBILIZE was mainly composed of asymptomatic DVTs (**Table 29**).

Table 29 RE-MOBILIZE - individual components of the primary efficacy outcome

	DBG 220mg	DBG 150mg	Enoxaparin
FAS	604	649	643
Total VTE and all-cause mortality, *N* (%)	188 (31.1)	219 (33.7)	163 (25.3)
Asymptomatic DVT	174 (28.8)	212 (32.7)	153 (23.8)
Symptomatic DVT	7 (1.2)	6 (0.9)	5 (0.8)
Nonfatal PE	6 (1.0)	0	5 (0.8)
Death, VTE cannot be ruled out	1 (0.2)	0	0
Death not associated with VTE	0	1 (0.2)	0

DBG, dabigatran etexilate; FAS = full analysis set, i.e. mITT (modified intention to treat) analysis

5.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 5.2.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- ***Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.***
- ***Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).***
- ***Provide an adequate description of the methods of statistical combination and justify their choice.***
- ***Undertake sensitivity analysis where appropriate.***
- ***Tabulate and/or graphically display the individual and combined results.***

Meta-analyses were performed for the primary efficacy endpoint (total VTE and all- cause mortality) and for the most clinically relevant secondary endpoint (major VTE and VTE-related death, including proximal DVT, symptomatic and well-documented non-fatal PE, and VTE related deaths), which EMEA guidelines recommend in order to support a claim of therapeutic non-inferiority. This endpoint was defined as a secondary efficacy endpoint in each individual trial, mainly due to sample size and feasibility concerns.

Each comparison consisted of one fixed effects meta-analysis with the combined European trials (RE-NOVATE and RE-MODEL), as well as one fixed and one random effects meta-analysis for the 3 trials combined (including RE-MOBILIZE). The data on which the meta-analyses are based are presented in the previous sub-section. Please refer to Section 5.9.2 for more detail on the reasons for this particular delination of the clinical trials.

Figure 9 through **Figure 11** present the meta-analyses of the primary endpoint for the comparison of DBG 220mg versus enoxaparin. **Figure 12** through **Figure 14** presents the corresponding analyses for DBG 150mg.

Figure 9 **Meta-analysis of the primary endpoint (DBG 220mg, European trials only, fixed effects)**

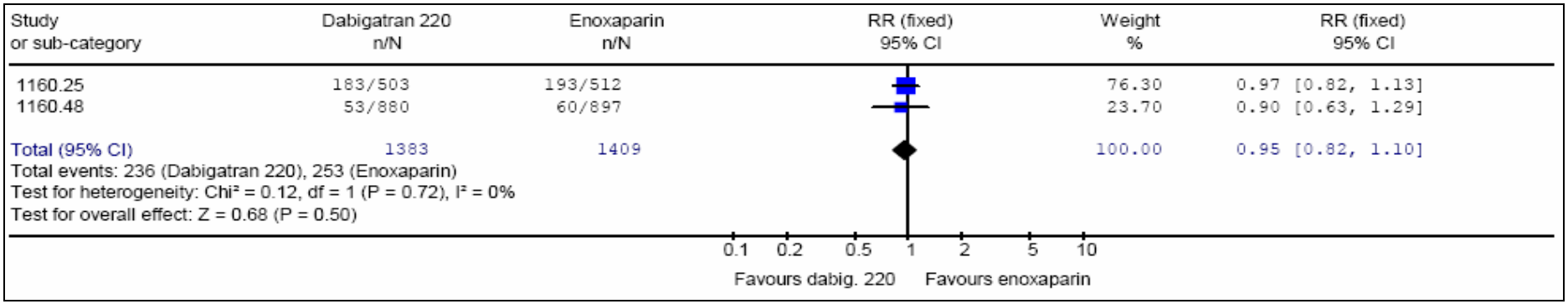


Figure 10 **Meta-analysis of the primary endpoint (DBG 220mg, all trials, fixed effects)**

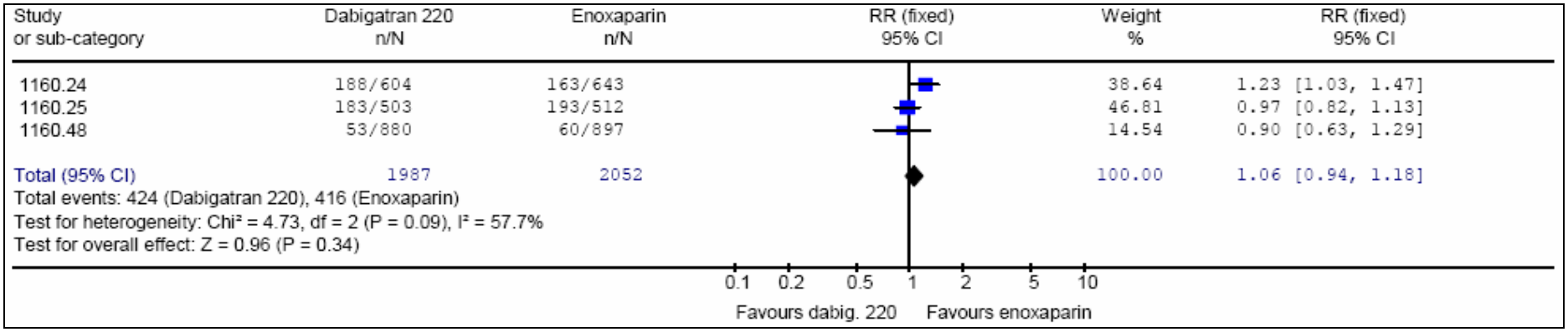


Figure 11 **Meta-analysis of the primary endpoint (DBG 220mg, all trials, random effects)**

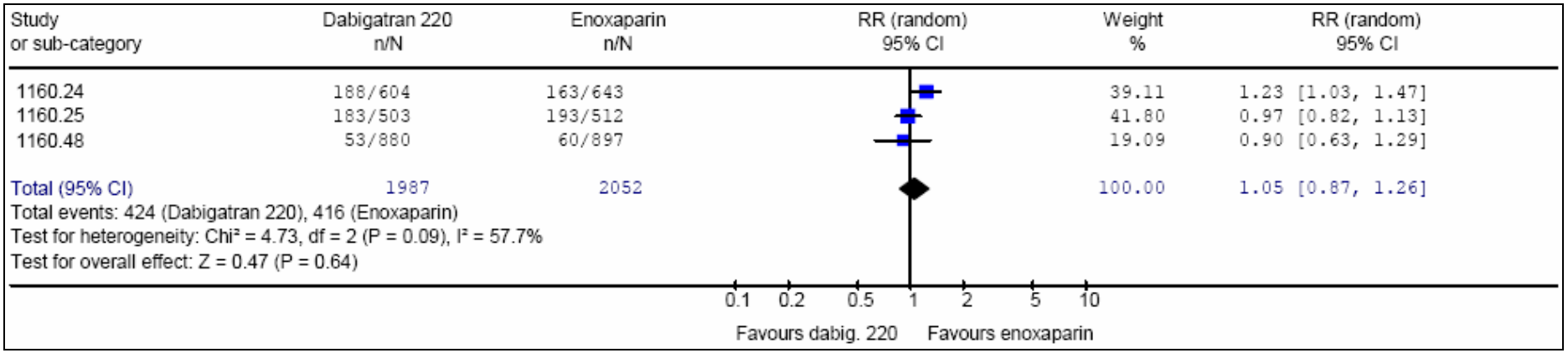


Figure 12 **Meta-analysis of the primary endpoint (DBG 150mg, European trials only, fixed effects)**

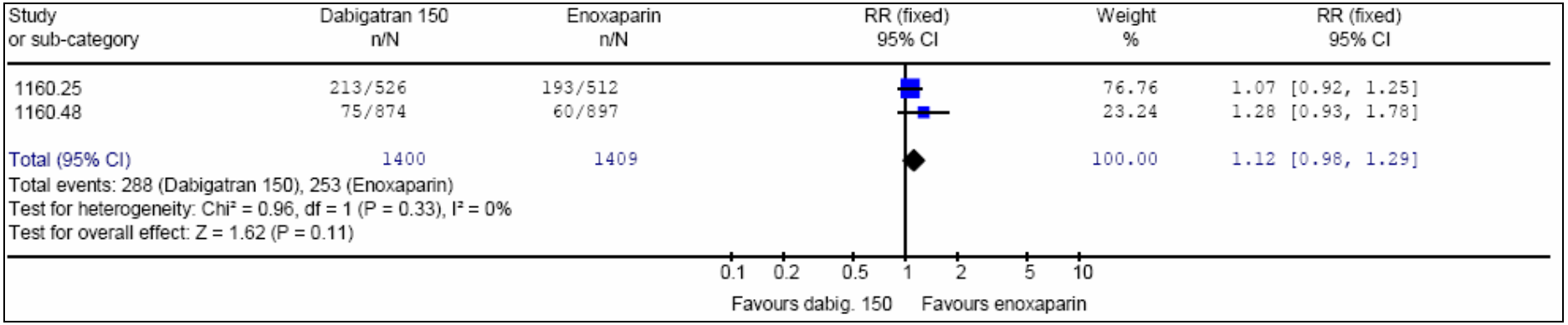


Figure 13 **Meta-analysis of the primary endpoint (DBG 150mg, all trials, fixed effects)**

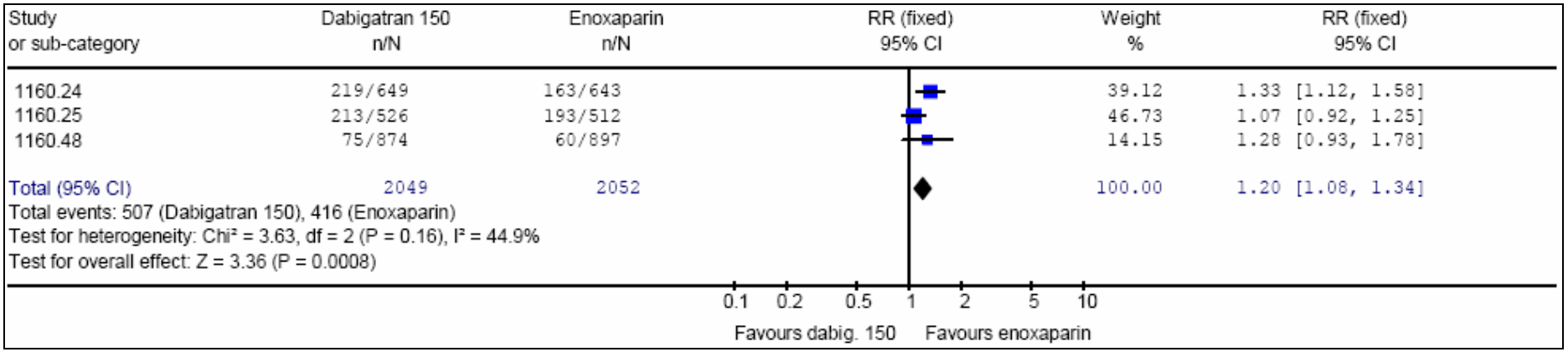
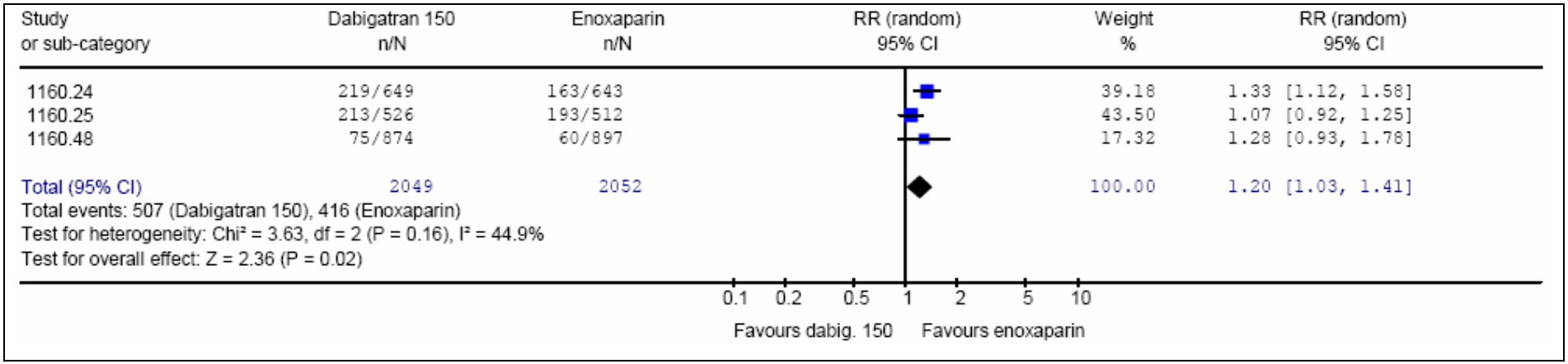


Figure 14 **Meta-analysis of the primary endpoint (DBG 150mg, all trials, random effects)**



For DBG 220mg, each of the pooled estimates supports the conclusion of non-inferiority. In the DBG 150mg comparisons, only pooled estimate from the meta-analysis of the European trials supports the conclusion of non-inferiority. In all cases, the inclusion of RE-MOBILIZE causes the pooled estimate to shift to the right. Further, the tests for heterogeneity reveal that the analyses including RE-MOBILIZE demonstrate more evidence of differences between the studies (although not statistically significant). This concurs with the differences in the RE-MOBILIZE trial design and treatment regimens outlined in the previous sub-sections.

Figure 15 through **Figure 17** present the meta-analyses of the secondary endpoint (major VTE and VTE-related death) for the comparison of DBG 220mg versus enoxaparin. **Figure 18** through **Figure 20** presents the corresponding analyses for DBG 150mg.

Figure 15 Meta-analysis of the major VTE and VTE-related death (DBG 220mg, European trials only, fixed effects)

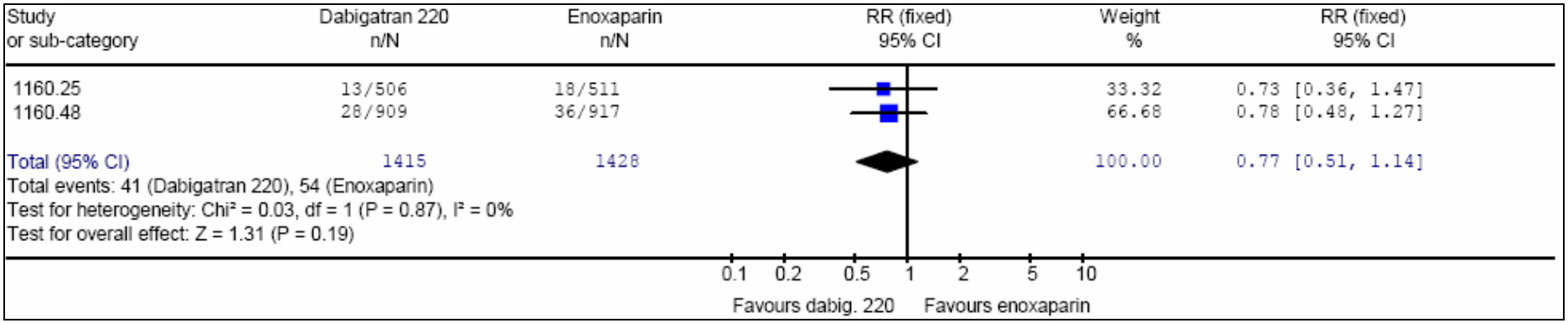


Figure 16 Meta-analysis of the major VTE and VTE-related death (DBG 220mg, all trials, fixed effects)

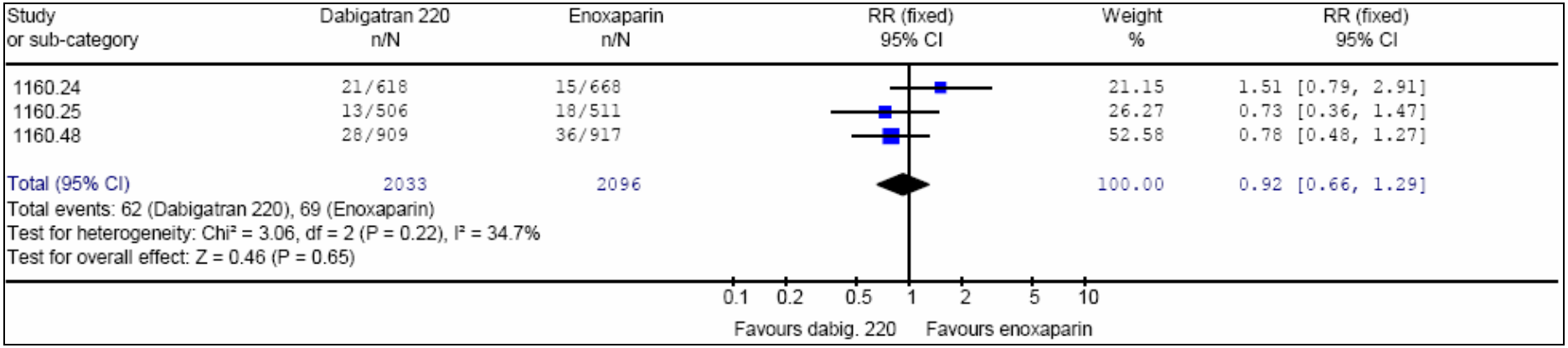


Figure 17 Meta-analysis of the major VTE and VTE-related death (DBG 220mg, all trials, random effects)

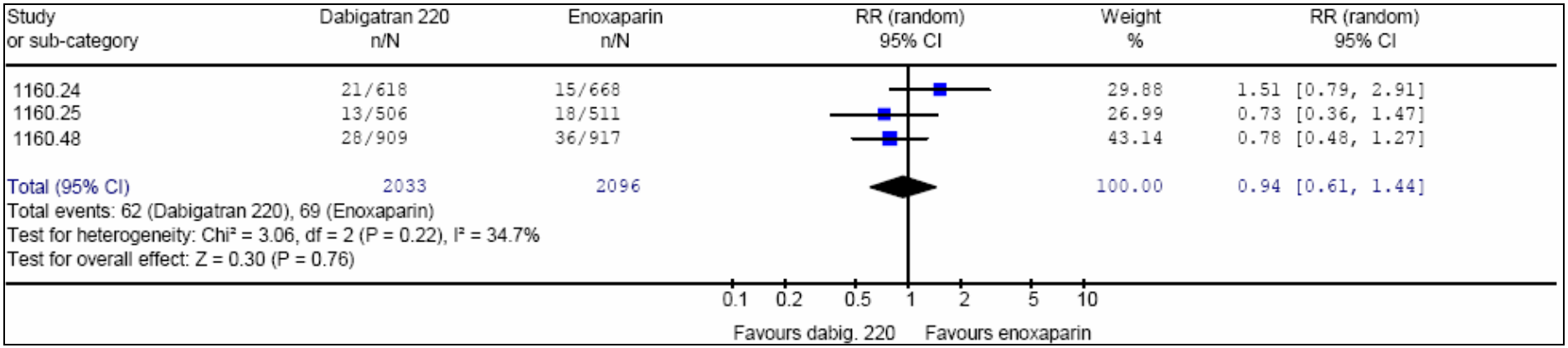


Figure 18 Meta-analysis of the major VTE and VTE-related death (DBG 150mg, European trials only, fixed effects)

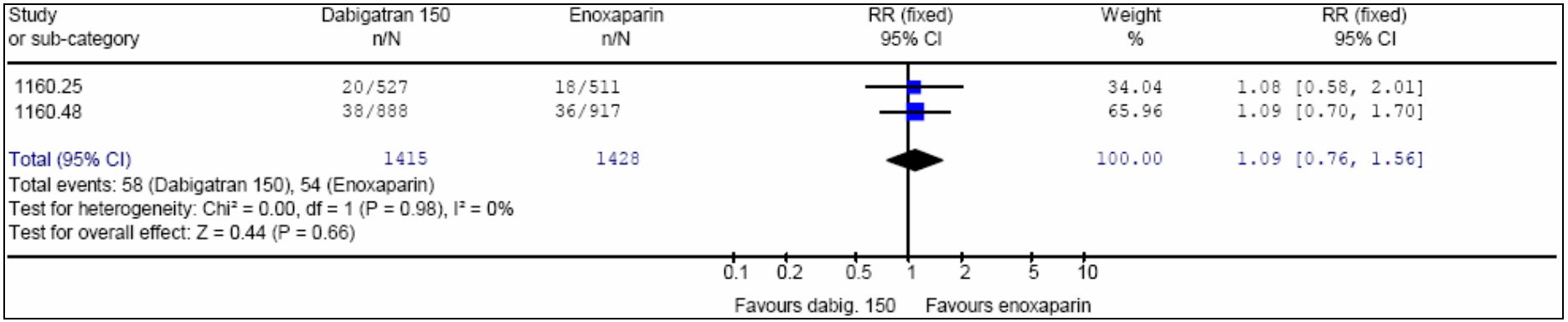


Figure 19 Meta-analysis of the major VTE and VTE-related death (DBG 150mg, all trials, fixed effects)

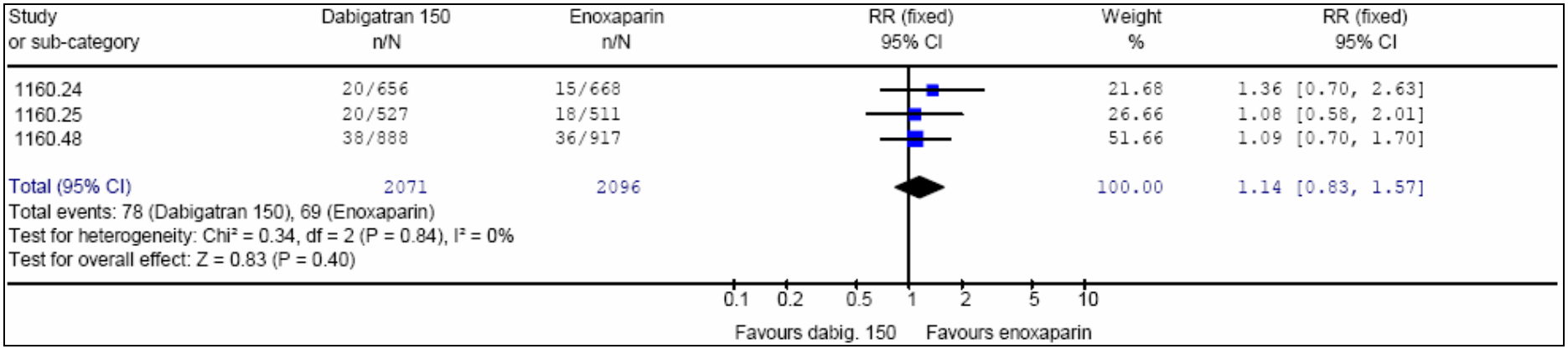
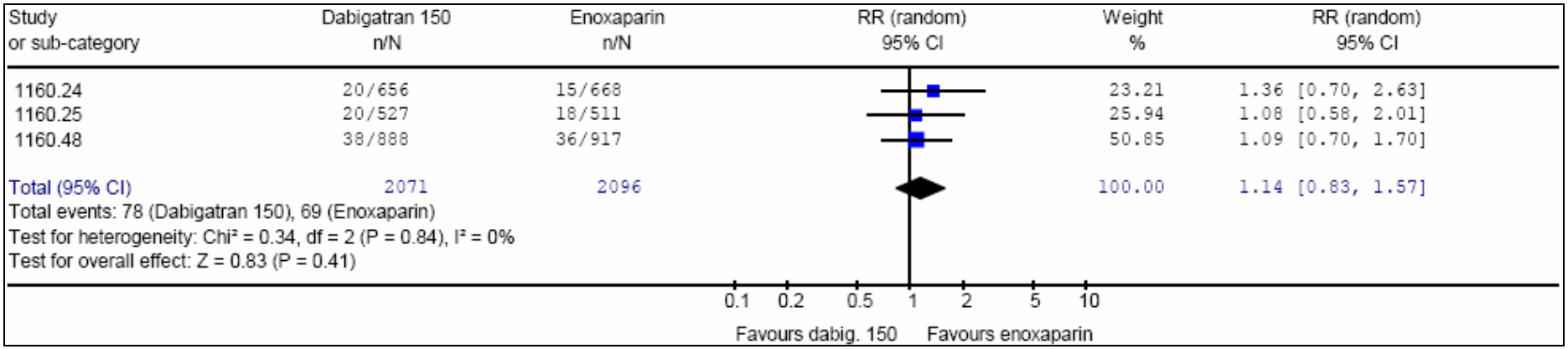


Figure 20 Meta-analysis of the major VTE and VTE-related death (DBG 150mg, all trials, random effects)



In all analyses, the pooled estimates support the conclusion of non-inferiority in this endpoint. There is little evidence of heterogeneity in the European trial analyses, with the inclusion of RE-MOBILIZE leading to a moderate increase in the chi-squared statistic (more pronounced in the DBG 220mg comparisons).

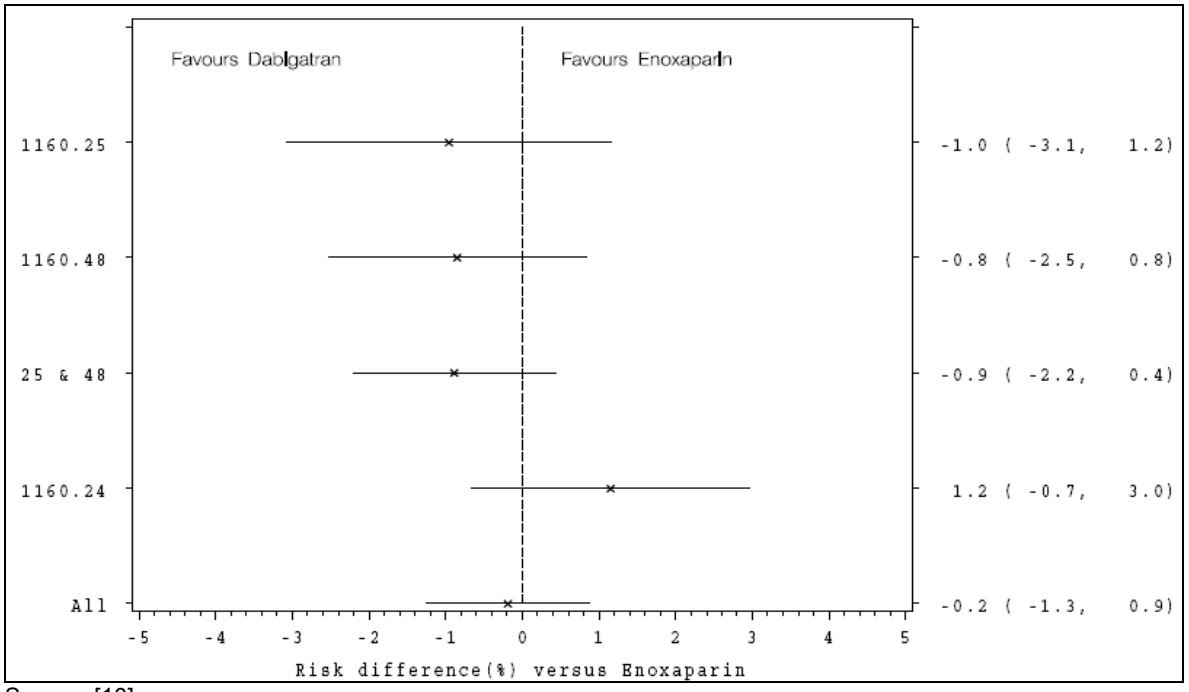
Pre-specified pooled analysis

The purpose of the pre-specified pooled analyses [40] was to evaluate efficacy outcomes using a larger patient population than the individual trials can provide. Similar to the secondary endpoint meta-analyses above, the efficacy outcome evaluated in the pooled analysis was the composite of major VTE and VTE-related mortality during the treatment period. The analyses in the pre-specified pooled analysis reported percentage risk difference as opposed to relative risk.

Methodologically, no confirmatory statistical hypothesis test was pre-specified. All analyses were exploratory and presented confidence intervals and descriptive *p*-values to compare each test therapy to enoxaparin.

A confidence interval plot illustrates the risk difference for DBG 220mg versus enoxaparin in terms of major VTE and VTE-related mortality (**Figure 21**). The two European trials, RE-MODEL and RE-NOVATE, show similar results. Pooling the results of these two trials decreases the width of the confidence interval although there is no change in the mean risk difference versus enoxaparin. The addition of the RE-MOBILIZE results decreases the mean risk difference to -0.2% (95% confidence interval: -1.3, 0.9).

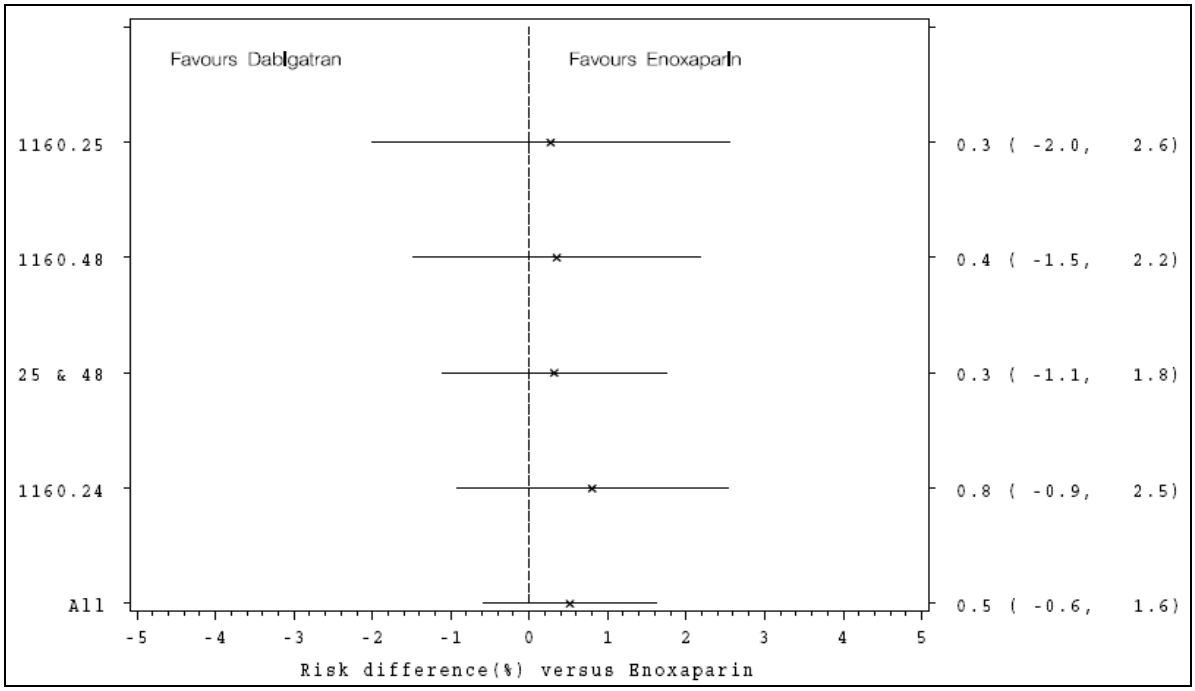
Figure 21 Pooled analysis results (220mg dabigatran etexilate)



Source: [10]
1160.25, RE-MODEL; 1160.48, RE-NOVATE; 1160.24, RE-MOBILIZE.

Similar results are seen for the 150mg DBG dose (**Figure 22**). Although the mean results appear to favour enoxaparin, all of the confidence intervals cross zero, indicating statistically non-significant differences for the risk for major VTE and VTE-related mortality.

Figure 22 Pooled analysis results (150mg dabigatran etexilate)



Source: [10]
1160.25, RE-MODEL; 1160.48, RE-NOVATE; 1160.24, RE-MOBILIZE.

Sensitivity analyses were conducted using different scenarios. The best case scenario imputed no events and the worst case scenario imputed an event for each instance of missing data across the treatment arms (**Table 30**). In most analyses, for both the 220mg and 150mg DBG doses, differences were not statistically significant. However, in most cases the upper limit of the confidence intervals is still quite low, even in the worst case scenario.

Table 30 Pooled analysis - sensitivity analysis results

Trial/analysis	Difference *versus* enoxaparin		95% confidence interval	
	220mg	150mg	220mg	150mg
Best case scenario				
RE-MODEL	-0.7	0.2	(-2.3, 0.9)	(-1.5, 2.0)
RE-NOVATE	-0.7	0.1	(-2.0, 0.7)	(-1.3, 1.6)
RE-MOBILIZE	0.7	0.6	(-0.6, 2.1)	(-0.8, 1.9)
RE-MODEL and RE-NOVATE	-0.7	0.2	(-1.7, 0.3)	(-0.9, 1.3)
All trials*	-0.2	0.3	(-1.0, 0.6)	(-0.5, 1.2)
Worst case scenario				
RE-MODEL	-1.1	-0.9	(-5.8, 3.7)	(-5.6, 3.8)
RE-NOVATE	-0.3	3.6	(-3.8, 3.1)	(0.1, 7.1)
RE-MOBILIZE	5.6	2.2	(1.4, 9.8)	(-1.9, 6.3)
RE-MODEL and RE-NOVATE	-0.6	2.0	(-3.4, 2.2)	(-0.8, 4.8)
All trials*	1.3	2.1	(-1.0, 3.6)	(-0.3, 4.4)

*Fixed effect model

5.6 Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest, consideration should be given to using indirect/mixed treatment comparisons. This analysis indirectly compares the proposed technology with the main comparator by comparing one set of RCTs in which participants were randomised to the intervention/common reference with another set of RCTs in which participants were randomised to the main comparator/common reference. The common reference is often placebo, but may be an alternative technology.

Before comparing the proposed technology with the main comparator, the comparability of the two sets of RCTs must be established. If the RCTs have not been described in the previous sections the methodology and results from the RCTs included in the analysis should be summarised using the format described in sections 5.3 and 5.4 Highlight any potential sources of heterogeneity between the RCTs included in the analysis.

Give a full description of the methodology used and provide a justification for the approach.

MIXED TREATMENT COMPARISONS META-ANALYSIS

Objectives and methodology

Routine practice of VTE thromboprophylaxis in major orthopaedic surgery demonstrates significant variation across countries. Whilst the phase-III clinical trial programme studied the direct comparison of DBG against the current gold standard of care (LMWH), there was a clear need for a series of indirect comparisons examining the relative treatment effect and safety of DBG versus the many other possible alternatives. To this end, Boehringer Ingelheim conducted a literature search to systematically identify the most up-to-date, comprehensive meta-analysis (or meta-analyses) available in the literature describing the efficacy and safety of antithrombotic medication for the prevention of VTE associated with total hip and knee replacement surgery.

The search strategy and full references of the included studies for the literature search of meta-analyses appropriate for the MTC is provided in Appendix 9.6.

Quality control for study inclusion

Secondary confirmation of included/excluded studies was performed by independent evaluation of all abstracts by a second person and reconciliation of discrepancies.

Results of the search

Study retrieval, inclusion and exclusion are described in **Figure 23**. A total of 246 articles were retrieved by the electronic searches (after elimination of duplicates) of which 205 were excluded (179 were not a meta-analysis of an included intervention, 8 were in an excluded patient group, 1 was in an excluded indication, 1 was not in English, and 16 were

duplicate reports. Two meta-analyses were identified within economic analyses retrieved as part of a separate search. A total of 43 meta-analyses therefore met the inclusion criteria.

Since the searches were conducted, one additional meta-analysis was identified, performed by the UK National Co-ordinating Centre for Acute Care (NCC-AC, 2007) [41] as part of the guideline development programme by the UK National Institute for Health and Clinical Excellence for VTE prevention in patients undergoing orthopaedic and other high risk surgery (NICE, 2007) [1]. This was added to the systematic review. Since this analysis was performed so recently, updating is unnecessary.

Details of the included meta-analyses are summarised in **Table 31**. Analyses in which only one included intervention were analysed are included as these may represent the best synthesis of data for that individual intervention. There were twelve of these in total, some of which compared different durations of prophylaxis or timing of initiation of prophylaxis for the same agent.

Of the 43 meta-analyses identified, only 7 reported data in a format that would allow the analysis to be updated (i.e. data were reported at the individual trial level for all study arms and at least some of the major endpoints relevant to our analysis). Details of these studies are summarised in **Table 32**. Of these 7 studies, 3 did not report any quality control procedures for data abstraction (Anderson [42], Martel [43], Turpie [44]). The accuracy of the data reported in these articles may therefore be open to question.

Figure 23 Study retrieval, inclusion and exclusion

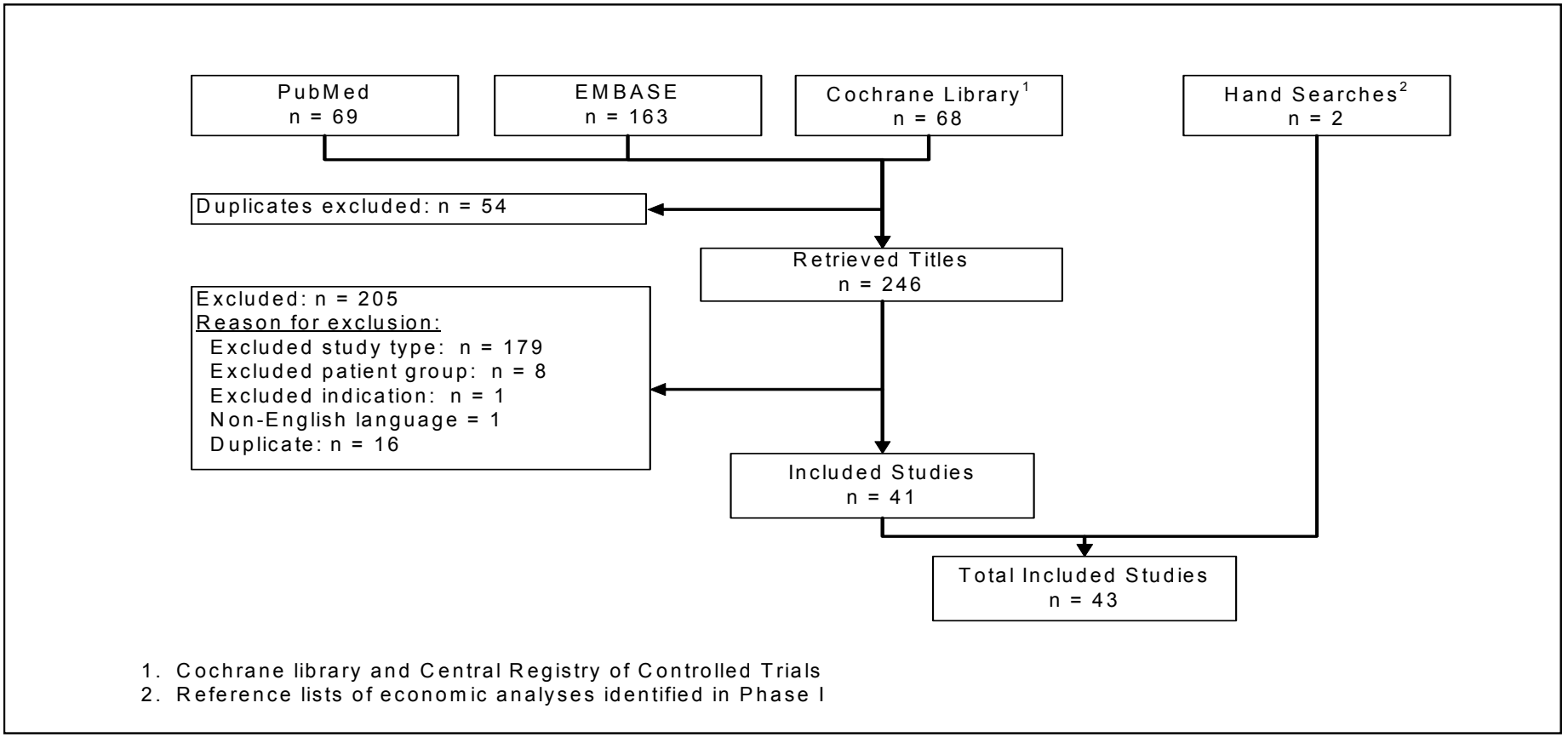


Table 31 Included Meta-Analyses

Study No.	Author, date	No. Relevant Interventions Analysed	Both THR & TKR Included	Efficacy and Safety Included	Data reported for individual Trials	ID
1	Mismetti, 2004	5	yes	yes	yes	MR013
2	Freedman, 2000	4	THR only	yes	no	MR040
3	Imperiale, 1994	4	THR only	yes	no	MR056
4	Mohr, 1993	4	THR only	efficacy only	no	MR062
5	Muntz, 2004	3	yes	safety (major bleed) only	RR only	MR010
6	Oster 1987	3	yes	efficacy only	no	H015
7	Anderson 1998	3	yes	yes	yes	R411
8	Westrich, 2000	3	TKR only	efficacy only	no	MR039
9	Palmer, 1997	3	yes	yes	no	MR050
10	Martel, 2005	2	yes	safety (thrombocytopenia) only	yes	MR007
11	Turpie, 2002	2	yes	yes	OR only	MR022
12	Douketis, 2002	2	yes	efficacy only	not in all study arms	MR023
13	Turpie, 2002	2	yes	yes	yes	MR029
14	Hull, 2001	2	THR only	yes	yes	MR033
15	Eikelboom, 2001	2	yes	yes	yes	MR035
16	Koch, 2001	2	yes	efficacy & wound haematoma only	no	MR036
17	Brookenthal 2001	2	TKR only	yes	no	MR037
18	Wade, 1999	2	THR only	na	not all arms	MR041
19	Koch, 1997	2	yes	yes	yes	MR049
20	Menzin, 1995	2	THR only	efficacy only	not all arms	MR055
21	Borris, 1994	2	THR only	unknown	na	MR057
22	O'Brien, 1994	2	THR only	unknown	not all arms	MR058
23	Anderson, 1993	2	THR only	yes	not all arms	MR061
24	Jorgensen, 1993	2	unknown	yes	na	MR063
25	Leizorovicz, 1992	2	unknown	yes	na	MR064
26	Nurmohamed, 1992	2	yes	yes	na	MR066
27	Lassen, 1991	2	THR only	efficacy only	1 end-point only	MR068
28	Botteman, 2002	2	THR only	efficacy only	1 end-point only	MR245
29	Hull, 1999	1	THR only	yes	not all arms	MR042
30	Urbankova, 2005	1	yes	efficacy only	na	MR005

Study No.	Author, date	No. Relevant Interventions Analysed	Both THR & TKR Included	Efficacy and Safety Included	Data reported for individual Trials	ID
31	Cohen, 2005	1	yes	yes	na	MR006
32	Zufferey, 2005	1	yes	yes	na	MR008
33	Iorio, 2005	1	yes	yes	na	MR009
34	Zufferey, 2003	1	yes	yes	na	MR019
35	O'Donnell, 2003	1	THR only	efficacy only	na	MR021
36	Strebel, 2002	1	THR only	yes	na	MR024
37	Ferriols-Lisart, 2002	1	yes	efficacy & wound haematoma only	na	MR026
38	Hull, 2001	1	THR only	yes	na	MR031
39	Vanek, 1998	1	yes	efficacy only	na	MR045
40	Howard, 1998	1	TKR	yes	na	MR046
41	na	na	na	na	na	MR141
42	Alikhan, 2001	na	TKR only	not available	na	MR038
43	Murray, 1996	1 (may be more)	THR only	fatal PE & death only	na	MR052
-	NCC-AC, 2007	9	yes	yes	yes	-

na, not available

Table 32 Meta-Analyses Reporting Trial-level Data for All Relevant Study Arms

Author, date	Relevant Interventions Included	THR & TKR	Adequacy of Retrieval	No. Studies	Quality of Data Abstraction	Relevant events reported at trial level	ID
Mismetti, 2004	warfarin v UH, LMWH, danaparoid, IPC	yes	Studies not including a VKA were excluded	29 (22 relevant)	4 abstractors, consensus reached	DVT, proximal DVT, PE, death, major haemorrhage, haematoma	MR013
Anderson 1998	LMWH v UH, warfarin	yes	Adequate for included interventions, included searches of SWETSCAN	16	QC procedures for data abstraction not reported	-	R411
Martel, 2005	LMWH v UH	yes	Studies not reporting HIT were excluded	15	QC procedures for data abstraction not reported	-	MR007
Turpie, 2002	fondaparinux v enoxaparin	yes	No searches performed	4	QC procedures for data abstraction not reported	-	MR029
Hull, 2001	LMWH (different dosing schedules) v oral AC	THR only	Only included trials comparing prolonged LMWH with placebo	7	Dual abstraction	All DVT, proximal DVT, symptomatic VTE	MR033
Eikelboom, 2001	extended heparin, warfarin v placebo	yes	Only included trials comparing prolonged LMWH/warfarin with placebo	9	Dual abstraction, consensus, sent to the primary investigator for verification.	Symptomatic VTE, symptomless VTE	MR035
Koch, 1997	LMWH v UH	yes	Adequate for included interventions	36 (11 relevant)	Dual abstraction & consensus.	DVT, death, PE, haemorrhage*	MR049
NCC-AC, 2007	All except desirudin	Yes**	Adequate for included interventions	248	Information not available	DVT, PE, Major Bleed	-

* bleeds reported separately haematoma and for those needing transfusion, reintervention, or resulting in withdrawal.
** included other surgery types also
Articles including only 1 relevant intervention or reporting trial-level data for only one end-point are not reported in the table since original articles would have to be abstracted for all other end-points of interest

The following 4 articles are also not appropriate for updating for the following reasons:

- Mismetti [45] excluded all studies that did not include a vitamin K antagonist, thus trials comparing for example enoxaparin and unfractionated heparin or fondaparinux were excluded;
- Hull [46] included only those trials comparing prolonged LMWH with placebo;
- Eikelboom [47] included only those trials comparing prolonged LMWH or warfarin with placebo; and
- Koch [48] did not report DVT events in sufficient detail; the distinction between venographic and symptomatic, and also proximal and distal is unclear.

Conclusions

The NCC-AC meta-analysis [41] was identified as the only analysis that would be appropriate for the project. Since it was performed very recently, updating is unnecessary.

NCC-AC meta-analysis

The mixed treatment comparison was based on a recent meta-analysis performed by the UK National Co-ordinating Centre for Acute Care (NCC-AC) [41], an analysis which underpinned the NICE clinical guideline for VTE prevention in patients undergoing orthopaedic and other high risk surgery [1].

This mixed treatment comparison (MTC) meta-analysis reported relative risk (RR) estimates for DVT (detected clinically or by venography, ultrasound or other diagnostic technique) and major bleed for the following comparators compared with nil (placebo or untreated control):

- aspirin
- vitamin K antagonists (warfarin)
- unfractionated heparin (UFH)
- low molecular weight heparin (LMWH)
- danaparoid
- fondaparinux
- graduated compression stockings (GCS)
- intermittent pneumatic compression (IPC) devices
- foot pumps (FP)

Relative risks for alternative LMWH regimens (pre- and post-operatively initiated, standard duration (≤14 days) and extended (>14 days)) were also reported.

While the risk for developing a DVT varies depending on the baseline risk for each type of surgery and patient specific risk factors, the NCC-AC meta-analysis did not find reliable

statistical evidence to be certain of a difference between surgical specialities with respect to the effectiveness of each method of prophylaxis. Consequently, to provide a reliable estimate of the relative effectiveness of different methods of prophylaxis, the RCTs for all surgical specialities were analysed together.

Whilst the results for DBG and fondaparinux are of primary importance in terms of this decision problem, the results for all alternatives are presented here as further evidence of the comparative efficacy and safety of DBG.

Supplementary meta-analyses

Unfortunately, the NCC-AC meta-analysis did not collect and analyse data on minor bleeds and heparin-induced thrombocytopenia (HIT). Therefore, an additional meta-analysis of studies reporting minor bleeds or HIT was also conducted for the interventions of interest (for full details see Appendix 9.7). The primary data source was the published full-text of the studies included in the NCC-AC analyses for major bleed. Studies that were not included in the NCC-AC analyses for major bleed were not reviewed on the assumption that they would not have reported minor bleeds or HIT. No additional analyses were performed for the mechanical devices (IPC, FP and GCS) as it is assumed that these do not increase the risk of bleeding or thrombocytopenia.

To complete the mixed treatment comparisons and supplement the global pooled analysis, separate meta-analyses for the three DBG trials were performed on the following endpoints:

- Major bleed
- Clinically relevant bleed
- Clinically relevant and minor bleed
- HIT
- Total VTE and all cause mortality

Further details concerning the approach and methodology used for the supplemental meta-analysis on safety endpoints can be found in the full report (Appendix 9.7).

Results

As in the meta-analyses and pre-specified pooled analysis reported in the previous sub-section, treatment effects are presented for each trial individually, for RE-MODEL and RE-NOVATE combined, and for all three trials combined. Results are also presented for the 220mg and 150mg doses.

The effects of each DBG dose and alternative prophylaxis regimes versus nil are shown in the following figures:

- Relative risk for DVT (**Figure 24**)
- Relative risk for major bleed (**Figure 25**)
- Relative risk for minor bleed (**Figure 26**)

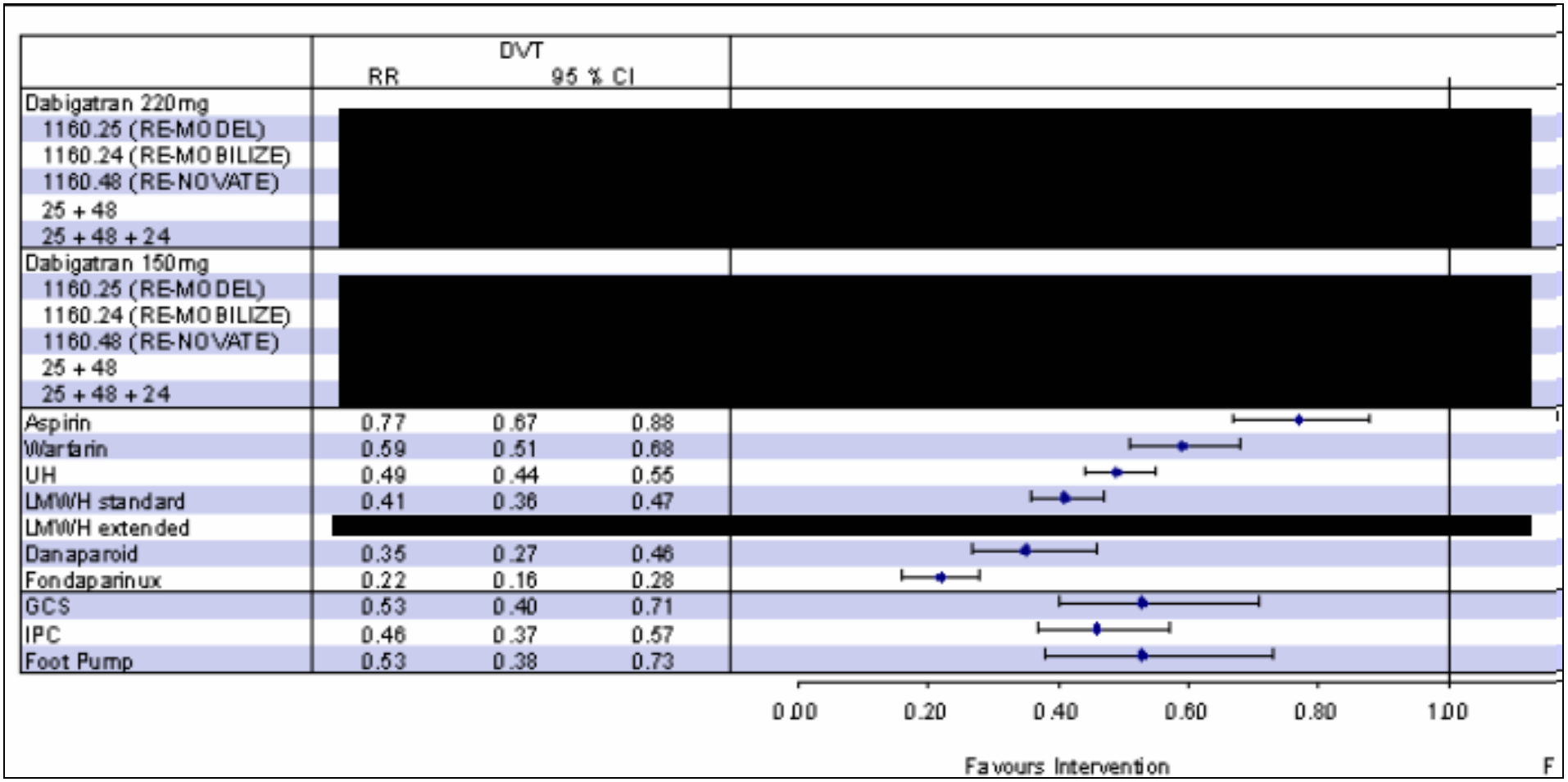
The results from the single intervention meta-analyses show that, among existing therapies, extended LMWH and fondaparinux perform best overall in terms of DVT prevention, with relative risks of [redacted] and [redacted], respectively, compared with no prophylaxis. The mechanical treatments (GCS, IPC and foot pumps) show a similar relative risk (0.53, 0.46 and 0.53, respectively) with overlapping confidence intervals. Results for DBG compare favourably, with the 220mg dose used for 28-35 days in the RE-NOVATE trial offering the smallest relative risk ([redacted]; 95% confidence interval [redacted]) versus no prophylaxis.

The results for the bleeding events highlight the trade-off between increased efficacy (reducing the risk of DVT) and increased bleeding. Fondaparinux, which was one of the most effective pharmacological treatments in reducing the risk of DVT, had the highest estimated relative risk for major bleeding (RR=2.22 *versus* nil) and was second only to unfractionated heparin (UFH) in terms of the risk for minor bleeding (RR=1.89 *versus* nil). DBG compares favourably with alternative pharmacological treatments in terms of bleeding risk. The relative risk for major bleed with DBG versus nil for all trials combined was [redacted] and [redacted] for the 150mg and 220mg doses, respectively. However, the broad confidence intervals for all the strategies overlap, making it difficult to distinguish between the different pharmacological prophylaxis options in terms of safety. It is interesting to note that, in terms of the relative risk for major bleed, the point estimate for RE-MOBILIZE is <1, favouring DBG. For all other chemical prophylaxis options, apart from aspirin, the relative risks are such that no intervention would be considered the preferred intervention.

The estimated pooled risk of HIT is just over 0.6% in the standard duration LMWH treatment group. Including data from the phase-III DBG trials reduced the risk of HIT in LMWH standard duration to 0.4% (95% confidence interval: 0.1%-0.7%).

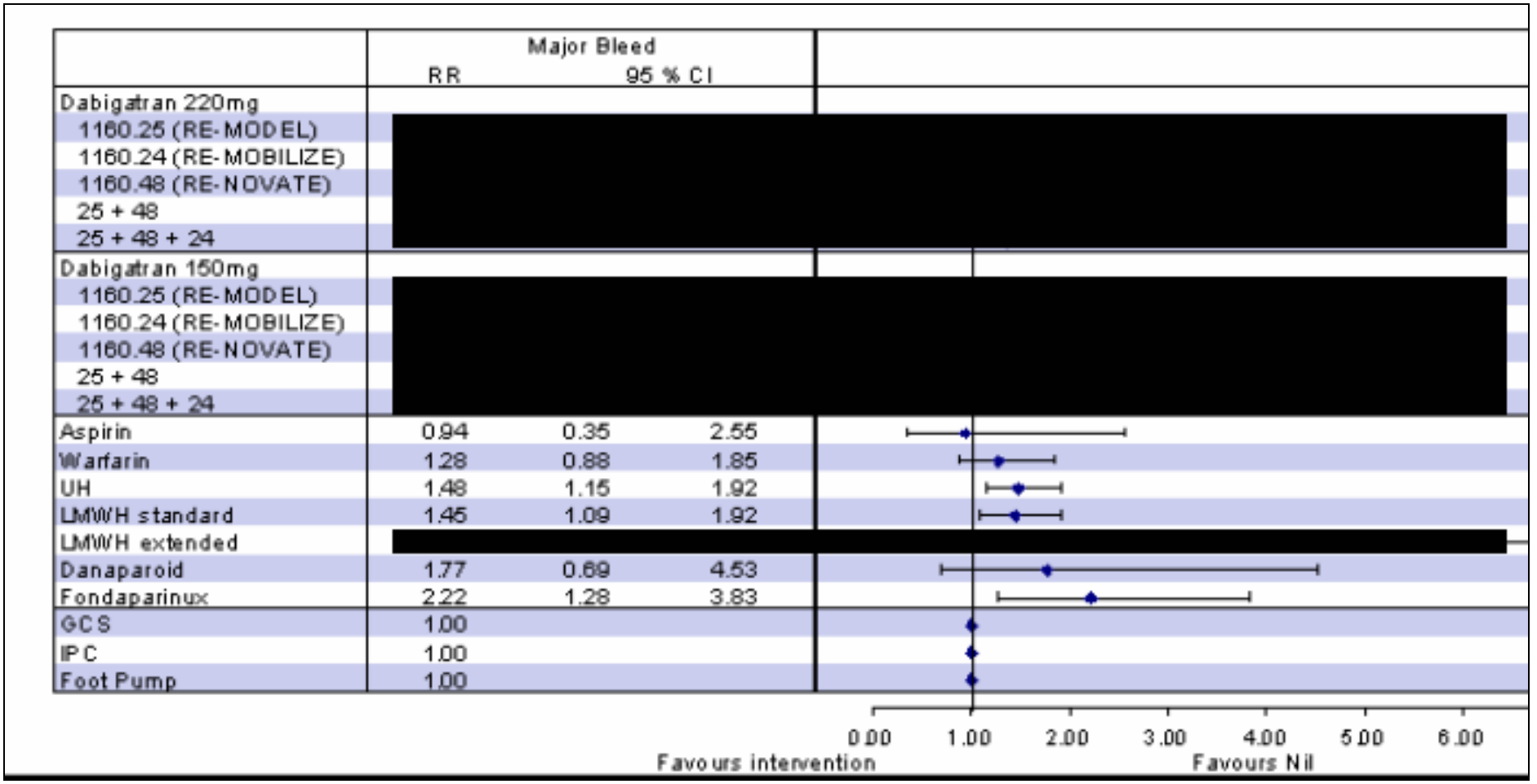
It can be concluded from this analysis that DBG compares favourably with existing alternatives in terms of both efficacy and safety. The estimates gained for DBG and fondaparinux can be applied to the economic evaluation in order to provide an estimate of the cost-effectiveness of DBG compared to fondaparinux.

Figure 24 Relative risks (RRs) for DVT – dabigatran etexilate and comparators *versus* nil



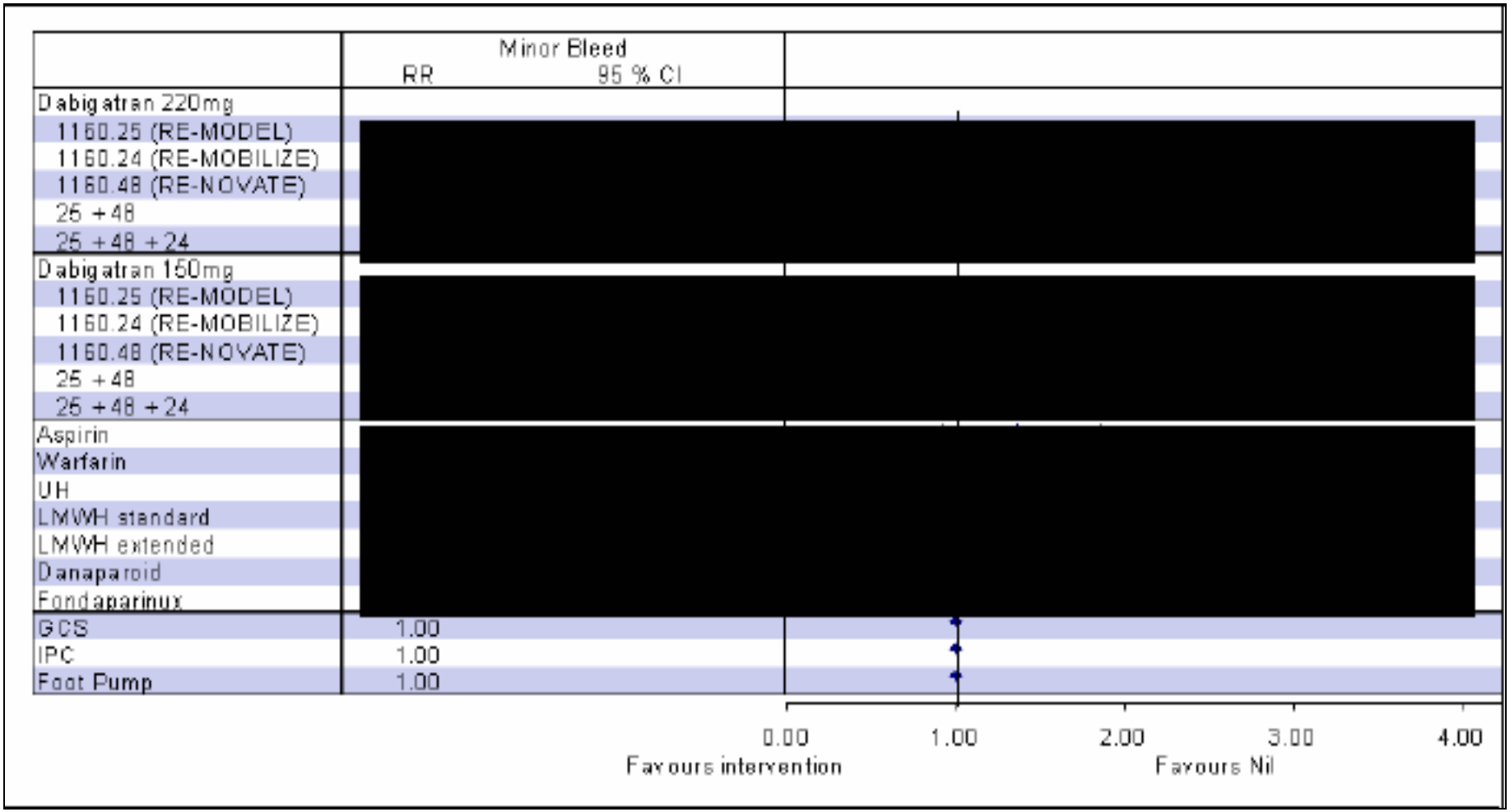
RRs for dabigatran etexilate and extended LMWH were estimated by adjusted indirect comparison
No adjustment of meta-analysed RRs was possible for the extended regimen in RE-NOVATE.

Figure 25 Relative risks (RRs) for major bleed – dabigatran etexilate and comparators *versus* nil



RRs for dabigatran etexilate and extended LMWH were estimated by adjusted indirect comparison
Mechanical interventions are assumed to have no impact on the risk of major bleed.
No adjustment of meta-analysed RRs was possible for the extended regimen in trial RE-NOVATE.

Figure 26 Relative risks (RRs) for minor bleed – dabigatran etexilate and comparators *versus* nil



RRs for dabigatran etexilate and extended LMWH were estimated by adjusted indirect comparison
Mechanical interventions are assumed to have no impact on the risk of minor bleed.
No adjustment of meta-analysed RRs was possible for the extended regimen in trial 1160.48 RE-NOVATE.

5.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

Extent of exposure

Table 33 presents the extent of exposure to study medication in each of the phase-III trials for the safety set (i.e. those patients who were randomised and received at least one dose of study medication).

Table 33 Treatment exposure in the phase-III clinical trials

Drug and trial	Number of days			Sample size
	Mean	Median	SD	N
DBG 220mg				
RE-NOVATE	31.3	32	8.4	1,146
RE-MODEL	7.6	8	1.5	679
RE-MOBILIZE	13.4	14	2.8	857
DBG 150mg				
RE-NOVATE	31.0	33	9.1	1,163
RE-MODEL	7.6	8	1.6	703
RE-MOBILIZE	13.6	14	2.5	871
Enoxaparin				
RE-NOVATE	30.8	32	9.2	1,154
RE-MODEL	7.2	7	1.9	694
RE-MOBILIZE	12.5	13	2.7	868

N, safety set analysis population.

Total exposure to active medication in each trial was as follows:

- RE-NOVATE: 96.5 years, 96.7 years and 97.4 years for DBG 220mg, DBG 150mg and enoxaparin respectively
- RE-MODEL: 13.8 years, 14.2 years and 13.6 years for DBG 220mg, DBG 150mg and enoxaparin respectively
- RE-MOBILIZE: 31.4 years, 32.5 years and 29.6 years for DBG 220mg, DBG 150mg and enoxaparin respectively

Bleeding

RE-NOVATE

In RE-NOVATE, the rate of major bleeding was similar between groups (**Table 34**) and the majority of events occurred at the surgical site. The rate of major bleeding plus clinically relevant bleeding was also similar between groups and the same was true for the rate of any bleeding.

Table 34 RE-NOVATE bleeding events during treatment

	DBG 220mg N=1,146	**DBG 150mg N=1,163**	**Enoxaparin N=1,154**
Major bleeding	23 (2.0%)	15 (1.3%)	18 (1.6%)
Major bleeding plus clinically-relevant bleeding	71 (6.2%)	70 (6.0%)	58 (5.0%)
Absolute difference *versus* enoxaparin (%)	1.2	1.0	
95% CI	(-0.7, 3.1)	(-0.9, 2.9)	
Any bleeding	141 (12.3%)	142 (12.2%)	132 (11.4%)
Absolute difference *versus* enoxaparin (%)	0.9	0.8	
95% CI	(-1.8, 3.5)	(-1.9, 3.4)	

CI = confidence interval; DBG, dabigatran etexilate

Two fatal bleeds occurred in RE-NOVATE, one in each of the DBG groups. Both events were assessed by the investigator as not related to study drug.

RE-MODEL

Compared with BISTRO II [26] (see Appendix 9.5), the lower doses of DBG used in RE-MODEL appear to contribute greatly to safety, with only 1.3-1.5% of patients experiencing major bleeding events (**Table 35**) compared with 3.8-4.7% of patients treated with the higher doses of DBG in the phase II trial.

The majority of bleeding events observed in RE-MODEL were at the surgical site. There were two critical site bleeds, one in each of the DBG groups. Three patients in the DBG 220mg group, one in the DBG 150mg group and one in the enoxaparin group required re-operation due to major bleeding.

Table 35 RE-MODEL bleeding events during treatment

Outcome	DBG 220mg N=679	DBG 150mg N=703	Enoxaparin N=694
Major bleeding (%)*	1.5	1.3	1.3
Major bleeding plus clinically-relevant bleeding (%)	7.4	8.1	6.6
Absolute difference *versus* enoxaparin (%)	0.7	1.5	
95% CI	(-2.0, 3.4)	(-1.3, 4.2)	
Any bleeding (%)	16.2	16.5	16.6
Absolute difference *versus* enoxaparin (%)	-0.4	-0.1	
95% CI	(-4.3, 3.5)	(-4.0, 3.8)	

* No fatal bleeding, one critical organ bleed in each of the dabigatran etexilate dose groups.
CI = confidence interval; DBG, dabigatran etexilate

RE-MOBILIZE

In RE-MOBILIZE, MBEs were infrequent but more common in the enoxaparin group compared with the DBG 220mg and 150mg groups (**Table 36**) although the study was not designed to test any hypothesis regarding differences in major bleeding events. It is important to note that the lower VTE rate seen in the enoxaparin group compared with patients receiving DBG is associated with potentially higher bleeding. The majority of MBEs occurred at the surgical site and within three days after surgery. In the enoxaparin group, one patient had a MBE that led to re-operation, while one had a MBE that resulted in discontinuation of study medication. In the DBG 220mg group, one MBE occurred in a critical organ (intraocular). Most of the bleeding events that were categorised as MBEs were associated with a decrease in haemoglobin and/or necessitated a greater than expected number of transfusions.

Table 36 RE-MOBILIZE bleeding events during treatment

Outcome	DBG 220mg N=857	DBG 150mg N=871	Enoxaparin N=868
Major bleeding	5 (0.6%)*	5 (0.6%)**	12 (1.4%)
Major bleeding plus clinically-relevant bleeding	28 (3.3%)	27 (3.1%)	33 (3.8%)
Absolute difference *versus* enoxaparin (%)	-0.5	-0.7	
95% CI	(-2.3, 1.2)	(-2.4, 1.0)	
Any bleeding	74 (8.6%)	72 (8.3%)	84 (9.7%)
Absolute difference *versus* enoxaparin (%)	-1.0	-1.4	
95% CI	(-3.8, 1.7)	(-4.1, 1.3)	

* *P*=0.1416 *versus* enoxaparin
** *P*=0.0942 *versus* enoxaparin
CI = confidence interval; DBG, dabigatran etexilate

Similar incidences of combined MBEs and CRBEs were demonstrated in all groups. An analysis of all bleeding events per treatment group showed a slightly higher incidence of

any bleeding event in the enoxaparin group. No statistically significant difference between the DBG groups and the enoxaparin group was detected. The rates of any bleeding observed in RE-MODEL (16.2%, 16.5% and 16.6%) were approximately twice as high as those seen in RE-MOBILIZE (8.6%, 8.3% and 9.7%). This may be due to the fact that randomization in RE-MOBILIZE was carried out post-surgery, meaning that patients with excessive bleeding during surgery would not have been included in the trial. In contrast, patients in RE-MODEL were randomised prior to surgery. Therefore, the bleeding rate includes bleeds that started before first administration of the study drug.

Blood loss

RE-NOVATE

In RE-NOVATE (**Table 37**) the proportions of patients receiving transfusions because of excessive blood loss were 2.5% (DBG 220mg), 1.6% (DBG 150mg), and 2.7% (enoxaparin). The number of patients who had an MBE and had received transfusions was similar in all treatment groups. The mean number of transfusions received by patients with an MBE was also similar in all treatment groups.

Table 37 RE-NOVATE blood loss and transfusion

	DBG 220mg	DBG 150mg	Enoxaparin
Treated	1146	1163	1154
Treated and operated	1137	1156	1142
Volume of blood loss during surgery			
Mean	457	435	463
Standard deviation	304	271	291
Blood transfusion			
Patients with at least one transfusion (%)	45.5	45.9	47.5
Patients with at least one non-autologous transfusion (%)	22.8	23.0	25.0
Units of non-autologous transfusion per patient (mean±SD)	2.5±1.7	2.3±1.5	2.5±1.4
Patients receiving transfusion associated with excessive blood loss (%)	2.5	1.6	2.7
Patients with MBE and transfused	1.9	1.0	1.6

DBG, dabigatran etexilate; MBE = major bleeding event; SD = standard deviation

RE-MODEL

In RE-MODEL, the amount of blood loss during surgery was similar in all treatment groups (**Table 38**). The proportion of patients receiving at least one transfusion was similar across all groups, as was the mean number of non-autologous transfusions per patient. The number of patients receiving transfusions because of excessive blood loss

was smaller in the DBG 220mg and 150mg groups than in the enoxaparin group. The number of patients who had an MBE and received transfusions was similar in all treatment groups, although the mean number of transfusions received by patients with an MBE was higher in the DBG groups (6.4 and 5.2) than in the enoxaparin group (2.0).

Table 38 RE-MODEL blood loss and transfusion

	DBG 220mg	DBG 150mg	Enoxaparin
Treated	679	703	694
Treated and operated	675	696	685
Volume of blood loss during surgery			
Mean	187	190	191
Standard deviation	258	250	254
Blood transfusion			
Patients with at least one transfusion (%)	35.9	36.4	38.7
Patients with at least one non-autologous transfusion (%)	12.9	12.4	17.5
Units of non-autologous transfusion per patient (mean±SD)	2.3±2.6	2.3±1.5	2.0±0.9
Patients receiving transfusion associated with excessive blood loss (%)	0.9	1.0	1.8
Patients with MBE and transfused (%)	1.0	1.0	0.9

DBG, dabigatran etexilate; MBE = major bleeding event; SD = standard deviation

RE-MOBILIZE

In RE-MOBILIZE, there were no differences between groups in terms of volume of blood loss during surgery, volume of post-operative drainage, percentage of patients requiring transfusion, or transfusion volume (**Table 39**). The number of patients receiving transfusions because of excessive blood loss was smaller in the 220mg and 150mg DBG groups than in the enoxaparin group. The number of patients who had a MBE and received transfusions was less in the two DBG groups than in the enoxaparin group although the mean number of transfusions received by patients with an MBE was slightly higher in the DBG 220mg group (3.7) than in the DBG 150mg group (2.3) and the enoxaparin group (2.7).

Table 39 RE-MOBILIZE blood loss and transfusion

	DBG 220mg	DBG 150mg	Enoxaparin
Treated	857	871	868
Treated and operated	857	871	868
Volume of blood loss during surgery			
Mean	119	115	115
Standard deviation	126	122	109
Blood transfusion			
Patients with at least one transfusion (%)	27.3	29.2	28.1
Patients with at least one non-autologous transfusion (%)	10.0	9.5	12.2
Units of non-autologous transfusion per patient (mean±SD)	1.9±0.8	2.0±1.1	2.0±0.9
Patients receiving transfusion associated with excessive blood loss (%)	0.8	0.7	1.5
Patients with MBE and transfused	0.5	0.5	1.4

DBG, dabigatran etexilate; MBE = major bleeding event; SD = standard deviation

Hepatic safety

In all three trials, the incidence of hepatotoxicity is similar to that seen with enoxaparin. There were no cases that met criteria for Hy's Law* (ALT>3x ULN and bilirubin >2 x ULN), which may indicate severe hepatotoxicity, that did not have a clear cause. LFT monitoring during DBG treatment is not necessary.

RE-NOVATE

Given that prophylaxis was for 4-5 weeks, liver enzyme data from RE-NOVATE (**Table 40**) are more relevant than data from RE-MODEL or RE-MOBILIZE. Although there were six patients with elevated ALT after the end of RE-NOVATE, they did not fulfil Hy's Law criteria and were evenly distributed across the treatment arms. Besides one patient with acute cholangitis, no clinical signs or symptoms were attributed to these abnormalities. All alanine aminotransferase concentrations returned to baseline or the upper limit of normal with additional follow-up. In one case, a 37-year-old patient in the group receiving DBG 150 mg in whom the baseline alanine aminotransferase concentration was 1.7 times the upper limit of normal had not returned to baseline or the upper limit of normal after 2 years of follow-up. This patient's alanine aminotransferase concentration was recorded as being greater than three times the upper limit of normal only once during the 2 years, and has since returned to baseline levels. One patient in each of the DBG groups had raised concentrations of alanine aminotransferase and a two-fold increase in bilirubin concentration. One of these patients was diagnosed with acute cholangitis but a definitive

* Hy's law is a prognostic indicator that a pure drug-induced liver injury (DILI) leading to jaundice, without a hepatic transplant, has a case fatality rate of 10% to 50%.

diagnosis was not made in the other patient. At all time points during treatment, the occurrence of raised liver enzymes with either dose of DBG was consistently lower than with enoxaparin.

Table 40 RE-NOVATE ALT and bilirubin elevations

ALT elevation – n (%)*	DBG 220mg N=1,117	DBG 150mg N=1,124	Enoxaparin N=1,122
ALT>3x ULN	34 (3.0)	34 (3.0)	60 (5.3)
ALT>5x ULN	9 (0.8)	18 (1.6)	20 (1.8)
ALT>3x ULN and BILI>2x ULN	1	1	0

*At any time during treatment and 3-month follow-up periods;
ALT = alanine aminotransferase; BILI = bilirubin; DBG, dabigatran etexilate; ULN = upper limit of normal range

RE-MODEL

In RE-MODEL, liver enzyme elevations were rare events; overall, there were 18 patients, 6 patients in each treatment group, with ALT-elevations above 5x the upper limit of the normal range (ULN; **Table 41**). However, the ALT-elevations had returned to baseline in all but one patient at the end of the study.

In this one patient, a definitive diagnosis could not be made and the liver enzymes returned to normal range within 4 weeks. Of note, this patient developed a similar enzyme elevation (ALT > 3 x ULN together with a > 2-fold increase in bilirubin) one year later when she underwent replacement of the contra lateral knee, at which time she was not participating in any trial. During follow-up, in 2 and 5 patients in the DBG 220 mg and 150 mg groups and three patients in the enoxaparin group, ALT was >3 x ULN for the first time. In all cases, the abnormalities returned to baseline or the ULN with additional follow-up.

Transaminase elevations during the early post-operative period are well documented and may be related to the surgical procedure and other drugs given peri- and post-operatively. Also, there is a known increase in transaminase levels with enoxaparin during the early post-operative period.

Table 41 RE-MODEL ALT and bilirubin elevations

ALT elevation – n (%)*	DBG 220mg N=654	DBG 150mg N=675	Enoxaparin N=670
ALT>3x ULN	18 (2.8)	25 (3.7)	27 (4.0)
ALT>5x ULN	6 (0.9)	6 (0.9)	6 (0.9)
ALT>3x ULN and BILI>2x ULN	0	1 (0.1)	0

*At any time during treatment and 3-month follow-up periods;
ALT = alanine aminotransferase; BILI = bilirubin; DBG, dabigatran etexilate; ULN = upper limit of normal range

RE-MOBILIZE

In RE-MOBILIZE, liver enzyme elevations were infrequent and returned to baseline values in all patients. Two patients in the DBG 220mg group and two in the enoxaparin group experienced ALT>3x ULN and total bilirubin>2x ULN at some time post baseline (**Table 42**); however in each of these four cases, a clear cause was documented:

- One patient in the DBG 220mg group was diagnosed with cholelithiasis. Following laparoscopic cholecystectomy all liver function tests were within normal limits
- Another in the DBG 220mg was diagnosed with a malignant distal common bile duct stricture
- One patient in the enoxaparin group was diagnosed with cholelithiasis via endoscopic retrograde cholangiopancreatography
- Another in the enoxaparin group was found to have cholecystitis with gall stones.

Liver function test monitoring was conducted when patients returned for their venography (i.e., 12-15 days post-surgery), thus avoiding much of the anticipated postoperative noise that could be present. The frequency of abnormal ALT values was comparable between the treatment groups or slightly numerically greater with enoxaparin treatment.

Table 42 RE-MOBILIZE ALT and bilirubin elevations

ALT elevation – n (%)*	DBG 220mg N=842	DBG 150mg N=859	Enoxaparin N=847
ALT>3x ULN	6 (0.7)	9 (1.0)	8 (0.9)
ALT>5x ULN	1 (0.1)	3 (0.3)	4 (0.5)
ALT>3x ULN and BILI>2x ULN	2 (0.2)	0	2 (0.2)

*At any time during treatment and 3-month follow-up periods;
ALT = alanine aminotransferase; BILI = bilirubin; DBG, dabigatran etexilate; ULN = upper limit of normal range

Adverse events and cardiac events leading to discontinuation

RE-NOVATE

The overall incidences of cardiac events during the RE-NOVATE treatment period were minimally higher in the DBG groups (DBG 220mg: 3.8%, DBG 150mg: 4.4%) than in the enoxaparin group (2.9%). Myocardial infarction and acute myocardial infarction occurred in 1 patient in the DBG 220mg group, and in 5 patients in both the DBG 150mg group and the enoxaparin group. Discontinuation due to cardiac adverse events was relatively uncommon (**Table 43**). The most frequent reason for discontinuation was the occurrence of gastrointestinal disorders, followed by general disorders and administration site conditions.

Table 43 RE-NOVATE cardiac AEs leading to discontinuation

	DBG 220mg N=1146	DBG 150mg N=1163	Enoxaparin N=1154
Patients with adverse events leading to discontinuation	74 (6.5)	88 (7.6)	66 (5.7)
All cardiac disorders	7 (0.6)	14 (1.2)	11 (1.0)
Atrial fibrillation	2 (0.2)	4 (0.3)	3 (0.3)
Cardiac arrest	2 (0.2)	0 (0.0)	1 (0.1)
Myocardial infarction	1 (0.1)	3 (0.3)	5 (0.4)
Acute myocardial infarction	0 (0.0)	2 (0.2)	0 (0.0)
Tachycardia	0 (0.0)	1 (0.1)	2 (0.2)

DBG, dabigatran etexilate

In the post-treatment period, cardiac disorders were rare events and there was no indication of a rebound effect upon discontinuation of study drug. Two patients in the DBG 220 mg group, 7 patients in the DBG 150 mg group and 6 patients in the enoxaparin group had an adverse event belonging to the system organ class of cardiac disorders. In the enoxaparin group 2 patients suffered from myocardial infarction compared with no patient in the DBG groups.

RE-MODEL

In RE-MODEL, the proportion of patients who discontinued due to adverse events was slightly lower with DBG treatment (3.7% in both dose groups) than with enoxaparin (4.6%). The most frequent reason for discontinuation was the occurrence of cardiac events, causing 5 patients (0.7%) in the DBG 220mg group, 8 patients (1.1%) in the DBG 150mg group, and 9 patients (1.3%) in the enoxaparin group to terminate study participation (**Table 44**).

Table 44 RE-MODEL cardiac AEs leading to discontinuation

	DBG 220mg N=679	DBG 150mg N=703	Enoxaparin N=694
Patients with adverse events leading to discontinuation	25 (3.7)	26 (3.7)	32 (4.6)
All cardiac disorders	5 (0.7)	8 (1.1)	9 (1.3)
Atrial fibrillation	3 (0.4)	2 (0.3)	4 (0.6)
Myocardial infarction	1 (0.1)	3 (0.4)	1 (0.1)
Angina pectoris	0 (0.0)	2 (0.3)	2 (0.3)

DBG, dabigatran etexilate

In the post-treatment period, there was no indication of a rebound effect upon discontinuation of study drug.

RE-MOBILIZE

In RE-MOBILIZE, the proportion of patients who discontinued the study because of adverse events was similar in the three treatment groups, but slightly lower in the DBG 150mg group (4.2%) compared with the DBG 220mg group (5.4%) and the enoxaparin group (5.9%). Cardiac disorders were the second most frequent reason for withdrawal from the study after gastrointestinal disorders (**Table 45**).

Table 45 RE-MOBILIZE cardiac AEs leading to discontinuation

	DBG 220mg N=857	**DBG 150mg N=871**	**Enoxaparin N=868**
Patients with adverse events leading to discontinuation	46 (5.4)	37 (4.2)	51 (5.9)
All cardiac disorders	8 (0.9)	6 (0.7)	7 (0.8)
Atrial fibrillation	6 (0.7)	2 (0.2)	2 (0.2)
Myocardial infarction	0 (0.0)	3 (0.3)	1 (0.1)
Tachycardia	0 (0.0)	0 (0.0)	2 (0.2)

DBG, dabigatran etexilate

In the post-treatment period, there was no indication of a rebound effect upon discontinuation of study drug.

Heparin-induced thrombocytopenia (HIT)

The binding of heparin to platelet factor 4 (PF4) may stimulate antibody formation, resulting in HIT. DBG does not bind to PF4, so would not be expected to cause HIT. Accordingly, there was no explicit requirement to record cases of HIT in the phase-III DBG trials. One case was reported in the enoxaparin treatment group of RE-MOBILIZE, representing an absolute risk of 0.1% (1/868). This estimate is low in comparison to other reported estimates for LMWH, the secondary meta-analysis of the trials included in the NCC-AC meta-analysis (Appendix 9.7) reported that the mean rate of HIT for LMWH was 0.6%.

5.8 Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The level of detail provided should be the same as for RCTs and where possible more than one independent source of data should be examined to explore the validity of any conclusions. Inferences about relative treatment effects drawn from observational evidence will necessarily be more circumspect from those from RCTs.

Not applicable.

5.9 Interpretation of clinical evidence

5.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Clinical relevance of efficacy outcomes

The relevance of the outcomes in the clinical trials was discussed in Section 5.3.4. In summary, the primary outcome assessed in the clinical trials was the incidence following major orthopaedic surgery (total hip or knee replacement) of total VTE (proximal & distal DVT based on venogram, objectively confirmed symptomatic DVT & PE) and all-cause mortality. Thus the studies used a composite endpoint combining clinical elements with asymptomatic venographic DVT.

The use of a composite endpoint combining clinical events with asymptomatic venographic VTE is advocated by several guidelines (ACCP [2], EMEA [29], NICE [1], SIGN [17]).

Appropriate endpoints to show clinically relevant benefits for studies of thromboprophylaxis are a subject of much debate. One school of thought is that studies should aim to detect all VTE events using contrast venography. Another is that assessment of efficacy should be based on reduction of all-cause mortality.

Screening venography has the advantage of being sensitive and yielding a high incidence of VTE, giving statistical power to relatively small trials. It is known that approximately 10-20% of calf thrombi propagate to the proximal veins and, particularly in patients undergoing major surgery involving the hip, isolated femoral vein DVT is common. Also, a strong association between asymptomatic DVT and the subsequent development of symptomatic VTE has been reported in several studies, as has strong concordance between the 'surrogate' outcome of asymptomatic DVT and clinically important VTE. With few exceptions, interventions that reduce asymptomatic DVT also show similar reductions in symptomatic VTE, suggesting that asymptomatic events provide a reliable surrogate endpoint. Venographically-detected asymptomatic VTE is often used in clinical trials as a surrogate measure for the clinical outcomes of symptomatic VTE and PE, and is recognised as a valid surrogate when comparing antithrombotic regimens in the same population. [2]

Clinical relevance of safety outcomes

Safety outcomes measure in the phase-III trials were focused on bleeding events, as is common in clinical trials of anticoagulants.

Given recent experience with ximelagatran (Exanta, AstraZeneca), a previous direct thrombin inhibitor withdrawn from the market due to hepatic safety concerns, special attention was also paid to hepatic toxicity events. In addition, due to some acute coronary events with ximelagatran believed to be caused by a rebound effect on thrombin production, coronary events were also specifically monitored. Crucially, all safety outcomes were recorded over an extended period of follow-up.

The safety outcomes measured in the clinical trials can be said therefore to be those of greatest clinical relevance in this indication. The results of the safety analyses from the DBG clinical trials are presented in detail in a previous sub-section.

5.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

Non-evaluable patients

The methodological approach employed for the RE-NOVATE, RE-MODEL and RE-MOBILIZE studies is one that has been used in all studies conducted in this therapeutic area over the last 20 years. It is a well defined approach that has been accepted by clinicians, consensus guidelines and regulatory authorities for testing the efficacy of a new prophylactic anticoagulant. However, this methodology has been criticised in the published literature with respect to the proportion of randomised patients who are counted as non-evaluable.

For example, in RE-NOVATE 24% of patients were non-evaluable due to venograms either not done, considered not readable by the blinded adjudication committee or the patients were not operated on or given any treatment. In an editorial accompanying the RE-NOVATE publication, Norrie [49] assesses the possible effect of this missing data. Importantly, Norrie demonstrated that in the worst case scenario (where if all data were present and the event rate was 100% higher in missing versus non-missing venographs), then the outcome of the trial is not affected (i.e. DBG was demonstrated to be non-inferior to enoxaparin). Norrie's analysis echoes the sensitivity analysis conducted by the RE-

NOVATE authors and concludes that the missing data does not change the results of the trial. Furthermore, it is important to note that follow-up was conducted on all non-evaluable patients in the RE-NOVATE trial and none had symptomatic events.

It can be argued that non-evaluable patients are an inevitable consequence of the study design adopted for VTE prevention trials, and the use of venography to detect asymptomatic deep-vein thrombosis at the end of the treatment period. It is not uncommon for patients to have their procedures cancelled or postponed, in addition to the risk that the venogram is unable to be adjudicated by the central blinded committee.

The proportion of patients not evaluable for the primary outcome in RE-NOVATE is lower than the 35% predicted at commencement of the study (27% of randomised patients were non-evaluable in both RE-MODEL and RE-MOBILIZE) and is consistent with similar estimates from those reported in previous studies using venographic deep-vein thrombosis as an endpoint. A study of fondaparinux and enoxaparin in hip fracture patients [50] reported that 27% of patients were non-evaluable. Similarly, in a study of the LMWH dalteparin in total hip replacement [51] 250 patients out of 991 entered into the study (25%) had non-evaluable venograms (indeed for a variety of reasons, only 569 patients (57%) were evaluated). A comparison of another LMWH preparation, bemiparin, with unfractionated heparin [52] reported that only 217 of the 298 randomised patients (73%) had evaluable venograms.

Whilst this approach can be criticised for adding to attrition of the final analysis set, it is the most pragmatic and clinically relevant solution to providing a meaningful outcome from the clinical trial. The rarity of symptomatic events would make the size of an appropriately powered clinical trial prohibitive. The method used in RE-NOVATE, RE-MODEL and RE-MOBILIZE is that advocated by the American College of Chest Physicians (ACCP) consensus statement and EMEA [29], which recommend the use of a composite endpoint combining clinical events with asymptomatic deep-vein thrombosis. Indeed, venographic deep-vein thrombosis is recognised to be a valid surrogate outcome when comparing antithrombotic regimens in the same patient population.

In support of the main study findings, sensitivity analyses were performed for the primary efficacy endpoint, using best and worst case scenarios (all treatment success or all treatment failure), to ensure that missing data did not affect the power of the trial or bias any estimation of the treatment effect. In addition, separate assessments of clinical endpoints showed results consistent with the primary efficacy outcome and none of the patients excluded from the primary efficacy analysis suffered a symptomatic event or died.

Treatment duration and dosing regimens

Whilst the pivotal trials (and RE-MOBILIZE) were designed to be as similar as possible to one another, there are several key differences in the dosing schedules and treatment durations that distinguish RE-MODEL and RE-NOVATE as applicable to the England and Wales setting, and RE-MOBILIZE inapplicable.

In Europe, dosing of enoxaparin is 40mg o.d. and starts in the evening of the day before the surgery (as in RE-NOVATE and RE-MODEL) while in North America the protocol is for enoxaparin 30mg b.i.d., starting 12–24 hours after surgery and only after adequate haemostasis has been established (as in RE-MOBILIZE). Similarly, the first (half) dose of DBG was administered 1–4 hours after surgery in RE-MODEL and RE-NOVATE, and 6–12 hours after surgery in the RE-MOBILIZE trial.

Furthermore, the durations of treatment are different in all three trials. The RE-NOVATE, RE-MODEL and RE-MOBILIZE studies had treatment durations of 28 to 35 days, 6 to 10 days and 12 to 15 days, respectively.

The regimens used in RE-NOVATE and RE-MODEL reflect standard UK practice and are in line with the proposed Summary of Product Characteristics for DBG (Appendix 9.1). RE-MOBILIZE is more consistent with a North American practice. The study populations and trial design of RE-MODEL and RE-NOVATE closely resemble routine clinical practice with LMWH in England and Wales [30]. The 30mg formulation of enoxaparin is not available in the UK. Major differences in the RE-MOBILIZE design make its results less applicable.

Patient characteristics

The populations enrolled in the RE-NOVATE and RE-MODEL and RE-MOBILIZE trials were similar to those described for patients undergoing hip or knee replacements in the National Joint Registry in terms of age and gender (**Table 46** and **Table 47**).

Table 46 Comparison of trial patient age with England and Wales patient population

Type of surgery	England and Wales patient population mean age[1]	Trial	Trial population mean age
THR	68 years	RE-NOVATE (THR)	63.9 years
TKR	70 years	RE-MODEL (TKR)	67.7 years
		RE-MOBILIZE (TKR)	66.1 years

THR, total hip replacement; TKR, total knee replacement
1. National Joint Registry [16]

Table 47 Comparison of trial patient gender with England and Wales patient population

Type of surgery	England and Wales patient population proportion male[1]	Trial	Trial population mean proportion male
THR	40 %	RE-NOVATE (THR)	43.6 %
TKR	43 %	RE-MODEL (TKR)	34 %
		RE-MOBILIZE (TKR)	42.3 %

THR, total hip replacement; TKR, total knee replacement
1. National Joint Registry [16]

Data from the 2001 UK Census [53] reveals that the ethnic breakdown of the British population (7.9% non-white), falls between the ethnic breakdown of the patients in the RE-MOBILIZE and the European trials. As may be expected, there was a higher proportion of Black and Asian patients in the North American RE-MOBILIZE trial, relative to white patients, than in RE-NOVATE and RE-MODEL (**Table 48**). However, it should be noted that there is evidence to suggest that the treatment effect of DBG does not vary across ethic groups [28].

Table 48 Breakdown of ethnicity of patients entered into the phase-III trials

	RE-MOBILIZE	RE-MODEL	RE-NOVATE
Race			
White	2242 (86.4)	2050 (98.7)	3441 (99.4)
Black	100 (3.9)	17 (0.8)	14 (0.4)
Asian	254 (9.8)	9 (0.4)	8 (0.2)

Current practice in England and Wales

In addition to mechanical methods of thromboprophylaxis such as graduated elasticated compression stockings, intermittent pneumatic foot compression or foot impulse devices, there are several pharmacological alternatives indicated for VTE prevention following major orthopaedic surgery. Those currently holding UK marketing authorisation for, or known to be used in this indication are as follows:

- Aspirin
- Vitamin K Antagonists such as warfarin sodium
- Low dose/Unfractionated Heparin
- Low Molecular Weight Heparins (LMWH)
    - Bemiparin sodium (Zibor)
    - Enoxaparin sodium (Clexane)
    - Dalteparin sodium (Fragmin)
    - Tinzaparin sodium (Innohep)
- Fondaparinux sodium (Arixtra)
- Danaparoid sodium (Orgaran)

Each of these pharmacological alternatives can be used in addition to mechanical methods of thromboprophylaxis and need not affect their usage.

Current practice varies considerably from centre to centre, and, often within centres. As presented earlier, the weight of opinion from the various published treatment guidelines indicates that the consensus "gold standard" of care is LMWH. In the UK, the recently published (April 2007) NICE clinical guidelines on the prevention of VTE in surgical inpatients [1] recommended that all major orthopaedic patients should receive LMWH or fondaparinux, with length of treatment determined by baseline risk factors. The most recent data for England and Wales from the National Joint Registry [16] suggests that LMWH is indeed the most widely used pharmacological alternative, and that the uptake of fondaparinux in this indication is extremely limited.

Table 49 Pharmacological thromboprophylaxis uptake; England and Wales (2006)

Medication	Proportion usage in THR	Proportion usage in TKR
Aspirin	25%	26%
Low dose heparin	2%	2%
Low molecular weight heparin	60%	57%
Pentasaccharide (fondaparinux)	1%	1%
Warfarin	2%	1%
Other chemical	2%	1%

Source: Adapted from the National Joint Registry 4th Annual Report [16]

Furthermore, as noted above the recent NICE guidelines propose recommendations that assume each of the LMWH preparations to be essentially bioequivalent. Therefore, with DBG compared to the LMWH enoxaparin in the phase-III clinical trials, one can be confident that the clinical trials represent the comparison most relevant to current practice in England and Wales.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

As dabigatran etexilate (DBG) is currently in the pre-license phase, the need for a *de novo* economic evaluation was clear. However, a systematic review of published economic evaluations was valuable in order to achieve the following objectives:

- To evaluate the design and source data of published analyses to inform the design of this economic evaluation and identify data for use in the model
- To identify key outcomes that should be included in the model (short-term and long-term)
- To identify key cost drivers (short-term and long-term) to guide focus of cost estimation in the economic analysis

The review was performed in 2006 as the initial phase of development for the economic evaluation presented in Section 6.2.

Methods

The following databases were searched:

- Pubmed
- EMBASE
- Cochrane Library (including DARE, NHS EED and HTA Database)
- Internet sources (NICE, SMC, CADTH/CCOHTA)
- BILIT (Boehringer Ingelheim's own database)

Articles were also identified by hand searching of the reference lists of included articles and reviews. Please see Appendix 3, section 9.3 for the full search strategy.

Inclusion and exclusion criteria

Studies were included or excluded based on title and abstract according to the following criteria.

Inclusion criteria

- Economic analyses of pharmacological agents in the primary prevention of VTE following THR or TKR
- Studies reporting resource utilisation or costs associated with DVT, PE, PTS or major bleed from a nationally representative sample
- Studies reporting the occurrence of long-term events (recurrent VTE, PTS)
- Studies reporting utility weights for DVT, PE, haemorrhage or PTS, obtained using standard gamble, time trade-off, EQ-5D or HUI
- 1985 to present unless determined to be a key article
- English language unless determined to be a key article

Exclusion criteria

- Excluded patient groups
    - idiopathic VTE
    - surgery other than THR or TKR, for example hip fracture surgery
    - other high risk groups e.g. pregnant women, cancer
    - acute medical patients
    - general medical conditions e.g. heart disease

  Analyses which considered both included and excluded patient populations were included if parameters and results for the included populations were presented separately from the excluded populations.
- Excluded indications
    - treatment of VTE
    - secondary prevention of recurrent VTE except to supplement data in primary prevention of VTE as required

  Economic analyses of treatments for VTE were not included as economic analyses in their own right, but were included as potential sources of resource use / cost estimates for VTE events.
- Excluded interventions
    - screening or diagnostic methods
- Other exclusions
    - non-English language unless determined to be a key article
    - Reviews (except to identify additional primary analyses)

Quality control for study inclusion

Secondary confirmation of included/excluded studies was performed by independent inclusion/exclusion of all abstracts by two members of staff and reconciliation of discrepancies.

Data abstraction and quality assessment

Due to the large number of economic analyses identified, abstraction was performed by two reviewers (each reviewing different articles). Data were extracted from full published articles using standardised data acquisition forms. Secondary confirmation of data extraction was performed for 20 key studies by an independent reviewer.

The methodological quality of each analysis was assessed independently by two reviewers (each reviewing different articles), using pre-specified criteria adapted from existing recognised systems. A scoring algorithm was developed to summarise the relative quality of individual analyses.

The scoring algorithm is presented in **Table 50**. Thirteen items were scored, grouped into three domains: Structure, Data and Analysis. The total score was calculated for each of the domains and expressed as a percentage of the maximum possible score. If this value fell below a threshold of 30% for one or more domain, the study was categorised as poor quality and the overall quality was reported as “X”. Otherwise, an overall quality score was calculated as the mean of the three domain scores.

Table 50 Quality assessment algorithm

Domain	Description	Score
Structure		
Model timeframe	> 5 yrs	2
	> 6 mths < 5 yrs	1
	<=6 mths	0
Outcomes included	DVT, PE, Death, AND bleed OR recurrent DVT, PE or PTS	2
	DVT, PE, Death	1
	One of the above (DVT, PE or Death)omitted	0
Recent publication	published after 2000	2
	published 1995 - 2000	1
	published before 1995	0
Validation	Model predictions validated against real data &/or other studies (e.g. trial data, long-term event rates, other economic analyses)	3
	Validated by KOL(s)	2
	Authors identify key strengths & weaknesses of the analysis / other reasonable validation	1
	No apparent validation	0
Data		
Efficacy data	Systematic meta-analysis	3
	Properly powered head-to-head RCT and/or Adjusted indirect comparison within model	2
	Other trial data	1
	Clinical opinion	0
Mortality rates	National data, appropriately adjusted to analysis population, and model time = 2	2
	Fulfils 2 of these criteria = 1	1
	Fulfils <2 of these criteria = 0	0
Other outcomes data*	Identified by systematic search & analysed appropriately & to a high quality (e.g. time-dependent hazard of recurrent VTE & PTS estimated from high quality data source) = 2	2
	Based on published data but not fulfilling the above criteria = 1	1
	Clinical opinion = 0	0

Domain	Description	Score
Data cont.		
Resource use / cost estimates**	Based on high quality naturalistic trial / high quality medical record abstraction study = 4	4
	Based on medical records database / RCT / lower quality naturalistic trial or medical record abstraction = 3	3
	Based on Delphi Panel / high quality survey of clinical opinion = 2	2
	Based on guidelines / consensus statements = 1	1
	Based on clinical opinion = 0	0
Analysis		
Appropriateness of CE metrics	Includes incremental cost / QALY	4
	Includes incremental cost / LYS but not /QALY	3
	Incremental cost / other relevant outcome only (e.g. VTE avoided)	2
	Cost-minimisation analysis, budget impact analysis	1
	Average cost-effectiveness or other metric	0
Efficacy data Synthesis***	Synthesis from multiple trials by appropriate adjusted indirect comparison methods	4
	Single trial using appropriate methods	3
	Inappropriate methods (e.g. unadjusted absolute values from several trials)	0
Sensitivity Analysis	Probabilistic, appropriate univariate/multivariate, examination of elasticity, examination of structural uncertainty	4
	Probabilistic but one of the above missing	3
	Less than the above but reasonably appropriate	2
	Poor or none	0
Sub-group analyses	Groupings clinically justified & efficacy data from population stratified for sub-group	2
	Included but criteria above not met	1
	None	0
Presentation of results	Disaggregated data allows analysis of key cost drivers, well presented base-case results & sensitivity analysis = 2	2
	Well presented base case results but one of these missing = 1	1
	Both of these missing = 0	0

*E.g. underlying risk of VTE, long-term risk of recurrent VTE & PTS

**Sources of resource use and cost estimates were scored for key cost drivers only. If these were not reported, they were assumed to be DVT, PE and hemorrhage.

***This score relates to the methods used to combine trial data to produce the estimates used in the analysis, as opposed to the robustness of the sources themselves. The latter is scored in the Data domain.

6.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

Study identification, inclusion and exclusion are presented in **Figure 27**.

Of the 128 articles included, 50 were economic analyses, 44 were resource use or cost studies, 30 reported rates of recurrent VTE or PTS and 4 were utility studies. Full articles were available for 125 of these. For the remaining 3 (all included as economic analyses), neither full articles nor abstracts were available on-line or from the British Library. Three formal health technology appraisals (HTAs) were identified.

Brief details of the identified economic analyses only are provided in **Table 51**. Where use has been made of other studies (resource use or cost studies; studies reporting the incidence of recurrent VTE and/or PTS, and studies reporting utility estimates) these will be referred to individually in the appropriate sub-section of the report to the *de novo* economic evaluation. Study ID numbers beginning with R denote studies identified from electronic searches and those beginning with H denote studies identified via hand-searching of reference lists.

In addition, the search of BILIT revealed one further article which was a review.

For the economic analyses, data relating to analysis structure, outcomes, data and results were abstracted from full articles for all 49 for which articles or abstracts were available.

Figure 27 Study identification, inclusion and exclusion

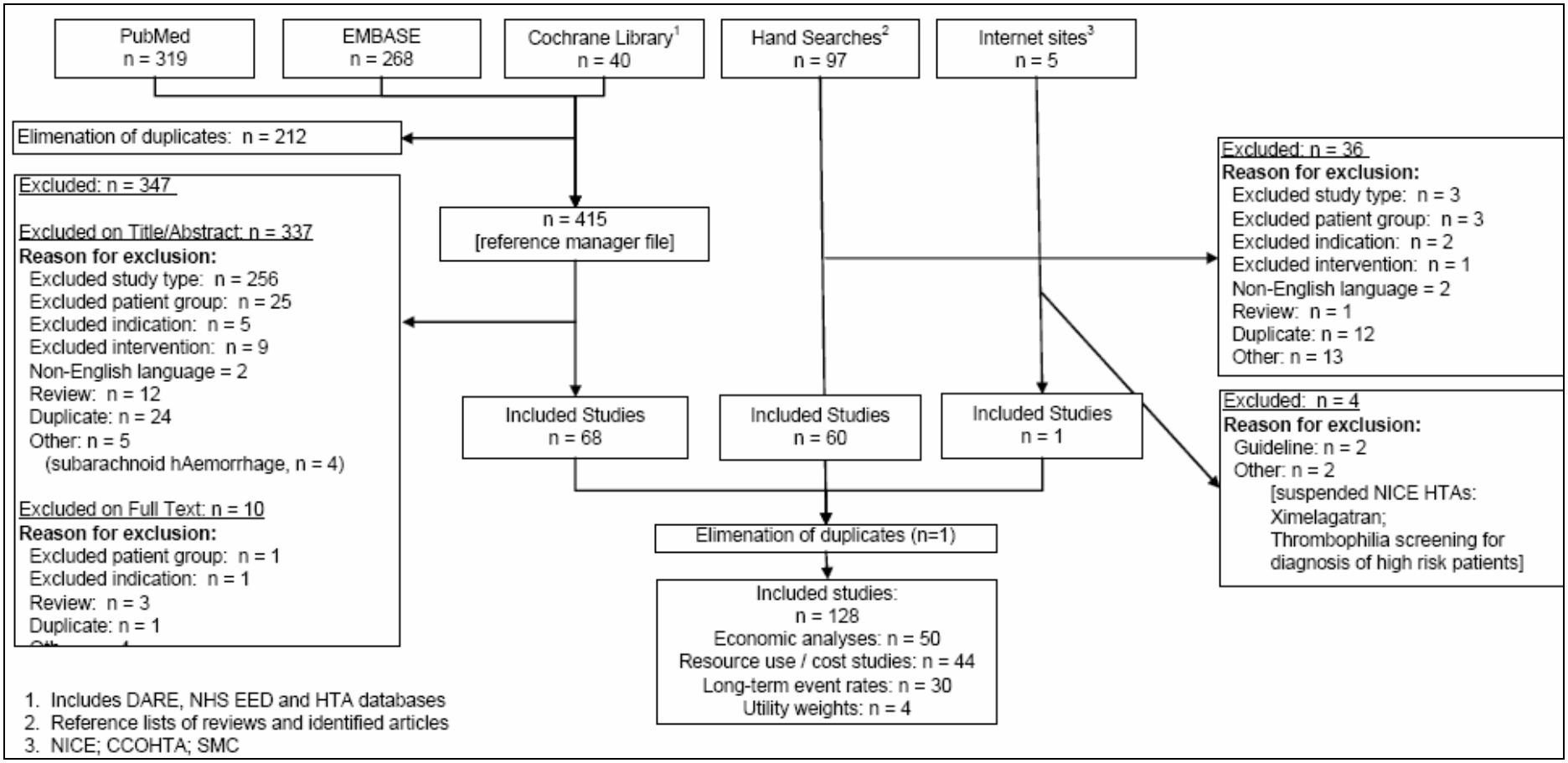


Table 51 Included economic analyses

Study No.	Author, date	Comparators	Country	ID
1	Honorato, 2004	bemiparin v enoxaparin	Spain	R075
2	Krotenberg, 2001	dalteparin v enoxaparin	USA	R123
3	Dahl, 2003	dalteparin: (prolonged / standard) v warfarin	Norway	R088
4	Wade, 1999	danaparoid v enoxaparin	USA	R207
5	Levin, 1998	desirudin v UH	Sweden	R232
6	Levin, 2001	desirudin v enoxaparin	Sweden	R148
7	Nicolaides, 1999	desirudin v enoxaparin	UK	R348
8	Hawkins, 1997	enoxaparin v heparin	USA	R242
9	Drummond, 1994	enoxaparin v UH	UK	H048
10	Menzin, 1994	enoxaparin v UH	USA	R282
11	Botteman, 2002	enoxaparin v warfarin	USA	R103
12	Hawkins, 1998	enoxaparin v warfarin	USA	R231
13	O'Brien, 1994	enoxaparin v warfarin (Low dose)	USA	R281
14	Menzin, 1995	enoxaparin v warfarin (Low dose)	USA	R274
15	Wade, 2000	enoxaparin v warfarin v combination	USA	R175
16	Nerurkar, 2002	enoxaparin/warfarin v no prophylaxis	USA	R109
17	Haentjens, 2004	enoxaparin: prolonged v standard	Belgium	R047
18	Davies, 2000	enoxaparin: prolonged v standard	UK	R155
19	Detournay, 1998	enoxaparin: prolonged v standard	France	R233
20	Olsen, 2005	fondaparinux v enoxaparin	Denmark	R024
21	Bjorvatn, 2005	fondaparinux v enoxaparin	Norway	R032
22	Annemans, 2004	fondaparinux v enoxaparin	Belgium	R043

Study No.	Author, date	Comparators	Country	ID
23	Spruill, 2004	fondaparinux v enoxaparin	USA	R048
24	Spruill, 2004	fondaparinux v enoxaparin	USA	R069
25	Sullivan, 2004	fondaparinux v enoxaparin	USA	H073
26	Lundkvist, 2003	fondaparinux v enoxaparin	Sweden	R081
27	Gordois, 2003	fondaparinux v enoxaparin	UK	R083
28	Sarasin, 2002	fondaparinux v enoxaparin (30mg started pre-op & 40mg started post-op)	Switzerland	R115
29	Wade, 2003	fondaparinux v enoxaparin (pre & post-operative)	USA	R091
30	Szucs, 2005	fondaparinux v LMWH	Switzerland	R322
31	Bischof, 2006	fondaparinux: 4 weeks v 1 week	Switzerland	H051
32	Oster, 1987	heparin v warfarin v other	USA	H015
33	Heaton, 1995	LMWH v UH	New Zealand	H022
34	Marchetti, 1999	LMWH v UH	USA	R201
35	Anderson, 1993	LMWH v UH	USA	R287
36	Bergqvist, 1993	LMWH v UH	Sweden	R292
37	Hauch, 1991	LMWH v UH	Denmark	R302
38	Borris, 1996	LMWH v UH, dextran & no prophylaxis	Denmark	R262
39	Borris, 1994	LMWH v UH, dextran & no prophylaxis	Denmark	R280
40	Bell, 2001	LMWH v warfarin	USA	R151
41	Saunders, 1998	LMWH v warfarin	USA	R215
42	Hull, 1997	tinzaparin v warfarin	USA & Canada	R246
43	Anderson, 1998	LMWH v warfarin	Canada	R411
44	Caprini, 2002	LMWH v warfarin v warfarin/UH/Mechanical	USA	R324
45	Abdool-Carmin, 1997	LMWH, UH+compression, aspirin v no prophylaxis	South Africa	R244
46	Bergqvist, 2000	enoxaparin: prolonged v standard	Sweden	R183

Study No.	Author, date	Comparators	Country	ID
47	Bergqvist, 1990	UH targeted to high risk patients v UH in all patients	Sweden	H038
48	Planes, 1999*	unknown [article not available]*	Unknown*	H023
49	Carter, 1996	unknown [article not available]	unknown	H047
50	Paiement, 1987	unknown [article not available]	unknown	R315

* Following receipt of the full text, this article is in fact a review

No analyses were identified which addressed the decision problem in this submission. Only 4 studies were conducted in the UK setting (Nicolaides, 1999 [54], Drummond, 1994 [55], Davies, 2000 [56] and Gordois, 2003 [57]). In terms of the objectives of the search, of the 47 analyses identified for which information were available, 28 were based on models, 16 were calculations and 3 were "costed trials". Of the 28 analyses based on models, the majority (23) were constructed as decision trees. Four analyses combined a decision tree with a Markov model, using the decision tree for the acute phase and the Markov model for the post-acute phase in order to model long-term events such as recurrent VTE and PTS. The final analysis was described as a cohort simulation model.

The quality score for each analysis based on a model, as well as the type of analysis, time-frame and events included, are provided in **Table 52**. Domain scores were calculated as a percentage of the maximum possible score in each domain. The overall quality rating was calculated as the mean of the three domain scores. Higher scores indicate analyses that include greater numbers of relevant short and long-term events and use higher quality data and analysis methods. More recent analyses also score higher than older ones. In addition, analyses estimating incremental cost per QALY were scored higher than those estimating incremental cost per life year saved which in turn scored higher than those estimating incremental cost per VTE avoided and so on.

The models reported by Oster [58] and Gordois [57] underpinned many of the analyses reported and were both decision trees. Of the models which combined a decision tree and Markov model, the Botteman model [3] scored highest in terms of structure.

Table 52 Included economic analyses based on models

Author, date	Type	Time Frame	Events Included	Quality Rating	ID
Analyses based on Markov Model / Decision Tree Combinations					
Botteman, 2002	CEA, CUA	lifetime	DVT, PE, DVT & PE-related death, recurrent VTE, PTS	65% [78%; 64%; 53%]	R103
Sarasin, 2002	CEA	3 months	DVT, PE, major haemorrhage, recurrent DVT	X [22%; 45%; 13%]	R115
Levin, 2001	CEA	lifetime	DVT, PE, DVT & PE-related death, recurrent VTE, PTS	58% [67%; 55%; 53%]	R148
Levin, 1998	CEA	lifetime	DVT, PE, DVT & PE-related death, recurrent VTE, PTS	58% [67%; 55%; 53%]	R232
Analyses based on Decision Tree Models					
Oster, 1987	CEA	not reported (short-term events only)	DVT, PE, DVT & PE-related death	41% [44%; 45%; 33%]	H015
Drummond, 1994	CEA	not reported (short-term costs & outcomes only)	DVT, PE, PE-related death	X [11%; 27%; 60%]	H048
Sullivan, 2004	CEA	5 years	DVT, PE, Haemorrhage, recurrent VTE, PTS, death	73% [89%, 64%, 67%]	H073
Olsen, 2005	CEA	acute phase: 3 months to chronic phase: 5 years	DVT, PE, DVT & PE-related death, major bleed, PTS	61% [100%; 36%; 47%]	R024
Bjorvatn, 2005	CEA	5 years	DVT, PE, DVT & PE-related death, haemorrhage, recurrent VTE, PTS	X [67%; 55%; 27%]	R032
Annemans, 2004	CCA	5 years	DVT, PE, DVT & PE-related death, haemorrhage, recurrent VTE, PTS	56% [89%; 45%; 33%]	R043
Haentjens, 2004	CEA CUA	1 year	DVT, PE, recurrent DVT, recurrent PE, PTS; DVT & PE-related death, haemorrhage	81% [78%; 73%; 93%]	R047
Honorato, 2004	CEA	6 weeks	DVT, PE, DVT & PE-related death, haemorrhage, thrombocytopenia, late complication, death (other causes)	X [44%; 18%; 53%]	R075
Lundqvist, 2003	CEA	acute: surgery-3 months; chronic: 3 months – 5 yrs	DVT, PE, DVT & PE-related death, haemorrhage, recurrent VTE, PTS	73% [100%; 73%; 47%]	R081
Gordois, 2003	CEA	acute: surgery-3 months; chronic: 3 months – 5 yrs	DVT, PE, DVT & PE-related death, haemorrhage, recurrent VTE, PTS	62% [67%; 73%; 47%]	R083

Author, date	Type	Time Frame	Events Included	Quality Rating	ID
Nerurkar, 2002	CEA	not reported (short term events included only)	DVT, PE, DVT & PE-related death, haemorrhage	48% [67%; 36%; 40%]	R109
Davies, 2000	CUA	short-term events only; survivors attributed life-expectancy	DVT, PE, DVT & PE-related death	64% [56%; 64%; 73%]	R155
Marchetti, 1999	CEA CUA	not reported, long-term events included	DVT, PE, PTS; PE-related death, haemorrhage, stroke, all cause mortality	69% [78%; 55%; 73%]	R201
Hawkins, 1998	CEA	costs: short term events only; outcomes: lifetime	Proximal & distal DVT, non-fatal PE, major bleed	57% [67%; 45%; 60%]	R231
Detournay, 1998	CEA	short-term costs, life years for expected remaining lifetime	DVT, PE, VTE-related death	65% [56%; 73%; 67%]	R233
Hawkins, 1997	CEA	not reported (short term events included only)	DVT, DVT & PE-related death, haemorrhage	43% [33%; 64%; 33%]	R242
Abdool-Carrin, 1997	CEA	short-term costs, life years for expected remaining lifetime	DVT, PE, VTE-related death, haemorrhage	X [78%; 18%; 40%]	R244
Borris, 1996	CEA	not reported (short term events included only)	DVT, PE, major bleed	X [22%; 27%; 60%]	R262
Menzin, 1995	CEA	not reported (short term events included only)	DVT, PE, PE-related death, death due to DVT treatment	X [33%; 27%; 33%]	R274
O'Brien, 1994	CEA	short-term events only; survivors attributed life-expectancy	DVT, PE, DVT & PE-related death; haemorrhage	X [67%; 45%; 27%]	R281
Szucs, 2005	CCA	5 years	DVT, PE, DVT & PE-related death, haemorrhage, recurrent VTE, PTS	71% [100%; 45%; 67%]	R322
Nicolaides, 1999	CEA	lifetime	DVT, PE, DVT & PE-related death	67% [78%; 64%; 60%]	R348
Anderson, 1998	CEA	3 months	DVT, PE, PE-related death, haemorrhage, haemorrhage-related death	56% [44%; 64%; 60%]	R411
Model type unclear (may be Markov or Individual Simulation)					
Bischof, 2006	CEA	short term (30 days) and up to 5 years	DVT, PE, fatal-PE, recurrent VTE, PTS, major bleed	71% [100%; 45%; 67%]	H051

Oster [58]

The four branches of the decision tree represent the following patient groups:

- Branch 1: clinically detected / symptomatic VTE (true-positive clinical diagnosis): Patients with VTE that is detected clinically were assumed to undergo tests, have the diagnosis confirmed and receive treatment;
- Branch 2: undetected /asymptomatic VTE (false-negative clinical diagnosis): Patients in this group may have a PE; they may die suddenly, before treatment can be initiated, or survive. Survivors may receive a clinical diagnosis, undergo tests to confirm the diagnosis and receive treatment. Still other patients with PE may survive an undetected embolic event, receive no treatment, and may experience recurrent PE (not shown in figure). Of those patients who do not have PE, some may nonetheless receive a clinical diagnosis of PE, which is not confirmed. The remaining patients with undetected VTE are assumed to undergo no additional tests or treatment.
- Branch 3: suspected unconfirmed VTE (false-positive clinical diagnosis): Patients who do not have VTE may nonetheless receive a clinical diagnosis of VTE. Because the diagnosis is incorrect, it will not be confirmed and no treatment will be initiated. Since VTE has been ruled out, it is assumed that these patients are not at risk of PE.
- Branch 4: no VTE (true-negative clinical diagnosis): Most of these patients undergo no additional tests or treatment. Some may nonetheless receive a clinical diagnosis of PE which is not confirmed and no treatment is received.

Events included in the model were therefore DVT, PE, and DVT / PE-related death. Haemorrhage was not included, and the long-term consequences of recurrent VTE and PTS were not modelled.

Gordois [57]

The structure is similar to that of the Oster model, with the addition of haemorrhage, recurrent DVT and PTS events. The structure represents three phases: the hospitalisation phase; post-discharge acute phase (up to 90 days); and chronic phase (90 days to 5 years). The possibility of haemorrhage is added as the first event in the decision tree such that all patients are at risk. VTE occurring after discharge was also included (up to day 30). The probability of recurrent VTE was derived from published data for the cumulative incidence at 5 years. The risk of PTS was assumed to begin at day 91 and was higher for those with a clinically detected VTE than those with an undetected VTE. It is unclear how the model caters for the time at which recurrent VTE and PTS occur.

Botteman [3]

The acute-phase was based on the Oster model and a Markov model was added to describe the post-acute phase. After THR surgery, patients who developed DVT could die from it or survive and enter the post-acute phase as survivors of a DVT. Patients who did

not develop DVT all survived and entered the post-acute-phase of the simulation via the no-DVT state.

The post-acute phase was modelled via a Markov model (which has also been used to estimate the burden of long-term complications of DVT by Caprini [59]). In the Markov model, patients who survived a DVT could remain in this post- DVT state, develop signs and symptoms of mild to moderate PTS syndrome (M/M PTS), develop signs and symptoms of severe PTS, or die. Patients who did not experience a DVT after surgery and were well were also assumed to be at risk for idiopathic PTS. When a patient developed PTS, the model established a distinction between the first and subsequent years with PTS to allow for differences in diagnostic and treatment patterns and associated costs. Once patients entered the PTS states, they remained in these states until death or the end of the simulation (age 100 years). All patients entering the severe PTS state for the first time were classified as severe, open ulcer; assuming an ulcer must be open before being healed. Although the model assumed that ulcers could heal, patients who developed an ulcer remained in the severe PTS health state for the remainder of their lives. Due to limited epidemiologic data, the model further assumed no movements of patients between the M/M PTS and severe PTS states.

6.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Attribute	Reference case	Section in 'Guide to the methods of technology appraisal'
Comparator(s)	The comparator that has been specified in the decision problem	5.3.2
Perspective costs	NHS and Personal Social Services	5.3.3
Perspective benefits	All health effects on individuals	5.3.3
Form of economic evaluation	Cost-effectiveness analysis	5.3.4
Time horizon	Sufficient to capture differences in costs and outcomes	5.3.5
Synthesis of evidence	Systematic review	5.4.1
Outcome measure	Quality-adjusted life years (QALYs)	5.5
Health states for QALY measurement	Described using a standardised and validated instrument	5.5

Benefit valuation	Time trade-off or standard gamble	5.5
Source of preference data	Sample of public	5.5
Discount rate	Health benefits and costs – both 3.5%	5.7.2
Equity	No additional weighting to QALYs	5.9.7
Sensitivity analysis	Probabilistic sensitivity analysis	5.9.3

6.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

The indication under consideration in the economic evaluation is that detailed in the dabigatran etexilate (DBG) summary of product characteristics (SPC) (Appendix 9.1), i.e. adult patients who have undergone elective total hip replacement (THR) surgery or total knee replacement (TKR) surgery.

As set out in the SPC, the dosing schedule for DBG is as follows:

- 220mg once daily taken as 2 capsules of 110 mg, initiated orally within 1 – 4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter

The duration of therapy varies depending on whether the patient has undergone THR or TKR. As the economic evaluation is based on the efficacy and safety results of the phase-III pivotal trials, the durations of therapy applied are based on the number of administrations actually recorded in the trials (**Table 53**).

Table 53 Number of drug administrations in RE-NOVATE and RE-MODEL

Drug and trial	Number of administrations			Sample size
	Mean	Median	SD	N
DBG 220mg				
RE-NOVATE	33	33	5.2	880
RE-MODEL	7.7	8	1.3	503
DBG 150mg				
RE-NOVATE	33.1	33	5.1	874
RE-MODEL	7.8	8	1.3	526
Enoxaparin				
RE-NOVATE	33.2	33	5.1	897
RE-MODEL	7.6	8	1.4	512

Source: Boehringer Ingelheim GmbH data on file, 2006 (analysis performed for this economic evaluation); FAS analysis population.
DBG, dabigatran etexilate

The number of administrations applied to each modelled patient is sampled from a normal distribution defined by the mean and standard error (in most cases, the mean was equal to the median to the nearest integer). The standard error was estimated from the standard deviation by dividing by the square root of the sample size (N).

The 220mg dose of DBG is the standard recommended dose. The 150mg dose is reserved for patients in the following special populations:

- Those with moderate renal impairment (creatinine clearance 30-50 ml/min)
- Elderly patients over the age of 75 years
- Patient receiving concomitant amiodarone

Therefore the 220mg dose will be considered in the base case analysis, with the 150mg dose considered in a subgroup analysis.

There are no other concomitant pharmacological therapies necessary during DBG treatment. Mechanical methods of thromboprophylaxis such as graduated elasticated compression stockings, intermittent pneumatic foot compression or foot impulse devices may be used concomitantly to therapy with DBG. However, the use of pharmacological agents need not affect the use of mechanical methods of thromboprophylaxis. Therefore mechanical thromboprophylaxis is assumed to be used equally in all patients and is not considered in this economic evaluation.

6.2.2 Patients

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

The patient population considered in the economic evaluation matches that of the licensed indication, that is, adult patients who have undergone elective THR or TKR surgery.

Patients are assumed to be either male or female and at least 18 years of age. The age and gender distribution of the population entering the model reflects that of patients undergoing THR and TKR, and are taken from the National Joint Registry's latest annual report (**Table 54**). [16]

Table 54 Age and gender distribution of major orthopaedic patients

	Total hip replacement		Total knee replacement	
	Number of patients (%)	Average age (years)	Number of patients (%)	Average age (years)
Male	18,376 (40%)	68	20,215 (43%)	70
Female	27,150 (60%)		26,834 (57%)	

Source: Adapted from the NJR 4th Annual Report [16]

The two surgery types are modelled as two separate groups in order to reflect the differing underlying risk of VTE in the two populations, any differences in age and gender distribution and differences in the duration of thromboprophylaxis.

6.2.2.2 ***Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?***

Yes, the 150mg dose is reserved for patients in the populations outlined above in section 6.2.1 and the analysis is presented for this subgroup. However, it is extremely important to note that the subgroup reserved for the 150mg dose is defined based on limited clinical experience as per the product SPC (Appendix 9.1). Estimation of treatment effect in these particular subgroups of patients would not be informative. The clinical trials studied the treatment effect of both this dose and the 220mg dose across the whole eligible patient population, and it will be this data for the 150mg dose that will underpin the subgroup analysis. Data from the GPRD [60] indicates that typically [redacted]% of THR and TKR patients are over the age of 75. The additional proportion of patients who are 75 or under and either receive concomitant amiodarone or have moderate renal impairment, is expected to be minimal.

6.2.2.3 ***Were any obvious subgroups not considered? If so, which ones, and why were they not considered?***

No.

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

All modelled patients enter and exit the model at the same points irrespective of treatment regimen. Patients enter the model at the point of admission for their index surgical procedure and exit at death.

6.2.3 Comparator technology

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

This economic evaluation compares DBG with two alternative pharmacological thromboprophylactics: LMWH and fondaparinux.

There are several thromboprophylactic alternatives available for use in this indication, please see Section 5.9.2 for the full list of licensed alternatives in the UK. As noted, pharmacological alternatives can be used in addition to mechanical methods of thromboprophylaxis and need not affect their usage. The introduction of DBG would not alter this aspect of care and therefore it would be incorrect to compare DBG directly to mechanical thromboprophylaxis in this economic evaluation. **Table 49** presented the relative split of pharmacological thromboprophylactic take-up for both THR and TKR in England and Wales during 2006. Approximately 60% of all THR and TKR patients receive LMWH therapy, which is recommended by the consensus of international clinical guidelines (see Section 4.6). Therefore it is clear that LMWH is an appropriate comparison.

Moreover, the recent NICE clinical guidelines [1] recommend the use of fondaparinux in this indication as a potential alternative to LMWH. The SMC have also approved fondaparinux for use in this indication in Scotland. Therefore this comparison should also be presented. Nevertheless, it is extremely important to note that the data presented in **Table 49** also reveals that the use of fondaparinux in this indication is negligible (approximately 1% of total pharmacological thromboprophylaxis). Therefore the relevance of this comparison to decision makers (based on current practice) may be questioned.

Despite accounting for approximately 25% of current practice, aspirin is now explicitly not recommended by clinical guidelines (see Section 4.6), including those recently published

by NICE [1], on the grounds of inferior efficacy. Aspirin is an outdated modality in this indication and therefore this comparison will not be presented.

No other pharmacological agents are recommended by clinical guidelines in this indication, nor is there any evidence that any other pharmacological alternative has a significant proportion of use in current practice. Therefore no further comparisons with other pharmacological agents will be presented in the economic evaluation.

6.2.4 Study perspective

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

The perspective of the economic evaluation is that of the NHS and PSS in England and Wales, as per the NICE reference case.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

The timeframe of the analysis was designed to encompass the lifetime of the patient cohort in order to capture the impact of differential VTE-related morbidity and mortality, health-related quality of life (HRQoL) impairment as well as that associated with drug-related adverse events. Estimates from the National Joint Registry [16] suggest that only 3-5% of THR and 1% of TKR patients are less than 45 years of age. Accordingly, the base case analysis assumes that the minimum age at operation is 40 years. The model timeframe is 60 years from surgery in order to capture the lifetime of the youngest patients up to 100 years of age.

Alternative analysis timeframes are also reported in sensitivity analysis:

- Acute phase (to 10 weeks post-surgery), reflecting the follow-up period of the pivotal clinical trials but excluding the impact of recurrent VTE, post-thrombotic syndrome (PTS) and long-term morbidity from intracranial bleeds
- 1 year
- 5 years

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

6.2.6.1 ***Please provide the following.***

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

Approach

In order to properly model the clinical pathway associated with this indication it is necessary to examine the potential journeys that patients may experience. Following the initial surgical procedure there is an acute phase where the patient is at greatest risk of VTE and where adverse outcomes are most likely. Prevention and management of these potential events is concentrated in the short-term acute phase following surgery.

Following the acute phase, health status of patients can be stratified by any chronic conditions they have acquired or by differing risk profiles associated with recurrent events, as a result of an event in the acute phase.

Therefore there is a distinct two-stage approach to modelling this clinical pathway. The approach adopted in this economic evaluation was to use a combination of a decision tree and a Markov model. Events in the peri-operative period (the acute phase) were modelled within the decision tree. The health status of patients as they exit the decision tree is then used to inform the longer term (chronic phase) events within the Markov model.

Acute phase (decision tree)

The layout of the decision tree is illustrated in **Figure 28** and **Figure 29**. **Figure 28** represents the pathway for VTE events and **Figure 29** shows the pathway for adverse events. Both parts of the decision tree are computed simultaneously, but are presented separately for ease of reference.

Figure 28 Schematic of acute phase decision tree (VTE events)

Figure 29 Schematic of acute phase decision tree (adverse events)

The decision tree component models the period of hospitalisation for the initial surgical procedure, and the period post-discharge (up to 10 weeks post-surgery) during which patients may be readmitted for symptomatic VTEs or adverse events.

All patients are at risk of VTE events and other post-surgical death (**Figure 28**) and also prophylaxis-related adverse events (**Figure 29**). The entire cohort was entered into the decision tree and the probability at each terminal node was then estimated and multiplied by costs and quality of life decrements for each terminal node.

[redacted]

All patients are also at risk of a prophylaxis-related bleeding event and heparin-induced thrombocytopenia (HIT). Bleeding events were categorised as major or minor; major bleeds are further categorised as shown in **Figure 29**. [redacted]

Patients experiencing adverse events were assigned the cost of treatment for the event, a QALY decrement for the duration of the event, and may survive or die as a result of the event. [redacted]

[redacted]

[redacted]

Chronic phase (Markov model)

The structure of the Markov model was based on that reported by Botteman et al. (2002) [3] in which the cycle length was 1 year. The structure of this model was modified by the addition of the asymptomatic VTE states and the "disabled" state resulting from intra-cranial bleed.

The Markov model schematic (**Figure 30**) is simplified for clarity. The untreated VTE state (b) actually represents three health states: asymptomatic and untreated proximal DVT, distal DVT and PE. The treated VTE state (c) also actually represents three health states: symptomatic and treated proximal DVT, distal DVT and PE. All patients in these and all subsequent health states are at risk of all-cause mortality (transition to the "Dead" state [k]).

Patients in the "Well" state (a) are assumed to be at risk of idiopathic DVT, PE and PTS (shown in dotted arrows).

Patients in the asymptomatic and untreated VTE states (b) may develop recurrent VTE (DVT [e] or PE [f]). These symptomatic events may or may not be confirmed.

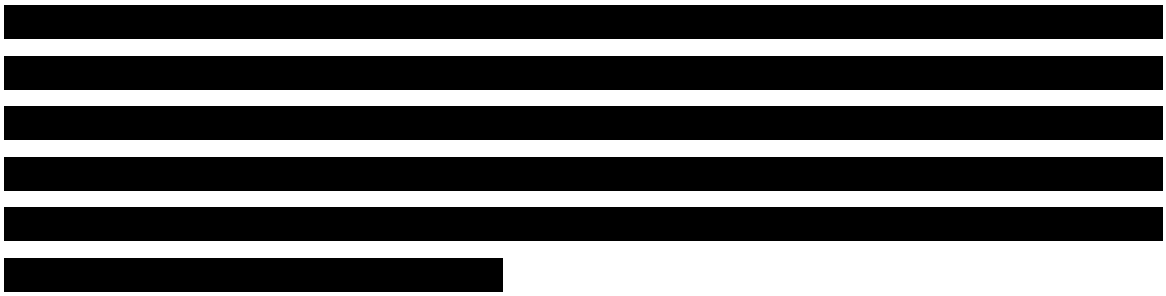


Figure 30 Stylised schematic of the chronic phase (Markov model)

The cycle length is 1 year.

[redacted]

Inclusion of distal DVT

Although many economic analyses have excluded distal DVT, making the assumption that is likely to be asymptomatic and untreated (e.g. Honorato *et al*.,2004 [63]), it was included in the model as an event in its own right for the following reasons:

- Although distal DVT is symptomatic in only an estimated 5% of cases [63-65], it is much more common than proximal DVT in venographic screens. For example, in the analysis by Nerurkar *et al*., (2002) [65], which pooled the results of 5 trials, the ratio of distal to proximal DVT was 3.6:1. An estimated 40% of proximal DVTs and 5% of distal DVTs were assumed to be symptomatic. If we consider a cohort of 100 patients with venographically confirmed DVT, using these figures, we would estimate that 78 patients would have distal DVT of which 4 would be symptomatic, and 22 would have proximal DVT of which 9 would be symptomatic. Thus, the number of symptomatic distal DVTs is expected to be significant, and only just less than half that for symptomatic proximal DVTs.

- Many economic analyses have assumed that distal DVT is usually not treated (e.g. Spruill *et al*., 2004b [66]). However, Nerurkar *et al*., 2002 [65] performed an analysis of the United States (US) Nationwide Inpatient Sample dataset (for 1995) which identified 400 patients who developed a distal DVT and 42,135 patients who did not develop a VTE complication after TKR. The excess length of stay in this symptomatic distal DVT population was 3.27 days (a mean 8.85 days versus 5.58 days for the no VTE population). This is evidence, then, that distal DVT may result in significant treatment costs.

- Distal DVT may also propagate to the proximal veins, and carries an increased risk of PE compared with no DVT which differs from that for proximal DVT [64-65] and PTS [62].

List of variables

For ease of reporting, the variables used in the economic model, along with their values and sources will each be listed in the appropriate sub-section later in the submission.

List of assumptions

1. All LMWHs are bioequivalent: This is supported by current literature, which suggests that dalteparin and tinzaparin are indistinguishable from enoxaparin (White and Ginsberg, 2003 [67]; Lopez, 2001 [68]; Anderson *et al*., 1998 [42]). The NICE clinical guidelines also recommend all LWMHs equally.

2. The efficacy of DBG, LMWH and fondaparinux is assumed to reflect combination prophylaxis with graduated compression stockings (GCS) in a proportion of patients: GCSs were permitted in all treatment groups in the phase-III DBG trials at clinicians' discretion, as is common in recent trials of pharmacological prophylaxis.

3. In the indirect comparison, the calculation of relative risks assumes that treatment effect is independent of surgery type: The NCC-AC meta-analysis [41] on which the indirect comparison is based included trials in many surgical populations. Trials were sub-grouped by surgical speciality and tests for heterogeneity within the subgroup analyses found no convincing evidence of a difference between surgery types. No evidence for a difference in treatment effect was identified in a review of other published meta-analyses.

4. In the acute phase, if a DVT (proximal or distal) is asymptomatic and untreated, the probability of it being fatal is 0.5%: In the absence of any data for this variable, a notional mortality rate is assumed. This is not treatment-specific.

5. The probability of recurrent VTE and PTS is the same for patients with treated and untreated VTE events: In the absence of data for these variables, this assumption is expected to be conservative assumption against effective interventions, since less effective interventions would be expected to result in more asymptomatic and untreated events. All events have a higher risk of recurrent VTE and PTS.

6. Patients in the PTS states do not transition out: Patients with either mild/moderate or severe PTS may suffer recurrent VTE but cannot return to the treated VTE states. This assumption is made in order to reflect the chronic nature of PTS and its impact on healthcare costs and quality of life.

7. Deaths occurring pre-discharge are assumed to occur at the time of discharge: A simplifying model assumption.

8. Deaths during the treatment period from events occurring post-discharge and asymptomatic events that are untreated were assumed to occur on day 14: A simplifying model assumption.

9. The probability of a minor bleed being fatal is zero: A reasonable assumption by definition given the nature of the event.

10. Minor bleeds and non-fatal HIT are assumed to have a negligible affect on quality of life: A reasonable assumption given the nature of the events.

11. Patients who suffer an intracranial haemorrhage and survive are permanently disabled: These patients may not transition to any other active model health state. Any costs and quality of life impacts associated with co-incident VTE events in these patients are likely to prove negligible compared to those of the “Disabled” heath state.

12. Patients unable or unwilling to self-administer LMWH or fondaparinux require daily community nurse visits to ensure compliance: In this case, and in the absence of a willing and capable carer, there is no other way of ensuring that patients prescribed an extended duration of LMWH or fondaparinux treatment receive their medication.

13. Patients able and willing to self-administer LMWH or fondaparinux require training in the correct method of self-administration: It is likely that the vast majority of patients will have little or no experience of self-administering a subcutaneous injection. It is reasonable to assume that such patients will require proper instruction from nursing staff prior to hospital discharge to ensure safe administration and compliance.

14. The length of stay of the primary hospitalisation is not affected by the choice of pharmacological prophylaxis: It is possible that patients receiving oral DBG may not need to be admitted the day before surgery since the first dose is administered post-operatively, unlike subcutaneous injections of LMWH which is initiated 12 hours pre-operatively. However, no difference is conservatively assumed in the base case analysis.

15. All detected DVTs incur a Doppler ultrasound procedure: In line with most previous UK economic evaluations.

16. All patients presenting with DVT symptoms post-discharge incur an outpatient visit: Model assumption.

17. All patients presenting with PE symptoms post-discharge incur an accident and emergency visit: Model assumption.

18. Non-clinically relevant minor bleeds incur no cost: A reasonable assumption given the nature of the event.

19. The cost of a surgical site bleed (requiring re-operation) is assumed to cost the same as a gastrointestinal (GI) bleed event: Reasonably assuming that such an event would require similar resource, in the absence of a specific reference cost estimate.

20. The minimum age at surgery is 40 years: Estimates from the National Joint Registry [16] suggest that only 3-5% of THR and 1% of TKR patients are less than 45 years of age.

6.2.6.2 *Why was this particular type of model used?*

As noted above, a two-stage approach to the modelling problem was most appropriate to capture the differences between the acute and chronic phases. The decision tree is necessary and sufficient to model the acute phase, where the patient is at greatest risk of VTE and adverse events, and to establish the most appropriate health status that the patient will carry forward into the chronic phase. From this point, a Markov model is most appropriate to track the (less frequent) potential changes in health status over the longer-term.

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

As described in Section 6.1, the primary objectives of the systematic review of published economic evaluations included compilation and critical appraisal of previous modelling approaches in this indication. From the reviews presented, the model reported by Botteman [3] stands out as the most comprehensive model structure with a life-time analysis horizon. With the addition of haemorrhage, the model would include all key events of interest (DVT, PE, DVT and PE-related death, haemorrhage, recurrent VTE and PTS). With one or two exceptions, it was determined that the model for this economic evaluation should be based on the same principles.

Of note, Botteman did not distinguish between proximal and distal DVT and used a rather crude method of pooling absolute rates of DVT across several non head-to-head trials. The model used in this economic evaluation will address both of these limitations.

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

Please refer to the responses to Section 6.1.2 and 6.2.6.3.

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

The model reflects all essential features of VTE and the adverse effects of thromboprophylaxis as set out above. The only outcome listed in the final scope which is not included in the economic model is “joint outcomes (medium and long-term), including joint infection”. This particular outcome has not been included in the other well conducted published economic evaluations reviewed in Section 6.1. Further, the follow-up in the DBG phase-III trials is insufficient to capture such longer-term outcomes. This economic model assumes that differential treatment effects are realised only in the acute phase, with the chronic phase progression being informed by the events experienced during the acute phase. The addition of this particular outcome would add little to the analysis and is therefore not included.

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

As described above, the acute phase decision tree covers the 10 week period post-surgery where the patient is most at risk of VTE and adverse events from thromboprophylaxis. The following chronic phase Markov model has annual cycles, reflecting the cycle length used in the Botteman economic evaluation. This choice of cycle

length seems to be appropriate when one considers the rare nature of the transitions between health states in the chronic phase and the way in which the long-term epidemiological data informing the transition probabilities is reported.

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

The model does not apply a half-cycle correction to the chronic phase of the model, justified by the length of the cycle (1 year) being short in relation to the model time-frame (60 years).

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

Yes, costs and clinical outcomes are extrapolated beyond the trial follow-up period, however as noted above differential treatment effects are assumed to occur only within the acute phase of the model (covered by the follow-up duration of the clinical trials). Extrapolation beyond the trial follow-up is performed using long-term epidemiological data from the published literature. No further interventional-specific probabilities are used following the acute phase.

b) Non-model-based economic evaluations

Not applicable.

6.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

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

Direct comparison (LMWH)

The baseline risk of a VTE event was assumed to be that associated with LMWH. That is, the rate of VTE events in the enoxaparin treatment groups in the appropriate clinical trial (RE-NOVATE in THR and RE-MODEL in TKR) provided the baseline risk of VTE for the economic model. **Table 55** presents these probabilities.

Table 55 Probabilities of VTE, Major Bleed and Minor Bleed for LMWH

Trial	VTE			Major bleed			Minor bleed		
	n	N	Probability	n	N	Probability	n	N	Probability
RE-MODEL	193	512	0.377	9	694	0.013	106	694	0.153
RE-NOVATE	60	897	0.067	18	1154	0.016	114	1154	0.099

N: number of events; N: number of patients in the study arm; p: probability
Sources: [23-24]

Probabilities were sampled in the probabilistic analysis from a beta distribution defined by the number of patients in the trials experiencing an event (n) and the number that did not (N-n). Estimates for VTE are for the primary clinical end-point "Total VTE and all-cause Mortality"; for Major Bleed are for the safety end-point "Major Bleed", and for Minor Bleed are for the end-points "Minor Bleed" and "Clinically Relevant Bleed" combined.

Indirect comparison (fondaparinux)

The indirect comparison drawn between DBG and fondaparinux is performed using the adjusted indirect comparison method of Bucher *et al*., (1997) [69]. The starting point is the underlying risk of events for patients undergoing THR or TKR. Relative Risk (RR) estimates for DBG and fondaparinux versus nil (placebo or untreated control) are applied to this underlying risk in order to estimate event probabilities.

Table 56 presents the estimates of underlying risk used as the basis for this approach.

Table 56 Underlying risk of VTE and bleeding events

Underlying risk	Probability (THR)	Probability (TKR)
VTE	0.440	0.270
Major Bleed	0.020	0.010
Minor Bleed	0.073	0.032

Source: [41]

6.2.7.2 ***How were the relative risks of disease progression estimated?***

Direct comparison (LMWH)

The probabilities of a VTE event, major bleed and minor bleed were derived by a simple calculation: application of a relative risk for DBG versus enoxaparin, to the probability the baseline risk outlined above.

The RR estimates are presented in **Table 57** and were taken from the individual DBG trial relevant to the analysis (base case) as presented in Section 5.4 or from the meta-analysis (sensitivity analysis). Probabilistic estimates were sampled from a normal distribution on the (natural) log scale defined by lnRR and the standard error of lnRR. Estimates for VTE

are for the primary clinical end-point "Total VTE and all-cause Mortality"; for Major Bleed are for the safety end-point "Major Bleed", and for Minor Bleed are for the end-points "Minor Bleed" and "Clinically Relevant Bleed" combined. Estimates from the meta-analysis were from a fixed effects model. Standard errors were estimated on the log scale as the confidence interval width of ln(RR) / 2x1.96.

Table 57 Relative Risks for VTE, Major Bleed and Minor Bleed for DBG vs LMWH

	VTE			Major bleed			Minor bleed		
	RR	95% CI		RR	95% CI		RR	95% CI	
DBG 220mg									
RE-MODEL	0.97	0.82	1.13	1.14	0.46	2.78	0.96	0.75	1.24
RE-NOVATE	0.90	0.63	1.29	1.29	0.70	2.37	1.04	0.82	1.33
Meta-analysis	0.95	0.82	1.10	1.24	0.75	2.05	1.00	0.84	1.20
DBG 150mg									
RE-MODEL	1.07	0.92	1.25	0.99	0.39	2.47	1.00	0.78	1.28
RE-NOVATE	1.28	0.93	1.78	0.83	0.42	1.63	1.11	0.87	1.40
Meta-analysis	1.12	0.98	1.29	0.88	0.51	1.52	1.05	0.89	1.25

Sources: [23-24], Section 5.5
CI: confidence interval; DBG, dabigatran etexilate; RR: Relative Risk;

Derivation of final probabilities for DBG is provided in **Table 58** and **Table 59**.

Table 58 Derivation of probabilities: DBG vs LMWH in THR

	VTE	Major bleed	Minor bleed
DBG 220mg			
Probability for LMWH	0.067	0.016	0.099
RR (DBG vs LMWH)	0.90	1.29	1.04
Probability for DBG	0.60	0.020	0.103
DBG 150mg			
Probability for LMWH	0.067	0.016	0.099
RR (DBG vs LMWH)	1.28	0.83	1.11
Probability for DBG	0.086	0.013	0.110

Table 59 Derivation of probabilities: DBG vs LMWH in TKR

	VTE	Major bleed	Minor bleed
DBG 220mg			
Probability for LMWH	0.377	0.013	0.153
RR (DBG vs LMWH)	0.97	1.14	0.96
Probability for DBG	0.366	0.015	0.147
DBG 150mg			
Probability for LMWH	0.377	0.013	0.153
RR (DBG vs LMWH)	1.07	0.99	1.00
Probability for DBG	0.403	0.013	0.153

The probability of HIT for LMWH was taken from a secondary meta-analysis of the trials included in the NCC-AC meta-analysis (Appendix 9.7) with the values from the three phase-III trials also incorporated. This results in a probability of HIT for enoxaparin of 0.004 (95% confidence intervals 0.001 to 0.007); however this may represent an underestimate as cases in the three DBG trials may not have been recorded. By definition, the probability of HIT is zero for DBG.

The data presented in **Table 58** and **Table 59** forms the entirety of intervention-specific probabilities used in the economic model (in addition to the probability of HIT).

Indirect comparison (fondaparinux)

RR estimates for DBG versus nil and aspirin versus nil were presented in Section 5.6 (NCC-AC meta-analysis [41] and a secondary analysis (Appendix 9.7)). The values for fondaparinux assume that treatment effects are independent of surgery type. The meta-analyses are described in detail in Section 5.6. **Table 60** presents the derivation of the event probabilities applied to the economic model in the indirect comparison.

It is extremely important to note that a relative risk for extended duration fondaparinux was not presented in Section 5.6. The only value for this regimen available from the published literature is from one relatively small, single trial of extended duration fondaparinux versus nil in hip fracture patients [70]. Moreover, this study reports the comparative risk of VTE for extended duration fondaparinux versus placebo *for days 9 to 31 post–surgery only*. That is, the rate reported in this study does not include any VTE experienced by either treatment group in the first 8 days post-surgery, both of which received fondaparinux for this period. Consequently, the relative risk reported from this study (0.01) is extremely low and leads to a VTE probability for fondaparinux of 0.004. Therefore extreme caution must be exercised when interpreting the results of the economic evaluation in this comparison. This value will also be examined closely in sensitivity analysis.

Table 60 Event probabilities in the indirect comparison

Treatment and parameter	Probability (Nil)	RR vs Nil[1]	Probability (treatment)[2]
Fondaparinux (THR)			
VTE	0.440	0.01	0.004
Major Bleed	0.020	6.70	0.134
Minor Bleed	0.073	[redacted]	[redacted]
Fondaparinux (TKR)			
VTE	0.270	0.22	0.059
Major Bleed	0.010	2.22	0.022
Minor Bleed	0.032	[redacted]	[redacted]
DBG 220mg (RE-NOVATE)			
VTE	0.440	[redacted]	[redacted]
Major Bleed	0.020		
Minor Bleed	0.073		
DBG 220mg (RE-MODEL)			
VTE	0.270		
Major Bleed	0.010		
Minor Bleed	0.032		
DBG 220mg (Meta-analysis- THR)			
VTE	0.440		
Major Bleed	0.020		
Minor Bleed	0.073		
DBG 220mg (Meta-analysis- TKR)			
VTE	0.270		
Major Bleed	0.010		
Minor Bleed	0.032		
DBG 150mg (RE-NOVATE)			
VTE	0.440		
Major Bleed	0.020		
Minor Bleed	0.073		
DBG 150mg (RE-MODEL)			
VTE	0.270		
Major Bleed	0.010		
Minor Bleed	0.032		
DBG 150mg (Meta-analysis – THR)			
VTE	0.440		
Major Bleed	0.020		
Minor Bleed	0.073		
DBG 150mg (Meta-analysis – TKR)			
VTE	0.270		
Major Bleed	0.010		
Minor Bleed	0.032		

1. The RR vs nil is calculated using the logarithm formula presented in the body text above.
2. The probability of event is calculated by multiplying the probably (nil) by the RR vs nil.

DBG: Dabigatran etexilate; RR, relative risk

Non-treatment specific probabilities (acute phase)

The probabilities in the previous sub-section advance the decision tree part of the way and serve to differentiate the two alternatives. In order to complete the patient pathway through the acute phase, the remaining parameters are assumed to be independent of thromboprophylaxis method employed.

For example, there is no reason to suspect that the chance of a VTE event either being detected prior to discharge or remaining undetected will be dependent on the thromboprophylaxis regimen employed. Similarly, the sequelae from any particular VTE or adverse event, or the sub-type of a major bleed, can be reasonably assumed to be independent of the thromboprophylaxis regimen.

Table 61 presents the full list of remaining parameters in the acute phase of the model.

Table 61 Non-treatment specific probabilities in the acute phase

Row	Parameter	Probability	Reference
	VTE event type		
A	Proximal DVT		
B	Distal DVT		1 – (A + C + D)
C	PE (fatal and non-fatal)		See note i
D	Death from other causes		
E	Distal DVT propagates to the proximal veins		
	Event is symptomatic		
F	Proximal DVT		
G	Distal DVT		
H	PE (excluding immediately fatal)		
	Symptomatic Events		
I			
J			
K			
L			
M			
	VTE Mortality		
N			
O			See note ii
P			
Q			
	Major bleed type		
R			See note iii
S			See note iii
T			See note iii
U			1 – (R + S + T)
	Adverse Event Outcomes		
V			
	Major bleed mortality		
W			
X			
Y			
Z			
AA	Minor bleed mortality	0	Assumption
AB			

i. The probabilities of PE were derived from a secondary analysis of data reported in the NCC-AC meta-analysis (Appendix 9.7).

ii. In the absence of a value from the literature for this probability, the value for this parameter is reasonably assumed to be greater than the corresponding probability for treated cases. The value is uplifted by the same proportion as for the corresponding probabilities for PE (rows P and Q).

iii. The type of major bleed was determined by conditional probabilities derived from a secondary analysis of the NCC-AC meta-analysis (Appendix 9.7).

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; HIT, heparin-induced thrombocytopenia

Chronic phase transition probabilities

Recurrent VTE

Separate sets of probabilities for recurrent VTE were applied for patients in the post-VTE health states (state type c in **Figure 30**), which incorporates three separate health states:

- Post proximal DVT;
- Post distal DVT; and
- Post PE.

Estimates were taken from a synthesis of studies identified via the systematic review of studies detailed in Section 6.1.

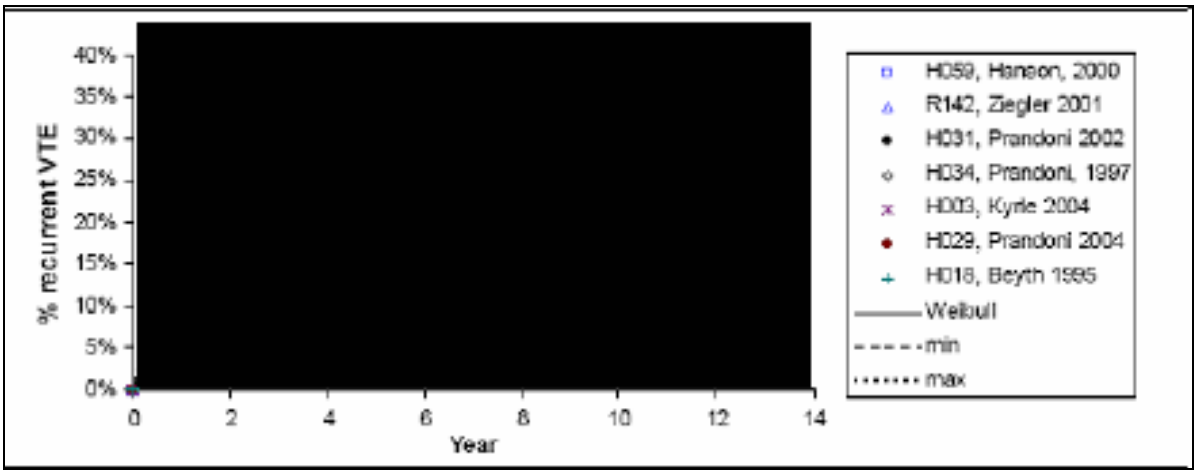
Of the 31 studies identified, 11 were excluded for the following reasons:

- Irrelevant populations were studied (3 studies);
- The same data were reported elsewhere, either for the same analysis or for a longer period of follow-up (4 studies);
- Reviews reporting data from other included studies (2 articles); and
- No relevant data were reported (2 studies).

Of the 20 included studies, 7 reported rates of recurrent VTE for patients that had experienced a DVT over a maximum period of 13 years. [75-81]

Incidence estimates from individual studies were extracted and synthesised by fitting a Weibull distribution (by minimisation of residuals). Two further distributions were fitted to data from the studies reporting the highest and lowest incidence estimates in order to derive high and low distributions (**Figure 31**). These were assumed to represent the upper and lower 95% confidence intervals of the distribution and were used to estimate a standard error for the Weibull scale parameter.

Figure 31 Incidence of recurrent VTE: published estimates and fitted Weibull function applied in the Markov model



In the probabilistic analysis, the Weibull lambda parameter (λ, scale) was sampled from a normal distribution defined by the mean and standard error. The gamma (γ, shape) parameter was assumed to be constant.

Table 62 Recurrent VTE: Weibull parameters

Parameter	Mean	95% CI
Lambda	[redacted]	[redacted]
Gamma*		

*The Gamma parameter was fixed in the probabilistic analysis.
CI, confidence interval

Time-dependent probabilities of a recurrent VTE event were estimated from the Weibull parameters as:

$$p = 1 - \exp[\lambda(t - u)^{\gamma} - \lambda t^{\gamma}]$$

where t is time in years and u is the cycle length (1 year).

No data were identified describing the incidence of recurrent VTE for patients with asymptomatic (and untreated) DVT. Probabilities of VTE were therefore assumed to be the same for patients with treated and untreated VTE events. This is expected to be a conservative assumption for more effective interventions, since less effective interventions would be expected to result in more asymptomatic and untreated events, and a higher risk of recurrent VTE is expected for untreated events.

The incidence of recurrent VTE is expected to be lower for patients that experienced a distal DVT as the primary VTE event [82]. In addition, the risk has been reported to be lower for females than for males [80]. The RRs for patients with a proximal DVT versus those with a distal DVT, and for males versus females, are presented in **Table 63**. These

parameters were fixed in the probabilistic analysis. No studies were identified that reported the incidence of recurrent VTE after a PE event. Probabilities were assumed to be the same as for a treated DVT.

Table 63 Relative risks for recurrent VTE by DVT location and gender

	RR	Source
Proximal vs Distal primary DVT	4.00	[82]
Males vs Females	3.60	[80]

Insufficient data were reported to include these parameters in the probabilistic analysis.

The probability that a recurrent VTE event will be a PE was estimated from four studies that reported the number of recurrent PEs and DVTs (**Table 64**). The probability was calculated as a simple average of the probabilities from each of the studies. In the probabilistic analysis, the probability derived from each study is sampled from a beta distribution defined by the number of patients with a VTE experiencing a PE and the number that did not.

Table 64 Type of recurrent VTE event

Study	n(DVT)	n(PE)	p(PE)	p(DVT)
[redacted]				
Average				

Patients that had no VTE event were assumed to be at the same risk of a VTE event as the general population (**Table 65**). Annual incidence estimates for DVT and PE were taken from the Prevention of Venous Thromboembolism, International Consensus Statement of 1997 (reported in [3]). The annual probability of an idiopathic VTE event was calculated by summing these incidence estimates and dividing by the population at risk. These parameters were fixed in the probabilistic analysis.

Table 65 Probability of idiopathic VTE

	Cases per 100,000 population	Probability applied to model
DVT	160	
PE	70	
VTE	**230**	**0.0023**

Source: [3]

PTS

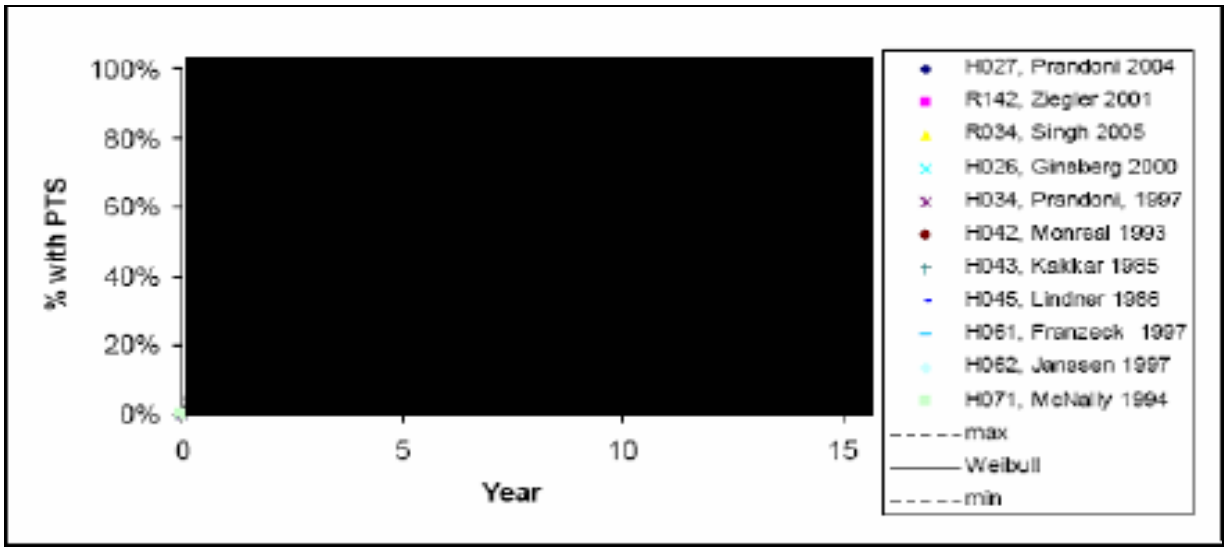
Estimates of the probability of PTS for patients with a treated VTE event were taken from a synthesis of studies identified via the systematic review of studies described in Section 6.1. Of the 20 included studies, 11 reported rates of PTS for patients that had experienced a DVT [5],[75],[79],[83-90].

Incidence estimates from individual studies reported over a period of 13 years were extracted and synthesised by fitting a Weibull distribution (by minimisation of residuals). The study that has been most widely used in economic analyses of VTE prophylaxis following orthopaedic surgery to estimate the probability of PTS [75] and a more recent study reporting very similar estimates [85] were selected to fit the central (deterministic) function. Two further distributions were fitted. The first was fitted to data from all identified studies and provided the high estimate. The second was fitted to the study reporting the lowest incidence estimates in order to derive a lower limit for the distribution (**Figure 32**). These were assumed to represent the upper and lower 95% confidence intervals of the distribution and were used to estimate a standard error for the Weibull scale parameter.

In the probabilistic analysis, the Weibull lambda parameter (λ, scale) was sampled from a normal distribution defined by the mean and standard error. The gamma (γ, shape) parameter was assumed to be constant. Time-dependent probabilities of a VTE event are estimated from the Weibull parameters as described in the previous sub-section.

The incidence of PTS for patients with asymptomatic (and untreated) DVT has been reported as 23.9% at a follow-up of 2 to 4 years [82] and 21% at a follow-up of 2 to 10 years [91]. These estimates are consistent with estimates for treated DVT reported by Prandoni and colleagues (1997) [75] for patients with a treated DVT. Probabilities of PTS are therefore assumed to be the same for patients irrespective whether the VTE event is treated or untreated.

Figure 32 Incidence of PTS: published estimates and fitted Weibull function applied in the Markov model



In the probabilistic analysis, the Weibull lambda parameter (λ, scale) was sampled from a normal distribution defined by the mean and standard error. The gamma (γ, shape) parameter was assumed to be constant (**Table 66**).

Table 66 PTS: Weibull parameters

Parameter	Mean	95% CI
Lambda	[redacted]	[redacted]
Gamma*		

*The Gamma parameter was fixed in the probabilistic analysis.
CI, confidence interval

Time-dependent probabilities of a PTS event were estimated from the Weibull parameters as described in the previous sub-section.

The incidence of PTS is expected to be lower for patients that experienced a distal DVT than for those who had a proximal DVT as the primary VTE event. The RR for patients with a proximal DVT versus those with a distal DVT is taken from Siragusa and colleagues (1997) [82]. This parameter is fixed in the probabilistic analysis.

Table 67 Relative risks for PTS by DVT location and gender

	RR	Source
Proximal vs Distal primary DVT	4.00	[82]

Insufficient data were reported to include these parameters in the probabilistic analysis.

Patients that had no VTE event are assumed to be at the same risk of developing PTS as the general population. Annual incidence estimates for venous stasis syndrome by age

group were taken from a US population-based study [92]. Probabilities were adjusted as patients aged with increasing time from surgery (**Table 68**). These parameters were fixed in the probabilistic analysis.

Table 68 Probability of idiopathic PTS by age group

Age group	Rate*	Probability
15-34	16.7	0.0002
35-44	42.7	0.0004
45-54	84.1	0.0008
55-64	120.8	0.0012
65-74	167.7	0.0017
75-84	326.3	0.0033
85+	349.7	0.0035

* (per 100,000 person years)
Annual probabilities were calculated by dividing the rate per 100,000 patient years by 100,000

For patients developing PTS, the probability that it is severe rather than mild-to-moderate was estimated as the simple average of estimates reported in eight studies (**Table 69**). This parameter was fixed in the probabilistic analysis.

Table 69 Probability that PTS is severe

Study	Mild to moderate	Severe	Total	p(Severe)
Singh and Masuda, 2005 [83]	29%	27%		0.483
Ziegler, 2001 [79]	75%	7%		0.083
Prandoni, 2004 [85]	87%	13%		0.130
Prandoni, 1997 [75]		3%	18%	0.150
		8%	30%	0.274
		8%	30%	0.272
Monreal, 1993 [86]	36%	20%		0.357
Kakkar and Lawrence, 1985 [87]	71%	17%		0.193
Franzeck, 1997 [89]	28%	5%		0.152
Janssen, 1997 [5]	73%	2%		0.027
Average				**0.233**

Death from other causes

Mortality rates by age and gender in 10-year age bands (**Table 70**) were taken from estimates for 2005 by the Office for National Statistics [93].

Table 70 Annual mortality rates

Age group	Annual mortality rate per 1,000	
	Males	Females
45-54	2.4	3.6
55-64	5.6	8.9
65-74	15.4	24.0
75-84	48.1	67.4
85+	152.7	171.6

Source: [93]

In order to estimate the rate for ages within each age band, an exponential equation was fitted to the data:

Mortality Rate (per 1,000 Females) = 0.0113 x e^ (0.1047 x age)
Mortality Rate (per 1,000 Males) = 0.0265 x e^ (0.0976 x age)

The probability of death in each yearly cycle (P) was calculated from the annual mortality rate per 1,000 patients (M) as: P = M / 1,000.

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

The quality of life of patients undergoing THR or TKR is expected to change during the time-frame of the model from pre-operative levels (when it will be poorer than that of the general population of the same age due to joint pathology) through the immediate post-surgical and hospitalisation period (when it will be poorer still due to the operation) and recovery period (by the end of which it is expected to return to levels similar to that of the general population). As the model follows patients for the remainder of their lifetimes, their quality of life is expected to decline a little, as is observed in the general population with increasing age.

Since changes in quality of life due to the surgery itself are expected to be the same regardless of the type of prophylaxis received, these may be excluded from the analysis. The model therefore focuses on the impact of VTE events, bleed events, HIT and death.

The impact of non-fatal VTE events, bleed events and HIT were modelled by applying a utility decrement for the period of time that quality of life is expected to be affected. All surviving patients were then attributed a utility weight which decreases over time to model the impact of ageing. Patients that survived an intracranial bleed but were disabled were attributed a utility decrement for the remainder of their lives to reflect the quality of life impairment from long-term disability.

This method is supported by the published literature on quality of life in such patients and by previous economic analyses in this indication. Exact sources will be detailed in the appropriate sub-sections later in the report.

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

Yes, as described above this is a cost-utility analysis considering the health effects associated with prevention of VTE and the adverse effects associated with bleeding events and HIT.

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

None of the clinical parameters were estimated via expert opinion.

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

Bioequivalency of LMWH

In the NCC-AC meta-analysis which accompanied the NICE clinical guideline [1], all LMWH agents were categorised as a single intervention. Similarly, other examples from the literature suggest that other LMWH agents such as dalteparin and tinzaparin are indistinguishable from enoxaparin [41],[67-68]. Thus, for the purposes of this economic evaluation, it is reasonably assumed that enoxaparin is equivalent in efficacy and safety to the aggregate of the agents included in the NCC-AC LMWH category. The mix of different LMWH agents used in current practice will be represented by the use of their respective acquisition costs to arrive at a weighted average for the mix.

Appropriate evidence base

As reported in the Section 5, there were two pivotal head-to-head clinical trials of DBG in this indication [23-24]. **Table 12** illustrated the key features of the trial designs, and it is extremely important to clarify why the design of the supporting RE-MOBILIZE study [25] differs significantly from the other two trials and where it is positioned.

Standard thromboprophylaxis practice in North America (particularly the United States) with respect to the administration of LMWH varies from that practiced in other parts of the world, especially in Europe. The dosing schedule for enoxaparin in RE-MOBILIZE is different to the that used in the UK (30mg b.i.d compared to 40mg o.d) as well as the

initiation (12-24 hours post-surgery compared to the evening before surgery) and the duration of treatment (12-15 days in TKR compared to 6-10 days).

Furthermore, the timing and duration of DBG treatment in RE-MOBILIZE does not reflect the intended marketing authorisation in the UK for TKR (initiated 12-24 hours post-surgery compared to 1-4 hours post-surgery, and 12-15 days duration compared to 10 days).

The RE-MOBILIZE trial was conducted with the specific purpose of satisfying the criteria for submission to the FDA for marketing authorisation in North America. As such, the design of RE-MOBILIZE makes it inapplicable to settings where alternative dosing and timing schedules of enoxaparin and DBG are appropriate.

The UK marketing authorisation for enoxaparin mirrors the design of RE-NOVATE [23] and RE-MODEL [24] in terms of dosing, initiation and duration of treatment. Similarly, the UK marketing authorisation for DBG, based on the positive opinion from the CHMP, will reflect the studied regimens from the RE-NOVATE study for THR and RE-MODEL study for TKR, and not the RE-MOBILIZE study. Therefore, in order to use the most appropriate evidence base this economic evaluation will consider the direct comparison of DBG and enoxaparin via the RE-NOVATE study for THR and RE-MODEL trial for TKR only.

Alternative approaches to derivation of symptomatic VTE event rate

The base case approach to the derivation of acute phase clinical inputs in the direct comparison uses the comparative rates of venographically confirmed VTE in the clinical trials to predict the number of symptomatic events, assuming a statistical link between the two. Conditional probabilities independent to the prophylaxis regimen are applied to predict the symptomatic events.

A second possible approach would be to use the symptomatic event data reported from the clinical trials directly. The base case approach facilitates a complete modelling of the whole epidemiological pathway and does not rely on estimates based on rare events. The main benefit of the second approach is that it would not assume that the type of DVT/PE event is independent of the thromboprophylactic agent used.

However, the rates of symptomatic events reported in clinical trials are typically extremely low (as in the DBG pivotal trials), therefore there is a large potential for the creation of bias using the second approach. The base case approach has also been extensively used

in previous economic evaluations (as determined by the systematic review described in Section 6.1).

6.2.8 Measurement and valuation of health effects

6.2.8.1 ***Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.***

The economic evaluation will report the following final outputs for each modelled patient cohort:

- Mean total expected costs per patient
- Mean total expected life years per patient
- Mean total expected QALYs per patient

These outputs will form the basis for the incremental cost-effectiveness ratios (ICERs) used to estimate the value for money of DBG versus the comparator medications.

In addition, the economic evaluation will also report the following secondary measures of health outcomes from the economic model:

- Mean total expected symptomatic VTE events per patient (including symptomatic proximal and distal DVT [first and recurrent events], PE and VTE-related death; PTS)
- Mean expected prophylaxis-related adverse events per patient: major bleeds; minor bleeds and HIT.

In each simulation, the model calculates the average number of events, time in each health state and overall survival for each treatment group in order to measure the relative health effects.

6.2.8.2 ***Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?***

The measured health effects detailed in the previous sub-section were valued in the economic model by assigning utility weights and decrements as appropriate to the various events and health states. This allows the model to arrive at a single set of final outcomes in each simulation, representing the average for the cohort in each treatment group, for use in the probabilistic analysis. This section details the utility weights and decrements used in the economic model.

VTE events

Utility decrements for VTE events were identified via the systematic review of economic evaluations described in Section 6.1.

One utility study was identified, Ingelgard (2002) [94], in which the EQ-5D was administered to 121 DVT patients undergoing warfarin treatment. The mean utility estimate for patients' current health state was 0.73, compared with 0.81 for a theoretical health state without DVT; the decrement associated with DVT was therefore estimated as 0.08.

The cost-utility analyses by Botteman *et al*. (2002) [3] and NCC-AC (2007) [41] assumed a decrement equal to the duration of hospitalisation for the event. The NCC-AC analysis applied a decrement of 0.01 associated with the inconvenience of warfarin treatment for the remainder of the treatment period.

In this analysis, a decrement equal to the duration of hospitalisation was assumed, and a decrement of 0.08 for the remainder of the treatment period based on Ingelgard (2002) [94]. Assumptions made in the calculation of utility decrements and the resulting estimates are presented in **Table 71**.

Table 71 Utility decrements for VTE events

Row	VTE events	Proximal DVT	Distal DVT	PE	Reference
	Occurring pre-discharge				
A	Duration of extended hospitalisation (days)				See note 1
B	Decrement during hospitalisation (QALdays)				A
C	Duration of treatment post-discharge (weeks)				
D	Utility decrement during treatment				
E	Total utility decrement (days)				(C x D x 7) + B
	Patients re-admitted for treatment (62%)				
F	Duration of re-hospitalisation (days)				F
G	Decrement during hospitalisation (QALdays)				
H	Duration of treatment post-discharge (weeks)				
I	Utility decrement during treatment				
J	Total utility decrement (days)				(H x I x 7) + G
	Patients treated at home (38%)				
K	Duration of treatment post-discharge (weeks)				
L	Utility decrement during treatment				
M	Total utility decrement (days)				K x L x 7

1. HES Tabulation Request, data year 2005/6 (Appendix 9.8).
2. NHS Reference Costs 2006 [95], elective and non-elective HRGs E20, E21, D10, D11

DVT, deep vein thrombosis; PE, pulmonary embolism; QALdays, quality-adjusted life days

PTS

Utility estimates for PTS were identified via the systematic review of economic evaluations described in Section 6.1. One study was identified which estimated the utility of mild-to-moderate and severe PTS, elicited from 30 Healthy volunteers and 30 physicians using Standard Gamble methods [96]. The utility weights were subtracted from that for perfect health (1.00), to calculate a decrement (**Table 72**) which is subtracted from the age and gender-adjusted utility weight for the model population.

Table 72 Utility decrements for PTS

Health state	PTS	No PTS	Utility decrement
Mild-to-moderate PTS	0.98	1.00	0.02
Severe PTS	0.93	1.00	0.07

Source:[96]

Bleed events and HIT

Utility estimates for PTS were identified via the systematic review of economic evaluations described in Section 6.1.

One utility study was identified [97] in which the standard gamble was administered to 54 atrial fibrillation patients undergoing warfarin treatment. The utility estimate for major bleed was 0.841 and for patients having warfarin treatment without major bleed was 0.941 (or 0.948 for general practice-managed treatment). The decrement is therefore estimated as 0.10 (0.941 - 0.841). The cost-utility analyses by the NCC-AC [41] assumed a decrement equal to the duration of hospitalisation for the event (4 days). No estimates were identified for minor bleed or non-fatal HIT.

In this analysis, a decrement of 0.10 [97] for the duration of in-patient stay for a gastrointestinal (GI) bleed (5.4 days; weighted average of elective and non-elective in-patient admissions for GI bleed with major procedure, F61 and F62) [95] was assumed.

Minor bleeds and non-fatal HIT are assumed to have a negligible effect on quality of life. For patients that are long-term disabled following an intracranial bleed, a utility decrement of 0.49 was applied for the remainder of their lifetime (based on the average of 109 published decrements reported for stroke, Appendix 9.9).

Fatal events

For fatal events occurring during the first 10 weeks (the period modelled by the decision tree), a utility decrement was applied that was equal to the number of days from death to the end of the 10-week period. Patients then enter the Markov model in the dead state and are assigned a utility weight of zero.

Deaths from events occurring pre-discharge were assumed to occur at the time of discharge. Death from events occurring post-discharge and asymptomatic events that are untreated were assumed to occur on day 14.

Quality of life for the aging population

All surviving patients were attributed a utility weight which decreases over time to model the impact of ageing (**Table 73**). Utility decrements for model events were subtracted from this baseline utility weight.

Age and gender-specific utility weights for the general population were taken from a national survey in England using the EQ-5D.

Table 73 General population utility weights by age and gender

Age group	Males	Females
55-64	0.80	0.78
65-74	0.80	0.76
75+	0.76	0.71

Source: [98]

6.2.8.3 ***Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?***

In all cases, utility weights and decrements were derived from studies that used methods consistent with the NICE reference case (EQ-5D, standard gamble), except in the decrement applied for the long-term disabled following intracranial haemorrhage. In this case, the utility decrement was based on an average of 109 published decrements for stroke (please see Appendix 9.9 for full details).

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

No health effects were excluded.

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

Health effects are expressed using QALYs.

6.2.9 Resource identification, measurement and valuation

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

The model measures the following disaggregated resources:

- The index surgical procedure
- Prophylaxis:
    - Drug acquisition
    - Drug administration
        - Nurse (ward or community)administration
        - Education in self-administration
- Treatment of VTE events:
    - Initial proximal DVT detected pre- or post-discharge
    - Initial distal DVT detected pre- or post-discharge
    - Initial PE detected pre- or post-discharge
    - Recurrent VTE (proximal DVT, distal DVT or PE)
    - PTS
- Treatment of prophylaxis-related adverse events:
    - Major bleeds
        - GI Bleed
        - Surgical site bleed (requiring re-operation)
        - Other major bleed
    - Minor bleeds
    - HIT
    - Long-term care of intracranial haemorrhage

6.2.9.2 ***How were the resources measured?***

Index surgical procedure

The introduction of oral DBG has the potential to reduce the length of stay of the primary hospitalisation at each end of the admission. Patients may not need to be admitted the day before surgery since the first dose is administered post-operatively, and may be discharged earlier than those receiving subcutaneous injections of LMWH because of the convenience of oral dosing. This will be examined in sensitivity analysis.

Length of stay was recorded in the phase-III DBG trials. However, because of the double blind, double dummy design no difference in length of stay would be expected between groups since all patients received subcutaneous injections of either enoxaparin or placebo. The base-case analysis therefore assumed the same length of stay for all prophylaxis interventions (except where it is extended due to a VTE or adverse event).

Prophylaxis

Drug acquisition

In the direct comparison, analyses were performed for both the base case (DBG 220mg) and the subgroup analysis (DBG 150mg) and enoxaparin (40mg o.d).

Since the efficacy data in the model reflects the number of doses administered in the phase-III trials, the cost of prophylaxis was based on the number of administrations (mean doses administered from the final analysis set used in the primary statistical analysis of the Phase III DBG trials; **Table 53**).

Table 74 Number of drug administrations in RE-NOVATE and RE-MODEL

Drug and trial	Number of administrations			Sample size
	Mean	Median	SD	N
DBG 220mg				
RE-NOVATE	33.0	33	5.2	880
RE-MODEL	7.7	8	1.3	503
DBG 150mg				
RE-NOVATE	33.1	33	5.1	874
RE-MODEL	7.8	8	1.3	526
Enoxaparin				
RE-NOVATE	33.2	33	5.1	897
RE-MODEL	7.6	8	1.4	512

Source: Boehringer Ingelheim GmbH data on file, 2006 (analysis performed for this economic evaluation); FAS analysis population.

All patients were assumed to receive the appropriate dosages to cover the mean durations of treatment reported in the clinical trials (NB: DBG patients receive a half dose on day 1). In the probabilistic analysis, the number of administrations was sampled from a normal distribution defined by the mean and standard error (In most cases, the mean was equal to the median to the nearest integer). The standard error was estimated from the standard deviation by dividing by the square root of the sample size (N).

In the indirect comparison, the SPC for fondaparinux [99] recommends that patients receive 2.5mg once daily for at least 5-9 days. Therefore in TKR, the duration of hospitalisation was assumed to equal the treatment duration. The NICE clinical guidelines [1] recommend that the vast majority of THR patients should continue therapy for 4 weeks (28 days) after surgery. Therefore an extended regimen of 28 days was assumed for THR patients.

Drug administration

Resource utilisation associated with drug administration of LMWH or fondaparinux could potentially include the following:

- The cost of nursing time for inpatient administration of subcutaneous injections;
- For patients able to self-administer outpatient prophylaxis:
    - patient/family training in self-administration;
    - a nurse home visit to check compliance.
- Nurse home visits for administration to those not able to self-administer.

For oral DBG the cost of administration was assumed to be zero.

There is considerable uncertainty as to the exact nature of in-hospital and post-discharge resources associated with the administration of LMWH or fondaparinux. It is clear that all patients expected to self-administer at home would need to receive adequate training from a nurse prior to discharge. It is also reasonable to assume that, given the largely elderly patient population in this indication, a significant proportion may experience some difficulty in self-administering their medication.

Resource use associated with post-discharge administration of subcutaneous injections has the potential to be a key differentiating cost parameter between DBG and LMWH/fondaparinux, and deserves close scrutiny. The debate does not surround the necessity for home visits where patients are unable to self-administer. If a patient is unable or unwilling to self-administer or has no access to a carer who is able to do so, and is prescribed a LMWH regimen that extends beyond discharge, then a daily home visit from a community nurse would be required to ensure compliance. The debate surrounds the following three points:

1. What proportion of patients is able and willing to self-administer, or has access to a carer who is able to administer the drug?

2. What proportion of patients, seemingly able and willing to self-administer, are wholly or partially non-compliant due to the inconvenience/discomfort associated with injections?

3. Whether the above issues create scenarios in practice where post-discharge LMWH or fondaparinux prophylaxis regimens are not actually prescribed.

In the absence of reliable data, points 2 and 3 are difficult to quantify and are therefore not considered in the base case analysis. Anecdotally, it can be reasonably argued that compliance with LMWH or fondaparinux therapy, as with any injectable medication, is likely to be lower than that of an oral therapy. However, as the economic model uses efficacy and safety data from clinical trials, where one should assume 100% compliance

with all therapies, this issue is one best kept for discussion outside the analysis. An analysis examining point 3 comparing extended DBG (28-35 days) with a standard LMWH/fondaparinux regimen (~8 days) in THR patients will be presented in sensitivity analysis.

With the base case assuming that THR patients receive an extended regimen of LMWH/fondaparinux, an estimation of the proportion of patients willing and able to self-administer in routine clinical practice will be key to the analysis. A systematic review was performed to identify estimates of the percentage of patients able to self-administer subcutaneous injections of VTE prophylaxis or treatment at home (see Appendix 9.10). A total of 26 full text sources were reviewed. Nine of these were excluded because no estimate of the proportion able to self-administer was reported. Details of the remaining 17 were reviewed in detail by two clinical specialists. Fifteen of these were rejected on the basis that nurse administration was enforced by the study design, patients were selected for ability to self-administer or were not representative of the THR/TKR population with respect to age, or estimates were assumptions not grounded in data.

Two relevant estimates were identified. Watts *et al*., (2006) [100] reported that 87% of patients receiving outpatient prophylaxis with fondaparinux were able to self-inject. This estimate may be considered as the upper end of the likely range for LMWH, as the fondaparinux injection system is designed to maximise ease of administration and is superior to injection systems available for LMWH in this respect.

The other relevant estimate was reported by Koopman *et al*., (1996) [101] 15% of patients receiving LMWH at home required help with administration (the remaining 85% were able to self-administer).

Therefore, the Watts estimate (87%) was adopted as the base case value for both LMWH and fondaparinux as a conservative approach. This implies that the economic model will consider 13% of THR patients as unable or unwilling to self-administer their medication, and therefore requiring a daily community nurse visit at home to administer the medication until the course is complete. This value was not sampled in the probabilistic analysis but will be tested in univariate sensitivity analysis.

Interventions administered by subcutaneous injection may also result in costs associated with sharps disposal, and costs and health consequences resulting from needlestick injuries. These have not been included in the base-case analysis, which may favour the injectable interventions slightly.

The resources associated with LMWH and fondaparinux administration in the base case are presented separately from their value in **Table 77**.

None of the economic analyses identified for the UK included platelet count monitoring for LMWH. The British Committee for Standards in Haematology guidance on diagnosis and treatment of HIT recommends carrying out a series of platelet counts up to day 14 to test for HIT [22], however the extent to which is done in practice in the UK is unclear. The economic analysis by the NCC-AC did not include costs of platelet counts, but did examine their addition in sensitivity analysis [41]. In this analysis, the cost of platelet count monitoring was excluded from the base case analysis.

VTE events

Resource utilisation for VTE and adverse events were based on the published literature (identified via the systematic review of economic analyses described in Section 6.1), recognised UK cost sources or non-controversial assumptions. Five analyses specific to the UK were identified [41],[54-57].

DVT detected prior to discharge

Diagnosis: All UK economic analyses assumed one Doppler ultrasound investigation (with the exception of the earliest analysis which assumed 1 venogram). All symptomatic DVT cases are therefore assumed to receive one Doppler ultrasound investigation.
Treatment of Confirmed Events: The increase in length of stay for patients with a confirmed DVT event identified during the primary hospitalisation was estimated from UK Hospital Episode Statistics (for the most recent data year at the time of analysis [2005/6]; HES Tabulation Request, 2006, Appendix 9.8). Other resource use estimates were taken from the economic analysis performed by the NCC-AC (2007) [41].

These resources are presented separately from their valuation in **Table 78**.

DVT detected post-discharge

Diagnosis: Patients presenting with DVT symptoms after discharge were assumed to incur an outpatient visit (adult follow-up attendance, clinical haematology) and receive one Doppler ultrasound investigation.
Treatment: Those with a confirmed event may either be treated at home or re-admitted for treatment. The percentage of patients that are re-admitted for treatment was taken from a UK economic analysis [56]. Resource use for extended treatment after discharge was

taken from NCC-AC (2007) [41]. Resource use for treatment of DVT for those patients that are treated at home was taken from NCC-AC (2007) and Davies and colleagues (2000) [56].

These resources are presented separately from their valuation in **Table 79**.

PE detected prior to discharge

PEs that are immediately fatal are assumed to be untreated and to incur no direct costs.

Diagnosis: Patients presenting with PE symptoms prior to discharge are assumed to receive diagnostic investigations. Resource use estimates for diagnosis of PE were taken from NCC-AC (2007) [41].
Treatment: Patients with confirmed events are assumed to receive an extended hospital stay and treatment with anticoagulants. The increase in length of stay was estimated from UK Hospital Episode Statistics (for the most recent data year [2005/6]; HES Tabulation Request, 2006, Appendix 9.8). Other resource estimates were taken from NCC-AC (2007) [41].

These resources are presented separately from their valuation in **Table 80**.

PE detected post-discharge

PEs that are immediately fatal are assumed to be untreated and to incur no direct costs.

Diagnosis: Patients presenting with PE symptoms after discharge are assumed to incur a visit to accident and emergency. Investigations received are taken from NCC-AC (2007) [41].
Treatment: Those with a confirmed event are assumed to be admitted for treatment. Resource use for extended treatment after discharge is taken from NCC-AC (2007) [41].

These resources are presented separately from their valuation in **Table 81**.

PTS

The resource use associated with diagnosis and management of PTS was assumed to be implicit within the valuations reported in an analysis of the economic burden of the long-term complications of DVT after total hip replacement surgery for the US [59]. These valuations are presented in **Table 82**.

Adverse events

Intracranial bleed

The resource use associated with acute care for intracranial haemorrhage was assumed to be implicit within the valuation derived from a retrospective study of 38 patients with a major bleed associated with warfarin treatment in the UK [102]. Similarly, the resource use associate with long-term care for intracranial haemorrhage was assumed to be implicit within the valuation taken from a cost of illness study based on resource use data collected for 457 stroke patients treated in a UK centre [103]. These valuations are presented in **Table 83**.

Other adverse events

It was assumed that resources associated with major bleeding events were reflected by the cost of an inpatient stay for such events.

For minor bleeds, the proportion that required medical attention was estimated from the proportion of all minor bleeds that were clinically relevant in the DBG trials. Resource use for clinically relevant minor bleeds was estimated as two out-patient visits (adult follow-up attendance, clinical haematology) based on clinical opinion. Other minor bleeds are assumed to result in negligible costs.

Resource utilisation for HIT was based on an economic analysis by Honorato *et al*. (2004) [63] and was applied to patients that survived the HIT event only.

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

With certain obvious exceptions (e.g. number of drug administrations) resource utilisation data was not routinely collected in the DBG phase-III trials and in some cases would not have been appropriate (i.e. no reliable estimate of self-administration capability can be derived from a clinical trial with enforced compliance). Therefore the measurement of resources in the acute treatment phase relied on the published literature, recognised cost sources and non-controversial assumption. In the chronic phase, due to the relatively short duration of follow-up in clinical trials, the resource measurement must necessarily rely heavily on the published literature.

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

Yes, the economic model considers all resources associated with VTE, adverse effects from thromboprophylaxis and their sequelae stemming from the index surgical procedure, whensoever they may occur.

6.2.9.5 ***What source(s) of information were used to value the resources?***

Index surgical procedure

The average costs of elective THR and TKR, and the average lengths of stay presented in **Table 75**, were taken from NHS National Reference Costs [95], calculated as a weighted average of procedures performed by NHS and non-NHS providers (for primary joint replacement, i.e. not including revision procedures). The cost per bed day was £251.11 (patients using a bed - cost per patient day: other medicine 2004, inflated to 2008 values) [104].

Table 75 Cost per episode and length of stay for THR and TKR

Description	Average cost	Average LOS	Number of episodes
NHS Hospital: Elective inpatient H80 - Primary Hip Replacement Cemented	£5,521	7.87	31,247
Non-NHS Hospital: Elective inpatient H80 - Primary Hip Replacement Cemented	£6,165	7.48	3,165
NHS Hospital: Elective inpatient H81 - Primary Hip Replacement Uncemented	£5,516	6.93	10,583
Non-NHS Hospital: Elective inpatient H81 - Primary Hip Replacement Uncemented	£6,825	5.32	749
Weighted Average for THR*	***£6,036***	***7.63***	
NHS Hospital: Elective inpatient H04 - Primary Knee Replacement	£5,843	7.38	52,378
Non-NHS Hospital: Elective inpatient H04 - Primary Knee Replacement	£6,928	5.35	4,354
Weighted Average for TKR*	***£6,389***	***7.38***	

Source: National Reference Costs, 2006 [95]
*Average was weighted for the number of episodes and inflated to 2008 values.
LOS, Length of Stay; THR, total hip replacement; TKR, total knee replacement.

Prophylaxis

Drug acquisition

Whilst the efficacy and safety results from the clinical trials are based purely on enoxaparin, in UK practice a mixture of the various LMWH preparations are used. As noted previously the recent NICE guidelines [1] propose recommendations that assume

each of the LMWH preparations to be essentially bioequivalent. For the purposes of this analysis, the assumption of bioequivalence affects only the unit costs applied to each enoxaparin administration in the clinical trials. Unit costs for the various DBG, LMWH and fondaparinux prophylaxis regimens available in the UK are presented in **Table 76**.

Table 76 Medication unit costs

Drug	Form	Strength	Pack size	Pack cost	Daily dose	Cost per dose
Dabigatran (Pradaxa)	Capsule	75mg	10	£21.00	150mg	£4.20
Dabigatran (Pradaxa)	Capsule	75mg	60	£126.00	150mg	£4.20
Dabigatran (Pradaxa)	Capsule	110mg	10	£21.00	220mg	£4.20
Dabigatran (Pradaxa)	Capsule	110mg	60	£126.00	220mg	£4.20
Enoxaparin (Clexane)	Syringe	40mg	1	£4.20	40mg	£4.20
Dalteparin (Fragmin)	Syringe	5000U	1	£2.82	5000U	£2.82
Tinzaparin (Innohep)	Syringe	4500U	1	£3.83	4500U	£3.83
Bemiparin (Zibor)	Syringe	3500U	1	£4.52	3500U	£4.52
Fondaparinux (Arixtra)	Syringe	2.5mg	1	£6.66	2.5mg	£6.66

Source: All comparator unit costs are NHS list prices drawn from BNF 54 [105]. Dabigatran etexilate unit costs are based on the proposed NHS list prices noted in Section1.

In the absence of accurate data from England and Wales on the share of the LMWH market attributable to each preparation in this indication, it is sufficient to make a conservative assumption (biased against DBG) that the cost of a LMWH regimen is a weighted average of the various preparations. With the exception of bemiparin, enoxaparin is the most expensive of the LMWH preparations. Therefore a weighted average that excludes bemiparin (which has been twice rejected by the SMC) will result in a cost per day that is lower than that of enoxaparin. The economic model therefore assumes the following notional market shares for LMWH in England and Wales:

- Enoxaparin, 80%
- Dalteparin, 10%
- Tinzaparin, 10%
- Bemiparin, 0%

Utilising these market shares results in a weighted average cost per day of £4.03, and this is the cost applied to the economic model base case.

Drug administration

The valuation of resources associated with LMWH and fondaparinux administration in the base case are presented in **Table 77**.

Table 77 Resources associated with administration of LMWH and fondaparinux

Resource	Units	Unit cost	Total cost
Patients unable/unwilling to self-administer (13% of THR patients)			
Community nurse visits per post-discharge administration[1]	1	£24	£24
In-patient administration (All patients)			
Nurse time per inpatient administration (min)[2]	2.14	£0.38	£0.82
Patients able/willing to self-administer (87% of THR patients)			
Nurse time for training (during inpatient stay, min)[3]	30	£0.37	£11

Costs are inflated to 2008 values.

1. *The unit cost of a community nurse visit is derived from Curtis (2007) [106], section 9.1*
2. *The time per administration is derived from Offord (2004) [107]. The unit cost of a staff nurse is derived from Curtis (2007) [106], section 13.3*
3. *The time for training is derived from NCC-AC (2007) [41]. The unit cost of a staff nurse is derived from Curtis (2007) [107], section 13.3*

VTE events

DVT detected prior to discharge

Table 78 presents the derivation of the costs for proximal and distal DVT events detected prior to discharge.

Table 78 Cost of DVT detected prior to discharge

	Proximal DVT		Distal DVT		Unit cost
	% of patients	Units	% of patients	Units	
Diagnosis					
Doppler Ultrasound[1]	100%	1	100%	1	£95.00
Total cost per suspected case	£87		£87		
Treatment of confirmed events					
Additional days: General Ward[2]	100%	4.9	100%	4.9	£263.55
LMWH (injections)[3]	100%	7	100%	7	£4.03
Nurse time (min)[4]	90%	30	90%	30	£0.38
Full Blood Count[1]	100%	2	100%	2	£3.04
GCS (pairs)[5]	100%	6	100%	6	£10.82
Warfarin (weeks)[6]	31%	26	69%	12	£0.70
Anticoagulation clinics[1]	100%	7	100%	5	£29.48
Ambulance transport to clinic[7]	5%	7	5%	5	£37.18
Total cost per confirmed case	£1,626		£1,563		

Costs are inflated to 2008 prices.

Unit cost sources:

1. NHS Reference Costs (2006) [95]
2. NHS Returns, 2003/04 [104]
3. Weighted average as described earlier in report
4. Curtis (2007) [106].
5. NHS Electronic Drug Tariff, Feb 2005 [108]
6. Based on cost per week: 7 days x £0.10 per day. Not exact due to rounding. Cost sourced from BNF 54 [105]
7. NCC-AC, 2007[41]

DVT detected post-discharge

Table 79 presents the derivation of the costs for proximal and distal DVT events detected post-discharge.

Table 79 Cost of DVT detected post-discharge

	Proximal DVT		Distal DVT		Unit cost
	% of patients	Units	% of patients	Units	
Diagnosis					
Outpatient visit[1]	100%	1	100%	1	£117.54
Doppler Ultrasound[1]	100%	1	100%	1	£95.00
Total cost per suspected case	£198.96		£198.96		
Treatment of confirmed events					
% of patients re-admitted	62%		62%		
Admitted patients					
Hospital stay for DVT treatment[1]	100%	1	100%	1	£1,165
Warfarin (weeks)[2]	31%	26	69%	12	£0.70
Anticoagulation clinics[1]	100%	7	100%	5	£29.48
Ambulance transport to clinic[3]	5%	7	5%	5	£37.18
Patients treated at home					
LMWH (injections)[4]	100%	5	100%	5	£4.03
Full Blood Count[1]	100%	1	100%	1	£3.04
GCS (pairs)[5]	100%	1	100%	1	£10.82
Warfarin (weeks)[2]	100%	12	69%	12	£0.70
Community nurse visits[6]	100%	8	90%	8	£25.10
Anticoagulation clinics[1]	100%	7	100%	5	£29.48
Ambulance transport to clinic[3]	5%	7	5%	5	£37.18
Total cost per confirmed case	£1,033		£970		

Costs are inflated to 2008 prices.

Unit cost sources:

1. NHS Reference Costs (2006) [95]
2. Based on cost per week: 7 days x £0.10 per day. Not exact due to rounding. Cost sourced from BNF 54 [105]
3. NCC-AC, 2007[40]
4. Weighted average as described earlier in report
5. NHS Electronic Drug Tariff, Feb 2005 [108]
6. Curtis (2007) [106]

PE detected prior to discharge

Table 80 presents the derivation of the costs for PE events detected prior to discharge.

Table 80 Cost of PE detected prior to discharge

	% of patients	Units	Unit cost
Diagnosis			
Computed tomography pulmonary angiogram[1]	100%	1	£91.06
Chest x-ray[1]	100%	1	£21.05
Electrocardiogram[1]	100%	1	£29.91
Total cost per suspected case	£142.02		
Treatment for confirmed cases			
Additional days: Intensive Care Unit[1]	10%	6	£1,438.05
Additional days: General Ward[2]	90%	6	£263.55
LMWH (injections)[3]	100%	7	£4.03
Nurse time (min)[4]	10%	30	£0.38
Full Blood Count[1]	100%	2	£3.04
GCS (pairs)[5]	100%	6	£10.82
Warfarin (weeks)[6]	100%	26	£0.70
Anticoagulation clinics[1]	100%	7	£29.48
Ambulance transport to clinic[7]	5%	7	£37.18
Total cost per confirmed case	£2,510		

Costs are inflated to 2008 prices.

Unit cost sources:

1. NHS Reference Costs (2006) [95]
2. NHS Returns, 2003/04 [104]
3. Weighted average as described earlier in report
4. Curtis (2007) [106]
5. NHS Electronic Drug Tariff, Feb 2005 [108]
6. Based on cost per week: 7 days x £0.10 per day. Not exact due to rounding. Cost sourced from BNF 54 [105]
7. NCC-AC, 2007[41]

PE detected post-discharge

Table 81 presents the derivation of the costs for PE events detected post-discharge.

Table 81 Cost of PE detected post-discharge

	% of patients	Units	Unit cost
Diagnosis			
A&E Visit[1]	100%	1	£146.18
Computed tomography pulmonary angiogram[1]	100%	1	£91.06
Chest x-ray[1]	100%	1	£21.05
Electrocardiogram[1]	100%	1	£29.91
Total cost per suspected case	£288.20		
Treatment for confirmed cases			
Hospital stay for PE treatment[1]	100%	1	£1,491.81
Warfarin (weeks)[2]	100%	26	£0.70
Anticoagulation clinics[1]	100%	7	£29.48
Ambulance transport to clinic[3]	5%	7	£37.18
Total cost per confirmed case	£1,729.34		

Costs are inflated to 2008 prices.
Unit cost sources:

1. NHS Reference Costs (2006) [95]
2. Based on cost per week: 7 days x £0.10 per day. Not exact due to rounding. Cost sourced from BNF 54 [105]
3. NCC-AC, 2007 [41]

PTS

The cost associated with diagnosis and management of PTS is derived from an analysis of the economic burden of the long-term complications of DVT after total hip replacement surgery for the US [59]. Costs in US dollars were converted to sterling using an exchange rate of 0.505 (10 January 2008) and inflated to current prices using the NHS Pay and Prices index.

Table 82 presents the derivation of the costs for PTS.

Table 82 Cost of PTS

Severity	Year 1	Year 2+
Mild to moderate	£541	£220
Severe	£2,461	£602

Costs are inflated to 2008 prices.
Source: Adapted from Caprini, 2003 [59].

Adverse events

Intracranial bleed

The cost of acute care for intracranial haemorrhage was based on a retrospective study of 38 patients with a major bleed associated with warfarin treatment in the UK [102]. The total cost of initial management of a major bleed was reported as £5,698 (95% confidence intervals £4,351 to £7,046; cost year 2002). These values were inflated to 2008 prices and sampled in the probabilistic analysis from a normal distribution (confidence intervals were symmetrical about the mean value).

Table 83 presents the derivation of the costs for intracranial bleed.

Table 83 Long-term care cost of intracranial bleed

Annual cost of care			
Institutionalised patients: (A)	£19,756		
Direct healthcare in-home: (B)	£1,663		
Informal care in-home: (C)	£6,975		
Annual cost of care by severity	**Mild**	**Moderate**	**Severe**
% of patients in institutional care: (D)	0%	1%	17%
% of patients cared for at home: (E)	100%	99%	83%
Direct care cost per patient: (A x D) + (B x E) = (F)	£1,663	£1,808	£4,775
Informal care cost per patient: (C x E) = (G)	£6,975	£6,919	£5,775
% of patients with each type of disability: (H)	0%	49%	16%
Average annual cost of long-term care: Σ[(F + G) x (H)]	**£5,953**		

Costs are inflated to 2008 prices.
Source: Bond, 2004 [102] (cost year 2002); Youman, 2003 [103].

Other adverse events

Cost estimates for bleed events were selected from available national cost estimates and published data by two UK clinical specialists.

The cost of GI bleeds was based on UK National Reference Costs (2006) [95] as follows:

- GI bleed episode: GI bleed with a major procedure (HRG F61 and F62).
- Surgical site bleed requiring re-operation: GI bleed with a major procedure (HRG F61 and F62).
- Other major bleeds: Inpatient admissions for a GI bleed without a major procedure (HRG F64 and F65).

Table 84 presents the derivation of the costs for other adverse events.

Table 84 Cost of other adverse events

Adverse event	Assumptions	Cost
GI bleed	Weighted average of HRGs F61 and F62	£2,355
Surgical site bleed (requiring re-operation)	As GI bleed	£2,355
Other major bleed	Weighted average of HRGs F64 and F65	£1,027
Minor bleed	Two outpatient visits	£89
HIT	One additional day in hospital plus one outpatient visit	£293

Costs are inflated to 2008 prices.
Sources: NHS Reference Costs (2006) [95] and NHS Returns, 2003/04 [104]

6.2.9.6 ***What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?***

The unit cost of DBG applied to the economic model is as presented in Section 1, please refer to **Table 76**.

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

Yes, costs relate to those under the control of the NHS and were valued using prices relevant to the NHS wherever possible. Drugs are valued at the NHS list price. The vast majority of resource use is informed either by the clinical trials or via the systematic review of economic evaluations. Non-controversial assumption is used in a few cases and expert opinion is avoided wherever possible.

6.2.9.8 ***Were resource values indexed to the current price year?***

Yes, resource values were indexed to 2008 prices using the NHS Pay and Prices Index. [106]

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

A full list of modelling assumptions is provided in Section 6.2.6.1.

6.2.10 Time preferences

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

Yes, costs and health benefits were both discounted to present value at a rate of 3.5% as per the NICE reference case. Alternative discount rates are examined in sensitivity analysis.

6.2.11 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

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

Apart from the probabilistic sensitivity analysis (PSA) described in Section 6.2.11.2, a range of univariate and scenario-based sensitivity analyses were also performed. During development of the economic model, areas of uncertainty were identified that would not necessarily be accounted for by PSA. For example, the relative risks applied for fondaparinux in THR were identified as a source of potential bias (Section 6.2.7.1), and with the confidence intervals also being derived from the same source PSA is unlikely to demonstrate the level of uncertainty with this estimate. In addition, uncertainty surrounds the level to which extended regimens of LMWH or fondaparinux are actually prescribed in UK practice (Section 6.2.9.2). Therefore, a separate analysis of extended DBG compared to standard duration LMWH/fondaparinux will also be presented to inform this debate.

Further sensitivity analyses were performed as follows:

- Substitution of the individual trial relative risks for DBG with the meta-analysed results of the combined trials
- Adjustment of the comparative length of stay to account for possible later admission/earlier discharge with DBG
- Adjustment of the self-administration proportion in THR patients receiving LMWH/fondaparinux and other administration assumptions
- Alternative model timeframes
- Discount rates

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

Yes, the economic model is designed to produce probabilistic results. Where model variables are sampled, the details of the chosen distributions and sources have been described in the relevant sub-section above. In summary:

- Absolute risks were sampled from beta distributions defined by the number of patients experiencing the event and the total number at risk;

- Relative risks taken from the NCC-AC meta-analysis (and DBG trials) were sampled from a log normal distribution, as the logarithm of the RR was reported to be normally distributed [41];
- Death from other causes which was sampled from a beta distribution defined by the number of patients with the event and the number without;
- Probabilities for the type of major bleed were sampled from a beta distribution defined by the number of patients experiencing an event of that type and the number that experienced another type of major bleed;
- Probabilities of recurrent VTE and PTS: the Weibull lambda parameters (scale) were sampled from normal distributions defined by the mean and standard error. The gamma (shape) parameters were assumed to be constant.
- The number of prophylaxis administrations for LMWH was sampled from a normal distribution defined by the mean and standard error observed in the phase-III trials. [In most cases, the mean was equal to the median to the nearest day];
- The cost of acute care for intracranial bleed was sampled from a normal distribution (confidence intervals were symmetrical about the mean estimate) defined by the mean and standard error reported by Bond *et al*., (2004) [102].

The analysis was performed by estimating the net monetary benefit (NMB) for each of 1,000 simulations of the probabilistic model at a series of incremental cost-effectiveness ratio (ICER) thresholds according to the following formula:

$$NMB = \Delta b \times ICERt - \Delta c$$

Where NMB is the net monetary benefit;
Δb is the incremental benefit;
ICERt is the ICER threshold; and
Δc is the incremental cost.

The probability of cost-effectiveness at each ICER threshold was estimated as the percentage of the 1,000 simulations for which NMB > 0. The probabilistic estimate of the ICER was generated by solving for the ICER threshold at which the mean net benefit is zero (using the GoalSeek function in MS Excel). The 95% confidence intervals were estimated in an analogous way, by solving for the ICER threshold at which the 95% confidence interval is zero.

6.2.11.2 *Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?*

The model structure employed has been extensively researched, described and supported as the most appropriate. Alternative model structures have not been investigated.

6.2.12 Statistical analysis

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

In the direct comparison, the rates of events recorded in the clinical trials are applied directly to the model given that the acute phase of the model accurately reflects the duration of follow-up in the clinical trial. In the indirect comparison, it is necessary to assume that the relative risks derived from the mixed treatment comparison apply equally to same period of time.

In the chronic phase, the transformation of the published long-term epidemiological data into probabilities using a Weibull function has been described above.

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

As described above, the transition probabilities used in the chronic phase are time-dependant.

6.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The economic model was developed by RTI Health Solutions, an independent non-profit research organisation. The initial model specification and the completed model were reviewed by a panel of clinical experts and amended to address their comments. Quality-control procedures were performed by staff not involved in the model development according to a pre-specified test plan including verification of all input data with the original source and programming validation by a senior health economist.

6.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- ***costs, QALYs and incremental cost per QALY***
- ***disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment***
- ***a statement as to whether the results are based on a probabilistic sensitivity analysis***
- ***cost-effectiveness acceptability curves***
- ***scatterplots on cost-effectiveness quadrants.***

6.3.1 Base-case analysis

6.3.1.1 *What were the results of the base-case analysis?*

Whilst results for both the 220mg and 150mg dose of DBG will be presented, it is important to note that the 220mg dose is the focus of the analyses presented. Positive CHMP opinion has been granted with 220mg the recommended dose for the vast majority of patients. The 150mg dose is intended to be reserved for patients who should be treated with caution due to limited clinical experience of such patients in the clinical trials.

Direct comparison with LMWH

THR

The results of the direct comparison of DBG with LMWH in THR, both for the main analysis of patients receiving DBG 220mg and the subgroup analysis of patients receiving DBG 150mg, based on the RE-NOVATE trial, are presented in the following tables and charts.

Table 85 presents the modelled lifetime costs per patient for LMWH and both doses of DBG, disaggregated by cost category.

Table 85 Comparative mean lifetime costs of DBG and LMWH in THR patients

Cost category	LMWH	DBG 220mg	Increment	DBG 150mg	Increment
Primary hospitalisation	£6,036	£6,036	£0	£6,036	£0
Prophylaxis	£233	£137	-£97	£137	-£96
Drug	*£134*	*£137*	*£3*	*£137*	*£3*
Administration	*£100*	*£0*	*-£100*	*£0*	*-£100*
VTE events	£227	£220	-£7	£248	£20
Proximal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	£29	£34	£5	£22	-£7
Major bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minor bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HIT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£6,525**	**£6,426**	**-£99**	**£6,442**	**-£83**

DBG, dabigatran etexilate; DVT, deep vein thrombosis; HIT heparin-induced thrombocytopenia; LMWH, low-molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; THR, total hip replacement.
Some numbers may have rounding error.

The economic model predicts that THR patients will accrue less healthcare costs over the course of their lifetime when treated with DBG compared to LMWH. Whilst medication costs are approximately the same, the administration costs associated with LMWH

patients drive the difference between the treatments. Costs incurred for VTE and adverse events are similar for both treatments. Nevertheless, it is interesting to note that the 220mg dose of DBG incurs slightly lower VTE event costs and slightly higher bleeding event costs compared to LMWH, with the opposite true for DBG 150mg. This points towards the delicate balance between efficacy and safety that characterises the practice of thromboprophylaxis.

Table 86 presents the modelled lifetime health outcomes per patient for LMWH and both doses of DBG, disaggregated by outcome category.

Table 86 Comparative mean lifetime health outcomes of DBG and LMWH in THR patients

Outcome category	LMWH	DBG 220mg	Increment	DBG 150mg	Increment
Symptomatic VTE	6.1%	5.9%	-0.2%	6.8%	0.7%
Non-fatal proximal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal distal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeds	1.6%	2.0%	0.5%	1.3%	-0.3%
Minor bleeds	9.9%	10.3%	0.4%	11.0%	1.1%
HIT	0.4%	0.0%	-0.4%	0.0%	-0.4%
Final outcomes					
Life years	**11.229**	**11.242**	**0.013**	**11.232**	**0.002**
QALYs	**8.422**	**8.432**	**0.010**	**8.423**	**0.001**

DBG, dabigatran etexilate; DVT, deep vein thrombosis; HIT heparin-induced thrombocytopenia; LMWH, low-molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QALY, quality-adjusted life year; THR, total hip replacement.
Some numbers may have rounding error.

The economic model predicts that THR patients will fare better over the course of their lifetime when treated with DBG compared to LMWH. Patients receiving DBG 220mg gain additional benefit due to less symptomatic VTE events; the slightly higher rate of bleeding events is partially offset by HIT events in LMWH patients.

Table 87 presents the incremental cost-effectiveness analysis based on these results.

Table 87 Incremental cost effectiveness of DBG compared to LMWH in THR patients

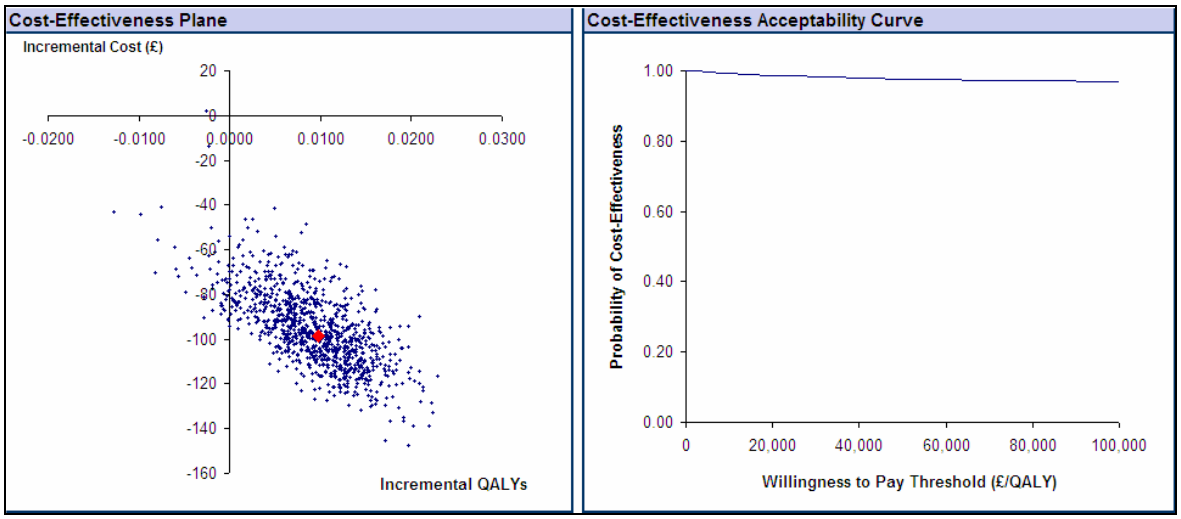
	Deterministic	Probability cost-effective at threshold:	
		£20,000/QALY	£30,000/QALY
DBG 220mg			
Incremental cost	-£99	99%	98%
Incremental QALYs	0.010		
ICER	DBG DOMINANT		
DBG 150mg			
Incremental cost	-£83	76%	71%
Incremental QALYs	0.001		
ICER	DBG DOMINANT		

DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; LMWH, low-molecular weight heparin; QALY, quality-adjusted life year; THR, total hip replacement.

In terms of incremental cost effectiveness, both DBG doses are associated with lower lifetime costs and improved outcomes over the average patient lifetime when compared to LMWH. This results in DBG dominating LMWH in both analyses. The robustness of these results can be examined diagrammatically with the cost-effectiveness planes and acceptability curves generated by the economic model, which in turn permits threshold analyses to be performed. **Figure 33** and **Figure 34** illustrate the cost-effectiveness planes and acceptability curves for each DBG dosage regimen.

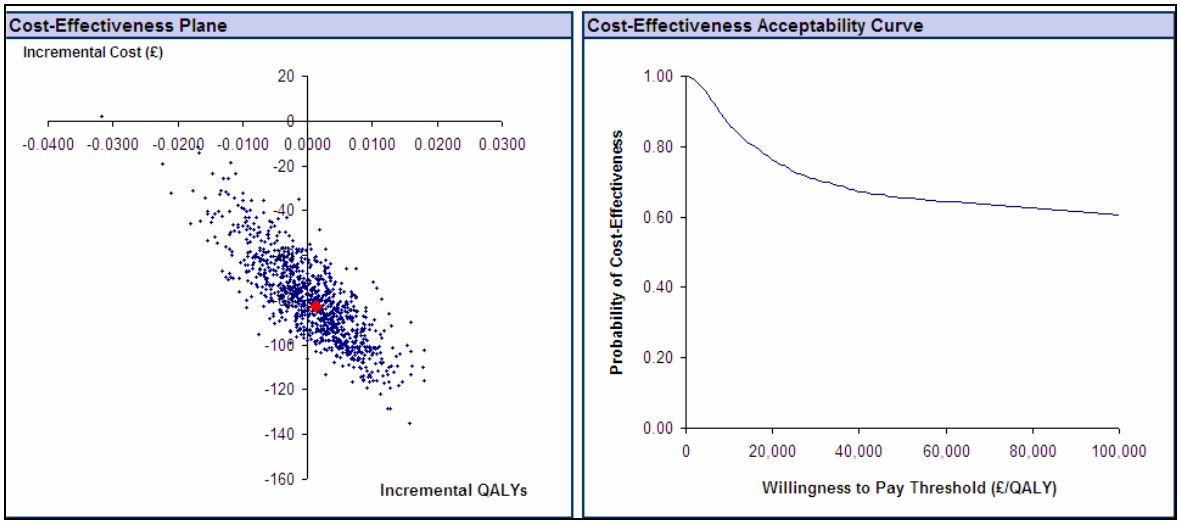
For DBG 220mg, the vast majority of model simulations are situated in the “south-east” quadrant where DBG is more effective and less costly. At a cost-effectiveness threshold of £20,000 per additional QALY gained, DBG is predicted to be cost-effective with a probability of 99%. For DBG 150mg the results are similar, although with slightly more simulations situated in the “south-west” quadrant where DBG is less effective and less costly, resulting in a corresponding cost-effectiveness probability of 76%.

Figure 33 Cost-effectiveness plane and CEAC for DBG 220mg in THR patients (LMWH)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; LMWH, low-molecular weight heparin; QALY, quality-adjusted life year; THR, total hip replacement.

Figure 34 Cost-effectiveness plane and CEAC for DBG 150mg in THR patients (LMWH)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; LMWH, low-molecular weight heparin; QALY, quality-adjusted life year; THR, total hip replacement.

Whilst these results appear positive for DBG, it is important to remember that the analyses are based on numerical (non-significant) differences between the regimens and that changes in health outcomes are extremely small when considered over the lifetime of the patient. The analysis effectively becomes a cost-minimisation exercise, with the results driven by the savings realised primarily by eliminating post-discharge LMWH administration costs in the acute phase.

TKR

The results of the direct comparison of DBG with LMWH in TKR, both for the main analysis of patients receiving DBG 220mg and the subgroup analysis of patients receiving

DBG 150mg, based on the RE-MODEL trial are presented in the following tables and charts.

Table 88 presents the modelled lifetime costs per patient for LMWH and both doses of DBG, disaggregated by cost category.

Table 88 Comparative mean lifetime costs of DBG and LMWH in TKR patients

Cost category	LMWH	DBG 220mg	Increment	DBG 150mg	Increment
Primary hospitalisation	£6,389	£6,389	£0	£6,389	£0
Prophylaxis	£37	£30	-£7	£31	-£6
Drug	*£31*	*£30*	*£0*	*£31*	*-£0*
Administration	*£6*	*£0*	*-£6*	*£0*	*-£6*
VTE events	£543	£531	-£12	£571	£28
Proximal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	£24	£25	£1	£22	-£3
Major bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minor bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HIT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£6,993**	**£6,976**	**-£18**	**£7,013**	**£19**

DBG, dabigatran etexilate; DVT, deep vein thrombosis; HIT heparin-induced thrombocytopenia; LMWH, low-molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; TKR, total knee replacement.
Some numbers may have rounding error.

The economic model predicts that TKR patients receiving DBG 220mg will accrue slightly less healthcare costs over the course of their lifetime compared to LMWH, due to a reduction in costs associated with VTE events. Costs incurred for adverse events are similar for both treatments.

Table 89 presents the modelled lifetime health outcomes per patient for LMWH and both doses of DBG, disaggregated by outcome category.

Table 89 Comparative mean lifetime health outcomes of DBG and LMWH in TKR patients

Outcome category	LMWH	DBG 220mg	Increment	DBG 150mg	Increment
Symptomatic VTE	16.3%	16.0%	-0.4%	17.2%	0.9%
Non-fatal proximal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal distal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeds	1.3%	1.5%	0.2%	1.3%	0.0%
Minor bleeds	15.3%	14.7%	-0.6%	15.3%	0.0%
HIT	0.4%	0.0%	-0.4%	0.0%	-0.4%
Final outcomes					
Life years	**10.247**	**10.261**	**0.014**	**10.246**	**-0.001**
QALYs	**7.636**	**7.647**	**0.011**	**7.634**	**-0.002**

DBG, dabigatran etexilate; DVT, deep vein thrombosis; HIT heparin-induced thrombocytopenia; LMWH, low-molecular weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QALY, quality-adjusted life year; TKR, total knee replacement.
Some numbers may have rounding error.

The economic model predicts that TKR patients will fare better over the course of their lifetime when treated with DBG 220mg compared to LMWH. Patients receiving DBG 220mg gain additional benefit due to less symptomatic VTE events; major bleeding is similar and DBG patients fare better in terms of minor bleeding events and HIT.

Table 90 presents the incremental cost-effectiveness analysis based on these results.

Table 90 Incremental cost effectiveness of DBG compared to LMWH in TKR patients

	Deterministic	Probability cost-effective at threshold:	
		£20,000/QALY	£30,000/QALY
DBG 220mg			
Incremental cost	-£18	82%	82%
Incremental QALYs	0.011		
ICER	DBG DOMINANT		
DBG 150mg			
Incremental cost	£20	38%	39%
Incremental QALYs	-0.002		
ICER	DBG DOMINATED		

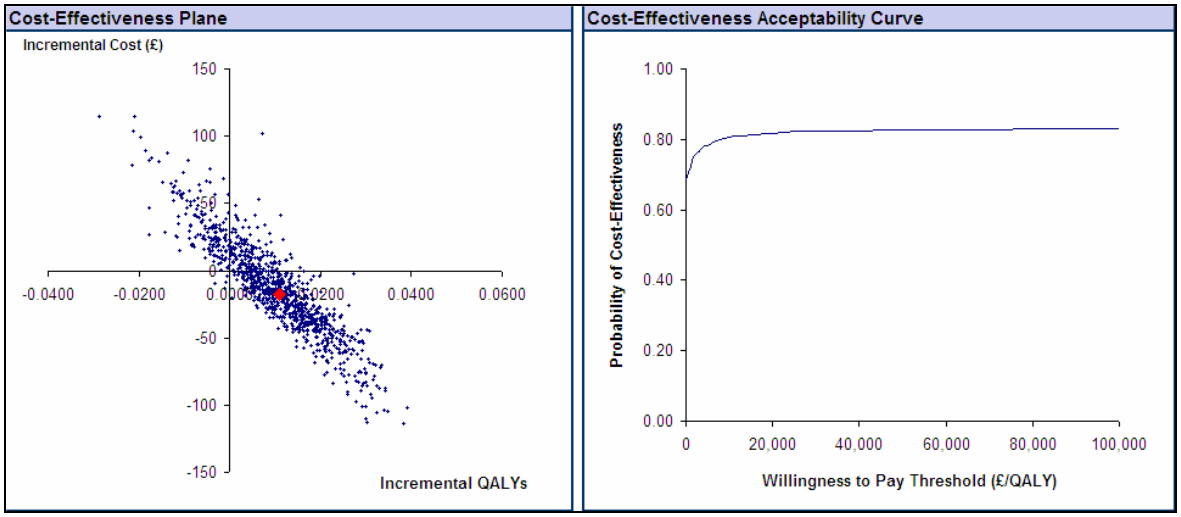
DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TKR, total knee replacement.

In terms of incremental cost-effectiveness, DBG 220mg is associated with slightly less lifetime costs and improved outcomes over the average patient lifetime when compared to LMWH; therefore DBG 220mg dominates LMWH. For DBG 150mg the situation is

reversed, with lifetime health outcomes approximately the same and slightly higher lifetime costs when compared to LMWH. In this instance DBG 150mg is dominated by LMWH. **Figure 35** and **Figure 36** illustrate the cost-effectiveness planes and acceptability curves for each DBG dosage regimen.

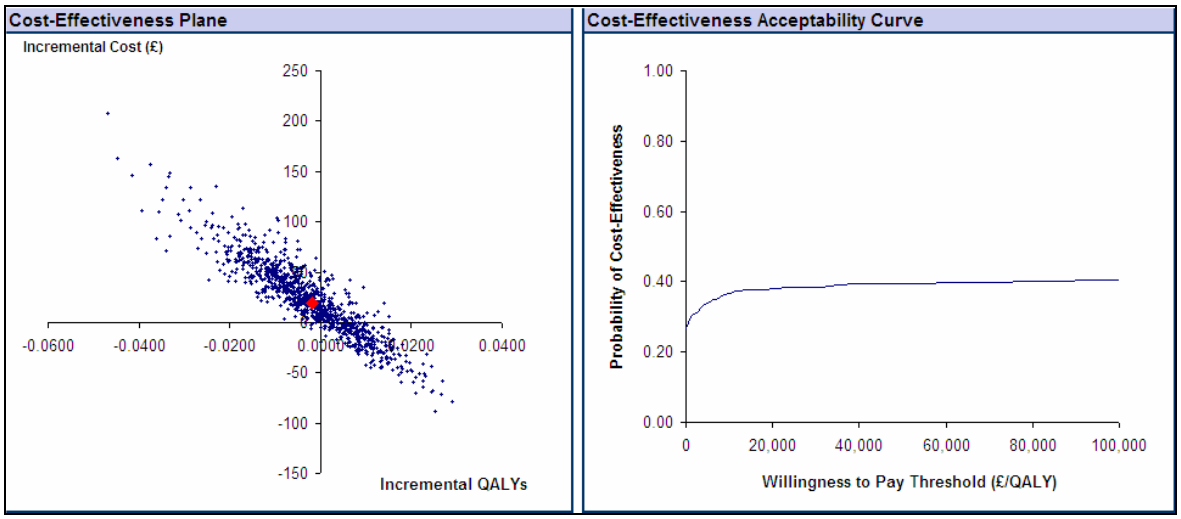
For DBG 220mg, the vast majority of model simulations are situated in either the "south-east" (where DBG is more effective and less costly) or "north-east" quadrant (DBG is more costly and more effective). At a cost-effectiveness threshold of £20,000 per additional QALY gained, DBG is predicted to be cost-effective with a probability of 82%. For DBG 150mg the results are less clear, with more simulations concentrated around the axis between the "north-east" and "north-west" quadrants (DBG is less effective and more costly), resulting in a corresponding cost-effectiveness probability of 38%.

Figure 35 Cost-effectiveness plane and CEAC for DBG 220mg in TKR patients (LMWH)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; LMWH, low-molecular weight heparin; QALY, quality-adjusted life year; TKR, total knee replacement.

Figure 36 Cost-effectiveness plane and CEAC for DBG 150mg in TKR patients (LMWH)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; LMWH, low-molecular weight heparin; QALY, quality-adjusted life year; TKR, total knee replacement.

The results are once again extremely positive for DBG 220mg however, as with THR, it is important to note the magnitude of the differences between the regimens, i.e. the analyses are based on numerical (non-significant) differences. In this analysis, the regimens are effectively cost-neutral and the results are driven by the improvement in health outcomes realised from slightly lower rates of VTE and minor bleed.

Indirect comparison with fondaparinux

THR

The results of the indirect comparison of DBG with fondaparinux in THR (with treatment effects based on the RE-NOVATE trial as described above) are presented in the following tables and charts.

Table 91 presents the modelled lifetime costs per patient for fondaparinux and both doses of DBG, disaggregated by cost category.

Table 91 Comparative mean lifetime costs of DBG and fondaparinux in THR patients

Cost category	Fondaparinux	DBG 220mg	Increment	DBG 150mg	Increment
Primary hospitalisation	£6,036	£6,036	£0	£6,036	£0
Prophylaxis	£269	£137	-£133	£137	-£132
Drug	*£186*	*£137*	*-£50*	*£31*	*-£50*
Administration	*£83*	*£0*	*-£83*	*£0*	*-£83*
VTE events	£159	£240	£80	£275	£116
Proximal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	£225	£77	-£148	£50	-£175
Major bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minor bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£6,689**	**£6,489**	**-£200**	**£6,497**	**-£192**

DBG, dabigatran etexilate; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; THR, total hip replacement.
Some numbers may have rounding error.

The economic model predicts that THR patients will incur less healthcare costs over the course of their lifetime when treated with DBG compared to fondaparinux. Whilst the cost of VTE events is higher for DBG, this is more than offset by the costs associated with fondaparinux administration and major bleeding, the natural consequence of greater efficacy in thromboprophylaxis.

Table 92 presents the modelled lifetime health outcomes per patient for fondaparinux and both doses of DBG, disaggregated by outcome category.

Table 92 Comparative mean lifetime health outcomes of DBG and fondaparinux in THR patients

Outcome category	Fondaparinux	DBG 220mg	Increment	DBG 150mg	Increment
Symptomatic VTE	3.9%	6.5%	2.6%	7.6%	3.8%
Non-fatal proximal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal distal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeds	13.4%	4.6%	-8.8%	3.0%	-10.4%
Minor bleeds	34.7%	12.9%	-21.8%	13.8%	-20.9%
Final outcomes					
Life years	**11.253**	**11.231**	**-0.022**	**11.218**	**-0.035**
QALYs	**8.440**	**8.422**	**-0.018**	**8.412**	**-0.028**

DBG, dabigatran etexilate; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QALY, quality-adjusted life year; THR, total hip replacement.
Some numbers may have rounding error.

The economic model predicts that THR patients will fare slightly less well over the course of their lifetime when treated with DBG compared to fondaparinux. Patients receiving DBG

experience slightly more VTE events on average. However the relatively high level of bleeding events with fondaparinux should be considered.

Table 93 presents the incremental cost-effectiveness analysis based on these results.

Table 93 Incremental cost effectiveness of DBG compared to fondaparinux in THR patients

	Deterministic	Probability cost-effective at threshold:	
		£20,000/QALY	£30,000/QALY
DBG 220mg			
Incremental cost	-£200	40%	35%
Incremental QALYs	-0.018		
ICER	DBG <£,<QALY		
DBG 150mg			
Incremental cost	-£192	32%	27%
Incremental QALYs	-0.028		
ICER	DBG <£, <QALY		

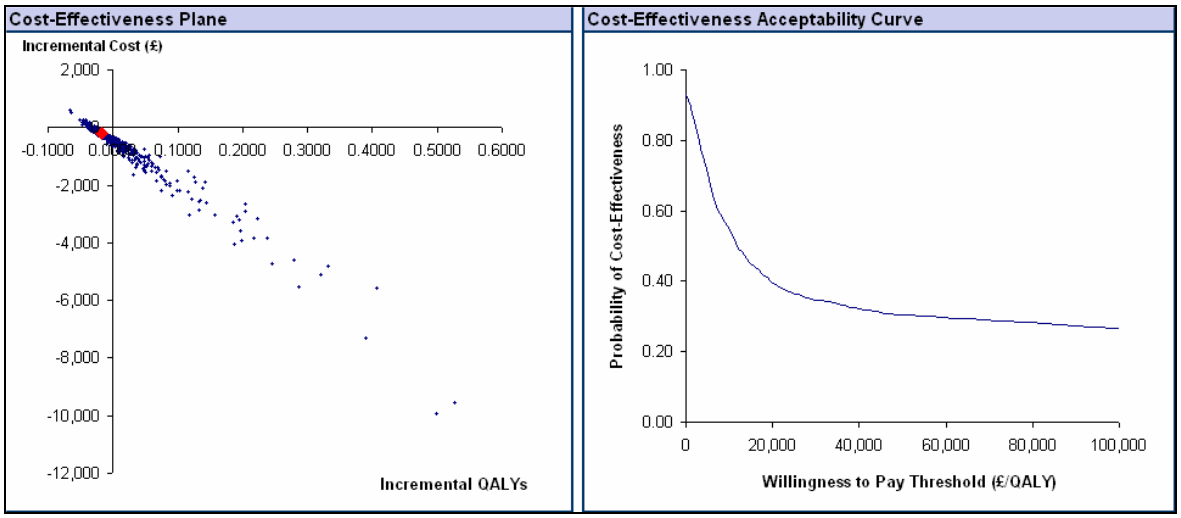
DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; THR, total hip replacement; <£, <QALY, lower costs and health effects.

In terms of incremental costs effectiveness, both DBG doses are associated with lower costs and slightly lower outcomes when compared to fondaparinux. **Figure 37** and **Figure 38** illustrate the cost-effectiveness planes and acceptability curves for each DBG dosage regimen.

For both DBG doses, most model simulations are situated in the “south-west” quadrant (where DBG is less costly and less effective). Although the clarity of the diagrams is compromised slightly by the scale used to account for some extreme outliers in the analysis, the plots demonstrate evidence of strong correlation between outcomes and costs in this analysis. DBG is predicted to be cost-effective with a probability of 40%.

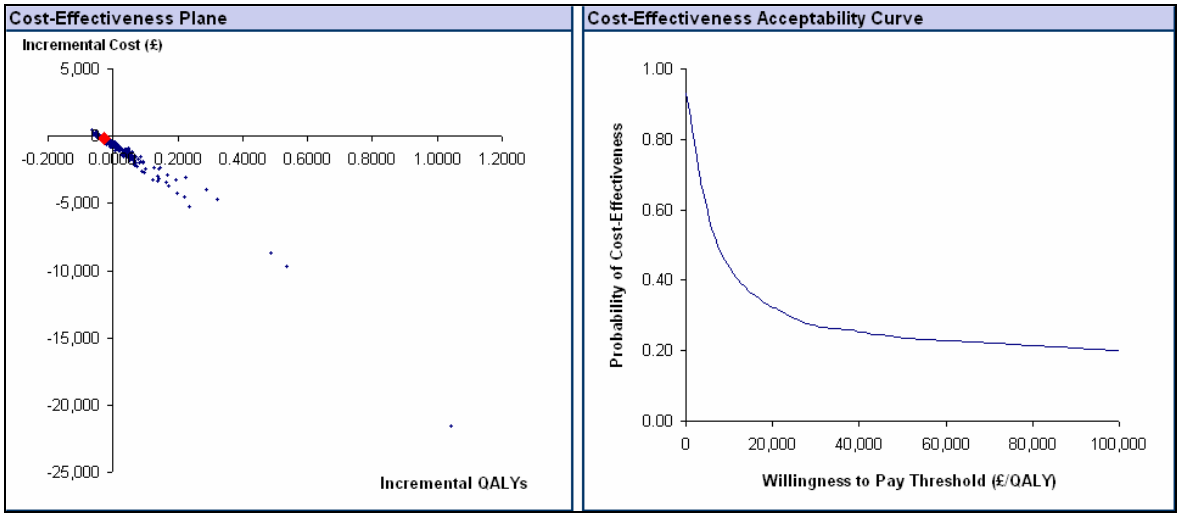
The difference in health outcomes in this analysis is driven by the slightly higher rate of VTE-related death in the DBG group (0.5% compared to 0.2%). This in turn is due to the extremely low relative risk of VTE for fondaparinux in this indication, which is based on a relatively small, single trial in hip fracture patients [70].

Figure 37 Cost-effectiveness plane and CEAC for DBG 220mg in THR patients (fondaparinux)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; QALY, quality-adjusted life year; THR, total hip replacement.

Figure 38 Cost-effectiveness plane and CEAC for DBG 150mg in THR patients (fondaparinux)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; QALY, quality-adjusted life year; THR, total hip replacement.

TKR

The results of the indirect comparison of DBG with fondaparinux in TKR (with treatment effects based on the RE-NOVATE trial as described above) are presented in the following tables and charts.

Table 91 presents the modelled lifetime costs per patient for fondaparinux and both doses of DBG, disaggregated by cost category.

Table 94 Comparative mean lifetime costs of DBG and fondaparinux in TKR patients

Cost category	Fondaparinux	DBG 220mg	Increment	DBG 150mg	Increment
Primary hospitalisation	£6,389	£6,389	£0	£6,389	£0
Prophylaxis	£55	£30	-£25	£31	-£25
Drug	*£49*	*£30*	*-£19*	*£31*	*-£18*
Administration	*£6*	*£0*	*-£6*	*£0*	*-£6*
VTE events	£208	£259	£51	£270	£62
Proximal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	£37	£28	-£10	£24	-£13
Major bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minor bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£6,690**	**£6,706**	**£16**	**£6,714**	**£25**

DBG, dabigatran etexilate; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; THR, total hip replacement.
Some numbers may have rounding error.

The economic model predicts that TKR patients will accrue slightly more healthcare costs over the course of their lifetime when treated with DBG compared to fondaparinux. The additional costs incurred from VTE events in DBG patients are partially offset by savings from fewer bleeding events and the elimination of administration costs.

Table 92 presents the modelled lifetime health outcomes per patient for fondaparinux and both doses of DBG, disaggregated by outcome category.

Table 95 Comparative mean lifetime health outcomes of DBG and fondaparinux in TKR patients

Outcome category	Fondaparinux	DBG 220mg	Increment	DBG 150mg	Increment
Symptomatic VTE	5.4%	7.1%	1.6%	7.5%	2.0%
Non-fatal proximal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal distal DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-fatal PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VTE-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PTS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major bleeds	2.2%	1.7%	-0.6%	1.4%	-0.8%
Minor bleeds	6.0%	4.9%	-1.2%	5.1%	-1.0%
Final outcomes					
Life years	**10.387**	**10.367**	**-0.019**	**10.363**	**-0.023**
QALYs	**7.750**	**7.734**	**-0.016**	**7.731**	**-0.019**

DBG, dabigatran etexilate; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QALY, quality-adjusted life year; THR, total hip replacement.
Some numbers may have rounding error.

The economic model predicts that TKR patients receiving fondaparinux will fare slightly better over the course of their lifetime than those receiving DBG. Although patients

receiving fondaparinux experience more bleeding events on average, this is offset by a reduction in symptomatic VTE events.

Table 93 presents the incremental cost-effectiveness analysis based on these results.

Table 96 Incremental cost effectiveness of DBG compared to fondaparinux in TKR patients

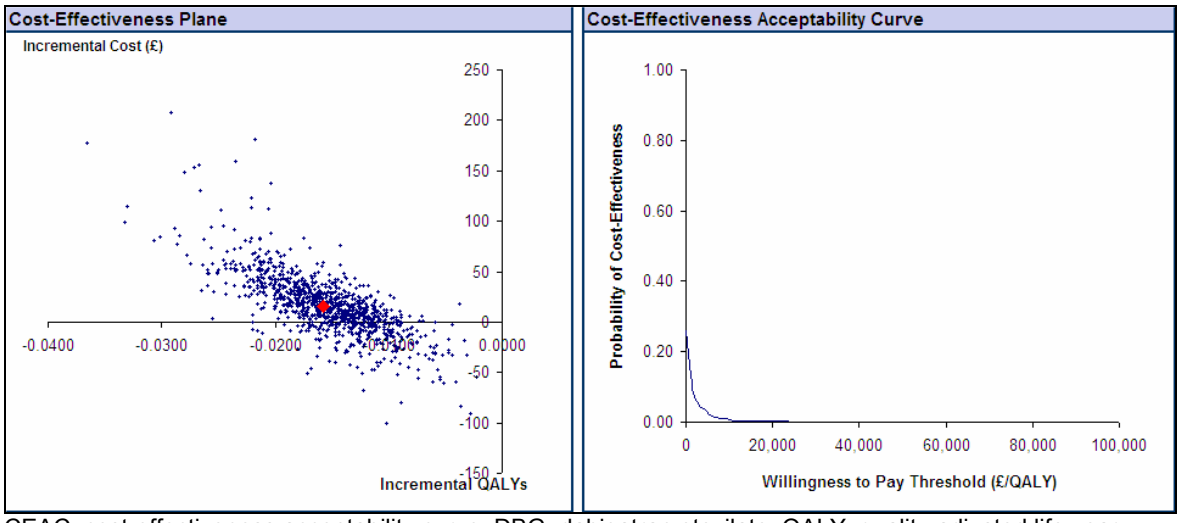
	Deterministic	Probability cost-effective at threshold:	
		£20,000/QALY	£30,000/QALY
DBG 220mg			
Incremental cost	£16	0%	0%
Incremental QALYs	-0.016		
ICER	DBG DOMINATED		
DBG 150mg			
Incremental cost	£25	0%	0%
Incremental QALYs	-0.019		
ICER	DBG DOMINATED		

DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; THR, total hip replacement.

In terms of incremental costs effectiveness, both DBG doses are associated with slightly higher costs and lower outcomes when compared to fondaparinux. **Figure 39** and illustrate **Figure 40** the cost-effectiveness planes and acceptability curves for each DBG dosage regimen.

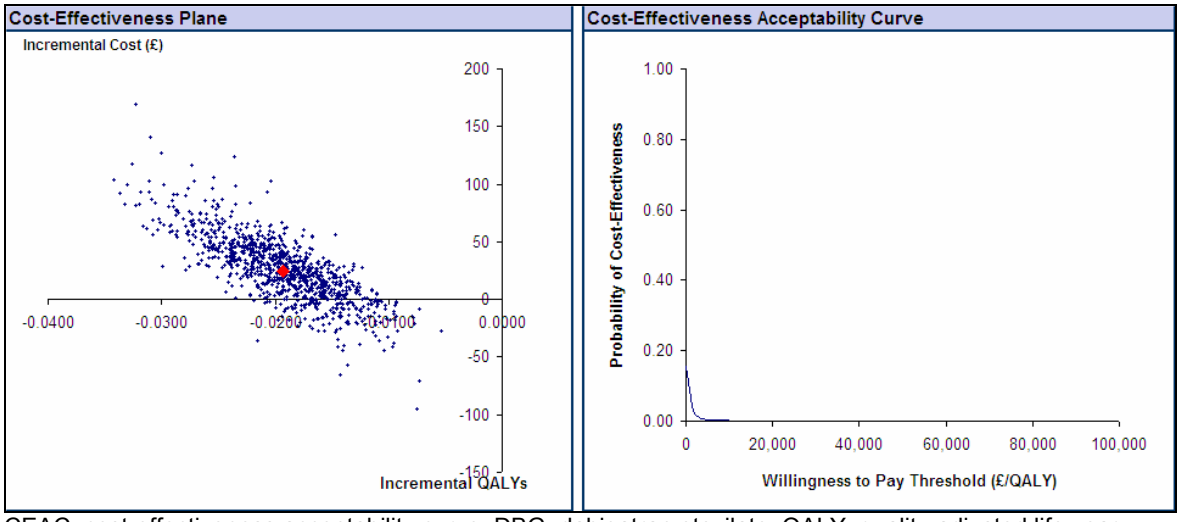
For both DBG doses, the model simulations are situated either in the “north-west” or “south-west” quadrants. It is worth noting however, that a significant proportion of simulations in the 220mg analysis are either in the “south-west” quadrant or clustered around the axis. This implies that the cost differences between the regimens are negligible.

Figure 39 Cost-effectiveness plane and CEAC for DBG 220mg in TKR patients (fondaparinux)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; QALY, quality-adjusted life year; TKR, total hip replacement.

Figure 40 Cost-effectiveness plane and CEAC for DBG 150mg in TKR patients (fondaparinux)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; QALY, quality-adjusted life year; TKR, total knee replacement.

6.3.2 Subgroup analysis

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

The subgroup analyses for the patient groups reserved for the reduced 150mg dose are presented in Section 6.3.1 alongside the base case results.

6.3.3 Sensitivity analyses

6.3.3.1 *What were the main findings of the sensitivity analyses?*

As described in Section 6.2.11.1, a range of univariate and scenario-based sensitivity analyses were performed to complement the base case probabilistic results. As a

pragmatic step, the sensitivity analyses were performed for the primary analysis only, i.e. the comparison of DBG 220mg with LMWH and fondaparinux, both for THR and TKR. The results for 220mg, as the recommended dose for the majority of patients, are of most interest and should suffice to demonstrate the sensitivity of the modelled results.

Direct comparison with LMWH

Table 97 presents the results of the sensitivity analyses, with associated probabilistic results (probability of cost-effectiveness at a threshold of £20,000 per QALY gained), for the direct comparison.

The first set of results (analyses A through E) show that the model results are insensitive to the choice of discount rate. This is not surprising when one considers the narrow margin between the efficacy and safety profiles of DBG and LMWH, and that the majority of cost activity occurs in the acute phase.

Analysis F examines the possibility that issues with subcutaneous injection in practice lead to extended LMWH prophylaxis regimens not actually being prescribed. Using a similar technique to that employed in the indirect comparison with fondaparinux, the relative risks from RE-NOVATE can be combined with the relative risks for extended LMWH versus standard LMWH to provide a comparison of extended DBG (33 days) with standard LMWH (7.6 days). This analysis shows that the additional cost of medication is more than offset by the benefits associated with prevented VTE events, with no additional administration costs; the associated ICER is £667 per QALY gained. This result corresponds with the recommendations from clinical guidelines that extended prophylaxis in THR is superior to standard duration.

Analyses G through I investigate the effect of LMWH administration costs on the results. Omission of the inpatient administration cost has little effect (analysis G). Interestingly, setting the proportion of patients able to self-administer to 100% is not enough in isolation to prevent LMWH being more costly than DBG (analysis I) and does not greatly affect the overall results.

Making the assumption that oral DBG may facilitate a shorter length of stay has the predictable effect of solidifying the cost-effectiveness of DBG (analysis J).

Analyses K, L and M show that the effect of equating the various relative risks between the two treatments does not affect the overall deterministic result, in this case the small proportion of HIT ensures that LMWH patients fare worse. Analysis N replaces the

individual relative risks for VTE, major and minor bleed from RE-NOVATE and RE-MODEL with the meta-analysed pooled estimates. Once again, this does not have any impact on the model conclusions.

Analyses O, P and Q test alternative model timeframes. The base case is a lifetime analysis based on the chronic nature of some of the VTE sequelae and bleeding events. Varying the model timeframe has no effect on the model conclusions in THR. In TKR patients, the model becomes more confident that DBG is cost-effective the longer the model timeframe. This should not be surprising; the cost differences between DBG and LMWH in the acute phase are smaller in TKR than THR, and the benefits of reduced VTE in the acute phase will be emphasised by lower ongoing complications with PTS the longer the model period. Nevertheless, the model still predicts DBG to be cost-effective with a probability of 73% based on the acute phase alone.

The range of analyses performed demonstrates that the results of the base case analysis can be regarded as extremely robust.

Indirect comparison with fondaparinux

Table 98 presents the associated results of the sensitivity analyses for the indirect comparison.

Analyses R through V show that the model results are insensitive to the choice of discount rate on costs, but move slightly in favour of DBG in THR when the rate on outcomes is increased and vice versa.

Analysis W examines the possibility that issues with subcutaneous injection in practice lead to extended fondaparinux prophylaxis regimens not actually being prescribed. This analysis shows that the additional cost of medication is more than offset by the benefits associated with prevented VTE events, with no additional administration costs. The associated ICER is £9,088 per QALY gained and the probability of cost-effectiveness rises to 63%. This result corresponds with the recommendations from clinical guidelines that extended prophylaxis in THR is superior to standard duration.

Analysis X shows the obvious effect of increasing the proportion unable to self-administer fondaparinux. Similarly, analysis Y demonstrates that the cost of surgery is a significant proportion of total costs and any reduction in length of stay due to DBG is influential.

Table 97 Sensitivity analyses (LMWH)

	Description of sensitivity analysis	Original value	New value	ICER (THR)	ICER (TKR)	Probability of CE (THR)	Probability of CE (TKR)
	Base case	**-**	**-**	**DOMINANT**	**DOMINANT**	**99%**	**82%**
	Discount rates						
A	Vary discount rate for both costs and health outcomes	3.5%	0%	DOMINANT	DOMINANT	99%	84%
B	Vary discount rate for costs only	3.5%	0%	DOMINANT	DOMINANT	99%	81%
C	Vary discount rate for costs only	3.5%	6%	DOMINANT	DOMINANT	99%	84%
D	Vary discount rate for health outcomes only	3.5%	0%	DOMINANT	DOMINANT	98%	82%
E	Vary discount rate for health outcomes only	3.5%	6%	DOMINANT	DOMINANT	99%	82%
	Duration of LMWH therapy						
F	Compare extended DBG with standard LWMH in THR	33.2 days	7.6 days	£667/QALY	N/A	100%	N/A
	LMWH administration assumptions						
G	Remove cost of inpatient administration	£0.82	£0.00	DOMINANT	DOMINANT	98%	81%
H	Vary proportion of THR patients able/willing to self-administer	87%	50%	DOMINANT	N/A	100%	N/A
I	Vary proportion of THR patients able/willing to self-administer	87%	100%	DOMINANT	N/A	94%	N/A
	Length of stay of primary hospitalisation						
J	Reduce DBG length of stay by 1 day	£6,036 (THR) £6,389 (TKR)	£5,772 (THR) £6,126 (TKR)	DOMINANT	DOMINANT	100%	97%
	Treatment effects						
K	No difference in treatment effect (VTE relative risk)	0.90 (THR) 0.97 (TKR)	1.00 (THR) 1.00 (TKR)	DOMINANT	DOMINANT	N/A	N/A
L	No difference in treatment effect (Major bleed relative risk)	1.29 (THR) 1.14 (TKR)	1.00 (THR) 1.00 (TKR)	DOMINANT	DOMINANT	N/A	N/A
M	No difference in any treatment effect (VTE, major or minor bleed)	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MJB: 1.04 (THR) 0.96 (TKR)	VTE: 1.00 (THR) 1.00 (TKR) MJB: 1.00 (THR) 1.00 (TKR) MJB: 1.00 (THR) 1.00 (TKR)	DOMINANT	DOMINANT	N/A	N/A
N	All DBG relative risks based on meta-analysis of RE-NOVATE and RE-MODEL	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MNB: 1.04 (THR) 0.96 (TKR)	VTE: 0.95 MJB: 1.24 MNB: 1.00	DOMINANT	DOMINANT	100%	90%
	Time horizon						
O	Model timeframe reduced to acute phase	Lifetime	10 weeks	DOMINANT	DOMINANT	100%	73%
P	Model timeframe reduced to 1 year	Lifetime	1 year	DOMINANT	DOMINANT	100%	77%
Q	Model timeframe reduced to 5 years	Lifetime	5 years	DOMINANT	DOMINANT	100%	81%

CE, cost-effectiveness; DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; LMWH, low molecular weight heparin; MJB, major bleeding; MNB, minor bleeding; N/A, not applicable; QALY, quality-adjusted life year; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism

Table 98 Sensitivity analyses (fondaparinux)

	Description of sensitivity analysis	Original value	New value	ICER (THR)	ICER (TKR)	Probability of CE (THR)	Probability of CE (TKR)
	Base case	**-**	**-**	**<£;<QALY**	**DOMINATED**	**40%**	**0%**
	Discount rates						
R	Vary discount rate for both costs and health outcomes	3.5%	0%	<£;<QALY	DOMINATED	40%	0%
S	Vary discount rate for costs only	3.5%	0%	<£;<QALY	DOMINATED	41%	0%
T	Vary discount rate for costs only	3.5%	6%	<£;<QALY	DOMINATED	42%	0%
U	Vary discount rate for health outcomes only	3.5%	0%	<£;<QALY	DOMINATED	36%	0%
V	Vary discount rate for health outcomes only	3.5%	6%	<£;<QALY	DOMINATED	44%	0%
	Duration of fondaparinux therapy						
W	Compare extended DBG with standard FNX in THR	33.2 days	7.4 days	£9,088/QALY	N/A	63%	N/A
	Fondaparinux administration assumptions						
X	Vary proportion of THR patients able/willing to self-administer	87%	50%	<£;<QALY	N/A	56%	N/A
	Length of stay of primary hospitalisation						
Y	Reduce DBG length of stay by 1 day	£6,036 (THR) £6,389 (TKR)	£5,772 (THR) £6,126 (TKR)	<£;<QALY	<£;<QALY	65%	28%
	Treatment effects						
Z	FNX relative risk of VTE raised	[redacted]	[redacted]	**<£;<QALY**	DOMINATED	N/A	N/A
AA	FNX relative risk of VTE raised	[redacted]	[redacted]	DOMINANT	**<£;<QALY**	N/A	N/A
BB	FNX relative risk of major bleed raised in TKR	[redacted]	[redacted]	**N/A**	**<£;<QALY**	N/A	N/A
CC	All DBG relative risks based on meta-analysis of RE-NOVATE and RE-MODEL	[redacted]	VTE: 0.95 MJB: 1.24 MNB: 1.00	**<£;<QALY**	DOMINATED	43%	0%
DD	VTE-related mortality halved	[redacted]	[redacted]	**<£;<QALY**	DOMINATED	61%	1%
	Time horizon						
EE	Model timeframe reduced to acute phase	Lifetime	10 weeks	<£;<QALY	<£;<QALY	96%	70%
FF	Model timeframe reduced to 1 year	Lifetime	1 year	<£;<QALY	<£;<QALY	92%	16%
GG	Model timeframe reduced to 5 years	Lifetime	5 years	<£;<QALY	DOMINATED	67%	1%

<£;<QALY, less expensive and less effective; Asy, asymptomatic; CE, cost-effectiveness; DBG, dabigatran etexilate; FNX, fondaparinux; DVT, deep vein thrombosis; ICER, incremental cost-effectiveness ratio; Imm, immediately fatal; MJB, major bleeding; MNB, minor bleeding; N/A, not applicable; PE, pulmonary embolism, QALY, quality-adjusted life year; THR, total hip replacement; TKR, total knee replacement; Tx, during treatment; VTE, venous thromboembolism

Analyses Z through BB show how sensitive the model conclusions are to the estimates of relative treatment effect, when a significant difference between the treatments is evident. Analyses Z and AA show the tipping point in the relative risk of VTE for fondaparinux, and that only small increases are sufficient to alter the conclusions of the model. This is extremely important to note, especially given the issues concerning the derivation of the relative risk for fondaparinux described in Section 6.2.7.2. Moreover, analysis BB illustrates the sensitivity of the major bleeding relative risk in TKR.

Analysis DD shows that changes to the epidemiological data informing VTE-related mortality do not affect the direction of the model conclusions in isolation, but do affect their magnitude (especially in THR). The impact of these values is intrinsically linked to the treatment-specific relative risks of VTE.

Analyses EE through GG concord with the discount rate analyses, and show the sensitivity of the model timeframe in this comparison. Where differences are evident in VTE risk, the model is sensitive to changes that affect the long-term outcomes. For instance, analysis V raises the health outcomes discount rate and erodes the longer term health outcome gains for fondaparinux due to reduced recurrent VTE and PTS. In analysis EE, DBG is clearly favoured in the acute phase in both indications given that the perceived longer term benefits of fondaparinux have not yet offset its initial acquisition and administration costs.

6.3.4 Interpretation of economic evidence

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

Direct comparison with LMWH

This economic evaluation has predicted that the recommended dose of dabigatran etexilate (DBG) is dominant when compared with low molecular weight heparin (LMWH) in the primary prevention of VTE in patients undergoing total hip and knee replacement surgery. Deterministic mean results are supported by the probabilistic analysis which attaches a high likelihood to their validity. That is, DBG can be confidently regarded as cost-effective compared to the current standard of care in England and Wales.

However, it can be argued that the key drivers of the results (additional administration costs with LMWH) could have been predicted *a priori*. Although we have gone to great

lengths to construct an economic model that accurately reflects the clinical pathway, the results of the analysis can be interpreted and contextualised in relatively simple terms. These are the important facts to note:

- DBG and LMWH have similar efficacy and safety profiles
- The acquisition costs of DBG and LMWH are the same
- Inpatient administration and the training of patients in self-administration of LMWH consumes resources that can be eliminated with DBG treatment
- Some LMWH patients will be unwilling or unable to self-administer their medication at home and will require expensive, daily assistance to ensure compliance
- An oral medication is likely to be preferred to subcutaneous injection by the vast majority of patients, resulting in improved compliance
- The introduction of an oral medication with proven efficacy may encourage some clinicians to prescribe extended thromboprophylaxis who may otherwise have been reticent due to issues with LMWH administration
- LMWH can be associated with other costs, e.g. platelet monitoring, needlestick injuries, sharps disposal. These costs are eliminated with DBG treatment

The intuitive combination of these factors serves to reinforce the findings of the economic model.

Similar rationale can be used to confirm the role of the reduced dose of DBG. The 150mg dose is reserved only for those patients in special populations. Each of the facts noted above can apply equally to the reduced dose, and accompanied by the results of the economic model, DBG is confirmed as cost-effective for such patients. Importantly, the economic evaluation (and the NHS price) provides no financial incentive for the 150mg dose to be used in patients where the 220mg is most appropriate.

Indirect comparison with fondaparinux

The indirect comparison produces more complex results which require careful interpretation. Contrasting this analysis with the direct comparison, one may suspect that fondaparinux would be regarded as cost-effective in a direct comparison with LMWH. As a first step, it is useful to look back to the published economic evaluations of fondaparinux in this indication to gain perspective:

- Gordois (2003) [57]: This analysis compared fondaparinux to enoxaparin in three populations (THR, TKR and hip fracture) in a UK setting. It concluded that

fondaparinux dominated enoxaparin in each surgery type. However the analysis concentrated heavily on VTE prevention, did not feature bleeding risk prominently and did not report QALYs or ICERs.

- Sullivan (2004) [109]: This analysis is based on the Gordois model and adapts it to a US setting. The conclusions are also similar.
- Lundkvist (2003) [110]: This analysis is based on the Gordois model and adapts it to a Swedish setting. It also reported that fondaparinux dominated enoxaparin in TKR and hip fracture and was associated with an ICER of €239 per VTE event prevented in THR.

Based on the results of these analyses, the economic evaluation in this submission would seem to concord. However, if fondaparinux does dominate LMWH, then two questions must be addressed:

1. Why did the NICE clinical guidelines [1] not recommend fondaparinux as the treatment of choice instead of recommending it as an *alternative* to LMWH?
2. Why does fondaparinux only account for approximately 1% of current practice if it is the most cost-effective alternative?

Referring to the analysis by the NCC-AC on which the guideline is based [41], the report states that based on direct evidence:

"Fondaparinux is more effective than low molecular weight heparin for reducing the risk of DVT and proximal DVT, however, it also significantly increases major bleeding. Extending fondaparinux beyond discharge reduces the risk of developing DVT and proximal DVT in this period without significantly increasing major bleeding." (Section 6.6.4)

However, it goes on to state that:

"The observed trade-off between DVT and major bleeding implies that a cost-effectiveness analysis, which explicitly evaluates the net impact of DVT, major bleeding and opportunity cost, is essential." (Section 12.5)

Consequently, the NCC-AC economic evaluation indicates that fondaparinux plus a mechanical method of prophylaxis is the most cost-effective option for THR patients. Nevertheless, its recommendations are that LMWH should be offered with fondaparinux as an *alternative*. Clearly the NCC-AC has exercised some caution, which is likely based on their extensive series of sensitivity analyses and the validity of one of their key assumptions, that the variation in the relative reduction in fatal and other symptomatic PE is similar to the relative reduction of DVT.

Further, in the face of such a weight of evidence of its cost-effectiveness, one may be surprised that fondaparinux has not been used more extensively in practice. Putting the relatively high acquisition cost to one side, this would seem to suggest that clinicians place a very high degree of importance on achieving the balance between efficacy and safety noted in Section 4.5. That is, the increased thromboprophylactic properties of fondaparinux come at a price of an increased risk of major bleeding. Indeed the ACCP guideline [2] explicitly places "a relatively low value on the prevention of venographic thrombosis, and a relatively high value on minimizing bleeding complications". It is not unreasonable to suppose that orthopaedic surgeons, historically wary of pharmacological thromboprophylaxis as a practice that increases the risk of bleeding, regard LMWH as striking the correct balance. In this case, fondaparinux tips the balance too far in that its increased efficacy is regarded as not worth the increased bleeding risk.

This, then, may call in to question the relative weights placed on VTE and bleeding in the economic evaluations. The economic evaluations (including this one) assume that VTE leads to longer-term complications and death more often than major bleeding, and where a difference exists in VTE prevention between treatments it is likely to drive the results. In this analysis, much of the data that determines the severity of VTE is derived from studies that are somewhat dated. [58,71]

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

Yes, this economic evaluation applies to all THR and TKR patients eligible for treatment with pharmacological prophylaxis.

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

This analysis is structurally robust, being based on a systematic review of published analyses in this indication and validated by an expert clinical panel. It includes all key outcomes and costs, considers the chronic nature of VTE and its sequelae and presents probabilistic results to test uncertainty.

However the analysis can only be as strong as the data that support it. The indirect comparison has shown that where a difference in efficacy or safety exists between two comparators, the model is sensitive to the data that informs the relative severity of VTE and major bleeding complications. As noted above in Section 6.3.4.1, much of the available longer-term epidemiological data is somewhat dated. For example, we have derived the probability of a symptomatic PE being immediately fatal from Oster (1987)

[58]. In turn Oster derived this value from two older studies, one from 1982 and one from 1975. Treatment of VTE (and PE in particular) is certainly more sophisticated now than it would have been over 30 years ago. More recent data on the type, severity and progression of VTE may lead to different conclusions. In the direct comparison, where DBG and LMWH are similar in efficacy and safety, this effect is less important.

Finally, the relative risk of VTE for fondaparinux in THR is a weak estimate. As noted in 6.2.7.2, this estimate was drawn from a single study in hip fracture which did not account for any VTE events in the first 8 days post-surgery. Therefore, careful interpretation of the results from this analysis is required.

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

Within the parameters of the model structure and data inputs presented, no further analyses would provide any additional information.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

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

Table 99 through **Table 102** present the total costs of treatment in England and Wales for THR and TKR, in the scenarios both with and without the introduction of DBG.

Table 99 Total cost of THR treatment without introduction of DBG

THR	2008	2009	2010	2011	2012
Patient population	46,741	47,444	48,176	48,910	49,652
Proportion treated	92%	92%	92%	92%	92%
Number treated	43,002	43,648	44,322	44,997	45,680
LMWH take-up	69.77%	71.77%	73.77%	75.77%	77.77%
LMWH number of patients	30,001	31,325	32,695	34,093	35,524
LMWH acquisition cost per course	£112.70	£112.70	£112.70	£112.70	£112.70
LMWH total acquisition cost	£3,381,148	£3,530,362	£3,684,752	£3,842,293	£4,003,517
LMWH administration cost per course	£78.25	£78.25	£78.25	£78.25	£78.25
LMWH total administration cost	£2,347,523	£2,451,122	£2,558,314	£2,677,695	£2,779,669
LMWH total cost	£5,728,671	£5,981,484	£6,243,066	£6,509,988	£6,783,240
Fondaparinux take-up	1.16%	1.16%	1.16%	1.16%	1.16%
Fondaparinux number of patients	500	508	515	523	531
Fondaparinux acquisition cost per course	£186.48	£186.48	£186.48	£186.48	£186.48
Fondaparinux total acquisition cost	£93,244	£94,646	£96,107	£97,570	£99,051
Fondaparinux administration cost per course	£78.25	£78.25	£78.25	£78.25	£78.25
Fondaparinux total administration cost	£39,125	£39,714	£40,327	£40,941	£41,562
Fondaparinux total cost	£132,369	£134,359	£136,433	£138,511	£140,613
Aspirin take-up	29.07%	27.07%	25.07%	23.07%	21.07%
Aspirin number of patients	12,501	11,816	11,111	10,381	9,625
Aspirin acquisition cost per course	£3.80	£3.80	£3.80	£3.80	£3.80
Aspirin total cost	£47,502	£44,899	£42,223	£39,447	£36,574
TOTAL COST OF TREATMENT	**£5,908,543**	**£6,160,742**	**£6,421,723**	**£6,687,946**	**£6,690,427**

DBG, dabigatran etexilate; LMWH, low molecular weight heparin; THR, total hip replacement.

Table 100 Total cost of THR treatment with introduction of DBG

THR	2008	2009	2010	2011	2012
Patient population	46,741	47,444	48,176	48,910	49,652
Proportion treated	92%	92%	92%	92%	92%
Number treated	43,002	43,648	44,322	44,997	45,680
DBG take-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBG number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBG acquisition cost per course	£126.00	£126.00	£126.00	£126.00	£126.00
DBG total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH take-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH acquisition cost per course	£112.70	£112.70	£112.70	£112.70	£112.70
LMWH total acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH administration cost per course	£78.25	£78.25	£78.25	£78.25	£78.25
LMWH total administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux take-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux acquisition cost per course	£186.48	£186.48	£186.48	£186.48	£186.48
Fondaparinux total acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux administration cost per course	£78.25	£78.25	£78.25	£78.25	£78.25
Fondaparinux total administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin take-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin acquisition cost per course	£3.80	£3.80	£3.80	£3.80	£3.80
Aspirin total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL COST OF TREATMENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DBG, dabigatran etexilate; LMWH, low molecular weight heparin; THR, total hip replacement; TKR, total knee replacement.

Table 101 Total cost of TKR treatment without introduction of DBG

THR	2008	2009	2010	2011	2012
Patient population	49,160	49,899	50,669	51,441	52,222
Proportion treated	88%	88%	88%	88%	88%
Number treated	43,261	43,911	44,589	45,268	45,955
LMWH take-up	67.86%	69.86%	71.86%	73.86%	75.86%
LMWH number of patients	29,356	30,675	32,040	33,434	34,860
LMWH acquisition cost per course	£32.20	£32.20	£32.20	£32.20	£32.20
LMWH total acquisition cost	£945,253	£987,743	£1,031,703	£1,076,568	£1,122,502
LMWH administration cost per course	£6.28	£6.28	£6.28	£6.28	£6.28
LMWH total administration cost	£189,275	£192,559	£206,129	£209,875	£218,830
LMWH total cost	£1,129,529	£1,180,301	£1,232,831	£1,286,443	£1,341,332
Fondaparinux take-up	1.19%	1.19%	1.19%	1.19%	1.19%
Fondaparinux number of patients	515	523	531	539	547
Fondaparinux acquisition cost per course	£53.28	£53.28	£53.28	£53.28	£53.28
Fondaparinux total acquisition cost	£27,440	£27,852	£28,282	£28,713	£29,149
Fondaparinux administration cost per course	£6.28	£6.28	£6.28	£6.28	£6.28
Fondaparinux total administration cost	£3,233	£3,282	£3,332	£3,383	£3,434
Fondaparinux total cost	£30,673	£31,134	£31,614	£32,096	£32,583
Aspirin take-up	30.95%	28.95%	26.95%	24.95%	22.95%
Aspirin number of patients	13,390	12,713	12,018	11,295	10,548
Aspirin acquisition cost per course	£3.80	£3.80	£3.80	£3.80	£3.80
Aspirin total cost	£50,883	£48,311	£45,668	£42,923	£40,082
TOTAL COST OF TREATMENT	**£1,211,085**	**£1,259,746**	**£1,310,114**	**£1,361,462**	**£1,413,997**

DBG, dabigatran etexilate; LMWH, low molecular weight heparin; TKR, total knee replacement.

Table 102 Total cost of TKR treatment with introduction of DBG

THR	2008	2009	2010	2011	2012
Patient population	49,160	49,899	50,669	51,441	52,222
Proportion treated	88%	88%	88%	88%	88%
Number treated	43,261	43,911	44,589	45,268	45,955
DBG take-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBG number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBG acquisition cost per course	£42.00	£42.00	£42.00	£42.00	£42.00
DBG total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH take-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH acquisition cost per course	£32.20	£32.20	£32.20	£32.20	£32.20
LMWH total acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH administration cost per course	£6.28	£6.28	£6.28	£6.28	£6.28
LMWH total administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LMWH total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux take-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux acquisition cost per course	£53.28	£53.28	£53.28	£53.28	£53.28
Fondaparinux total acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux administration cost per course	£6.28	£6.28	£6.28	£6.28	£6.28
Fondaparinux total administration cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fondaparinux total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin take-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin acquisition cost per course	£3.80	£3.80	£3.80	£3.80	£3.80
Aspirin total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL COST OF TREATMENT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DBG, dabigatran etexilate; LMWH, low molecular weight heparin; TKR, total knee replacement.

Table 103 consolidates the above results and presents the estimate of overall budget impact for the total patient population for the years 2008 to 2012.

Table 103 Overall budget impact

	2008	2009	2010	2011	2012
Total cost with introduction of DBG in THR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost with introduction of DBG in TKR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost with introduction of DBG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost without introduction of DBG in THR	£5,908,543	£6,160,742	£6,421,723	£6,687,946	£6,960,427
Total cost without introduction of DBG in TKR	£1,211,085	£1,259,746	£1,310,114	£1,361,462	£1,413,997
Total cost without introduction of DBG	**£7,119,627**	**£7,420,488**	**£7,731,836**	**£8,049,408**	**£8,374,424**
OVERALL BUDGET IMPACT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DBG, dabigatran etexilate; LMWH, low molecular weight heparin; THR, total hip replacement; TKR, total knee replacement.

The analysis estimates that the introduction of DBG will lead to a relatively low budget impact to the NHS in England and Wales of just over [redacted] in 2008, rising modestly to just over [redacted] in 2012.

There are two factors evident from this analysis worthy of note. Firstly, if clinical practice does phase out aspirin in the manner suggested then total costs will increase by approximately £1.25 million over the period, even without the introduction of DBG. That is, in this indication the NHS in England and Wales must expect an increase in spending for clinical practice to fall into line with clinical guidelines irrespective of the relative take-up of LMWH and DBG.

Secondly, the budget impact of the introduction of DBG depends largely on the relative rate of substitution of LMWH and aspirin. In the above analysis it is assumed that DBG patients are gained equally from both LMWH and aspirin. In THR, every patient that receives DBG will result in a net saving to the health economy if that patient would have otherwise received LMWH. This effect serves to partially offset the additional costs incurred by DBG patients in TKR and by those in either THR or TKR who would have otherwise received aspirin. To illustrate the point, consider the alternative analyses presented in **Table 104** and **Table 105**. In these analyses, the relative rate of substitution is modified such that DBG gains patients on a two-thirds to one-thirds basis from the two comparators (firstly for aspirin then for LMWH).

Table 104 Scenario analysis of overall budget impact (2/3 from aspirin)

	2008	2009	2010	2011	2012*
Total cost with introduction of DBG in THR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost with introduction of DBG in TKR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost with introduction of DBG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost without introduction of DBG in THR	£5,908,543	£6,160,742	£6,421,723	£6,687,946	£6,960,427
Total cost without introduction of DBG in TKR	£1,211,085	£1,259,746	£1,310,114	£1,361,462	£1,413,997
Total cost without introduction of DBG	**£7,119,627**	**£7,420,488**	**£7,731,836**	**£8,049,408**	**£8,374,424**
OVERALL BUDGET IMPACT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* In 2012, the rate of substitution would lead to a negative value for the take-up of aspirin. Therefore it is set to zero.

DBG, dabigatran etexilate; LMWH, low molecular weight heparin; THR, total hip replacement; TKR, total knee replacement.

Table 105 Scenario analysis of overall budget impact (2/3 from LMWH)

	2008	2009	2010	2011	2012
Total cost with introduction of DBG in THR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost with introduction of DBG in TKR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost with introduction of DBG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost without introduction of DBG in THR	£5,908,543	£6,160,742	£6,421,723	£6,687,946	£6,960,427
Total cost without introduction of DBG in TKR	£1,211,085	£1,259,746	£1,310,114	£1,361,462	£1,413,997
Total cost without introduction of DBG	**£7,119,627**	**£7,420,488**	**£7,731,836**	**£8,049,408**	**£8,374,424**
OVERALL BUDGET IMPACT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DBG, dabigatran etexilate; LMWH, low molecular weight heparin; THR, total hip replacement; TKR, total knee replacement.

These analyses show that the budget impact is sensitive to the relative rate of substitution. In **Table 104** each patient receiving DBG is creating a greater budget impact than the original analysis, given the greater difference between the acquisition costs of DBG and aspirin. Conversely, the analysis in **Table 105** shows how DBG patients will generate savings to the health economy relative to a LMWH patient on a one for one basis. Indeed in this analysis, DBG is cost saving overall in THR.

Importantly, in each analysis the overall budget impact is modest and the health economy gains irrespective of the relative rate of substitution. For each patient that substitutes from aspirin, the modest increase in budget can easily be justified by the health gains and cost savings associated with VTE events that will prevented due to the greater efficacy of DBG compared to aspirin. For each patient that substitutes from LMWH, costs are reduced by eliminating the need for LMWH administration assistance, without any loss in efficacy.

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

According the most recent report from the National Joint Registry [16], for the year ending March 31st 2007 (the most recent data available) there were 46,741 hip replacement procedures and 49,160 knee replacement procedures performed by the NHS in England and Wales. This includes procedures performed in NHS hospitals and NHS treatment centres (but does not include procedures in independent hospitals and treatment centres).

For the purposes of this analysis, it was assumed that the number of procedures will increase in line with the expected increase in the proportion of the England and Wales population aged over 45 years.

Population projections were obtained from the Government Actuary's Department [111], presented in **Table 106**.

Table 106 England and Wales population projection, age 45 and over (thousands)

Age group	2007	2008	2009	2010	2011	2012
45-49	3,746	3,834	3,930	4,025	4,089	4,136
50-54	3,285	3,350	3,416	3,500	3,597	3,689
55-59	3,319	3,215	3,173	3,149	3,161	3,201
60-64	3,099	3,234	3,296	3,324	3,322	3,182
65-69	2,385	2,438	2,508	2,591	2,706	2,926
70-74	2,088	2,124	2,165	2,190	2,184	2,197
75-79	1,751	1,761	1,764	1,774	1,791	1,822
80-84	1,298	1,301	1,313	1,331	1,353	1,372
85-89	785	826	846	846	845	852
90-94	295	283	289	319	352	378
95-99	76	79	82	84	84	83
100+	10	10	11	11	12	12
Total	**22,138**	**22,454**	**22,791**	**23,143**	**23,495**	**23,852**
Growth*	**100%**	**101%**	**103%**	**105%**	**106%**	**108%**

* Growth relative to 2007
Source: GAD [111]

Utilising these figures to estimate the growth rate of procedures, with 2006 as the base year, results in the estimates presented in **Table 107**.

Table 107 Projection of procedures applied to analysis

Year	THR	TKR
2008	46,741	49,160
2009	47,444	49,899
2010	48,176	50,669
2011	48,910	51,441
2012	49,652	52,222

THR, total hip replacement; TKR, total knee replacement.

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

The National Joint Registry [16] estimates that in 2006/07 92% of THR patients and 88% of TKR received some form of pharmacological thromboprophylaxis. It can be speculated that the remaining proportion are simply prescribed mechanical prophylaxis only, either due to absolute contraindications to anti-thrombotic medication or clinician/patient choice. In this analysis, these estimates will be applied as a basis for calculation of medication take-up in future years.

This analysis will consider only pharmacological thromboprophylaxis, including the two comparators from the economic evaluation (LMWH and fondaparinux). In addition, aspirin (as a considerable proportion of current practice) will also be included for the purposes of budget impact.

As a starting point, the shares of current practice as presented in **Table 5** are assumed. These shares are then uplifted to represent a total of 100% of current practice. That is, LMWH, fondaparinux and aspirin account for 86% and 84% of current practice in THR and TKR respectively. Of those cumulative shares, each treatment represents the following:

- LMWH: 69.77% in THR (60% divided by 86%) and 67.86% in TKR
- Fondaparinux: 1.16% in THR and 1.19% in TKR
- Aspirin: 29.07% in THR and 30.95% in TKR

These are the current practice shares applied to the model as a starting point.

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

In order to calculate the budget impact of DBG, two alternative scenarios are considered: a "world without" DBG and a "world with" DBG. The analysis makes the following dynamic assumptions:

- Aspirin will be gradually "phased out" as practice shifts towards the recommendations from clinical guidelines
- In the "world without" DBG, 2% of aspirin patients "switch" to LMWH annually
- In the "world with" DBG, patients receiving DBG are substituted equally from those who would otherwise received LMWH and aspirin (this assumption is varied in sensitivity analysis)
- Fondaparinux market share remains constant irrespective of the scenario or year. This assumption is based on the extremely low current take-up of fondaparinux, indicating that its use is specialised and unlikely to be affected

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

The unit costs of DBG and each of the principal alternatives were presented in **Table 76**. In this analysis, the durations of therapy most likely to be applied in England and Wales practice are considered.

- DBG: 30 days (THR), 10 days (TKR)
- LMWH and fondaparinux: 28 days (THR), 8 days (TKR)
- Aspirin: 35 days (both THR and TKR)

For DBG, advice from a pharmaceutical advisory panel (personal communication) indicated that in practice patients will be dispensed whole packs (which will not be split) and expected to complete the course. Therefore 30 days in THR and 10 days in TKR are the durations which represent the least costly combination of whole packs to cover the recommended duration of therapy[*].

For LMWH and fondaparinux, 28 days therapy in THR is based on the NICE Clinical Guideline [1] recommendation that LMWH and fondaparinux therapy should be continued for four weeks following surgery. In TKR patients, 8 days represents the average length of stay in England and Wales for TKR. It is important to note that this assumes all THR patients receiving LMWH and fondaparinux are prescribed in line with the recommended duration of therapy. As discussed in Section 6, it could be argued that difficulties associated with outpatient administration of LMWH and fondaparinux may currently dissuade some clinicians from prescribing extended prophylaxis. Nevertheless, in the absence of reliable data to support this claim it would be inappropriate to make such an assumption in this analysis. Therefore it is assumed that THR patients prescribed LMWH receive the appropriate duration of therapy.

In addition, given that aspirin forms a considerable proportion of current practice, it is also considered in this analysis. It is assumed that aspirin will be dispensed for 35 days in both THR and TKR.

The resultant costs of medication acquisition are detailed in **Table 108**.

[*] In practice, with a recommended duration of therapy of 28-35 days, it is reasonable to assume that most patients would be dispensed a single 30-day pack.

Table 108 Medication cost per course

Medication	Cost per day	Days of therapy (THR)	Days of therapy (TKR)	Cost per course (THR)	Cost per course (TKR)
DBG	£4.20	30	10	£126.00	£42.00
LMWH	£4.03	28	8	£112.70	£32.20
Fondaparinux	£6.66	28	8	£186.48	£53.28
Aspirin	£0.11*	35	35	£3.80	£3.80

* Aspirin unit cost is sourced from BNF 54 [105], £1.52 per pack of 28 tablets, equating to ~£0.11 per day.
DBG, dabigatran etexilate; LMWH, low molecular weight heparin; THR, total hip replacement; TKR, total knee replacement.

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

This analysis does not consider the costs of the index surgical event but simply examines the costs of thromboprophylaxis that may differentiate between the various pharmacological alternatives, as per the base case assumptions of the economic model. That is, the costs of drug acquisition and the costs associated with administration. It does not consider any potential future cost offsets due to treatment of VTE or adverse events. The dosing schedule assumed in this analysis is outlined in Section 7.5.

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

As in the economic model, it is assumed that all LMWH and fondaparinux patients incur inpatient costs related to the nurse time required to administer the medication. In addition, all THR receiving LMWH or fondaparinux are assumed to either require inpatient training if they are able and willing to self-administer (87% [100]) or daily community nurse visits to administer the medication if they are unable or unwilling to self-administer (13%). **Table 109** presents the average costs per patient applied to the analysis.

Table 109 Cost of LMWH and fondaparinux administration

Parameter	Value
Inpatient administration cost per day	£0.78
Length of stay (days)	8
Inpatient administration cost per patient	£6.28
Proportion of THR patients able/willing to self-administer	87%
Cost of training in self-administration	£11.00
Average cost of self-administration training per THR patient	£9.57
Proportion of THR patients unable/unwilling to self-administer	13%
Average days of outpatients prophylaxis required	20
Unit cost of community nurse visit	£24.00
Average cost of outpatient administration per THR patient prescribed LMWH	£62.40
Average total administration cost per THR patient	£78.25
Average total administration cost per TKR patient	£6.28

LMWH, low molecular weight heparin; THR, total hip replacement.

As DBG has no requirement for monitoring and can be administered in a convenient oral dose, these costs represent direct savings when a patient who would otherwise have been prescribed LMWH or fondaparinux, is instead prescribed DBG.

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

Unlike LMWH which is initiated 12 hours pre-operatively, DBG is initiated post-operatively. Therefore there is the potential to reduce the length of stay of the index surgical procedure, which has not been considered here. In addition, LMWH and fondaparinux are administered by subcutaneous injection. This analysis does not consider any potential costs associated with needlestick injury or sharps disposal.

8 References

Please use the Vancouver style (that is, consecutive numbering throughout the main text):

1. National Institute for Health and Clinical Excellence (NICE). Venous thromboembolism. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery). NICE clinical guideline 46. April 2007.
2. Geerts WH, Pineo GF, Heit JA *et al*. Prevention of venous thromboembolism: The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004. 126;338S–400S
3. Botteman MF, Caprini J, Stephens JM *et al*. Results of an economic model to assess the cost-effectiveness of enoxaparin, a low-molecular-weight heparin, versus warfarin for the prophylaxis of deep vein thrombosis and associated long-term complications in total hip replacement surgery in the United States. *Clin Ther* 2002;24(11):1960-86.
4. Bergqvist D, Jendteg S, Johansen L, Persson U, Odegaard K. Cost of long-term complications of deep venous thrombosis of the lower extremities: an analysis of a defined patient population in Sweden. *Ann Intern Med* 1997; 126(6): 454-7.
5. Janssen MC, Haenen JH, van Asten WN, Wollersheim H, Heijstraten FM, de Rooij MJ, Thien T. Clinical and haemodynamic sequelae of deep venous thrombosis: retrospective evaluation after 7-13 years. *Clin Sci (Lond)* 1997; 93(1): 7-12.
6. Schulman S, Lindmarker P, Holmstrom M, Larfars G, Carlsson A, Nicol P, Svensson E, Ljungberg B, Viering S, Nordlander S, Leijd B, Jahed K, Hjorth M, Linder O, Beckman M. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost* 2006; 4(4): 734-42.
7. Fitzmaurice DA, Murray E. Thromboprophylaxis for adults in hospital. BMJ 2007; 334(7602): 1017-8
8. Siddique RM, Siddique MI, Connors AF Jr, Rimm AA. Thirty-day case-fatality rates for pulmonary embolism in the elderly. *Arch Intern Med* 1996; 156(20): 2343-7.
9. Goldhaber SZ, Visani L, DaRosa for ICOPER. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353: 1386–9.
10. Eichlisberger R, Widmer MT, Frauchiger B, Widmer LK, Jager K. [The incidence of post-thrombotic syndrome]. [Article in German] *Wien Med Wochenschr* 1994; 144(10-11): 192-5.
11. Murray DW, Britton AR, Bulstrode CJ. Thromboprophylaxis and death after total hip replacement. *J Bone Joint Surg Br* 1996; 78(6): 863-70.
12. Kahn SR, Ducruet T, Lamping DL, Arsenault L, Miron MJ, Roussin A, Desmarais S, Joyal F, Kassis J, Solymoss S, Desjardins L, Johri M, Shrier I. Prospective evaluation of health-related quality of life in patients with deep venous thrombosis. *Arch Intern Med* 2005; 165(10): 1173-8.
13. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. *Arch Intern Med* 2002; 162(10): 1144-8.
14. Carpenedo M, Monzini M, Perelli Cippo P, Mantovani L, Moia M. Quality of life (QoL) in patients receiving vitamin k antagonists (VKA): a study using EQ-5D questionnaire. *J Thromb Haemost* 2005; 3 Suppl 1: 02482.
15. van Korlaar IM, Vossen CY, Rosendaal FR, Bovill EG, Cushman M, Naud S, Kaptein AA. The impact of venous thrombosis on quality of life. *Thromb Res* 2004; 114(1): 11-8.
16. National Joint Registry 4th Annual Report (2007). Available at http://www.njrcentre.org.uk/
17. Scottish Intercollegiate Guidelines Network. 62. Prophylaxis of venous thromboembolism. A national clinical guideline. Available at http://www.sign.ac.uk
18. Proposed review of SIGN guideline 2005 consultation form. SIGN 62: Prophylaxis of venous thromboembolism. Available at http://www.sign.ac.uk
19. Consensus statement. Cardiovascular Disease Educational and Research Trust; Cyprus Cardiovascular Disease Educational and Research Trust; European Venous Forum; International Surgical Thrombosis Forum; International Union of Angiology; Union Internationale de Phlebologie. Prevention and treatment of venous

thromboembolism. International Consensus Statement (guidelines according to scientific evidence). *Int Angiol* 2006; 25(2): 101-61.
20. British Orthopaedic Association. Primary Total Hip Replacement: A Guide to Good Practice, 1999; revised 2006.
21. British Orthopaedic Association. Knee Replacement: A Guide to Good Practice 1999.
22. Keeling D, Davidson S, Watson H; Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The management of heparin-induced thrombocytopenia. *Br J Haematol* 2006; 133(3): 259-69.
23. Eriksson BI, Dahl OE, Rosencher N, *et al.* for the RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 370 (9604), 2004 (2007)
24. Eriksson BI, Dahl OE, Rosencher N, *et al.* for the RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost*. 2007 Nov;5(11):2178-85.
25. Friedman RJ, Caprini JA, Comp PC, *et al*. Dabigatran etexilate versus enoxaparin in preventing venous thromboembolism following total knee arthroplasty. 21st Cong of the International Society on Thrombosis and Haemostasis (ISTH), Geneva, 6 - 12 Jul 2007 *J Thromb Haemost* 5 (Suppl 2), (2007).
26. Eriksson BI, Dahl OE, Buller HR, *et al*. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* 2005; 3(1): 103-11.
27. Boehringer Ingelheim GmbH. Clinical trial 1160.50, clinical study report. Data on file, December 2007.
28. Nippon Boehringer Ingelheim Co., Ltd. Study PK0747E: A pharmacokinetic comparison between Japanese and Caucasians for dabigatran etexilate – Across study evaluation of pharmacokinetic data obtained in Phase I and Phase II trials. Study report. Data on file, November 2007.
29. Committee for Propriety Medicinal Products (CPMP). Points to consider on the clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk. European Medicines Agency (EMEA), June 2000. Available at http://www.emea.europa.eu/pdfs/human/ewp/070798en.pdf
30. Enoxaparin sodium (Clexane) summary of product characteristics (EU).
31. Graafsma YP, Prins MH, Lensing AWA, deHaan RJ, Huisman MV, Buller HR. Bleeding Classification in clinical trials: Observer variability and clinical relevance. *Thromb Haemost* 1997;78: 1189-1192.
32. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr *et al*. Prevention of venous thromboembolism. *Chest* 2001; 119:132S-175S.
33. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ *et al*. A randomized controlled trial of a low-molecular-weight-heparin (enoxaparin) to prevent deep vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986;315: 925-929.
34. Kalodiki EP, Hoppensteadt DA, Nicolaides AN, Fareed J, Gill K, Regan F *et al*. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. *Int. Angiology* 1996;15: 162-168.
35. Samama CM, Clergue F, Barre J, Montefiore A, Ill P, Samii K. Low molecular weight heparin associated with spinal anesthesia and gradual compression stockings in total hip replacement surgery. *Br J Aneasth* 1997; 78: 660-665.
36. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N *et al*. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. *Thromb Haemost* 2003;89:288-296.
37. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P *et al*. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement. *J Thromb Haemost* 2003;1:2490-2496.
38. Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F, *et al*. Prevention of deep vein thrombosis after major knee surgery - a randomized, double-blind trial

comparing a low molecular weight heparin fragment (enoxaparin) to placebo. 13th Cong of the International Society on Thrombosis and Haemostasis, Amsterdam *Thromb Haemost* 1992 ;67 (4) :417 -423.
39. Levine MN, Gent M, Hirsh J, Weitz J, Turpie AG, Powers P, *et al*. Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism: a randomized trial in patients undergoing knee surgery. *Arch Intern Med* 1996 ;156 :851 -856.
40. Caprini JA, Hwang E, Hantel S, *et al*. The oral direct thrombin inhibitor, dabigatran etexilate, is effective and safe for prevention of major venous thromboembolism following major orthopedic surgery. 21st Cong of the International Society on Thrombosis and Haemostasis (ISTH), Geneva, 6 - 12 Jul 2007. *J Thromb Haemost* 5 (Suppl 2), (2007).
41. National Collaborating Centre for Acute Care. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. April 2007. Available at http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11006.
42. Anderson DR, O'Brien B, Nagpal S. Economic evaluation comparing low molecular weight heparin with other modalities for the prevention of deep vein thrombosis and pulmonary embolism following total hip or knee arthroplasty. Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1998.
43. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005 Oct 15;106(8):2710-5. Epub 2005 Jun 28.
44. Turpie AG, Eriksson BI, Lassen MR *et al*. A meta-analysis of fondaparinux versus enoxaparin in the prevention of venous thromboembolism after major orthopaedic surgery. *J South Orthop Assoc*. 2002 Winter;11(4):182-8.
45. Mismetti P, Laporte S, Zufferey P *et al*. Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: a meta-analysis. *J Thromb Haemost.* 2004 Jul;2(7):1058-70.
46. Hull RD, Pineo GF, Stein PD *et al*. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med*. 2001 Nov 20;135(10):858-69.
47. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet.* 2001 Jul 7;358(9275):9-15.
48. Koch A, Bouges S, Ziegler S *et al*. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. *Br J Surg*. 1997 Jun;84(6):750-9.
49. Norrie J, Trials of venous thromboembolism prevention, *Lancet* 2007. 370(9591);915-917.
50. Eriksson BI, Bauer KA, Lassen MR *et al*. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip fracture surgery. *N Engl J Med* 2001; 345(18):1298-1305.
51. Hull RD, Pineo GF, Francis C *et al*. Low-Molecular-Weight Heparin Prophylaxis Using Dalteparin Extended Out-of-Hospital vs In-Hospital Warfarin/Out-of-Hospital Placebo in Hip Arthroplasty Patients *Arch Intern Med* 2000; 160: 2208-2215.
52. Kakkar VV, Howes J, Sharma V, Kadziola Z. A Comparative, Double-blind, Randomised Trial of a New Second Generation LMWH (Bemiparin) and UFH in the Prevention of Post-operative Venous Thromboembolism. *Thromb Haemost* 2000; 83:523-9
53. National Statistics. Breakdown of the UK population by ethnic group. UK Census 2001. Available at: http://www.statistics.gov.uk/cci/nugget.asp?id=273
54. Nicolaides A, Bosanquet N. Cost-effectiveness of desirudin in the prevention of the thromboembolic complications of surgery. *J Med Econ* 1999;(2):155-66.
55. Drummond M, Aristides M, Davies L *et al*., Economic evaluation of standard heparin and enoxaparin for prophylaxis against deep vein thrombosis in elective hip surgery. *Br J Surg* 1994; 81:1742-6.
56. Davies LM, Richardson GA, Cohen AT. Economic evaluation of enoxaparin as postdischarge prophylaxis for deep vein thrombosis (DVT) in elective hip surgery. *Value Health* 2000;3(6):397-406.

57. Gordois A, Posnett J, Borris L *et al*. The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery. *J Thromb Haemost* 2003;1(10):2167-74.
58. Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep-vein thrombosis in major orthopedic surgery. *JAMA* 1987;257:203-8.
59. Caprini JA, Botteman MF, Stephens JM *et al*. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value.Health* 2003;6(1):59-74.
60. Boehringer Ingelheim Ltd. Analysis of GPRD data 2003-2005: Proportion of Total Hip and Knee Replacement Patients Over the Age of 75. Data on File, February 2007.
61. Muntz J, Scott DA, Lloyd A, Egger M. Major bleeding rates after prophylaxis against venous thromboembolism: systematic review, meta-analysis, and cost implications. *Int J Technol.Assess.Health Care* 2004;20(4):405-14.
62. Marchetti M, Liberato NL, Ruperto N, Barosi G. Long-term cost-effectiveness of low molecular weight heparin versus unfractionated heparin for the prophylaxis of venous thromboembolism in elective hip replacement. *Haematologica* 1999;84(8):730-7.
63. Honorato J, Gomez-Outes A, Navarro-Quilis A *et al*. Pharmacoeconomic analysis of bemiparin and enoxaparin as prophylaxis for venous thromboembolism in total knee replacement surgery. *Pharmacoeconomics* 2004;22(13):885-94.
64. Haentjens P, De GK, Annemans L. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. A cost-utility analysis. *Arch Orthop.Trauma Surg* 2004;124(8):507-17.
65. Nerurkar J, Wade WE, Martin BC. Cost/death averted with venous thromboembolism prophylaxis in patients undergoing total knee replacement or knee arthroplasty. *Pharmacotherapy* 2002;22(8):990-1000.
66. Spruill WJ, Wade WE, Leslie RB. Cost analysis of fondaparinux versus enoxaparin as venous thromboembolism prophylaxis in elective hip replacement surgery. *Blood Coagul Fibrinolysis* 2004b;15(7):539-43.
67. White RH, Ginsberg JS. Low-molecular-weight heparins: are they all the same [review]? *Br J Haematol* 2003 Apr;121(1):12-20.
68. Lopez LM. Low-molecular-weight heparins are essentially the same for treatment and prevention of venous thromboembolism [review]. *Pharmacotherapy* 2001 Jun;21(6 pt 2):56S-61S, 71S-72S.
69. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683-91.
70. Eriksson BI, Lassen MR; for the PENTasaccharide in Hip-FRActure Surgery Plus (PENTHIFRA Plus) Investigators. Duration of Prophylaxis Against Venous Thromboembolism With Fondaparinux After Hip Fracture Surgery. *Arch Intern Med*. 2003;163:1337-1342.
71. Menzin J, Colditz GA, Regan MM *et al*. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. *Arch Intern Med* 1995;155(7):757-64.
72. White RH, Romano PS, Zhou H *et al*. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. *Arch Intern Med*. 1998 Jul 27;158(14):1525-31.
73. Lieberskind DS. Intracranial Hemorrhage In: e-medicine, Saver JL, Talavera F, Kirxhner H eds. 2006. http://www.emedicine.com/neuro/topic177.htm Accessed 04 February 2008.
74. Almeida JI, Coats R, Liem TK, Silver D. Reduced morbidity and mortality rates of the heparin-induced thrombocytopenia syndrome. *J Vasc Surg*. 1998 Feb;27(2):309-14.
75. Prandoni P, Villalta S, Bagatella P *et al*. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica* 1997 Jul-Aug;82(4):423-8.
76. Prandoni P, Lensing AW, Piccioli A *et al*. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002a Nov 15;100(10):3484-8.
77. Prandoni P, Lensing AW, Prins MH *et al*. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. *Ann Intern Med* 2002c Dec 17;137(12):955-60.

78. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med* 2000 Mar 27;160(6): 769-74.
79. Ziegler S, Schillinger M, Maca TH, Minar E. Post-thrombotic syndrome after primary event of deep venous thrombosis 10 to 20 years ago. *Thromb Res* 2001;101(2):23-33.
80. Kyrle PA, Minar E, Bialonczyk C *et al*. The risk of recurrent venous thromboembolism in men and women. *N Engl J* Med 2004 Jun 17;350(25):2558-63.
81. Beyth RJ, Cohen AM, Landefeld CS. Long-term outcomes of deep-vein thrombosis. *Arch Intern Med* 1995;155:1031-7.
82. Siragusa S, Beltrametti C, Barone M, Piovella F. Clinical course and incidence of post-thrombophlebitic syndrome after profound asymptomatic deep vein thrombosis. Results of a transverse epidemiologic study. *Minerva Cardioangiol* 1997 Mar;45(3):57-66.
83. Singh H, Masuda EM. Comparing short-term outcomes of femoral-popliteal and iliofemoral deep venous thrombosis: early lysis and development of reflux. *Ann Vasc Surg* 2005;19(1):74-9.
84. Ginsberg JS, Turkstra F, Buller HR *et al*. Postthrombotic syndrome after hip or knee arthroplasty: a cross-sectional study. *Arch Intern Med* 2000 Mar 13;160(5):669-72.
85. Prandoni P, Bernardi E, Marchiori A *et al*. The long term clinical course of acute deep vein thrombosis of the arm: prospective cohort study. *BMJ*. 2004 Aug 28;329(7464):484-5. Epub 2004 Jul 15.
86. Monreal M, Martorell A, Callejas JM *et al*. Venographic assessment of deep vein thrombosis and risk of developing post-thrombotic syndrome: a prospective study. *J Intern Med* 1993 Mar;233(3):233-8.
87. Kakkar VV, Lawrence D. Hemodynamic and clinical assessment after therapy for acute deep vein thrombosis. A prospective study. *Am J Surg* 1985 Oct 8;150(4A):54-63.
88. Lindner DJ, Edwards JM, Phinney ES *et al*. Long-term hemodynamic and clinical sequelae of lower extremity deep vein thrombosis. *J Vasc Surg* 1986 Nov;4(5):436-42.
89. Franzeck UK, Schalch I, Bollinger A. On the relationship between changes in the deep veins evaluated by duplex sonography and the post-thrombotic syndrome 12 years after deep vein thrombosis. *Thromb Haemost* 1997; 77:1109-12.
90. McNally MA, McAlinden MG, O'Connell BM, Mollan RA. Postphlebitic syndrome after hip arthroplasty: 43 patients followed at least 5 years. *Acta Orthop Scand* 1994 Dec;65(6):595-8.
91. Wille JP, Jorgensen LN, Crawford M. Asymptomatic postoperative deep vein thrombosis and the development of postthrombotic syndrome. A systematic review and meta-analysis. *Thrombosis Haemostasis* 2005, 93(2):236-41.
92. Heit JA, Rooke TW, Silverstein MD *et al*. Trends in the incidence of venous stasis syndrome and venous ulcer: a 25-year population-based study. *J Vasc Surg*. 2001 May;33(5):1022-7
93. Office for National Statistics (ONS). Mortality rates 2001, deaths 2001: rates per 1000 population by age-group and sex in the UK. Taken from Table 6 published in Mortality Statistics, general, 2001 (series DH1, No. 34). 2007.
94. Ingelgard A, Hedner E, Stigendal J, Carlsson J. Patient-reported outcomes in patients with deep vein thrombosis treated with warfarin. Poster presentation at the 17th International Congress on Thrombosis (ICT), 26-30 October 2002, Bologna, Italy. Abtract published in *Pathophysiology of Haemostasis and Thrombosis* 2002, Vol. 32, Suppl. 2
95. NHS National Reference Costs (2006). Department of Health
96. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. *J Am Med Inform.Assoc* 1997;4(1):49-56.
97. Robinson A, Thomson R, Parkin D *et al*. How patients with atrial fibrillation value different health outcomes: a standard gamble study. *J Health Serv Res Policy* 2001;6(2):92-8.
98. Prescott-Clarke P, Primatera P (eds). The Health Survey for England 1996. London: The Stationary Office, 1998.
99. Fondaparinux sodium (Arixtra) 2.5mg/0.5ml, summary of product characteristics (EU).

100. Watts AC, Howie CR, Simpson AH. Assessment of a self-administration protocol for extended subcutaneous thromboprophylaxis in lower limb arthroplasty. *J Bone Joint Surg* [Br] 2006;88-B:107-10.
101. Koopman MM, Prandoni P, Piovella F *et al*. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. *N Engl J Med* 1996 Mar 14;334(11):682-7. Erratum in: *N Engl J Med* 1997 Oct 23;337(17):1251.
102. Bond S, Rhodes S, James R *et al*., Healthcare costs of treating bleeding and other complications associated with warfarin treatment of atrial fibrillation and venous thromboembolism in the UK. Poster presentation at the British Society for Haematology 44th Annual Scientific Meeting, 19-21 April 2004, Cardiff, Wales. Abstracts published in *British Journal of Haematology* April 2004:Vol. 125 Issue s1;1-78
103. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics*. 2003;21 Suppl 1:43-50.
104. NHS Returns 2003/4. NHS Executive.
105. British National Formulary 54. September 2007. Available at http://www.bnf.org
106. Curtis L. Unit costs of health and social care 2007. University of Kent: Personal Social Services Research Unit; 2007.
107. Offord R, Lloyd AC, Anderson P, Bearne A. Economic evaluation of enoxaparin for the prevention of venous thromboembolism in acutely ill medical patients. *Pharm World Sci*. 2004 Aug;26(4):214-20.
108. NHS Electronic Drug Tariff (2007). Department of Health, London http://www.ppa.org.uk/ppa/edt_intro.htm
109. Sullivan SD, Davidson BL, Kahn SR, Muntz JE *et al*. Cost-Effectiveness Analysis of Fondaparinux Sodium Compared with Enoxaparin Sodium as Prophylaxis Against Venous Thromboembolism. Use in Patients Undergoing Major Orthopaedic Surgery. *Pharmacoeconomics* 2004; 22 (9): 605-620
110. Lundkvist J, Bergqvist D, Jönsson B. Cost-effectiveness of fondaparinux vs.enoxaparin as venous thromboembolism prophylaxis in Sweden. *Eur J Health Econom* 2003 4:254–262.
111. Government Actuary's Department. Population projection for England and Wales, base year 2006. Available at http://www.gad.gov.uk/

9 Appendices

9.1 Appendix 1: Summary of Product Characteristics

Pradaxa SPC (CONFIDENTIAL).pdf

9.2 Appendix 2: search strategy for section 5

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library.***

Table 110 presents the details of the searches performed to obtain clinical data relevant to the decision problem.

Table 110 Details of searches performed

Database	Service provider	Date of search	Data span of search
Embase	Ovid	08/02/08	1988-2008 week 05
Medline (R)	Ovid	08/02/08	2004-2008 Jan week 5
Medline In-process	Ovid	11/02/08	1996- Feb 11 2008
Cochrane Library	Wiley	08/02/08	Whole database
Boehringer Ingelheim Product Literature (BILIT) and pre-BILIT	None	08/02/08	Whole database

9.2.2 The date on which the search was conducted.

See **Table 110**.

9.2.3 The date span of the search.

See **Table 110**.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

EMBASE

DABIGATRAN ETEXILATE/ or DABIGATRAN/ or dabigatran.mp.
AND
TOTAL HIP PROSTHESIS/ or HIP ARTHROPLASTY/ or HIP SURGERY/ or HIP/ or TOTAL KNEE REPLACEMENT/ or KNEE/ or KNEE PROSTHESIS/ or KNEE ARTHROPLASTY/ or KNEE SURGERY/
AND
study.mp

MEDLINE

dabigatran.mp
AND
Hip/ or Arthroplasty, Replacement, Hip/ or Hip Prosthesis/ or Knee Joint/ or Knee/ or Arthroplasty, Replacement, Knee/ or Knee Prosthesis/
AND
study.mp.or trial.mp

MEDLINE IN-PROCESS

dabigatran.mp
AND
study.mp.or trial.mp

COCHRANE LIBRARY

dabigatran
and
Hip/ or Arthroplasty, Replacement, Hip/ or Hip Prosthesis/ or Knee Joint/ or Knee/ or Arthroplasty, Replacement, Knee/ or Knee Prosthesis/

9.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

BILIT & pre-BILIT

About BILIT

Content

The Boehringer Ingelheim Literature database (BILIT) contains all publications on Boehringer Ingelheim products, licensed drugs or developmental compounds. The database covers clinical medicine, pharmacology, toxicology, biochemistry, analytics, immunology etc.

All indexing is done with special reference to the BI product(s) mentioned in the paper. The main aspects in the publication relevant to our drug(s) are represented in the chosen indexing terms, e.g. indication treated and dosage used.

Sources

Sources screened include international journals, books, conference proceedings, reports and thesis. For completeness of the database external files from Medline and Embase are evaluated. BI operating units contribute to the comprehensiveness by supplying copies from national appearing papers. The turnaround time from publication to database input is generally about two weeks. Updates occur daily.

Producer

Corporate Medical Documentation & Information (CMDI), Boehringer Ingelheim GmbH

Search strategy:

FIND (GN='Dabigatran etexilate' AND.T CL='MAJOR') AND.R DT=('ABSTRACT' OR 'THESIS' OR 'ORIGINAL') AND.R ST=('DRUG THERAPY') AND.R DE=(CT(knee$).OR. (hip$))

9.2.6 The inclusion and exclusion criteria.

As presented in Section 5.2.2.

9.2.7 The data abstraction strategy.

Data relating to both study design and quality were extracted by one reviewer and checked for accuracy by a second reviewer. Disagreements were resolved through consensus and if necessary a third reviewer was consulted.

Data from all the trials identified as relevant are presented, supplemented where necessary with information from the unpublished company clinical trial reports.

9.3 Appendix 3: search strategy for section 6

The following information should be provided.

9.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***Health Economic Evaluation Database***

- ***NHS Economic Evaluation Database (NHS EED).***

Table 111 presents the details of the searches performed.

Table 111 Searches performed

Database	Service Provider	Date of Search	Date Span of Search
EMBASE	Ovid	15/09/2006	1985-2006
PubMed	Ovid	15/09/2006	1985-2006
Cochrane (DARE, NHS EED, HTA)	None	15/09/2006	1985-2006
BILIT	None	14/02/2008	Whole database
NICE, SMC, CADTH/CCOHTA	None	15/09/2006	Whole database

9.3.2 The date on which the search was conducted.

See **Table 111.**

9.3.3 The date span of the search.

See **Table 111.**

9.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

EMBASE and PubMed: Free-text terms

Interventions

- anticoagulant OR anti-coagulant OR heparin OR warfarin OR enoxaparin OR ardeparin OR fondaparinux OR desirudin OR Celaxane OR Normiflo OR Arixtra OR Revasc OR Iprivasc OR dihydroergotamine OR dextran OR bivalirudin OR ximelagatran OR Exanta OR antithrombin OR "graduated compression stocking" OR "compression stocking" OR "mechanical compression" OR "pneumatic compression " OR "elastic stocking" OR "foot pump"

Disease

- thrombosis OR thromboembolism

Indication

- "hip replacement" OR "hip arthroplasty" OR "knee replacement" OR "knee arthroplasty"

Events

- ”intercranial haemorrhage” OR “intercranial haemorrhage” OR “intercranial bleed” OR haemorrhage OR haemorrhage OR "major bleed" OR "post-thrombotic syndrome" OR "post thrombotic syndrome" OR "post thrombotic leg syndrome"

Economics

- Cost* OR economic OR burden OR modelling OR “cost analysis” OR pharmacoeconomic OR “resource use” OR utilization OR utilisation OR “resource utilisation” OR “resource utilization” OR “health care” OR budget OR GPRD OR “general practice research database” OR Mediplus OR “Doctors independent network” OR DIN-LINK OR “prescribing patterns” OR MEMO OR HODaR OR IMS OR database OR chart OR Medicare OR QALY

Utilities

- “standard gamble” OR “time trade off” OR SG OR TTO OR EuroQol OR EQ5D OR EQ-5D OR “quality of well being” OR “health utility index” OR “health utilities index” OR QALY OR “Quality adjusted life year”

Term group combinations

- drugs & economics & disease & indication
- events & economics & disease*
- events & utilities

* “events” terms combined with the “economics” terms resulted in 2,282 hits in PubMed alone; “disease” terms were therefore added.

PubMed: MeSH search

"Economics"[MeSH] OR "Costs and Cost Analysis"[MeSH]

AND

"Arthroplasty, Replacement, Knee"[MeSH] OR "Knee Prosthesis"[MeSH] OR "Arthroplasty, Replacement, Hip"[MeSH] OR "Hip Prosthesis"[MeSH]

AND

"Anticoagulants"[MeSH] OR "Warfarin"[MeSH] OR "Drug Therapy"[MeSH]

AND

"Venous Thrombosis"[MeSH] OR "Pulmonary Embolism"[MeSH] OR "Thromboembolism"[MeSH]

Cochrane

Cochrane databases including DARE, NHS EED, and HTA were searched for relevant references on anti-coagulant prophylaxis relating to TKR and THR.

BILIT

#econom# AND GN=dabigatran and.t CL=major

NICE

Completed health technology appraisals were searched; all appraisals of anticoagulant prophylaxis relating to TKR and THR were retrieved.
http://www.nice.org.uk/page.aspx?o=cat.diseaseareas

SMC

Completed medicines assessments were searched, all assessments of anticoagulant prophylaxis relating to TKR and THR will be retrieved.
http://www.scottishmedicines.org.uk/medicines/default.asp

CADTH/CCOHTA

HTA reports and publications were searched for the following terms

- Thromboembolism
- Thrombosis
- VTE

http://www.cadth.ca/index.php/en/hta/reports-publications

9.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

Not applicable.

9.4 Appendix 4: EPAR


Appendix 4 - Draft EPAR.doc

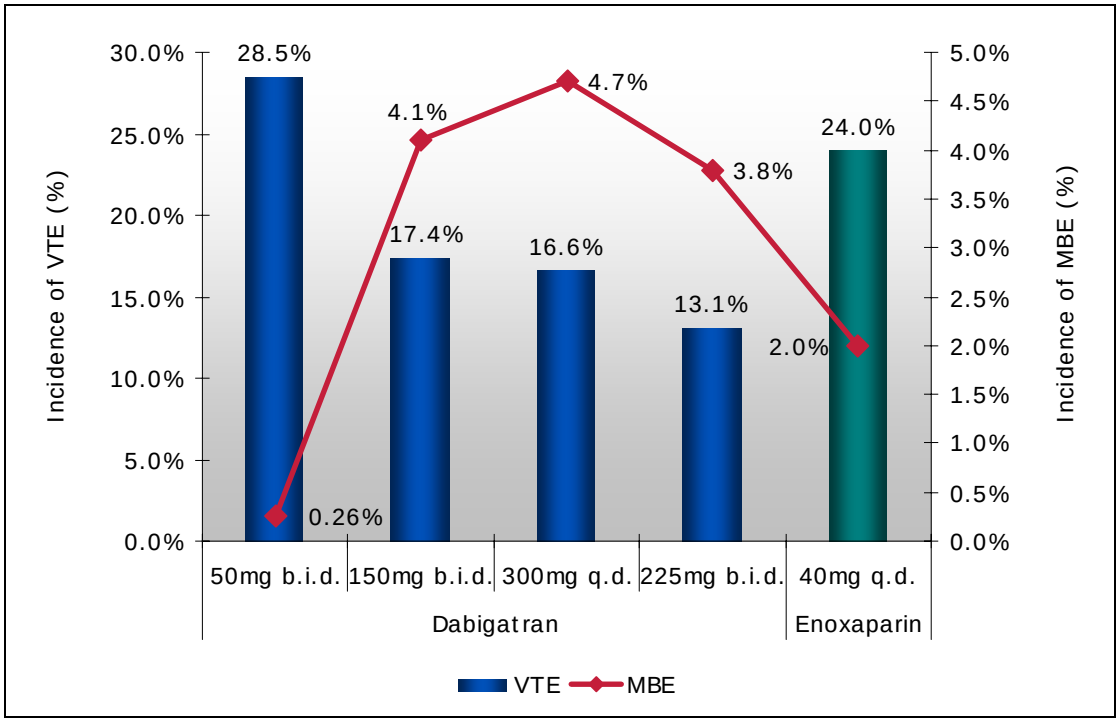
9.5 Appendix 5: BISTRO II

BISTRO II [26] was a phase-II dose-ranging study in 1,973 patients undergoing THR or TKR surgery. Four doses of DBG (50mg b.i.d., 150mg b.i.d., 300mg o.d. and 225mg b.i.d.) were compared with 40mg o.d. enoxaparin. The primary efficacy endpoint was the incidence of VTE and the primary safety endpoint was the incidence of major bleeding (MBE). Patients treated with 50mg b.i.d. DBG were found to have fewer MBEs than enoxaparin-treated patients with incidences of 0.26% and 2.0%, respectively (P<0.05) but

had a numerically higher incidence of VTEs: 28.5% versus 24.0% (*P*=0.24) (**Figure 41**). In contrast, patients treated with higher DBG doses of 150mg b.i.d., 300mg o.d. or 225mg b.i.d. had significantly lower incidences of VTE *versus* enoxaparin: 17.4% (*P*=0.04), 16.6% (*P*=0.02), and 13.1%, (*P*=0.0007) respectively. However, there was a trend towards increased bleeding rates in each of the higher DBG dose groups with MBE incidences of 4.1%, 4.7%, and 3.8% for the 150mg b.i.d., 300mg o.d., and 225mg b.i.d. dose groups respectively compared with 2.0% in the enoxaparin group. In the 300mg o.d. group, the difference in the incidence of MBEs *versus* enoxaparin was statistically significant (*P*<0.05).

The efficacy and safety of the 150mg b.i.d. DBG dose was not significantly different from that of the 300mg o.d. dose, as was expected due to the relatively long half life of DBG (14–17 hours). Since patients receiving a DBG 50mg b.i.d had fewer MBEs than enoxaparin-treated patients but numerically more VTEs, it was concluded that this dose was not optimal. Conversely, as patients receiving DBG doses of 150mg b.i.d and 225mg b.i.d had lower VTE rates than enoxaparin-treated patients but had numerically more bleedings, these doses were thought to be excessive.

Figure 41 Results of BISTRO-II



MBE, major bleeding event; q.d, once daily dosing; VTE, venous thromboembolism.

To optimise the DBG dose it was decided to compare two daily doses between 100 and 300mg in subsequent phase-III trials, namely 150mg and 220mg with enoxaparin as an active control. To minimise the risk of MBEs, of which about three quarters occur within

the first 24 hours following surgery, only one half of the dose was to be given on the day of surgery.

9.6 Appendix 6: Search strategy and full references of the included studies for the literature search of meta-analyses

Appendix 6

9.7 Appendix 7: Supplementary meta-analyses

9.8 Appendix 8: HES tabulation request

Appendix 8

9.9 Appendix 9: Stroke utility weights

9.10 Appendix 10: Self-administration rates