Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: A Single Technology Appraisal

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Contributions of authors
The review of the clinical evidence was undertaken by Chris Carroll, the review of the cost-effectiveness evidence was undertaken by Mike Holmes. Diana Papaioannou carried out the searches.

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Abbreviations

ALT	alanine aminotransferase
b.i.d.	twice daily
BILI	bilirubin
CRBE	clinically relevant bleeding event
DBG	dabigatran etexilate
DVT	deep vein thrombosis
ERG	evidence review group
GCS	graduated compression stockings
HIT	heparin-induced thrombocytopenia
LMWH	low molecular weight heparin
MBE	major bleeding event
MS	manufacturer's submission
NCC-AC	National Collaborating Centre for Acute Care
o.d.	once daily
PE	pulmonary embolism
PTS	post-thrombotic syndrome
RCT	randomized controlled trial
THR	total hip replacement
TKR	total knee replacement
ULN	under limit of normal
VTE	venous thromboembolic events

1 SUMMARY

1.1 Scope of the submission

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

The ERG would like to comment on the quality of the MS. The MS contains 222 pages, this is much longer than the 70-100 pages recommended by NICE. The length of the MS make the review by the ERG more difficult than it should have been and this was compounded by the lack of a table of contents. The MS contained some information that was extraneous to the submission and omitted information that was important to the submission. For this important information the ERG was directed by the MS to two large documents produced by organisations independent to the manufacturers. This information should have been contained within the MS.

1.2 Summary of submitted clinical effectiveness evidence

- The main evidence in the submission is derived from three head-to-head, phase III, multi-arm, randomised, double blind, controlled, non-inferiority trials (RE-NOVATE, RE-MODEL and RE-MOBILIZE). These trials compared the efficacy and safety of DBG at doses of 220mg and 150 mg once daily (o.d) with enoxaparin (40mg o.d. in RE-NOVATE and RE-MODEL trials, 30mg twice daily (b.i.d.) in the RE-MOBILIZE trial) in patients undergoing TKR (RE-MODEL and RE-MOBILIZE) or THR (RE-NOVATE). Follow-up was 12-14 weeks.

- Evidence from post-hoc sub-group analyses of the included trials indicates that the 150mg o.d. dose may be less effective in terms of incidence of total VTE and all-cause mortality than the 220mg o.d. dose in the special populations indicated for this dose, and for whom this lower dose is specifically licensed: the elderly (aged 75 years and older), and those with moderate renal impairment. Safety outcomes were not reported for these sub-groups.

- The meta-analysis of the primary efficacy outcome across all three trials (RE-NOVATE, RE-MODEL and RE-MOBILIZE), and across combinations of these trials, appears to show that the intervention, DBG, at the dose of 220mg o.d. was not inferior to the comparator, enoxaparin (at either 40mg o.d or 30mg b.i.d), in reducing levels of total venous thromboembolism (VTE) and all-cause mortality among patients undergoing THR and TKR.

- The meta-analyses of the two TKR trials combined (RE-MODEL and RE-MOBILIZE) and the three TKR and THR trials combined (RE-NOVATE, RE-MODEL and RE-MOBILIZE) appear to show that the 150mg o.d. dose of DBG is inferior to the comparator, enoxaparin (at both 40mg o.d and 30mg b.i.d), in reducing levels of total VTE and all-cause mortality among patients undergoing TKR and THR.

- The meta-analysis of the RE-MODEL and RE-NOVATE trials appears to show that the 150mg o.d. dose of DBG is not inferior to the comparator, enoxaparin (at either 40mg o.d and 30mg b.i.d), in reducing levels of total VTE and all-cause mortality among patients undergoing TKR and THR.

- DBG (at both 220mg o.d. and 150 mg o.d.) does not appear to be inferior to enoxaparin (40mg o.d. and 30mg b.i.d.) in terms of the secondary efficacy outcome of major-VTE or VTE-related events.

- A mixed treatment comparison (MTC) analysis compared the results of these trials of DBG with all other available interventions for patients undergoing surgery and at risk of DVT and found that DBG compared favourably with the other interventions, with the exception of extended LMWHs and fondaparinux, which appear to be more effective.

- The adverse event profile was not significantly different in those receiving DBG compared to those receiving enoxaparin. The primary safety endpoint was major

bleeding. Clinically-relevant bleeding, any bleeding and liver function were also measured (secondary endpoints).

1.3 Summary of submitted cost-effectiveness evidence

The model developed by Boehringer Ingelheim has an acute phase which starts at time of surgery and ends at 10 weeks post-surgery and a chronic phase with a lifetime horizon. The model compares DBG with LMWH and fondaparinux in both THR and TKR. The acute phase model is a decision tree that predicts the health states patients will be in at 10 weeks based on evidence from phase III trials for DBG compared to LMWH and a mixed treatment comparison for DBG compared to fondaparinux. At 10 weeks patients enter a chronic phase Markov model in the same health state in which they terminated the decision tree model. No further treatment effect is applied in the chronic phase model. Transition between states in the chronic phase model is dependent on VTE recurrence rates obtained from the literature.

The health states, costs, utilities and recurrence rates used within the model are considered to be appropriate for the required analysis.

The Boehringer Ingelheim model estimated that:

- At the licensed dose of 220mg o.d. DBG dominates LMWH in both THR and TKR.

- At the lower dose of 150 mg o.d. (licensed for patients with mild or moderate kidney problems, patients over 75 years of age and for patients taking amiodarone), DBG dominates LMWH in THR, and LMWH dominates DBG in TKR.

- DBG is less cost-effective than fondaparinux in THR at both doses of DBG. The cost/QALY is £11,111 and £6,857 respectively, for the higher and lower doses of DBG (please note that these ICERs are in the “south/west quadrant of the cost-effectiveness plane).

- In TKR, both DBG doses are dominated by fondaparinux.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

- The manufacturer conducted a limited but systematic search for clinical and cost-effectiveness studies of DBG for the prevention of VTE in patients undergoing TKR and THR. It appears unlikely that any additional trials would have met the inclusion criteria had the search been widened to include more free text terms or to include other databases.

- The three identified trials, which represent the main clinical efficacy evidence, were of reasonable methodological quality (with some limitations, see section 4.1.5), and measured a range of outcomes that were appropriate and clinically relevant.

- The meta-analyses demonstrated the non-inferiority of DBG 220mg o.d. *versus* the LMWH enoxaparin in terms of the efficacy and safety endpoints, and acknowledged the apparent inferiority of the 150mg o.d. dose in terms of the primary efficacy outcome.

- The model structure is appropriate and allows sensitivity analysis to be carried out easily.

- The model assumptions are reasonable.

- The univariate sensitivity analysis is extensive and is performed on appropriate parameters.

- The PSA is performed correctly.

1.4.2 Weaknesses

- The processes undertaken by the manufacturer for screening studies, data extraction and applying quality assessment criteria to included studies are not made explicitly clear in the MS. These factors limit the robustness of the systematic review.

- Quality assessment of the included studies should have been undertaken using a checklist appropriate to the types of study included (non-inferiority randomised trials).

- One of the trials used in the clinical effectiveness section is published only as an abstract (RE-MOBILIZE); much of the key data employed are unpublished.

- A simple pooled analysis of the patient level data, from the two pivotal trials, as well as all three head-to-head trials, was reported. However, the methods used for this data pooling were not described; the statistical approach for combining the data appears to be inappropriate as it fails to preserve randomisation and introduces bias and confounding. The resulting pooled data should therefore be treated with caution.

- Elements of the mixed treatment comparison (MTC) reported in the MS are reproduced from documents produced by organisations other than the manufacturer, rather than specifically in response to the scope. The key details of trials included in the MTC, and issues relating to heterogeneity of trials, are neither reported nor discussed. The resulting MTC should therefore be treated with caution.

- The economic results for DBG compared to LMWH in THR and TKR both rely on one trial each. These trials indicate that DBG is not inferior to LMWH. The small numerical difference seen in these trials is reproduced in the model in terms of both incremental costs and incremental health benefits. A small change in the direction of the trial results would result in a similar change in the direction of the model results.

- The economic results for DBG versus fondaparinux in THR are based on one study for which the manufacturers appear to have used an incorrect relative risk (RR) estimate.

- VTE recurrence rates, post-thrombotic syndrome (PTS) rates and quality of life utilities used in the model are based on a literature review limited to economic studies. It is therefore possible that non-economic studies reporting this data in sources such as Medline have not been identified.

- Some input parameters into the modelling process are incorrect. The impact of this is unknown.

1.4.3 Areas of uncertainty

- There is uncertainty around the clinical and cost effectiveness of DBG in comparison with other relevant treatments included in the scope, especially

fondaparinux, and other standard and extended LMWHs, especially with respect to the 150mg o.d. dose.

- The 150mg o.d. dose may be less effective than the 220mg o.d. dose for the special populations for whom this lower dose is licensed.

- The economic results for DBG compared to LMWH in THR and TKR both rely on one trial each. The small numerical difference seen in these trials is reproduced in the model in terms of both incremental costs and incremental health benefits. A small change in the direction of the trial results would result in a similar change in the direction of the model results.

1.5 Key issues

- The external validity of the evidence is limited. Only a single randomised controlled trial (RCT) using a comparator and dose applied in England and Wales has been conducted on each of the relevant THR and TKR populations. The addition of evidence from any future RCTs may alter the results regarding the non-inferiority of DBG. Small changes in key parameters could markedly alter the conclusions with respect to cost and clinical effectiveness.

- The results of the RE-MOBILIZE TKR trial indicates that both the 220mg o.d. and the 150mg o.d. dose of DBG are inferior to the LWMH enoxaparin in terms of the primary efficacy outcome of total-VTE and all-cause mortality. When the pivotal trials (RE-MODEL and RE-NOVATE) are combined with this trial in a meta-analysis the 150mg o.d. dose of DBG is found to be inferior to the LWMH enoxaparin in terms of the primary efficacy outcome. The 150mg o.d. dose may therefore not be suitable for use in the special populations indicated. Post-hoc sub-group analyses for total VTE and all-cause mortality conducted on the special populations indicated also suggest that this dose may be less effective than the 220mg o.d. dose in terms of the primary efficacy outcome.

- The economic results for DBG compared to LMWH in THR and TKR both rely on one trial each. These trials indicate that DBG is not inferior to LMWH. The small numerical difference seen in these trials is reproduced in the model in terms of both incremental costs and incremental health benefits. A small

change in the direction of the trial results would result in a similar change in the direction of the model results.

- The cost-effectiveness analysis based on a meta-analysis of RE-MODEL plus RE-MOBILIZE reverses the direction of the results, i.e. DBG is now dominated by LMWH for both doses. However it is the manufacturers opinion that the RE-MOBILIZE study is not generalisable to the England and Wales setting. This is also the opinion of the clinical advisors to the ERG.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of the underlying health problem lacks some detail. A description of VTE disease characteristics is included with reference to complications, recurrence and mortality rates. However, it is unclear whether or not this description refers to VTEs as a result of hip and knee surgery or from other causes.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of current service provision is adequate although further discussion around specific points is required. The MS includes a discussion of a key issue in the provision of pharmacological thromboprophylaxis. That is, the considerable disparity between relevant clinical guidelines and actual practice. This is a potentially contentious issue and relates to clinicians' concerns over the trade-off between efficacy and safety. This issue should have been discussed in more detail. The MS suggests that there is also a problem with patient compliance due to the delivery mode of current treatment (i.e. subcutaneous injection) and also suggests that this may result in a reluctance to prescribe by clinicians. This is a potentially relevant issue which is unfortunately not backed up with any firm data in the MS.

The percentage of individuals currently receiving the comparator employed in the reported trials (enoxaparin) is omitted, and no data are provided in this section on the percentage of patients currently receiving the other comparator of the scope, fondaparinux. A discussion regarding the relative levels of use of these two comparators has not been provided.

3 Critique of manufacturer's definition of decision problem

A summary of the decision problem addressed by the MS is shown in Table 1.

Table 1: Decision problem as issued by NICE and addressed by the MS

	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 in terms of incremental cost per	The economic evaluation will present a cost-utility analysis with cost effectiveness expressed in terms of incremental cost per quality-adjusted

	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.	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.

3.1 Population

The manufacturer's statement of the decision problem appropriately defines the population as adults undergoing elective total hip replacement (THR) or total knee replacement (TKR) surgery. The submission identifies the following contraindications to DBG therapy:

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 DBG is 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.

3.2 Intervention

DBG (Pradaxa®) is an oral direct thrombin inhibitor, a type of anticoagulant. DBG is indicated for the primary prevention of venous thromboembolism (VTE) in adult patients who have undergone THR or TKR surgery. Marketing authorisation for DBG was granted by the European Medicines Agency on March 18, 2008. The proposed course of treatment varies between elective total hip replacement (THR) and elective total knee replacement (TKR). For THR the recommended dose of DBG is 220 mg o.d. taken as two capsules of 110 mg. Treatment is to be initiated orally within 1 – 4 hours of completed surgery with a single capsule, and to continue with two capsules o.d. thereafter for a total of 28-35 days. For TKR the recommended dose of DBG is 220 mg o.d. taken as two capsules of 110 mg. Treatment is to be initiated orally within 1 – 4 hours of completed surgery with a single capsule, and to continue with two capsules o.d. thereafter for a total of 10 days.

Ttreatment in patients with severe renal impairment (creatinine clearance < 30 ml/min) is contraindicated, and patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials, so the use of DBG is not recommended in this population. For the elderly (>75 years) and patients with moderate renal impairment (creatinine clearance 30-50 ml/min), caution is advised and the recommended dose is 150mg. The MS states that there is limited clinical experience in these populations.

3.3 Comparators

The decision problem addressed in the MS states that the standard comparators to be considered are LMWHs and fondaparinux. The ERG acknowledges that LMWHs and fondaparinux are appropriate pharamacological comparators for DBG.

3.4 Outcomes

The decision problem outlines eight relevant outcomes to be assessed. Four of these eight outcomes are reported in the clinical effectiveness section of the MS (mortality, incidence of DVT, incidence of PE, adverse events [including bleeding]), and the

omission of only one of the excluded outcomes (joint outcomes) is addressed in the statement of the decision problem in the MS. The remaining outcomes outlined by the final scope issued by NICE are considered in the cost- effectiveness section of the MS, these are; post DVT complications, including post-thrombotic syndrome, length of hospital stay, and health-related quality of life. A summary of the measures used in the principal trials supporting the MS are shown in Table 2.

Table 2: Outcome measures in trials

Outcome	Outcome measures use in principal trials providing supportive evidence in MS		
	RE-NOVATE	RE-MODEL	RE-MOBILIZE
Primary efficacy endpoint	• A composite endpoint consisting of total venous thromboembolic events* (VTEs) and all-cause mortality during the treatment period		
Secondary efficacy endpoint	• Composite of major VTE (defined as proximal DVT and PE) and VTE-related mortality • Proximal DVT • Total DVT • Symptomatic DVT • Pulmonary Embolism (PE) • Death		
Safety	• Incidence of bleeding events • Major Bleeding Events (MBE) • MBE and clinically-relevant bleeding events • Any bleeding events (major, clinically-relevant, and minor) • Volume of blood loss • Number and type of blood transfusions • Incidence of adverse events • Incidence of discontinuations due to adverse events • Laboratory measures, especially changes in liver function tests • Results of physical examinations		
Joint outcomes, PTS, length of stay	• Not reported		
Health related quality of life	• Not reported		

*** 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.

The MS notes that all the measures, especially the composite endpoint combining clinical events with asymptomatic venographic VTE, as well as the clinical and laboratory procedures used, especially screening venography, are standard and generally accepted (pp.47-48, MS). The MS also provides a discussion of the controversies surrounding the procedures used (p48, MS). The ERG acknowledges that the procedures and measures used to evaluate the clinical outcomes are appropriate, as long as adequate sample sizes are achieved, and appropriate analyses are conducted, to counteract the limitations of these procedures[1,2].

The metric used for the evaluation of the interventions is cost per cost per quality-adjusted life-year (QALY) gained, which is in accordance with the NICE reference case.

3.5 Time frame

The follow-up period in the two trials evaluating the effectiveness of dabigatran etexilate for the prevention of VTEs in hip or knee replacement was 12-14 weeks. No longer-term studies were identified in the MS.

The manufacturer's health economic model has a two-stage time frame. The first stage models the acute phase following surgery (10 weeks) and the second stage models the chronic phase and has a lifetime horizon of 60 years from surgery. Given a starting age of 69 in the model, a horizon of 60 years is difficult to justify. However, adequate sensitivity analysis is performed for shorter time periods for which there is reasonable evidence of the risks of disease recurrence.

3.6 Other relevant factors

No other relevant factors were identified.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The searches undertaken by the manufacturer to identify all relevant randomised controlled trials (RCTs) were conducted in February 2008. The search strategy utilises terms to identify the patient group (hip and knee replacement surgery), the intervention (dabigatran etexilate) and the type of evidence (study, trial). No language restrictions appear to have been applied. The strategy is simple and reasonably effective, but a form of methodological filter is applied (study.mp or trial.mp), even though it is clearly stated that the strategy was intended not to identify a particular study design (MS, p.25). The filter used is not validated nor is its efficacy reported elsewhere, and given the small number of citations retrieved, these terms could have been omitted, without greatly increasing the work involved. The resulting strategy would have been more sensitive and less vulnerable to criticism.

Only five databases were searched (Medline, Medline in-process, Embase, The Cochrane Library and the manufacturer's own in-house database, BILIT / pre-BILIT); key data may therefore have been missed, particularly regarding unpublished data (no research registers, such as the National Research Register or Current Controlled Trials, were searched, other than the manufacturer's own in-house database). Key databases overlooked include the Science Citation Index (Web of Science) and BIOSIS. The searches also applied date limits, which were not justified in the MS (eg. Medline 2004-2008, MS p.215). The range reported to be searched for Medline in-process (1996-2008, MS p.215) is not congruent with the scope of the database.

No methods, other than the searching of the above electronic databases, were used to identify studies (eg. handsearching of journals, reference and citation tracking). The use of such supplementary methods is required by the QUORUM checklist (Moher 1999). The MS fails to report the use of such methods, or to explain why these methods were not used.

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

Details of the inclusion and exclusion criteria, as reported in the MS, is reproduced in Table 3 (p27, MS)

Table 3: Inclusion/exclusion criteria in the MS clinical effectiveness study selection

	Clinical effectiveness
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 criteria	• 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

The inclusion/exclusion criteria appear to be appropriate, but the rationale behind the stated inclusion and exclusion criteria was not given.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded?

The MS identifies three direct head-to-head, phase III, randomised, blinded, non-inferiority trials (RE-NOVATE,[3] RE-MODEL[4] and RE-MOBILIZE[5]. Two of these trials are described as pivotal (MS pp.36, 47), one for THR (RE-NOVATE) and one for TKR (RE-MODEL), because the dosing regimen, and the timing of first dose, of both DBG and the comparator are apparently applicable to England and Wales (however, see section 4.1.7 below, for the inconsistent timing of first dose applied in these studies). The remaining TKR trial (RE-MOBILIZE) is described as a supporting trial because, unlike the pivotal trials, its dosing regimen and timing of first dose are applicable to North America, and is different from that used in England and Wales. This trial is currently only published as an abstract, a fact not highlighted in the MS.

Of the 19 citations identified by the search of electronic databases, 16 were correctly excluded for the following reasons:

- RCT with inappropriate dose of DBG (1)
- 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)

The remaining three studies were included. Details of the study design and patient characteristics of the included studies are summarised in Table 4. A summary of the results are presented later in the report.

The MS also identified one recently completed, but unpublished TKR trial (1160.50) (p.30 MS) comparing 220mg and 150mg o.d. doses of DBG with placebo. The trial was smaller than the other trials reported in the MS and preliminary results indicated that, compared to placebo, these doses of DBG were significantly more effective at preventing total VTE and all cause mortality and did not significantly increase bleeding events.

Table 4: Characteristics of studies

Study	Design	Participants	Interventions (n=treated)	Outcomes	Duration (planned)
RE-NOVATE	Phase III, multi-centre (n=115), randomised, double-blind, active-controlled, parallel-group, non-inferiority, trial (n=3494) in Europe, Australia and South Africa	• Patients scheduled for primary, unilateral elective total hip replacement surgery. • Male or female patients of 18 years or older. • Patients weighing at least 40 kg. • Patients who provided written informed consent for study participation	T1: dabigatran etexilate 75mg o.d. 1-4 hours after surgery, day 1; 150 mg o.d. day 2 and on (n=1163) T2: dabigatran etexilate 110mg o.d. 1-4 hours after surgery, day 1; 220 mg o.d. day 2 and on (n=1146) T3 : enoxaparin 40 mg o.d. in the evening of the day before the surgery, then day 1 on ; although in some countries treatment was started post-operatively to reflect local practice (n=1154)	Primary efficacy endpoint: • Composite of Total VTE (proximal & distal DVT based on venogram, objectively confirmed symptomatic DVT & PE) and all-cause mortality Secondary endpoints: o Composite of major VTE (defined as proximal DVT and PE) and VTE-related mortality o Proximal DVT o Total DVT o Symptomatic DVT o Pulmonary Embolism (PE) o Death o Major Bleeding Events (MBE) o MBE and clinically-relevant bleeding events o Clinically-relevant bleeding events o Any bleeding events (major, clinically-relevant, and minor) o Volume of blood loss o Number and type of blood transfusions o Incidence of adverse events o Incidence of discontinuations due to adverse events o Laboratory measures, especially changes in liver function tests	28-35 days

Study	Design	Participants	Interventions (n=treated)	Outcomes	Duration (planned)
RE-MODEL	Phase III, multi-centre (n=105), randomised, double-blind, active-controlled, parallel-group, non-inferiority, trial (n=2101) in Europe, Australia and South Africa	• Patients scheduled for primary, unilateral elective total knee replacement surgery • As RE-NOVATE	T1: As RE-NOVATE (N=679) T2: As RE-NOVATE (N=703) T3 : As RE-NOVATE (N=694)	As RE-NOVATE	6-10 days
RE-MOBILIZE	Phase III, multi-centre (not reported), randomised, double-blind, controlled, non-inferiority, trial (n=2615) in USA and Canada	• Patients scheduled for primary, unilateral elective total knee replacement surgery • As above	T1: dabigatran etexilate 75mg o.d. 6-12 hours after surgery, day 1; 150 mg o.d. day 2 and on (N= 857) T2: dabigatran etexilate 110mg o.d. 6-12 hours after surgery, day 1; 220 mg o.d. day 2 and on (N=871) T3 : enoxaparin 30 mg b.i.d., starting 12–24 hours after surgery, day 1; and on (N=868)	As RE-NOVATE	12-15 days

The participant flowcharts provided in the MS (pp.44-46, Figures 6-8) were not entirely in accordance with the requirements of the CONSORT flowchart or point 13 on the CONSORT checklist (http://www.consort-statement.org), nor were the stages reported consistent across the three flowcharts (eg. overall number of patients randomised is not provided in all flowcharts). At the request of the ERG, the sponsor provided some of the missing data (Addendum to MS) (eg. reasons for withdrawals between randomisation stage and treatment stage, numbers analysed for efficacy and safety endpoints, and numbers excluded from analysis with reasons). However, these data were not reported in the form of a CONSORT flowchart, as requested, and numbers for all sub-groups were reported, rather than only the primary efficacy and safety endpoints, as required. Not all of the reported endpoints were defined in the additional material.

The MS states that no clinically relevant differences were observed across treatment groups. However, this was not apparent in the MS. At the request of the ERG (Addendum to MS), the sponsor reported the baseline demographic and clinical characteristics of each study group in each trial, and discussed similarities between groups in accordance with point 14 on the CONSORT checklist (http://www.consort-statement.org).

4.1.4 Details of any relevant studies that were not included in the submission?

The ERG performed searches using the manufacturer's strategy but without the study design filter, in order to increase the sensitivity of the search (including searching within research registers eg. http://www.clinicaltrials.gov). No more relevant trials were identified. The ERG is confident that all relevant studies were included in the MS and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported.

4.1.5 Description and critique of manufacturers approach to validity assessment

There is some confusion in the MS about included studies. The application of the stated inclusion criteria ultimately results in the identification of the three trials. However, the MS initially identifies four trials as satisfying the stated inclusion criteria, including the dose-response BISTRO II trial (p.27 MS)[6]. This is clearly contradictory. The BISTRO II trial is then rejected as it does not employ a relevant DBG dose. According to the MS, the criteria being applied therefore appear to differ at different stages in the study screening process. The application of the inclusion criteria makes

necessary the immediate exclusion of the BISTRO II trial, its inclusion, and later rejection after screening, confuses the reported study screening process.

At the request of the ERG, full details of the results of the search of the sponsor's in-house database were provided, in order to validate the searches performed. The searches were validated and the reasons provided for excluding studies were all justified.

The MS contained a flow diagram relating to the literature searches, conforming to the QUORUM statement flow diagram[7]. However, the process by which the recently completed, unpublished trial (p.30, MS) was identified is not reported, nor is the process by which data were extracted from the included studies, as required by the QUORUM checklist[7]. This may introduce bias into the results.

A completed table recording decisions regarding trial quality assessment was not in the MS. A completed validity assessment form for the three trials, provided at the request of the ERG, is reproduced in Table 5.

The critical appraisal of the trials conducted in the MS is based on the full details of the trials, as reported in the MS, rather than the published details. For example, data about efforts to protect blinding (eg. database lock) were not reported in the published papers. There are also three issues with the submitted critical appraisal.

Firstly, Table 5 states that each patient received "twice daily subcutaneous injections", but the published papers of the RE-NOVATE and RE-MODEL trials state that only a single daily subcutaneous injection was given[3,8].

Secondly, the dosing regimens described for the RE-NOVATE and RE-MODEL trials are not reported accurately. The published papers report the pre-operative dosing regimen for enoxaparin, as described, i.e. on the evening before surgery, but also state that "in some countries treatment was started post-operatively to reflect local practice". [3,8] It is not clear what percentage of the sample received a post-operative dose as the first dose, but the treatment regimen employed in the trials clearly, to some degree, does not, as suggested, completely reflect practice in England and Wales (i.e. pre-operative dose of enoxaparin).

Finally, the MS reports on efforts to ensure blinding, but does not report if any of these studies assessed the success of blinding, as required by point 11 on the

CONSORT checklist (http://www.consort-statement.org/). The assessment of the ERG is that they did not.

The MS correctly reports on the potential for confounding from venography for identifying DVT. However, none of the three trials monitors or controls for non-pharmacological techniques of prophylaxis such as graduated compression stockings (GCS). The two pivotal trials permit the background use of GCS by participants, but the use and duration of use of GCS are not reported for each trial. GCS are known to reduce the risk of DVT significantly when used as adjuvant therapy in conjunction with pharmacological means of prophylaxis, as demonstrated by sensitivity analyses published in a recent NCC-AC report on the prevention of DVT[9]. This limitation is not acknowledged in the MS. The apparent overall effect of the test therapies may therefore appear to be greater or worse than they actually are, because it is not clear whether there were differences between trial arms in terms of use of GCS, with possible implications for the margin of non-inferiority.

The MS states that the participants in the pivotal trials were similar to the UK population (see tables 46-48 in MS). The ERG notes that the mean age of the participants in the THR (RE-NOVATE) trial was 63.9 years compared to 68 years in the UK National Joint Registry Annual Report[10], and that the mean ages for the TKR trials (RE-MODEL and RE-MOBILIZE) were 67.7 and 66.1 years respectively compared to 70 years in the UK National Joint Registry Annual Report[10]. The trial populations were therefore slightly younger, and therefore may have possibly demonstrated greater efficacy of the intervention and comparator therapies in the trial population: sub-group analyses reported for the RE-MODEL, RE-NOVATE and RE-MOBILIZE trials all indicate that DBG is potentially more effective in younger patients (MS, Tables 22, 24 and 26). The MS did not report if there was a statistically significance difference between the mean age of the trial population and the likely population for THR and TKR in England and Wales.

Table 5. Validity assessment of completed trials included by the manufacturer

Trial aspect	RE-NOVATE	RE-MODEL	RE-MOBILIZE
How was allocation concealed?	Each phase-III trial had a double blind, double dummy design. Randomisation was blinded to both investigators and patients. 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. Prior to database lock, procedures were in place to ensure that individuals associated with the conduct of the studies 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 teams nor were they entered into the trial databases until after database lock.		
What randomisation technique was used?	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.		
Was a justification of the sample size provided?	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. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.	Depending on the assumed incidence rates, sample sizes were calculated to achieve 90% power to state non-inferiority with a margin of 9.2% difference for total VTE and all-cause mortality. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.	Depending on the assumed incidence rates, sample sizes were calculated to achieve 90% power to state non-inferiority with a margin of 9.2% difference for total VTE and all-cause mortality. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.
Was follow-up adequate?	Yes. Follow up to 3 months. Mean duration of study 94 days. Haematology & clinical chemistry tests performed at 2 & 3months with focus on LFTs.	Yes. Follow up for 3 months. Haematology & clinical chemistry tests performed at 3 months with focus on LFTs.	Yes. Patients were followed up for 12-14 weeks.
Were the individuals undertaking the	No. The independent VTE endpoint adjudication committees performed their work blinded to randomised treatment		

outcomes assessment aware of allocation	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.		
Was the design parallel-group or crossover?	Parallel	Parallel	Parallel
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?	Multinational. No UK centres. European, Australian & S African populations. Similar to recommended UK practice, refer to NICE clinical guideline (reference 1 of the main submission).	Multinational. No UK centres. European, Australian & S African populations. Similar to recommended UK practice, refer to NICE clinical guideline (reference 1 of the main submission).	No, conducted in North America (with the exception of three UK patients). 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.	Population similar to UK population based on UK census data (please refer to tables 46 to 48 and accompanying text in the main submission).	Population similar to UK population (please refer to tables 46 to 48 and accompanying text in the main submission).	Broadly similar, though with a higher proportion of black patients, and slightly older age group (please refer to tables 46 to 48 and accompanying text in the main submission).
What dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	DBG: 220mg or 150mg od, starting with a half dose 1-4 hours after surgery Enoxaparin: 40mg od, starting the day before surgery. Both are in line with UK SPCs.	DBG: 220mg or 150mg od, starting with a half dose 1-4 hours after surgery Enoxaparin: 40mg od, starting the day before surgery Both are in line with UK SPCs.	DBG: 220mg or 150 mg od, starting 6-12 hours after surgery This is the same dose as UK SPC, but initiation is outside marketing authorisation. Enoxaparin: 30mg bd, starting 12-24 hours after surgery. This is a higher dose and later initiation than the UK SPC (but complies with the American label). Duration was 12-15 days for both treatments, which is outside the UK

			SPCs.
Were the study groups comparable?	Yes. Demographic and surgical characteristics were similar across treatment groups within each study.		
Were the statistical analyses used appropriate?	Yes. The endpoints considered and the non-inferiority design complies with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission).		
Was an intention-to-treat analysis undertaken?	The primary analysis was based on the Full Analysis Set (FAS) that was comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, and had an evaluable venogram or confirmed symptomatic DVT, PE, or death. This set is regarded as a modified intention to treat population in this type of study.		
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	The inclusion criteria were selected to allow entry of a representative yet homogeneous sample of patients undergoing primary elective total hip or knee replacement surgery. The exclusion criteria prevented entry of patients with significant co-morbidities or those whose participation might have represented a health risk for the patient. There is debate around the use of venographically confirmed VTE as the primary endpoint. It can be argued that symptomatic VTE and VTE-related mortality is a more clinically relevant outcome. However the problems associated with the use of this endpoint are well documented (i.e. the rarity of the event) and the primary endpoint adheres with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission).	The inclusion criteria were selected to allow entry of a representative yet homogeneous sample of patients undergoing primary elective total knee replacement surgery. The exclusion criteria prevented entry of patients with significant co-morbidities or those whose participation might have represented a health risk for the patient. There is debate around the use of venographically confirmed VTE as the primary endpoint. It can be argued that symptomatic VTE and VTE-related mortality is a more clinically relevant outcome. However the problems associated with the use of this endpoint are well documented (i.e. the rarity of the event) and the primary endpoint adheres with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission).

		As discussed, the dosing regimens, points of initiation and treatment durations in this study confound the results with respect to the UK setting.

DBG, dabigatran etexilate; DVT, deep vein thrombosis; LFT, liver function test; PE, pulmonary embolism; PK/PD, pharmacokinetic/pharmacodynamic; od, once daily dosing; SPC, summary of product characteristics; VTE, venous thromboembolism.

The validity assessment tool used in the MS is not referenced and the questions are not entirely adequate. The trials included were all non-inferiority trials, and an appropriate validity assessment tool is available for assessing the quality of such trials, see Table 6[2]. The tool used in the MS appears to be appropriate for assessing superiority trials only.

The RE-MOBILIZE trial is currently published only as an abstract (the manufacturer has recently indicated that the full paper is to be published soon: Addendum to MS). The trial's details and full results are those reported in the MS, rather than an independently peer-reviewed paper. The validity assessment of the RE-MOBILIZE trial performed by the ERG is therefore based on the trial as it is reported in the MS. However, the validity assessment of the RE-NOVATE and RE-MODEL trials reported by the ERG is based on the published papers. The results of the validity assessment of the ERG are reported in Table 7 (the item numbers correspond to the item numbers and questions outlined in Table 6).

Table 6: Validity assessment tool for non-inferiority studies

Paper Section and Topic	Item Number	Descriptor (Adapted for Noninferiority or Equivalence Trials)
Title and abstract	1*	How participants were allocated to interventions (eg, "random allocation," "randomized,"or "randomly assigned"), *specifying that the trial is a noninferiority or equivalence trial.*
Introduction Background	2*	Scientific background and explanation of rationale, *including the rationale for using a noninferiority or equivalence design*
Methods Participants	3*	Eligibility criteria for participants *(detailing whether participants in the noninferiority or equivalence trial are similar to those in any trial[s] that established efficacy of the reference treatment)* and the settings and locations where the data were collected.
Interventions	4*	Precise details of the interventions intended for each group, *detailing whether the reference treatment in the noninferiority or equivalence trial is identical (or very similar)to that in any trial(s) that established efficacy,* and how and when they were actually administered.
Objectives	5*	Specific objectives and hypotheses, *including the hypothesis concerning noninferiority orequivalence.*
Outcomes	6*	Clearly defined primary and secondary outcome measures, *detailing whether the outcomes in the noninferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).
Sample size	7*	How sample size was determined, *detailing whether it was calculated using a noninferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.* When applicable, explanation of any interim analyses and stopping rules *(and whether related to a noninferiority or equivalence hypothesis)*.
Randomization Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.
Statistical methods	12*	Statistical methods used to compare groups for primary outcome(s), *specifying whether a 1- or 2-sided confidence interval approach was used*. Methods for additional analyses, such as subgroup analyses and adjusted analyses.
Results Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the trial protocol, and analyzed for the primary outcome. Describe protocol deviations from trial as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.
Baseline data	15	Baseline demographic and clinical characteristics of each group.
Numbers analyzed	16*	Number of participants (denominator) in each group included in each analysis and whether *"intention-to-treat" and/or alternative analyses were conducted*. State the results in absolute numbers when feasible (eg, 10/20, not 50%).
Outcomes and estimation	17*	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% confidence interval). *For the outcome(s) for which noninferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.*
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.
Adverse events	19	All important adverse events or side effects in each intervention group.
Comment Interpretation	20*	Interpretation of the results, taking into account the *noninferiority or equivalence hypothesis and any other* trial hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.
Generalizability	21	Generalizability (external validity) of the trial findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

* and *italics* denote expansion on corresponding item on CONSORT checklist (http://www.consort-statement.org)

Table 7: Validity assessment of included studies

Item	RE-NOVATE	RE-MODEL	RE-MOBILIZE*
1	Yes, reported	As RE-NOVATE	As RE-NOVATE
2	Background reported, but rationale for non-inferiority design not given	As RE-NOVATE	As RE-NOVATE
3	Eligibility criteria and data collection reported; similarity of participants to those in the trial that established efficacy of the reference treatment is not reported	As RE-NOVATE	As RE-NOVATE
4	Yes details of intervention given; however dose of reference treatment in trial that established efficacy, not reported	As RE-NOVATE	As RE-NOVATE
5	Yes, reported	As RE-NOVATE	As RE-NOVATE
6	Outcomes, measures and their validation reported, but no detail on whether outcomes and measures are the same as those used in the trial that established efficacy of the reference treatment	As RE-NOVATE	As RE-NOVATE
7	Yes, done (see Table 5)	As RE-NOVATE	As RE-NOVATE
8	Yes, reported (see Table 5)	As RE-NOVATE	As RE-NOVATE
9	Not reported	As RE-NOVATE	As RE-NOVATE
10	Computer-generated sequence (see Table 5)	As RE-NOVATE	As RE-NOVATE
11	Participants and outcome assessors blinded. Blinding not evaluated.	As RE-NOVATE	As RE-NOVATE
12	Yes. 2-sided Confidence Intervals used. No sub-group analysis.	As RE-NOVATE. Pre-specified subgroup analyses cited but data not reported	As RE-NOVATE. Subgroup analyses described and reported.
13	Yes, reported in full. However, the numbers of patients reported in the flow diagram randomised to the 3 patient groups do not all add-up to the total number of	As RE-NOVATE, except the numbers are correct.	The diagram provided is not in complete accordance with the CONSORT flowchart (eg.

	patients randomised. The numbers are otherwise consistent.		numbers analysed for primary efficacy outcome are not given)
14	Not reported	As RE-NOVATE	As RE-NOVATE
15	Yes, reported in full.	As RE-NOVATE	As RE-NOVATE
16	Yes. Full Analysis Set (FAS) reported**	As RE-NOVATE	As RE-NOVATE
17	Yes, reported	As RE-NOVATE	As RE-NOVATE
18	None reported	As RE-NOVATE	As RE-NOVATE
19	Yes, reported	As RE-NOVATE	As RE-NOVATE
20	Yes, reported, but possible confounding by co-interventions (eg. ECS) not considered.	As RE-NOVATE	As RE-NOVATE
21	Good, but with limits. Although regimens generally reflect those to be used (DBG), or being used in the UK (for enoxaparin), the timing by which the reference treatment (enoxaparin) was delivered was sometimes different from that used in the UK (i.e. pre-operatively). The number of participants receiving either pre-operative or post-operative dose is unknown / not reported.	As RE-NOVATE	As RE-NOVATE
22	Good evidence of non-inferiority of DBG to enoxaparin in THR surgery, with potentially good external validity to UK, but there are limitations in the published reporting of this type of trial.	As RE-NOVATE, but for TKR	Evidence of inferiority of DBG to enoxaparin in TKR surgery, with limited external validity to UK. There are also limitations in the reporting of this type of trial in the MS.

* The appraisal of the RE-MOBILIZE trial was based on the published abstract and the data reported in the MS
** For the definition of a Full Analysis Set[11]

The overall methodological quality of the included trials was good, but a more appropriate validity assessment tool was available and could have been used in the MS.[2] The relevant extension of the CONSORT statement regarding the reporting of non-inferiority trials was available both at the time of the publication of the RE-NOVATE and RE-MODEL trials and for validity assessment of the trials included in the MS.

The additional issues raised by assessing the trials with this tool principally relate to both the reporting of the trials and whether the participants, interventions and outcomes in those trials used to establish efficacy of the reference treatment (i.e. enoxaparin), and the non-inferiority margins calculated, were indeed the same as or similar to those used in the non-inferiority trials themselves (RE-NOVATE, RE-MODEL and RE-MOBILIZE).

The participants in the RE-NOVATE and reference treatment trials[12,13,14] were generally similar, although there were some differences: to be eligible, the participants in one reference treatment trial were heavier (45kg and above vs 40kg and above),[14] and in two trials all wore Graduated Compression Stockings (GCS),[13,14] a mechanical prophylaxis of known efficacy[9], where-as the wearing of GCS was optional in the RE-NOVATE trial.

The reference treatment was not identical between the trials used to establish efficacy and the RE-NOVATE trial. The reference treatment dose and regimen was generally the same, but one trial employed the 30mg b.i.d. dose,[12] and there were no trials of the reference treatment *versus* placebo for a duration similar to the RE-NOVATE trial (28-35 days), so trials with a treatment duration of 8-14 days were used. Also, the timing of the first dose of the reference treatment was different (it was administered post-operatively in two trials,[12,14] and pre-operatively in another[13]. In the RE-NOVATE trial most, but not all patients appear to have received enoxaparin post-operatively. The outcomes and measures used by the trials were all similar, although the reference treatment trials measured DVT and PE as efficacy outcomes (rather than total VTE, which includes DVT and PE), and did not measure any mortality outcomes.

The RE-MODEL trial cites a TKR reference treatment trial used to calculate the non-inferiority margin[15], but this information is not given for the RE-MOBILIZE trial. It is assumed that RE-MOBILIZE employed the same reference trial (the non-inferiority

margin is the same), but this is not made clear in the MS. The participants and surgery in the RE-MODEL and RE-MOBILIZE and reference treatment trials appear to be similar. The reference treatment was identical between the trial used to establish efficacy and the RE-MOBILIZE trial (30mg b.i.d post-operatively), but differed from the RE-MODEL trial (40mg o.d.). The duration of treatment was also more similar between the RE-MOBILIZE trial and the reference trial (12-15 days and 14 days respectively), but different from the RE-MODEL trial (6-10 days). These similarities are most likely due to the fact that both trials were performed in North America. The RE-MODEL and RE-MOBILIZE trials permitted the use of GCS, where-as the patients in the reference trial were not permitted to receive any other form of venous thrombosis prophylaxis. The outcomes and measures used by these TKR trials were all similar, although the reference treatment trial measured DVT as the efficacy outcome (rather than total VTE, which includes DVT), and did not measure any mortality outcome.

The non-inferiority trials of DBG were therefore not identical to the trials used to establish the efficacy of the reference treatment, enoxaparin, and the resulting non-inferiority margin, but there were similarities between these trials, especially in terms of population, elements of the dose and regimen, and certain outcomes.

4.1.6 Description and critique of manufacturers outcome selection

The main outcome measures selected by the manufacturer are summarised in Table 8.

Table 8: Manufacturer's main outcome selection

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
Safety	Major Bleeding Events (MBE) MBE and clinically-relevant bleeding events Clinically-relevant bleeding events Any bleeding events (major, clinically-relevant, and minor) Volume of blood loss Number and type of blood transfusions Incidence of adverse events Incidence of discontinuations due to adverse events Laboratory measures, especially changes in liver function tests Results of physical examinations

***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. Debates around the appropriateness of the endpoints used were acknowledged (pp.47-48, MS) although no references were provided to substantiate the range of views in the debate. The efficacy endpoints is composite, including both mortality and venous thromboembolic events, because rates of mortality are so low that very large studies would be required, if they were to have sufficient power to measure mortality as an outcome. The studies are therefore led by the outcome of venous thromboembolic events. Although the MS does not consider all of the outcomes recommended by the NICE scope, the ERG considers the manufacturer's outcome selection (a further critique on the appropriateness of these outcomes is discussed in section 3.4.) to be relevant and appropriate.

4.1.7 Describe and critique the statistical approach used

The MS contained a series of meta-analyses. It reported relative risks (RR) for fixed effects models of the 2 pivotal trials combined (RE-NOVATE and RE-MOBILIZE) and all three trials combined, and a random effects model for all three trials combined. At the request of the ERG, the manufacturer also provided a random effects model meta-analysis of the 2 pivotal trials combined. At the request of the ERG, the manufacturer also provided risk differences (RD; absolute risk reductions) in both fixed and random effects models for the two pivotal trials, and all three trials combined, as required in the MS.

At the request of the ERG, the manufacturer also provided fixed and random effects models for both RR and RD for the two TKR trials combined (RE-MODEL and RE-MOBILIZE). For the results of these meta-analyses, see section 4.2.2.

The ERG accepts that the dosing regimen and treatment duration employed in the North American RE-MOBILIZE TKR trial is slightly different from that used in England and Wales, but requested meta-analysis of the two TKR trials combined (RE-MODEL and RE-MOBILIZE) in order to inform the decision-making process. This was requested for three reasons: 1) As the population in these two TKR trials was the same, the risk of VTE and the treatment duration were comparable or similar, whereas the baseline risk varies between hip and knee surgery; 2) in the absence of additional relevant RCTs the effectiveness data was otherwise based only on a single pivotal trial for each population (THR and TKR), so it made sense to utilise data from a second, supporting TKR trial of the treatment and comparator drugs, albeit a trial with more limited external validity to England and Wales; 3) the timing of the first dose of the comparator in the TKR trial conducted in Europe, Australia and South Africa (RE-MODEL) did not comply completely with UK practice (i.e. in an unknown number of cases, the first dose was given post-operatively, rather than pre-operatively, therefore commensurate with North American rather than UK practice), so the two trials were arguably not quite as different as they otherwise appeared, and as argued in the MS.

A pooled analysis of RD for the two pivotal trials was reported in the MS (pp.78-80). The rationale for presenting and pooling individual patient data was not reported. The analyses themselves appear to have been reproduced from a source external to the MS and were only performed on the secondary efficacy outcome (no explanation for this was given). The statistical methods of pooling were not made explicit in the MS.

Sensitivity analyses presenting best and worst case scenarios were also performed, imputing no events for missing trial data, or an event for each piece of missing data, respectively, as well as a pooled analysis of all three trials using a fixed effects model only (p.80, MS). The rationale for pooling the 3 trials in this way, with a fixed effects model only, was not given. In a worst case scenario for the RE-MOBILIZE trial, there was a significant difference between the 220mg dose of DBG and the 30mg b.i.d dose of enoxaparin (95% Confidence Interval did not cross 1, indicating significance), and the upper level of the 95% Confidence Interval (1.4-9.8) exceeded the non-inferiority margin of 9.2% established for this trial (p.57, MS). Neither the related p value nor the exceeding of the non-inferiority margin was explicitly reported for this worst case scenario.

The ERG also notes that the pooling of data is viewed as inadequate for the assessment of efficacy. A pooled analysis focuses on treatment groups rather than on studies, ignores validity of the comparisons and is subject to bias termed 'Simpson's paradox in probability.[16,17] A more satisfactory statistical technique for combining the results from two or more separate studies is meta-analysis.[16,18,17] All efficacy and safety meta-analyses requested by the ERG were provided by the manufacturer.

4.1.8 Summary statement

The manufacturer's search strategy was adequately reported but limited, although the submission appears to contain all of the relevant head-head RCTs. Processes and validation of study screening and data extraction were not reported in full, and the validity assessment tool used was not entirely appropriate or adequate, although the application of a more appropriate tool did not greatly alter judgments on the overall quality of the included trials. The outcomes selected were relevant and appropriate. Statistical methods were explicitly described for the meta-analyses and all required meta-analyses were performed. Pooled analyses were also reported, although they were not described fully and may be inappropriate.

4.2 Summary of submitted evidence

Two pivotal trials (RE-NOVATE and RE-MODEL) and one supporting trial (RE-MOBILIZE) were identified in the effectiveness section of the MS. The RE-NOVATE study (n=3613) was a phase III, three-arm, randomised, double-blind, multi-centre, non-inferiority trial comparing the efficacy and safety of DBG (220mg and 150mg o.d) with enoxaparin (40mg o.d.) in patients undergoing elective THR. Duration of

treatment was 28-35 days. The RE-MODEL trial (n=2183) was a phase III, three-arm, randomised, double-blind, multi-centre, non-inferiority trial comparing the efficacy and safety of DBG (220mg and 150mg o.d) with enoxaparin (40mg o.d.) in patients undergoing elective TKR. Duration of treatment was 6-10 days. The supporting RE-MOBILIZE trial (n=3016) was a phase III, three-arm, randomised, double-blind, multi-centre, non-inferiority trial comparing the efficacy and safety of DBG (220mg and 150mg o.d) with enoxaparin (30mg b.i.d.) in patients undergoing elective TKR. Duration of treatment was 12-15 days. All trials had a follow-up of 12-14 weeks.

It should be noted that the participants who received the two doses of DBG (220mg o.d. and 150mg o.d.) in all three included trials were identical in terms of baseline characteristics (i.e. participants were randomised to treatment arm regardless of age or degree of renal impairment; it is not the case that the 150mg o.d. dose was reserved only for the special populations listed in the licence).

4.2.1 Summary of results

This section presents the main clinical efficacy evidence, as reported in the MS. Some of these analyses, however, were not produced for the MS, but rather appear to have been generated for other reports produced by third parties. This is the case with the MTC. The full details of the MTC and its included trials were not reported in the MS.

Efficacy

This section presents the main clinical efficacy evidence. In the MS, it is difficult to compare the results of the analyses directly as the results of the trials were tabulated separately, rather than together (as requested). A full tabulated summary of the data provided in the MS, and constructed by the ERG, is presented in Table 9.

The MS reported that in the two pivotal trials, RE-NOVATE (THR) and RE-MODEL (TKR), both DBG doses demonstrated non-inferiority to enoxaparin (40 mg o.d.) in terms of the primary endpoint, with confidence intervals falling within pre-defined non-inferiority margins. However, in the supporting TKR RE-MOBILIZE trial, the rate of total-VTE and all-cause mortality favoured the comparator, enoxaparin. DBG was therefore found to be inferior to enoxaparin in terms of the primary efficacy outcome in this trial.

Post-hoc sub-group analyses indicated that age was a possible predictor of higher incidence of total VTE and all-cause mortality in all trials, and there was a trend

towards a higher incidence of total VTE and all-cause mortality among those patients with higher Body Mass Index in the two TKR trials (RE-MODEL and RE-MOBILIZE) (MS, Tables 22, 24 and 26).

Table 9: Summary of the primary efficacy endpoint results

	Full analysis set N	Total VTE and all-cause mortality n(%)	Risk difference *versus* enoxaparin	95% CI (%)	p value	Relative risk *versus* enoxaparin	95% CI (%)	p value
RE-NOVATE								
DBG 220mg	880	NR (6)	-0.7	(-2.9, 1.6)	0.5648	0.9	(0.63, 1.29)	NR
DBG 150mg	874	NR (8.6)	1.9	(-0.6, 4.4)	0.1339	1.28	(0.93, 1.78)	NR
Enoxaparin	897	NR (6.7)						
RE-MODEL								
DBG 220mg	503	NR (36.4)	-1.3	(-7.3, 4.6)	0.6648	0.97	(0.82, 1.13)	NR
DBG 150mg	526	NR (40.5)	2.8	(-3.1, 8.7)	0.3553	1.07	(0.92, 1.25)	NR
Enoxaparin	512	NR (37.7)						
RE-MOBILIZE								
DBG 220mg	604	NR (33.1)	5.8	(0.8, 10.8)*	0.0234	1.23	(1.03, 1.47)	NR
DBG 150mg	649	NR (33.7)	8.4	(3.4, 13.3)*	0.0009	1.33	(1.12, 1.58)	NR
Enoxaparin	643	NR (25.3)						

*** Upper CI limit exceeds the non-inferiority margin of 9.2%**

CI, confidence interval; DBG, dabigatran etexilate; VTE, venous thromboembolism; NR, not reported.

Critique of efficacy data reported

There are a number of issues with the efficacy data reported in the MS. Median time of follow-up is not given, as required. Numbers of patients experiencing an event are not given, as required, only percentages. Only risk differences (RD) are accompanied by p values; these are not given for relative risk. Sub-group analyses were exploratory and apparently supported by univariate and multivariate logistic regression analyses, but with the exception of the results relating to age in the RE-NOVATE trial, the results of these analyses (and accompanying p values) are not given. Consequently, only "trends" based on incidence are reported.

The post-hoc sub-group analyses do not consistently (Tables 22, 24 and 26 of MS) support the licensing indication of the 150mg o.d. dose for the indicated special populations of the elderly (≥75 years) and those with moderately impaired renal function. In the RE-NOVATE (THR) trial only, the 150mg o.d. dose of DBG does appear to be potentially more effective for people aged 75 years or more than for those aged less than 75 years (Table 22, MS: 5.3% *versus* 9.3% [65-75 years] and 8.9% [<65 years]). However, this difference is not apparent for those aged 70 years or more in this trial (8% [≥70 years] *versus* 8.8% [<70 years]).

It is also not clear whether there is a significant difference in this trial for the primary efficacy outcome between the 220mg and 150mg dose (i.e. that the 150mg dose is better-suited to the elderly, aged 75 years or older). This comparison is not reported. However, it is apparent from this THR trial that in the other special population group, those with a creatinine clearance of 30-50 mL/min, the sample receiving the 150mg o.d. dose have a much higher incidence of total-VTE and all-cause mortality (9.8%) than those receiving the 220mg o.d. dose (3.8%) (p value not given) (Table 22, MS). This suggests that this lower dose is less efficacious than the higher 220mg o.d. dose in this population (who are licensed to receive the lower dose of 150mg o.d.).

In the TKR trials (MS, Tables 24 and 26), the subgroup analyses appear to show that the 220mg o.d. dose produces a lower incidence of total VTE and all-cause mortality than the 150mg o.d. in those over 75 years of age: 35.6% versus 41.3% (RE-MODEL) and 37% *versus* 39% (RE-MOBILIZE), and with no difference or a potentially significant difference in those with a creatinine clearance of 30-50 mL/min: 44.4% *versus* 44.4% (RE-MODEL) and 17.3% *versus* 32.3% (RE-MOBILIZE). These data suggest that caution should be exercised regarding efficacy of the licensed 150mg o.d. dose for the special populations. No safety outcomes were reported for

the sub-groups to determine whether significantly better bleeding outcomes might be reported for these special populations receiving the lower 150mg o.d. dose.

The secondary endpoints reported in the results section (pp.68-69, MS) do not correspond with the secondary endpoints as defined earlier in the MS (pp.47 and 55), but rather are only the individual components of the primary efficacy outcome. Finally, it must be remembered that the sample size and inferiority margin calculations were derived for the primary efficacy outcome only.

Safety and tolerability

The MS reports safety data from all three trials. In the MS, it is difficult to compare the results of the analyses directly as the results of the trials were tabulated separately, rather than together (as requested). A full tabulated summary of the data provided in the MS, constructed by the ERG, is presented in Table 10. The rates of major bleeding, and of major and clinically relevant bleeding combined, as reported in the MS, were comparable between treatment groups in all three trials. The majority of major bleeding events in the three trials occurred at the surgical site. Although the incidence of bleeding events appears higher for enoxaparin than DBG in the RE-MOBILIZE trial, the MS states that no statistically significant difference between the DBG groups and the enoxaparin group was detected (p value not given). The rates of any bleeding observed for the DBG 220mg, DBG 150mg, and enoxaparin 40mg doses in RE-MODEL (16.2%, 16.5% and 16.6% respectively) were approximately twice as high as those seen in RE-MOBILIZE (8.6%, 8.3% and 9.7%). The MS suggests that this may be due to the fact that randomisation 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.

The amount of blood loss during surgery was similar for DBG and enoxaparin in all trials, as was the number of patients who received transfusions. In all three trials the incidence of hepatotoxicity for DBG is similar to that seen with enoxaparin. The MS also reported data on cardiac events and discontinuation due to adverse events: the most frequent reasons for discontinuation was the occurrence of gastrointestinal disorders (RE-NOVATE and RE-MOBILIZE), cardiac events (RE-MODEL and RE-MOBILIZE), general disorders and administration site conditions (RE-NOVATE). There were no cases that met the criteria for severe hepatotoxicity.

Table 10: Summary of the primary safety endpoint results

	N	Major bleeding n(%)	Major bleeding, plus clinically relevant bleeding n(%)	Absolute difference *versus* enoxaparin	95% CI (%)	p value	Any bleeding n(%)	Absolute difference *versus* enoxaparin	95% CI (%)	p value
RE-NOVATE										
DBG 220mg	1,146	23 (2.0)	71 (6.2)	1.2	(-0.7, 3.1)	NR	141 (12.3)	0.9	(-1.8, 3.5)	NR
DBG 150mg	1,163	15 (1.3)	70 (6.0)	1.0	(-0.9, 2.9)	NR	142 (12.2)	0.8	(-1.9, 3.4)	NR
Enoxaparin	1,154	18 (1.6)	58 (5.0)				142 (12.2)			
RE-MODEL										
DBG 220mg	679	NR (1.5)	NR (7.4)	0.7	(-2.0, 3.4)	NR	NR (16.2)	-0.4	(-4.3, 3.5)	NR
DBG 150mg	703	NR (1.3)	NR (8.1)	1.5	(-1.3, 4.2)	NR	NR (16.5)	-0.1	(-4.0, 3.8)	NR
Enoxaparin	694	NR (1.3)	NR (6.6)				NR (16.6)			
RE-MOBILIZE										
DBG 220mg	857	5 (0.6)	28 (3.3)	-0.5	(-2.3, 1.2)	NR	74 (8.6)	-1.0	(-3.8, 1.7)	NR
DBG 150mg	871	5 (0.6)	27 (3.1)	-0.7	(-2.4, 1.0)	NR	72 (8.3)	-1.4	(-4.1, 1.3)	NR
Enoxaparin	868	12 (1.4)	33 (3.8)				84 (9.7)			

CI, confidence interval; DBG, dabigatran etexilate; VTE, venous thromboembolism; NR, not reported.

Critique of safety data reported

The reporting and interpretation of the safety and tolerability data is good. However, the MS consistently failed to report numbers of patients with events, rather than simply percentages (RE-MODEL), and also failed to report p values, especially for comparisons where the data do indicate a relationship that is close to being statistically significant (eg. the DBG 150mg dose in the RE-MOBILIZE trial). Also, not all adverse events are reported. The ERG appreciates that the major adverse events are reported (eg. bleeding, cardiac events and hepatic safety), but all reported adverse events are required. These are tabulated below by the ERG (Table 11. Note: only the RE-NOVATE trial reported other adverse events). No definition of serious adverse events was given in the RE-NOVATE study.

Table 11: Adverse events n (%) (RE-NOVATE trial only)

	DBG 220mg o.d. (n=1146)	DBG 150mg o.d. (n=1163)	Enoxaparin 40mg o.d. (n=1154)
Adverse events during treatment			
Serious adverse events	89 (8)	91 (8)	82 (7)
Total with adverse events	879 (77)	895 (77)	892 (77)
Adverse events leading to treatment discontinuation	74 (6)	88 (8)	66 (6)
Adverse events during treatment with an incidence of ≥3% or a difference of ten or more events between any treatment group			
Nausea	238 (21)	258 (22)	289 (25)
Vomiting	194 (17)	186 (16)	191 (17)
Constipation	146 (13)	141 (12)	150 (13)
Pyrexia	123 (11)	142 (12)	162 (14)
Wound secretion	102 (9)	96 (8)	63 (5)
Hypotension	81 (7)	77 (7)	83 (7)
Insomnia	77 (7)	88 (7)	80 (7)
Peripheral oedema	65 (6)	81 (7)	56 (5)
Anaemia	47 (4)	39 (3)	44 (4)
Dizziness	38 (3)	38 (3)	49 (4)
Wound complication	40 (3)	37 (3)	47 (4)
Deep Vein Thrombosis	33 (3)	55 (5)	36 (3)
Diarrhoea	30 (3)	49 (4)	36 (3)
Blister	40 (3.5)	43 (4)	30 (3)
Headache	37 (3)	37 (3)	39 (3)
Urinary retention	25 (2)	25 (2)	35 (3)
Post-procedural haematoma	17 (1)	34 (3)	26 (2)
Dyspepsia	22 (2)	12 (1)	17 (1)
Tachycardia	9 (0.8)	15 (1)	5 (0.4)
Dysuria	4 (0.3)	8 (0.7)	14 (1)
Haemorrhage	12 (1)	2 (0.2)	11 (1)

4.2.2 Critique of submitted evidence syntheses

Meta-analysis

The MS reported the following meta-analyses for both the primary and secondary efficacy outcomes: fixed effects models of relative risks (RR) for the two pivotal trials combined (RE-NOVATE and RE-MOBILIZE) and for all three trials combined, and a random effects model for all three trials combined. At the request of the ERG, the sponsors also provided a random effects model meta-analysis of the two pivotal trials combined, as required, as well as risk differences (RD; absolute risk reductions) in both fixed and random effects models for the two pivotal trials, and for all three trials combined, as required in the outline of section 5.5 in the MS (Addendum to MS).

The MS therefore failed to provide all of the required meta-analyses. The reported meta-analyses also labelled the trials by trial number, rather than trial name. Consistency in the reporting of trials by name or number is required in the MS. The ERG has therefore tabulated the results using the appropriate trial names in Tables 12 and 13 below.

At the request of the ERG, the sponsor also provided fixed and random effects models for both RR and RD for the two TKR trials combined (RE-MODEL and RE-MOBILIZE) for the primary and secondary efficacy outcomes. For the reasons behind the request for these additional analyses, see Section 4.1.7 above. For the results of all of the efficacy outcome meta-analyses, see Tables 12 and 13 (pp. 49-50) below.

The MS (pp.78-79) also presents a pooled analysis of data from the RE-MODEL and RE-NOVATE trials and treats them as one large study. The data are presented in a different format (STATA) from that used in previous analyses (Review Manager) and the analysis appears to be reproduced from another source, rather than being produced for the purposes of the MS, in accordance with the agreed scope. Also, the reference provided in the MS for the source of this analysis is incorrect (p.79, MS). The pooled analysis also labels the trials by trial number, rather than trial name. The analysis is neither described nor explained in the MS (eg. whether the data were appropriate for pooling, especially given that the analysis pools data from both hip and knee trials). The MS reports a pooled analysis for risk difference only, for both the 220mg and 150mg doses of DBG, using the fixed effects model only (reported in Addendum to MS, but not reported in MS), and for the secondary efficacy endpoint only. There is no explanation in the MS why only the secondary efficacy endpoint is

analysed, but the manufacturer has subsequently argued that the secondary efficacy outcome is more relevant than the primary efficacy outcome because numbers of events are much less rare for the former (Addendum to MS).

Sensitivity analyses presenting best and worse case scenarios, including pooling of data from all 3 trials using a fixed effects model only, have also been presented (p.80, MS), but no description of the rationale or details behind the analyses has been given, other than the best case scenario imputing no events for missing trial data, and the worse case scenario imputing an event for each missing piece of data. It is not clear whether the analyses relate to the primary or secondary efficacy outcome. The comment in the MS on these analyses is limited to the statement (p.80) that, "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". However, it is clear that there is a significant difference between DBG 220mg and enoxaparin in the worst case scenario for the RE-MOBILIZE trial (95% CI 1.4, 9.8; p value not given).

As noted in section 4.1.7, the ERG considers this type of data pooling to be inappropriate as it fails to preserve randomisation and introduces bias and confounding. The pooled analyses as presented in the MS also have a range of limitations and so should be treated with caution. A more satisfactory statistical technique involves combining the results from two or more separate studies in a meta-analysis. The results of such meta-analyses in the form of relative and absolute risk reductions (risk difference) using the both the fixed and random effects models were subsequently all provided by the manufacturer, following a request from the ERG (see Tables 12 and 13).

It is the conclusion of the MS that, for DBG 220mg, the meta-analyses support the conclusion of non-inferiority in terms of both the primary and secondary efficacy outcomes. In the DBG 150mg comparisons, however, only the meta-analysis of the pivotal RE-NOVATE and RE-MODEL trials supports the conclusion of non-inferiority. The inclusion of the supporting RE-MOBILIZE trial causes the pooled estimate to favour the comparator, enoxaparin, in terms of the primary efficacy outcome (there is no difference between DBG 150mg and enoxaparin in terms of the secondary efficacy outcome in any of the analyses). The 150mg dose of DBG is therefore inferior to the comparator enoxaparin for the primary efficacy outcome in many of the

analyses that include the supporting RE-MOBILIZE trial (i.e. in analyses combining all three trials, as well as those that combine the two TKR trials only (for relative risk fixed effects model only, and risk difference, both fixed and random effects models).

Table 12. Meta-analysis of primary efficacy endpoint for DBG versus enoxaparin (40mg o.d. or 30mg b.i.d)

Trials (and dose)	Relative risk (fixed effects, 95% CI)	Relative risk (random effects, 95% CI)	Risk difference (fixed effects, 95% CI)	Risk difference (random effects, 95% CI)
220mg o.d. DBG				
RE-NOVATE and RE-MODEL	0.95 (0.82, 1.10)	0.95 (0.82, 1.10)	-0.01 (-0.03, 0.02)	-0.01 (-0.03, 0.01)
RE-MODEL and RE-MOBILIZE	1.08 (0.96, 1.22)	1.09 (0.86, 1.37)	0.03 (-0.01-0.06)	0.02 (-0.05, 0.09)
RE-NOVATE, RE-MODEL and RE-MOBILIZE	1.06 (0.94, 1.18)	1.05 (0.87, 1.26)	0.01 (-0.01, 0.04)	0.01 (-0.03, 0.06)
150mg o.d. DBG				
RE-NOVATE and RE-MODEL	1.12 (0.98, 1.29)	1.11 (0.97, 1.27)	0.02 (0.00, 0.05)	0.02 (0.00, 0.04)
RE-MODEL and RE-MOBILIZE	1.19 (1.06, 1.33) †	1.08 (0.96, 1.22)	0.06 (0.02, 0.10) †	0.06 (0.00, 0.11)*
RE-NOVATE, RE-MODEL and RE-MOBILIZE	1.20 (1.08, 1.34) ‡	1.20 (1.03, 1.41)*	0.04 (0.02, 0.07) ‡	0.04 (0.00, 0.09)

*$p \leq 0.05$; † $p \leq 0.01$; ‡ $p \leq 0.001$
Note: RR>1 indicates that the results favour the comparator (enoxaparin)

Table 13. Meta-analysis of secondary efficacy endpoint for DBG versus enoxaparin (40mg o.d. or 30mg b.i.d)

Trials (and dose)	Relative risk (fixed effects, 95% CI)	Relative risk (random effects, 95% CI)	Risk difference (fixed effects, 95% CI)	Risk difference (random effects, 95% CI)
220mg o.d. DBG				
RE-NOVATE and RE-MODEL	0.7 (0.51-1.14)	0.77 (0.51-1.14)	-0.01 (-0.02, 0.00)	-0.01 (-0.02, 0.00)
RE-MODEL and RE-MOBILIZE	1.08 (0.67, 1.73)	0.60 (0.52, 2.17)	0.00 (-0.01-0.02)	0.00 (-0.02, 0.02)
RE-NOVATE, RE-MODEL and RE-MOBILIZE	0.92 (0.66-1.29)	0.94 (0.61-1.44)	0.00 (-0.01, 0.01)	0.00 (-0.02, 0.01)
150mg o.d. DBG				
RE-NOVATE and RE-MODEL	1.09 (0.76-1.56)	1.09 (0.76, 1.56)	0.00 (-0.01, 0.02)	0.00 (-0.01, 0.02)
RE-MODEL and RE-MOBILIZE	1.20 (0.76, 1.89)	1.20 (0.76, 1.89)	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.02)
RE-NOVATE, RE-MODEL and RE-MOBILIZE	1.14 (0.83-1.57)	1.14 (0.83-1.57)	0.00 (-0.01, 0.02)	0.01 (-0.01, 0.02)

Note: RR>1 indicates that the results favour the comparator (enoxaparin)

Indirect/ mixed treatment comparisons

The MS presented the results of a mixed treatment comparison (MTC) meta-analysis. A literature search was reported for meta-analyses describing the efficacy and safety of anti-thrombotic medication for the prevention of VTE associated with THR and TKR. The aim was to identify meta-analyses reporting the treatment effect of alternatives to DBG (p.81, MS). It is not clear why the search aimed to identify only meta-analyses, rather than individual trials. Also, some elements of the search are unclear. For example, the QUORUM diagram specifies that the Cochrane library and the Central Register of Controlled Trials was searched (p.83, MS), but it is not clear why the manufacturer would search a register of controlled trials for meta-analyses, or which other components of the Cochrane library were searched, especially as some are irrelevant (eg. Cochrane Methodology Register).

The search and study selection identified only a single relevant meta-analysis (detailed inclusion criteria for the study screening process were not given). Even though the MS acknowledges that LMWH and fondaparinux are "of primary importance in terms of this decision problem" (p.88), the results for all alternatives to DBG are reported in the MTC. This goes beyond the scope of the decision problem, as well as the actual inclusion criteria described by the MS for this section (i.e. anti-thrombotic medication only, p.81), as it includes elastic or graduated compression stockings (GCS), intermittent pneumatic compression (IPC) and foot pumps. Aspirin is also included, even though this therapy's lack of efficacy is stressed elsewhere in the MS (pp.14, 22, 23, 24). The manufacturer has subsequently stated that the MS was drafted with all countries and therapies in mind, rather than within the limits of the NICE scope only (Addendum to MS). However, the ERG does not understand why therapies not specified in the scope could not be removed from this section, especially as the results of the MTC for the alternative therapies appear to have been derived from a previously published NCC-AC report[9].

An MTC is presented comparing relative risks of DBG and all available alternatives *versus* nil for the following outcomes: DVT, major bleed, and minor bleed. The trials of the alternative therapies included in the MTC have not been summarised, as required for such a comparison, nor have any potential sources of heterogeneity between these trials and the RE-NOVATE, RE-MODEL and RE-MOBILIZE trials been highlighted or discussed, again, as required. For example, the trials used to generate the data on fondaparinux (assuming that the relative risk data used in the MTC are derived from the five trials cited in the clinical effectiveness section (6.6) of

the recent NCC-AC report[9] – although this is not made explicit) were undertaken on patients undergoing abdominal and hip fracture surgery,[19,20] as well as THR and TKR surgery Such potential sources of heterogeneity are neither assessed nor acknowledged in the MS. The manufacturer has subsequently argued that the MTC is based on the assumption that treatment effect is independent of both treatment duration and type of surgery, as these are the apparent assumptions made by those conducting the MTC as published in the NCC-AC report on VTE (Addendum to MS). The manufacturer has directed the ERG to the document from which the data are derived for all such details (Addendum to MS). The required data are therefore absent from the MS. In the absence of this information, it is not possible adequately to appraise this analysis.

For all trials other than RE-NOVATE, RE-MODEL and RE-MOBILIZE, the MTC for DVT and major bleed appears to be based on the MTC reported by the NCC-AC for these outcomes. The MS states that the MTC for minor bleed was performed for the MS, using data from relevant trials cited by the NCC-AC. However, the rationale for the type of MTC presented in the MS is not given, and the efficacy outcome (DVT) does not correspond to the primary or secondary efficacy outcomes reported previously in the MS. It is not clear if the results for the RE-NOVATE, RE-MODEL and RE-MOBILIZE trials have been revised to take account of DVT as the only outcome, in order to validate the comparison presented in the MTC, or if the primary efficacy outcome is an equivalent to the DVT outcome being measured for all trials in the MTC. The means by which the relative risks of DBG *versus* nil were calculated for the RE-NOVATE, RE-MODEL and RE-MOBILIZE trials are not described in this section of the MS, but rather are referenced briefly elsewhere (p.139, MS). The MTC also includes the results of pooled analyses of the RE-NOVATE, RE-MODEL and RE-MOBILIZE trials, which are arguably inappropriate as it involves the pooling of individual patient data from potentially heterogeneous trials (see Section 4.1.7 and 4.2.2 above). The results of this MTC must therefore be treated with caution.

The MTC presented in the MS reports that extended LMWH and fondaparinux perform best overall in terms of relative risk of DVT prevention, and that the extended regime of the RE-NOVATE trial compares favourably with these interventions (pp.89-90, MS). However, the RR of DVT presented by the results of the RE-MODEL and RE-MOBILIZE trials are less comparable with the most efficacious pharmacological treatments, and rather more comparable with the various forms of mechanical prophylaxis included in the analysis (eg. GCS, IPC and foot pumps). According to

this MTC, the risk of experiencing DVT is [redacted] less likely with fondaparinux compared to nil, and [redacted] (RE-NOVATE extended duration THR trial), [redacted] (RE-MODEL) and [redacted] (RE-MOBILIZE) less likely with the 220mg o.d. dose DBG compared to nil, and [redacted], [redacted] and [redacted] respectively with the 150mg o.d. dose DBG.

However, it is not possible to determine from this MTC whether fondaparinux is significantly more or less effective than, or no different from DBG. This would require an indirect comparison of the two treatments. Consequently, the comparative efficacy and safety of DBG and fondaparinux is not made very clear in the MS. However, fondaparinux is known to be more effective than LMWH[9], and the MS indicates that 220mg o.d. DBG is to be considered as non-inferior to LMWH, potentially suggesting a likely significant difference between fondaparinux and DBG in favour of fondaparinux.

In terms of bleeding, the MS reports that DBG compares favourably with alternative pharmacological treatments, but, given its characteristics as an anti-coagulant, understandably has higher relative risk of bleeding compared to mechanical prophylaxis or doing nothing. Fondaparinux, the most effective therapy in preventing DVT, appears to present the greatest risk for a major bleed (p.91, MS).

4.2.3 Summary

Overall the evidence from the two pivotal trials in the MS indicates that the 220mg o.d. dose of DBG is not inferior to the comparator enoxaparin, a LMWH, in terms of total VTE and all-cause mortality. LMWHs are the principal form of pharmacological anti-coagulant used in England in Wales. However, this is not the case for the supporting RE-MOBILIZE TKR trial, in which both the 220mg and 150mg o.d. doses are inferior to the comparator enoxaparin. The 220mg o.d. dose of DBG is not inferior to enoxaparin when combining both pivotal trials, and the supporting trial, in meta-analysis. However, there is greater uncertainty about the efficacy of the 150mg o.d. dose of DBG, which appears in meta-analysis to be inferior to enoxaparin in terms of the primary efficacy outcome of total VTE and all-cause mortality when the results of the RE-MOBILIZE trial are included in any analyses. Evidence from the sub-group analyses of the included trials also indicates that the 150mg o.d. dose may be less effective in terms of incidence of total VTE and all-cause mortality than the 220mg o.d. dose in the special populations indicated for this lower dose by the licence: the elderly (aged 75 years and older), and those with moderate renal impairment. Safety outcomes were not reported for these sub-groups.

Both doses of DBG are also likely to be less effective than the other named comparator in the scope, fondaparinux, although the MTC reported does not demonstrate this particularly clearly. However, both DBG doses were comparable to enoxaparin in terms of both the secondary efficacy outcome, major VTE and VTE-related death, and also the safety outcomes of major, clinically-relevant and minor bleeding. The intervention was also similar in terms of all other safety outcomes.

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

The economic evaluation model has two components:

- Short term acute phase. Two decision tree models run simultaneously. The first estimates expected costs and (Quality Adjusted Life Years Saved) QALYS associated with VTE events. In the second, patients experiencing adverse events are 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. The time horizon for these models is 10 weeks. Following the initial surgery, it is in this acute phase of the model where the patient is at most risk of VTE and where adverse events are most likely. The differential effects of treatment are only realised in this phase of the model. The ERG consider the structure of the short-term model to be appropriate. However, the ERG are unsure as to whether important correlations are lost by using two separate decision trees instead of one combined decision tree.
- Long-term chronic phase. A Markov model of disease progression is used to generate estimates of QALYs and costs over a 60 year time horizon. The proportion of patients in each starting health state is the proportion in these states at the end on the acute phase model. As stated above there is no differential treatment effect in this phase of the model. Movement between states is defined by VTE recurrence rates. These were obtained from literature reviews.

The health states in the long-term model are:

- Well
- Three asymptomatic untreated VTE states (proximal DVT, distal DVT and PE)
- Three treated VTE states for patients surviving after symptomatic: proximal DVT, distal DVT and PE
- Recurrent DVT or PE.
- Mild to moderate PTS (a distinction is made between year 1 and subsequent years)
- Severe PTS (a distinction is made between year 1 and subsequent years)
- Disabled due to intracranial bleed
- Death

The health states used within the model are considered to be appropriate for the required analysis. However, it should be noted that previously published models have included progression from distal to proximal DVT,[21] the impact of including this progression in the MS model is unknown.

The model structures and health states for both the short-term and long-term models is shown in figures 1 to 3, below.

Figure 1: Boehringer Ingelheim short-term VTE event model structure

Figure 2: Boehringer Ingelheim short-term adverse-event model structure

Figure 3: Boehringer Ingelheim long-term model structure

The following is a list of the key assumptions in the model taken directly from the MS. These have been checked by the ERGs clinical advisors and were considered to be reasonable:

1. All LMWHs are bioequivalent: This is supported by current literature, which suggests that dalteparin and tinzaparin are indistinguishable from enoxaparin [22,23,24]. 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[9]

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 heparin-induced thrombocytopenia (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[10] suggest that only 3-5% of THR and 1% of TKR patients are less than 45 years of age.

5.1.1 Clinical evidence

The comparison of DBG 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). This is referred to throughout the MS as the direct comparison.

There are no head-to-head trials comparing DBG with fondaparinux. This comparison is based on the relative efficacy and safety as derived from a mixed treatment comparison meta-analysis. This is referred to throughout the MS as the indirect comparison.

5.1.2 Natural history

5.1.2.1 Direct comparison (DBG versus LMWH)

In the direct comparison, the baseline risk of a VTE event was assumed to be that associated with LMWH. 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. These probabilities are presented in Table 14, below.

Table 14: 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: [4,3]

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. The ERG queried the manufacturer as to why major bleed is reported combined with clinically relevant bleed in the effectiveness section of the MS (pgs 94-95) but in the economic analysis minor bleed is combined with clinically relevant bleed. The justification provided by the manufacturer is that this was the closest match to the endpoints in the original study reports for the comparison with fondaparinux. It is the opinion of the ERG that this adjustment of bleeding definitions is unlikely to provide any advantage to DBG in the comparison with LMWH or fondaparinux.

5.1.2.2 Indirect comparison (DBG versus fondaparinux)

The baseline risk of DVT and major bleed is taken from a literature review and MTC conducted by the National Collaborating Centre for Acute Care (NCC-AC)[9] Probabilities are estimated as the number of patients with an event divided by the sample size from the no prophylaxis arm of the RCTs identified in this review. As minor bleed or HIT was not an outcome in the NCC-AC review, the manufacturers performed an additional meta-analysis using the published studies identified in the NCC-AC. Studies included were those reporting the endpoint of major bleed under the assumption that studies not reporting major bleed were unlikely to report minor bleed or HIT. This appears to be a reasonable assumption to the ERG. It is unknown to the ERG how many studies reporting these endpoints have been published since the NCC-AC review was published and how this may impact the final results. A brief description of the methodology of the NCC-AC study and the manufacturer's additional MTC should have been provided in the MS. As this was not done the ERG cannot comment on the quality of these two studies.

The probabilities for VTE in Table 15 are probabilities reported for DVT from the no prophylaxis arm of the RCTs in the NCC-AC report. The MS does not acknowledge this and does not discuss the implications of using DVT instead of VTE. See section 4.2.2 of this report for more comments.

The estimates of underlying risk derived from this methodology are shown in Table 15, below.

Table 15: Underlying risk of DVT and bleeding events

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

Source: [9]

5.1.3 Treatment effectiveness within the submission

5.1.3.1 Direct comparison (DBG versus LMWH)

The probabilities of a VTE event, major bleed and minor bleed for DBG were derived by applying the relative risk for DBG versus enoxaparin from the relevant THR or TKR trial, to the baseline risks shown in Table 14.

The RR estimates are presented in Table 16. 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.

Table 16: 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
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

The probability of HIT for LMWH (p=0.004, 95% CI 0.001 to 0.007) was taken from a secondary meta-analysis of the studies included the NCC-AC review (as described in 5.1.2.2.) values from the three DBG versus LMWH phase III trials were also included. It is the manufacturers' opinion that the inclusion of the three phase III trials may represent an underestimate of HIT. However, it appears from the published study reports that there was no occurrence of HIT in the LMWH arms of any of these trials and claims of an underestimation effect are not justifiable.

5.1.3.2 Indirect comparison

Relative risks for treatment versus no treatment were taken from the two MTCs described in section 5.1.2.2. The RRs and derived event probabilities for treatment are reproduced from the MS in Table 17. The RR versus no treatment for fondaparinux in THR is reported as 0.01. This was taken from a single study[25]. This study reports the incidence of VTE as 3/208 and 77/220 for the fondaparinux and placebo arm, respectively. This results in a RR of 0.04. The ERG are unsure of the source of the RR used in the model and if it is incorrect are unsure of the impact on the cost-effectiveness results.

Table 17: Event probabilities in the indirect comparison

Treatment and parameter	Probability (Nil)	RR vs Nil	Probability (treatment)
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	[redacted]	[redacted]
Minor Bleed	0.073	[redacted]	[redacted]
DBG 220mg (RE-MODEL)			
VTE	0.270	[redacted]	[redacted]
Major Bleed	0.010	[redacted]	[redacted]
Minor Bleed	0.032	[redacted]	[redacted]
DBG 220mg (Meta-analysis- THR)			
VTE	0.440	[redacted]	[redacted]
Major Bleed	0.020	[redacted]	[redacted]
Minor Bleed	0.073	[redacted]	[redacted]
DBG 220mg (Meta-analysis- TKR)			
VTE	0.270	[redacted]	[redacted]
Major Bleed	0.010	[redacted]	[redacted]
Minor Bleed	0.032	[redacted]	[redacted]
DBG 150mg (RE-NOVATE)			
VTE	0.440	[redacted]	[redacted]
Major Bleed	0.020	[redacted]	[redacted]
Minor Bleed	0.073	[redacted]	[redacted]
DBG 150mg (RE-MODEL)			
VTE	0.270	[redacted]	[redacted]
Major Bleed	0.010	[redacted]	[redacted]
Minor Bleed	0.032	[redacted]	[redacted]
DBG 150mg (Meta-analysis – THR)			
VTE	0.440	[redacted]	[redacted]
Major Bleed	0.020	[redacted]	[redacted]
Minor Bleed	0.073	[redacted]	[redacted]
DBG 150mg (Meta-analysis – TKR)			
VTE	0.270	[redacted]	[redacted]
Major Bleed	0.010	[redacted]	[redacted]
Minor Bleed	0.032	[redacted]	[redacted]

5.1.4 Chronic phase transition probabilities

5.1.4.1 Recurrent VTE

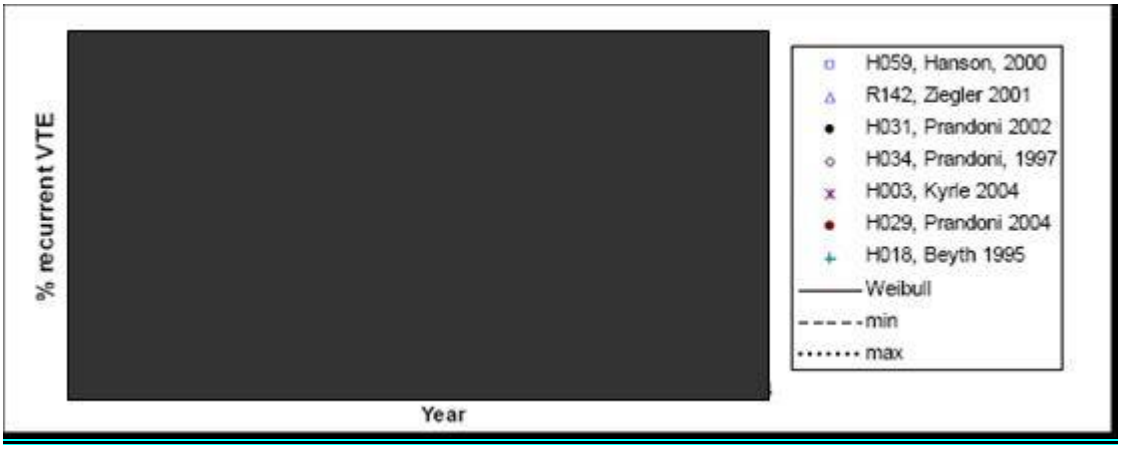
Estimates of transition probabilities for recurrent VTE events were obtained from a review of cost-effectiveness studies undertaken by the manufacturers. This review did not include databases such as Medline. It is therefore possible that some studies

reporting recurrent VTE events were not identified in this review. The impact of this is unknown.

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 4. 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.

It is the view of the ERG that a preferred method would have been to use statistical software (such as Stata) that would report multivariate distributions with CI's.

Figure4 Incidence of recurrent VTE: published estimates and fitted Weibull function applied in the Markov model



As no data was identified describing the incidence of recurrent VTE for patients with asymptomatic DVT probabilities were assumed to be the same as for patients with treated VTE. This is a reasonable assumption given the lack of evidence.

The MS reports that the incidence of recurrent VTE is expected to be lower for patients that experienced a distal DVT as the primary VTE event[26] and that, the risk has been reported to be lower for females than for males[27]. The RRs used in the model are shown in Table 18, below.

Table 18: Relative risks for recurrent VTE by DVT location and gender

	RR	Source
Proximal vs Distal primary DVT	4.00	[26]
Males vs Females	3.60	[27]

As no studies were identified by Boehringer Ingelheim that reported the incidence of recurrent VTE after a PE event, probabilities were assumed to be the same as for a treated DVT. This was considered to be a reasonable assumption by the ERG clinical advisors.

The MS identified four studies that reported recurrence rates for types of VTE events, The probability that a recurrent VTE event will be a PE was estimated from these studies. The probability was calculated as a simple average of the probabilities from each of the studies. The ERG consider this to be the wrong approach as it does not take into account the size of the trial. A weighted average should be used which results in probabilities of p(PE)=0.271 and p(DVT)=0.729. The values used in the MS are in Table 19.

Table 19: Type of recurrent VTE event

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

An assumption was made in the MS that patients that had no VTE event were assumed to be at the same risk of a VTE event as the general population, Table 20. Annual incidence estimates for DVT and PE were taken from the Prevention of Venous Thromboembolism, International Consensus Statement of 1997.[31] 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.

It is the opinion of the ERG that risks that are the same as the general population could be left out of the modelling process, for the same reason that we would not expect to include the risk of other diseases, such as cancer. However, the ERG consider that this will have little impact on the results.

Table 20: Probability of idiopathic VTE

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

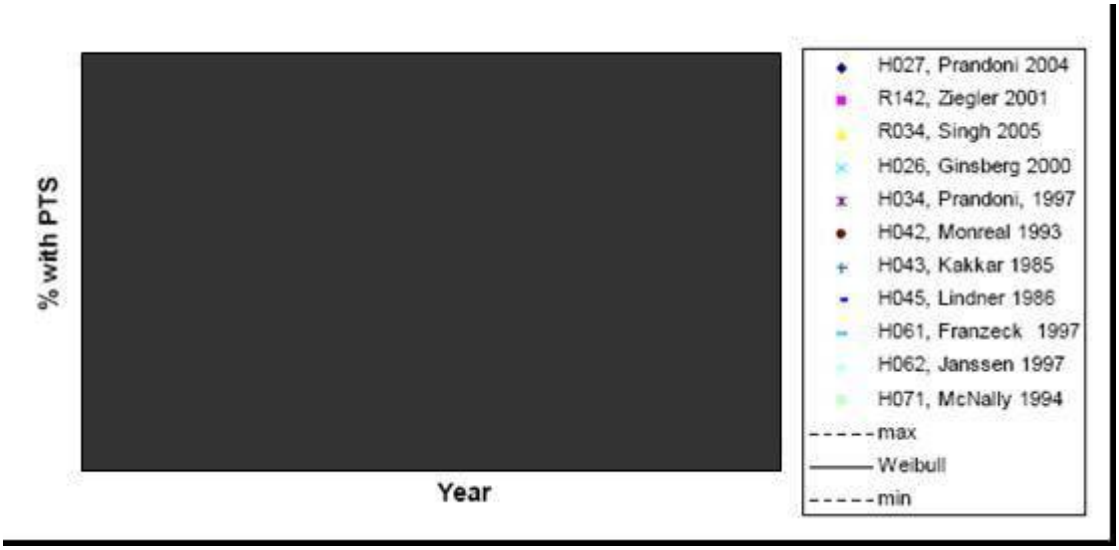
5.1.4.2 PTS

In the MS, estimates of the probability of PTS for patients with a treated VTE event were taken from a literature review. The same caveat applies here as above, i.e. some studies may have been missed by not including such databases as Medline. The impact of this is unknown.

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 5. 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.

As stated above, it is the view of the ERG that a preferred method would have been to use statistical software (such as Stata) that would report multivariate distributions with CI's.

Figure 5: Incidence of PTS: published estimates and fitted Weibull function applied in the Markov model



The MS identified evidence that 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), Table 21.[26]

Table 21: Relative risks for PTS by DVT location and gender

	RR	Source
Proximal vs Distal primary DVT	4.00	[26]

The MS assumes that patients with no VTE event are 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.[32] Probabilities were adjusted as patients aged with increasing time from surgery, Table 22. As stated above, it is the opinion of the ERG that risks that are the same as the general population could be left out of the modelling process, for the same reason that we would not expect to see the risk of other diseases, such as cancer, included. However, the ERG consider that this will have little impact on the results.

Table 22: 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

The MS identifies eight studies that report the probability of a PTS being severe rather than mild-to-moderate. A simple average of estimates reported in these studies was used. No reference is given as to how these studies were identified. The ERG assumes it was from the same review described earlier and therefore the same caveat applies.

The ERG consider that taking a simple average is the wrong approach as it does not take into account the size of the trial. A weighted average should be used which results in a probability of p(Severe)=0.194. The values used in the MS are in Table 23.

Table 23: Probability that PTS is severe

Study	Mild to moderate	Severe	Total	p(Severe)
Singh and Masuda, 2005[33]	29%	27%		0.483
Ziegler, 2001[29]	75%	7%		0.083
Prandoni, 2004[34]	87%	13%		0.130
Prandoni, 1997[30]		3%	18%	0.150
		8%	30%	0.274

		8%	30%	0.272
Monreal, 1993[35]	36%	20%		0.357
Kakkar and Lawrence, 1985[36]	71%	17%		0.193
Franzeck, 1997[37]	28%	5%		0.152
Janssen, 1997[38]	73%	2%		0.027
Average				**0.233**

5.1.4.3 Death from other causes

Mortality rates by age and gender in 10-year age bands were taken from estimates for 2005 by the Office for National Statistics.[32] It is not clear from the MS why 10-year age bands were chosen instead of 1-year bands.

5.1.5 Health related quality of life

Studies reporting health related utility estimates were identified via a systematic review of economic evaluations. It appears that the main aim of this review was to identify cost-effectiveness studies. Studies reporting utility values are often but not always economic studies. It is therefore possible that utility studies were missed in this review by failing to search databases such as Medline. The extent to which studies were missed is unknown and the impact this could have on the cost-effectiveness analysis cannot be assessed.

5.1.5.1 VTE events

Only one study reporting a utility for DVT was identified in the MS.[39] In this study 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 MS therefore uses a decrement associated with DVT of 0.08.

The MS follows the methodology used in two studies (Botteman et al. (2002)[31] and NCC-AC (2007)[9]) in which a decrement equal to the duration of hospitalisation for the event is assumed.

In the MS 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)[39] was applied. Assumptions made in the calculation of utility decrements and the resulting estimates are presented in Table 24 (taken directly from the MS).

This methodology of applying a utility decrement based on hospitalisation and length of treatment appears to be a reasonable way of measuring quality of life in the acute phase of the model.

Table 24: 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)				
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)				
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,[41], elective and non-elective HRGs E20, E21, D10, D11

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

5.1.5.2 PTS

Only one study was identified in the MS which reported utility values for PTS. In this study, the utility of mild-to-moderate and severe PTS was elicited from 30 Healthy volunteers and 30 physicians using Standard Gamble methods.[42] The utility weights were subtracted from that for perfect health (1.00), to calculate a decrement (Table 25) which is subtracted from the age and gender-adjusted utility weight for the model population.

Table 25: 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[42]

5.1.5.3 Bleed events and HIT

Only one utility study[43] was identified in the MS for major bleed. In this study the standard gamble method of elicitation was used on 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. The decrement therefore used in the MS was estimated as 0.10 (0.941 - 0.841).

The MS uses a similar methodology to the cost-utility analyses by the NCC-AC[9] in which a decrement equal to the duration of hospitalisation for the event (4 days) was assumed.

In the MS, a decrement of 0.10[43] for the duration of in-patient stay for a gastrointestinal (GI), bleed was assumed. This duration was obtained from NHS national reference costs[41] A weighted average of elective and non-elective in-patient admissions for GI bleed with major procedure (5.4 days) was assumed.

No estimates were identified in the MS for minor bleed or non-fatal HIT. 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, (MS Appendix 9.9)).

5.1.5.4 Fatal events

For fatal events occurring during the acute phase of the model (10 weeks) 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 value 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.

The ERG consider this to be a reasonable method to account for death and quality of life in the acute phase model.

5.1.5.5 Quality of life for the aging population

All surviving patients were attributed a utility value which decreases over time to model the impact of ageing (Table 26). Utility decrements for model events were subtracted from this baseline utility value.

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

Table 26: General population utility values 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: [44]

The ERG consider this to be a reasonable methodology.

5.1.6 Resources and costs

5.1.6.1 Drug acquisition

In order to maintain the link between efficacy and drug dosage in the Phase III DBG trials the MS has based the cost of prophylaxis on the number of administrations in the trials, Table 27.

Table 27: 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.

In the indirect comparison for TKR, the manufacturer's have assumed that the duration of hospitalisation equals the treatment duration recommended in the SPC for fondaparinux. For THR, the MS have assumed an extended regimen of 28 days based on the length of therapy recommended by NICE clinical guidelines.[45]

5.1.6.2 Drug administration

It is reasonable to assume that there will be resource use implications in the administration of subcutaneous injections (LMWH or fondaparinux) compared to oral DGB. The MS has correctly identified that the proportion of patients willing and able to self-administer in routine clinical practice is a key driver in the analysis. A

systematic review was performed by the manufacturer to identify estimates of the percentage of patients able to self-administer subcutaneous injections of VTE prophylaxis or treatment at home. Two studies were identified, Watts *et al*.,[46] reported that 87% of patients receiving outpatient prophylaxis with fondaparinux were able to self-inject and Koopman *et al*.,[47] reported that 15% of patients receiving LMWH at home required help with administration (the remaining 85% were able to self-administer).

In the MS the Watts estimate (87%) was adopted as the base case value for both LMWH and fondaparinux and is considered to be 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.

Interventions administered by subcutaneous injection may also result in costs associated with sharps disposal, and costs and health consequences resulting from needlestick injuries. The MS takes a conservative approach and does not include these in the base-case analysis.

The MS has assumed a cost for inpatient nurse administration of subcutaneous injections and nurse time for training. The resources use and costs associated with LMWH and fondaparinux administration are shown in Table 28, below.

Table 28: 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),[48] section 9.1*
2. *The time per administration is derived from Offord (2004).[49] The unit cost of a staff nurse is derived from Curtis (2007),[48] section 13.3*
3. *The time for training is derived from NCC-AC (2007).[9]. The unit cost of a staff nurse is derived from Curtis (2007),[48] section 13.3*

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,[50] 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.[9] In this analysis, the cost of platelet count monitoring was excluded from the base case analysis.

5.1.6.3 VTE events

DVT detected prior to discharge

Table 29, presents the derivation of the costs for proximal and distal DVT events detected prior to discharge used in the MS.

Table 29: 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)[41]
2. NHS Returns, 2003/04[51]
3. Weighted average as described earlier in report
4. Curtis (2007)[48]
5. NHS Electronic Drug Tariff, Feb 2005[52]
6. Based on cost per week: 7 days x £0.10 per day. Not exact due to rounding. Cost sourced from BNF 54[53]
7. NCC-AC, 2007[9]

DVT detected post-discharge

Table 30 presents the derivation of the costs for proximal and distal DVT events detected post-discharge.

Table 30: 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)[41]
2. Based on cost per week: 7 days x £0.10 per day. Not exact due to rounding. Cost sourced from BNF 54[53]
3. NCC-AC, 2007[54]
4. Weighted average as described earlier in report
5. NHS Electronic Drug Tariff, Feb 2005[52]
6. Curtis (2007)[48]

The ERG sought clinical advice to confirm that it is reasonable to expect the cost of pre-discharge DVT to be more than the cost of post-discharge DVT. The opinion of the clinical advisors was that it is reasonable. A pre-discharge diagnosis would incur the same costs of diagnosis and treatment but would likely prolong duration of in-patient stay, while post-discharge diagnosis would likely be treated as an out-patient and would not incur excessive hospitalisation costs.

PE detected prior to discharge

Table 31 presents the derivation of the costs for PE events detected prior to discharge.

Table 31: 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)[41]
2. NHS Returns, 2003/04[51]
3. Weighted average as described earlier in report
4. Curtis (2007)[48]
5. NHS Electronic Drug Tariff, Feb 2005[52]
6. Based on cost per week: 7 days x £0.10 per day. Not exact due to rounding. Cost sourced from BNF 54[53]
7. NCC-AC, 2007[9]

PE detected post-discharge

Table 32 presents the derivation of the costs for PE events detected post-discharge.

Table 32: 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)[41]
2. Based on cost per week: 7 days x £0.10 per day. Not exact due to rounding. Cost sourced from BNF 54[53]

NCC-AC, 2007[9]

The ERG sought clinical advice to confirm that it is reasonable to expect the cost of pre-discharge PE to be more than the cost of post-discharge PE. The opinion of the clinical advisors was that it is reasonable. A pre-discharge diagnosis would incur the same costs of diagnosis and treatment but would likely prolong duration of in-patient stay, while post-discharge diagnosis would likely be treated as an out-patient and would not incur excessive hospitalisation costs. The ERG also asked the clinical advisors if it was reasonable to expect no ICU costs to be included in the treatment of PE post-discharge. Their response was that some massive PE post-discharge may be expected to survive to admission and require ITU/ thrombolysis/ embolectomy. The cost of this has not been included in the MS.

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.[55] 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 33 presents the derivation of the costs for PTS.

Table 33: 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.[55]

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.[56] 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).

According to the NICE reference case, costs should relate to resources that are under the control of the NHS and PSS. The cost of informal care in-home (and possibly direct health care in-home, depending on what this refers to) should therefore not be included in the basecase analysis. However, if these costs are substantial it is reasonable to include them in a sensitivity analysis. If the cost of informal care in-home were not included, the average annual cost of long-term care would be £1,662, using the numbers presented in the MS (Table 33).

Table 34 presents the derivation of the costs for intracranial bleed, from the MS .

Table 34: 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[56] *(cost year 2002); Youman, 2003*[57].

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)[41] 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 35 presents the derivation of the costs for other adverse events.

Table 35: 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)[41] and NHS Returns, 2003/04[51]

5.1.7 Discounting

Boehringer Ingelheim have assumed a discount rate for both costs and health benefits of 3.5% per annum. This is in line with current NICE guidance.

5.1.8 Sensitivity analyses

Boehringer Ingelheim carried out a univariate and probabilistic sensitivity analysis (PSA). The following parameters were included in the univariate analysis:

- 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

Table 36, (reproduced from the MS) shows the parameters included in the univariate sensitivity analysis with both the original and new values.

Table 36: Parameters included in the univariate sensitivity analysis

Parameter	Original value	New value
Discount rates		
Vary discount rate for both costs and health outcomes	3.5%	0%
Vary discount rate for costs only	3.5%	0%
Vary discount rate for costs only	3.5%	6%
Vary discount rate for health outcomes only	3.5%	0%
Vary discount rate for health outcomes only	3.5%	6%
Duration of LMWH therapy		
Compare extended DBG with standard LWMH in THR	33.2 days	7.6 days
LMWH administration assumptions		
Remove cost of inpatient administration	£0.82	£0.00
Vary proportion of THR patients able/willing to self-administer	87%	50%
Vary proportion of THR patients able/willing to self-administer	87%	100%
Length of stay of primary hospitalisation		
Reduce DBG length of stay by 1 day	£6,036 (THR) £6,389 (TKR)	£5,772 (THR) £6,126 (TKR)
Treatment effects		
No difference in treatment effect (VTE relative risk)	0.90 (THR) 0.97 (TKR)	1.00 (THR) 1.00 (TKR)
No difference in treatment effect (Major bleed relative risk)	1.29 (THR) 1.14 (TKR)	1.00 (THR) 1.00 (TKR)
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)
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
Time horizon		
Model timeframe reduced to acute phase	Lifetime	10 weeks
Model timeframe reduced to 1 year	Lifetime	1 year
Model timeframe reduced to 5 years	Lifetime	5 years

The following is a summary of the sampling distributions used in the PSA:

- 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[9];
- Death from other causes which was sampled from a beta distribution defined by the number of patients dead and the number alive;

- Probabilities for major bleed (intracranial, surgical site and gastrointestinal) were sampled from a beta distribution defined by the number of patients experiencing the event and the total number at risk.
- 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 ERG considers that this assumption will underestimate the uncertainty.
- 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).[56]

As described in section 5.1 the main driver in the chronic phase of the model is VTE recurrence rates. It would therefore have been useful if this had been included as a parameter in the univariate analysis however these parameters are sampled within the PSA.

5.1.9 Model validation

The MS describes internal pre-specified quality control checks of all input data and programming and external validation by a panel of clinical experts.

The ERG are not aware of any further trials or models against which the Boehringer Ingelheim model could be validated.

5.2 Critique of approach used

The decision tree/state transition model which Boehringer Ingelheim used is considered to be appropriate for the economic analysis.

5.3 Results included in MS

5.3.1 Summary of baseline results

- At the licensed dose of 220mg once a day DBG dominates LMWH in both THR and TKR.

- At the lower dose of 150 mg once a day (licensed for patients with mild or moderate kidney problems, patients over 75 years of age and for patients taking amiodarone), DBG dominates LMWH in THR, and LMWH dominates DBG in TKR.

- At the licensed dose of 220mg once a day DBG is less cost-effective than fondaparinux in THR. The cost/QALY is £11,111 (this ICER is in the "south/west" quadrant of the cost-effectiveness plane).

- At the licensed dose of 150mg once a day DBG is less cost-effective than fondaparinux in THR. The cost/QALY is £6,857 (this ICER is in the "south/west" quadrant of the cost-effectiveness plane).

- In TKR, both DBG doses are dominated by fondaparinux.

5.3.2 Baseline results: DBG and LMWH in THR patients

Table 37 shows the baseline mean lifetime costs for DBG and LMWH in THR patients.

Table 37: 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.

Table 38 presents the modelled lifetime health outcomes per patient for LMWH and both doses of DBG, disaggregated by outcome category.

Table 38: 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.

Table 39 presents the incremental cost-effectiveness analysis based on the above results.

Table 39: 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.

For both doses of DBG the probability of cost effectiveness decreases as the threshold increases. The ERG has examined the data and believes this can be explained by the fact that as the monetary value of a QALY increases then the incremental net benefit tends towards zero as the cost savings diminish.

5.3.3 Baseline results: DBG and LMWH in TKR patients

Table 40 shows the baseline mean lifetime costs for DBG and LMWH in TKR patients.

Table 40: 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.

Table 41 presents the modelled lifetime health outcomes per patient for LMWH and both doses of DBG, disaggregated by outcome category.

Table 41: 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.

Table 42 presents the incremental cost-effectiveness analysis based on these results.

Table 42: 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.

5.3.4 Baseline results: DBG and fondaparinux in THR patients

Table 43 presents the modelled lifetime costs per patient for fondaparinux and both doses of DBG, disaggregated by cost category.

Table 43: 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.

Table 44 presents the modelled lifetime health outcomes per patient for fondaparinux and both doses of DBG, disaggregated by outcome category.

Table 44: 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.

Table 45 presents the incremental cost-effectiveness analysis based on these results.

Table 45: 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	£11,111*		
DBG 150mg			
Incremental cost	-£192	32%	27%
Incremental QALYs	-0.028		
ICER	£6,857*		

DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; THR, total hip replacement; <£, <QALY, lower costs and health effects.
*Please note this ICER is in the "south/west" quadrant of the cost-effectiveness plane.

5.3.5 Baseline results: DBG and fondaparinux in TKR patients

Table 46 presents the modelled lifetime costs per patient for fondaparinux and both doses of DBG, disaggregated by cost category.

Table 46: 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.

Table 47 presents the modelled lifetime health outcomes per patient for fondaparinux and both doses of DBG, disaggregated by outcome category.

Table 47: 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.

Table 48 presents the incremental cost-effectiveness analysis based on these results.

Table 48: 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.

Table 49 presents a summary of all the deterministic and PSA results.

Table 49: Summary of deterministic and PSA results

	Deterministic	Probability cost-effective at threshold:	
		£20,000/QALY	£30,000/QALY
DBG compared to LMWH in THR patients			
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 compared to LMWH in TKR patients			
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 compared to fondaparinux in THR patients			
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 compared to fondaparinux in TKR patients			
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		

5.3.6 Univariate sensitivity analysis

Boehringer Ingelheim conducted an extensive univariate sensitivity analysis. For the comparison of DBG with LMWH none of the parameters resulted in a significant difference to the basecase results. For the comparison of DBG with fondaparinux the

parameters that did have a noticeable effect are summarised below and are shown in Table 50, below:

- Reducing the number of days of fondaparinux administration from 30 to 7 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.

- Increasing the RR of VTE for fondaparinux results in DBG dominating in THR and being less costly and less effective in TKR.

- Increasing the RR of major bleed for fondaparinux results in DBG being less costly and less effective in TKR.

These results are fairly predictable and the RR changes highlight how sensitive the model conclusions are to the estimates of relative treatment effect. This is potentially important given the issues concerning the derivation of the RRs for fondaparinux discussed in section 4.2.2.

Table 50: Univariate Sensitivity analyses (fondaparinux)

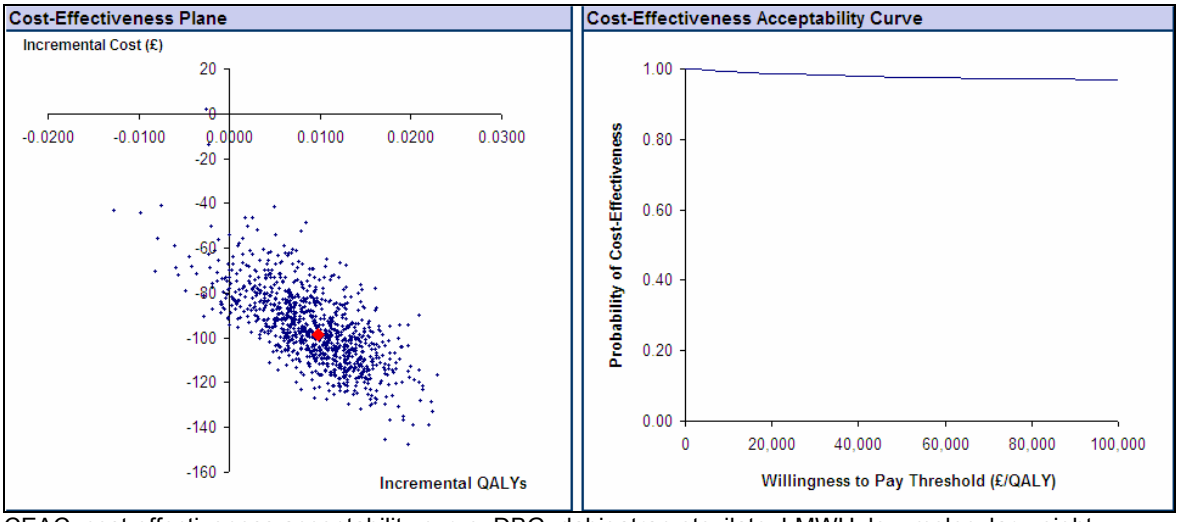
Description of sensitivity analysis	Original value	New value	ICER (THR)	ICER (TKR)	Probability of CE (THR)	Probability of CE (TKR)
Base case	**-**	**-**	**£11,111***	**DOMINATED**	**40%**	**0%**
Duration of fondaparinux therapy						
Compare extended DBG with standard FNX in THR	33.2 days	7.4 days	£9,088	N/A	63%	N/A
Treatment effects						
FNX relative risk of VTE raised	0.01 (THR) 0.22 (TKR)	[redacted]	DOMINANT	**<£;<QALY****	N/A	N/A
FNX relative risk of major bleed raised in TKR	2.22	[redacted]	**N/A**	**<£;<QALY****	N/A	N/A

*Please note this ICER is in the "south/west" quadrant of the cost-effectiveness plane.
** Actual numbers not reported in MS

5.3.7 PSA analysis

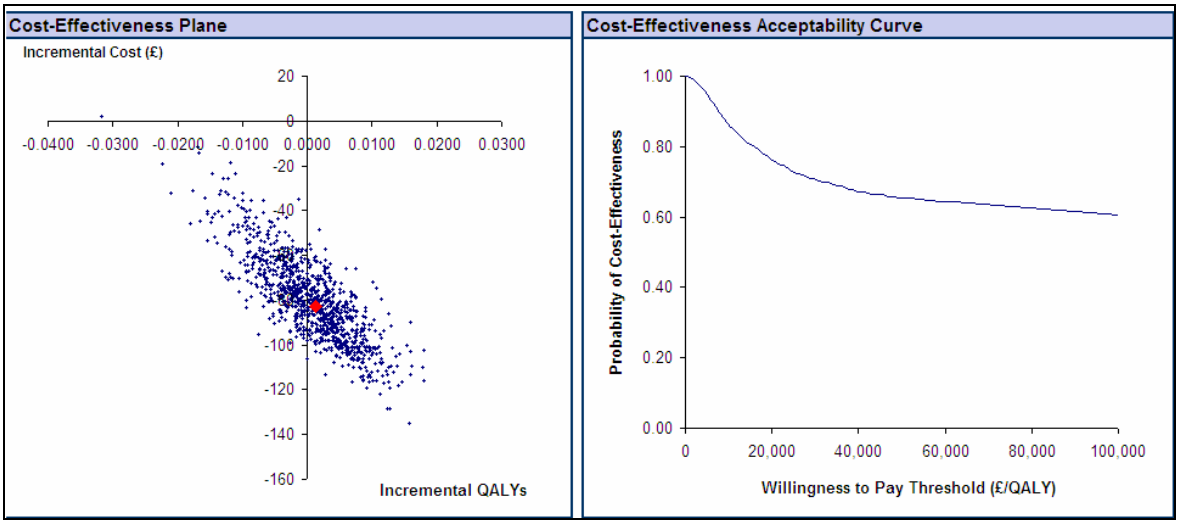
The cost-effectiveness planes and CEACs presented below are taken directly from the MS.

Figure 6: 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 7: Cost-effectiveness plane and CEAC for DBG 150mg in THR patients (LMWH)

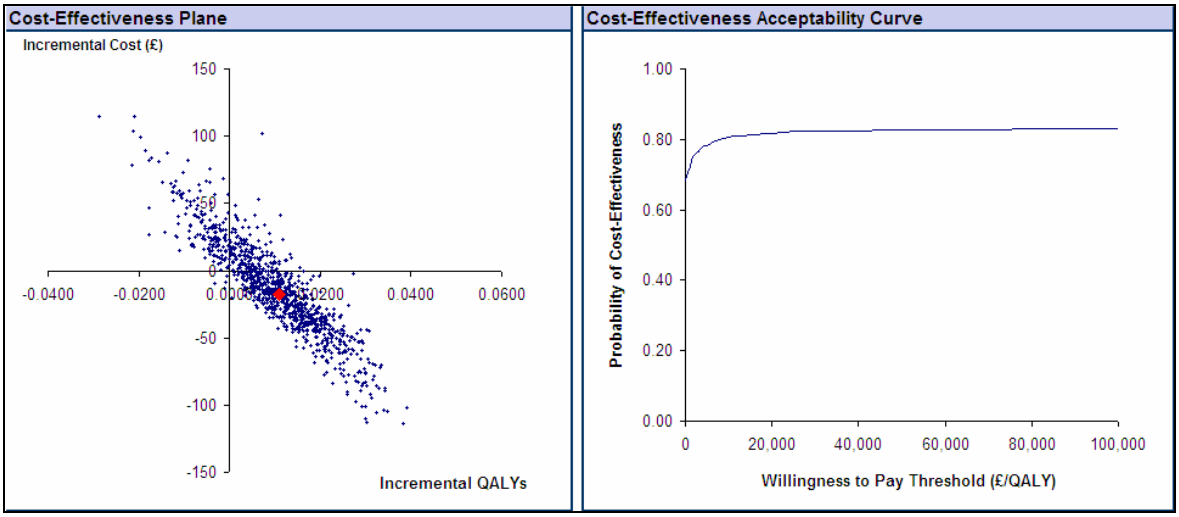


CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; LMWH, low-molecular weight heparin; QALY, quality-adjusted life year; THR, total hip replacement.

For both doses of DBG the probability of cost effectiveness decreases as the threshold increases. The ERG has examined the data and believes this can be explained by the fact that as the monetary value of a QALY increases then the incremental net benefit tends towards zero as the cost savings diminish.

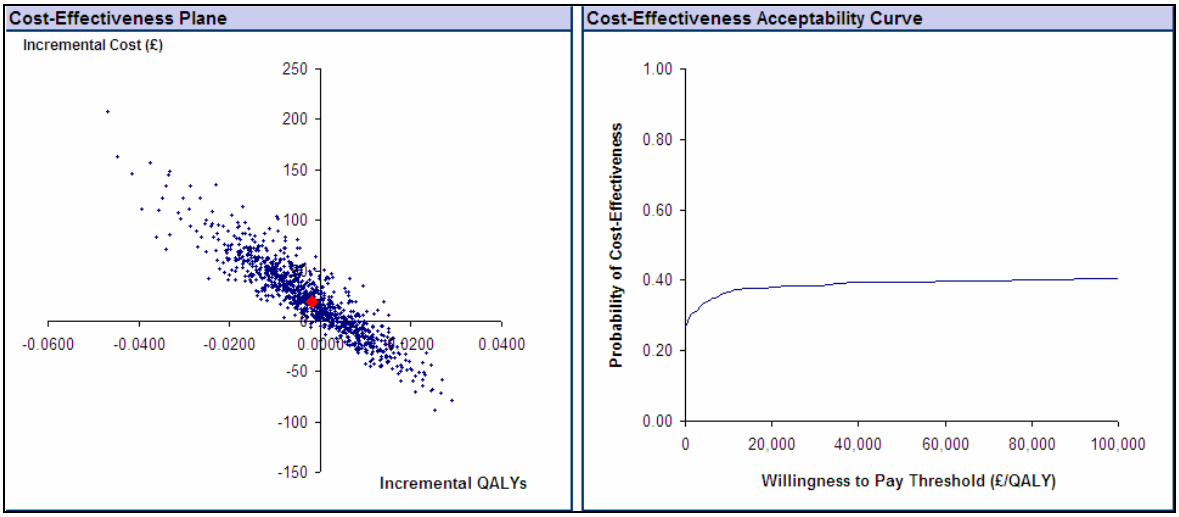
As noted in the MS, these results are based on non-significant differences between the regimens. The changes in health outcomes and the cost differences are extremely small when considered over the lifetime of the patient.

Figure 8: 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.

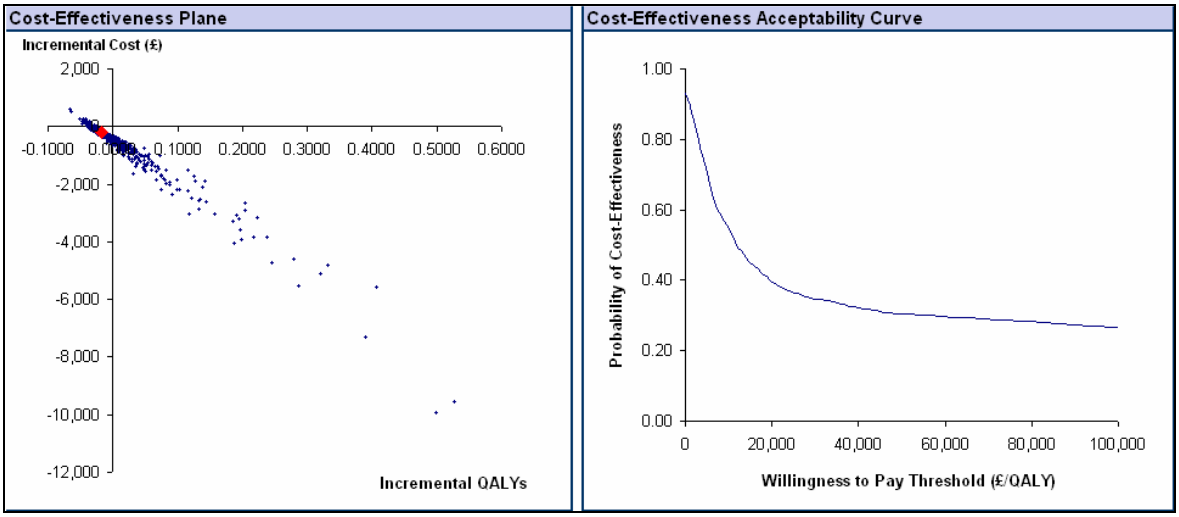
Figure 9: Cost-effectiveness plane and CEAC for DBG 150mg in TKR patients (LMWH)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; LMWH, low-molecular weight heparin; QALY, quality-adjusted life year; TKR, total knee replacement.

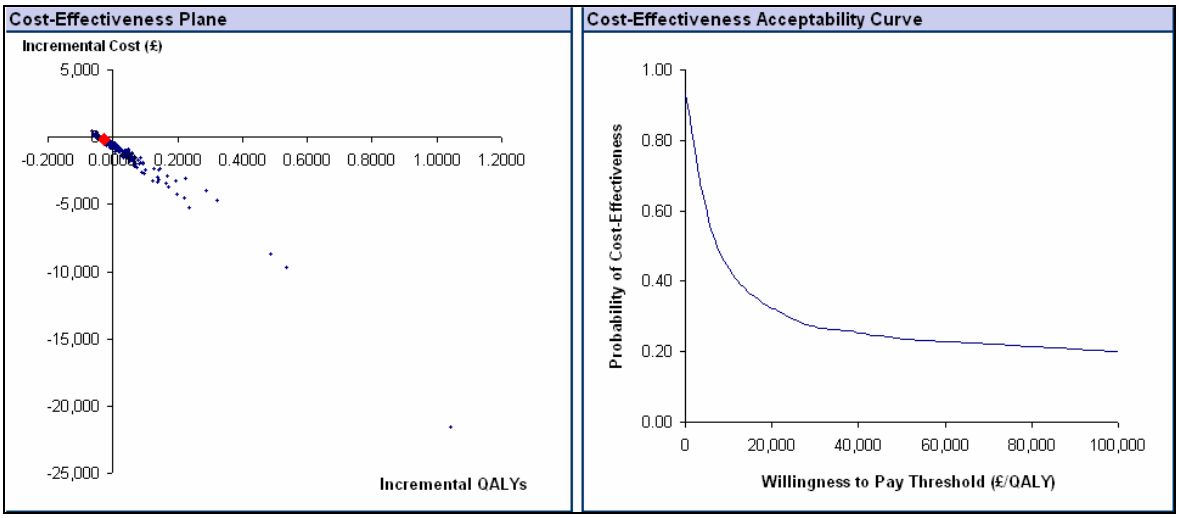
Although the results are extremely positive for DBG 220mg the same caveat applies here as with the THR results. The results are based on non-significant differences between the regimens and the changes in health outcomes and cost differences are extremely small when considered over the lifetime of the patient.

Figure 10: 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.

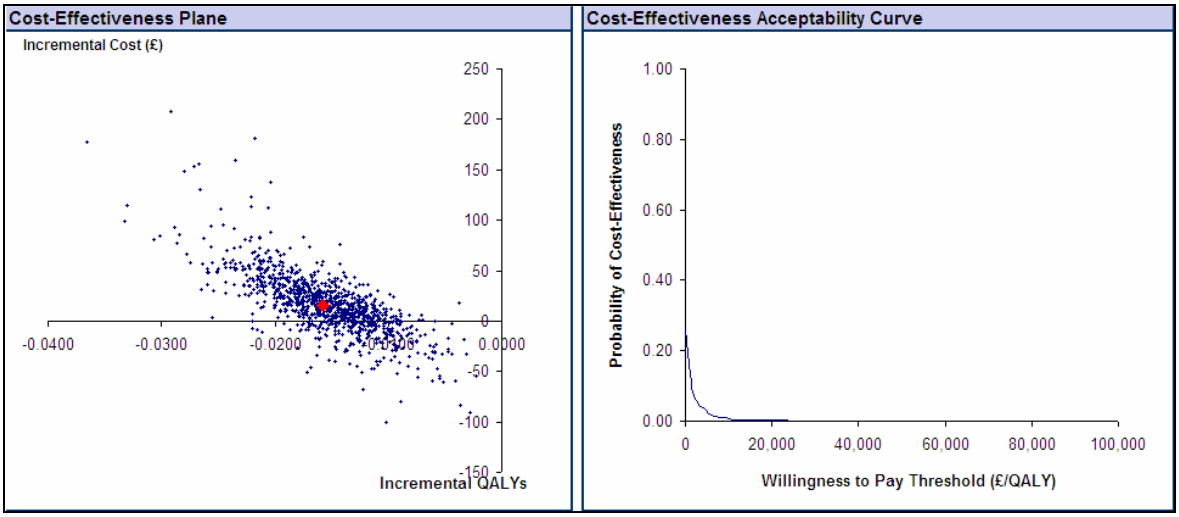
Figure 11: Cost-effectiveness plane and CEAC for DBG 150mg in THR patients (fondaparinux)



CEAC, cost-effectiveness acceptability curve; DBG, dabigatran etexilate; QALY, quality-adjusted life year; THR, total hip replacement.

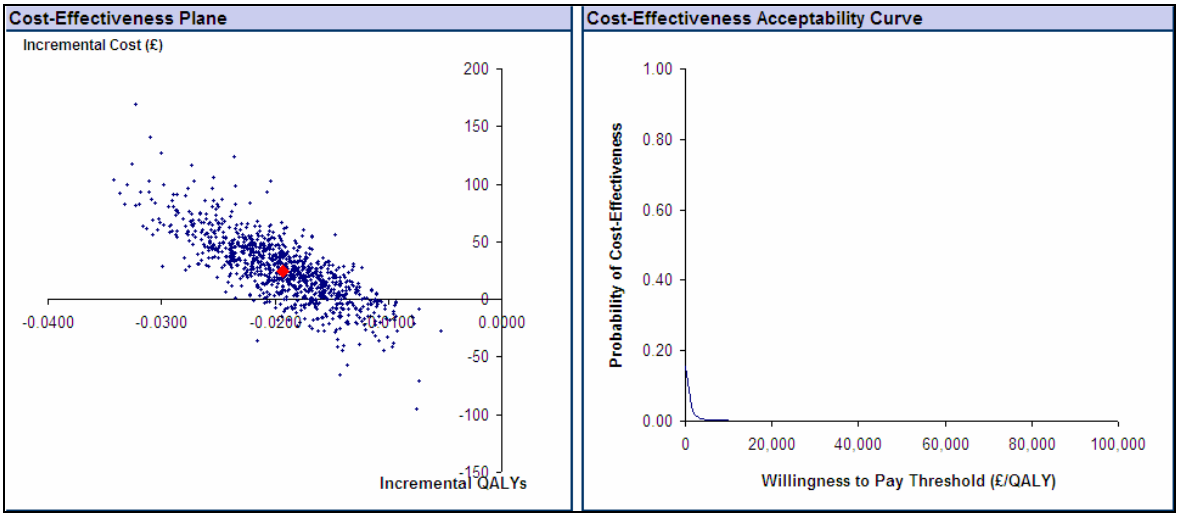
For both DBG doses, most points on the cost-effectiveness plane are situated in the "south-west" quadrant, where DBG is both less costly and less effective. At willingness to pay thresholds of above approximately £15,000 for DBG 220mg and £10,000 for DBG 150mg, DBG is predicted to be less cost-effective than fondaparinux.

Figure 12: 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 13: 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.

For both doses of DBG, the points on the cost-effectiveness plane are situated in either the “north-west” or “south-west” quadrants. At all willingness to pay threshold, DBG is predicted to be less cost-effective than fondaparinux.

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

The modelling methodology is considered to be appropriate for the economic analysis. The differential treatment effects only apply to the acute phase of the model (10 weeks). This is considered reasonable by the ERG as this is the phase where patients are at the greatest risk of VTE and adverse events. In the chronic phase of

the model, transition between states is driven primarily by VTE recurrence rates. The same rates apply to both treatment arms. Any incremental cost or health benefit accrued in the acute phase therefore remains relatively constant throughout the lifetime of the model.

The treatment effect in the acute phase is based on trials in which no statistically significant difference was found between treatments, and where the numerical difference between treatments is small, the incremental costs and health benefits seen in the acute phase of the model are therefore also small.

As no treatment effects are seen in the chronic phase, the cumulative incremental costs and health benefits remain small over the lifetime of the model. The incremental results observed at the end of the acute phase of the model are similar in magnitude to those seen at any time point in the chronic phase.

For the comparison of DBG with LMWH, the baseline results suggest that DBG 220mg once a day is both less costly and more effective than LMWH in both THR and TKR. At the lower dose DBG dominates LMWH in THR, and LMWH dominates DBG in TKR.

For the comparison of DBG with fondaparinux, DBG is less cost-effective than fondaparinux in THR at both doses of DBG. The cost/QALY is £11,111 and £6,857 respectively, for the higher and lower doses of DBG (please note that these ICERs are in the “south/west quadrant of the cost-effectiveness plane). In TKR, both DBG doses are dominated by fondaparinux.

However, the economic results for DBG compared to LMWH in THR and TKR both rely on one trial each. These trials indicate that DBG is not inferior to LMWH. The small numerical difference seen in these trials is reproduced in the model in terms of both incremental costs and incremental health benefits. A small change in the direction of the trial results would result in a similar change in the direction of the model results.

The economic results for DBG versus fondaparinux in THR are based on one study[25] and the RR used in the MS is different from that estimated by the ERG from this study.

It is the opinion of the ERG that the following input parameters are incorrect:

- The underlying risk of VTE for the comparison of DBG with fondaparinux is actually the underlying risk of DVT (5.1.3.1.)
- The RR for fondaparinux versus no treatment appears to have been wrongly estimated (5.1.3.2.)
- Recurrence rates for VTE events are wrongly estimated (5.1.4.1.)
- The probability of PE being severe is wrongly estimated (5.1.4.2)
- ICU costs should be included in PE post discharge (5.1.6.3)
- The cost of informal care should not be included (5.1.6.3)

Ideally, these numbers should all be corrected and the model re-run. The impact of re-running the model with the correct numbers is unknown.

5.5 Summary of uncertainties and issues

With regards to the chronic phase model there is an issue with how evidence used to populate the model was identified. It is a requirement of the STA process that a review of published economic evaluations is undertaken in the MS in order to retrieve and evaluate relevant cost-effectiveness studies. It appears however, that this review was also used as the basis for retrieving studies to inform VTE recurrence rates, PTS rates and quality of life utilities used in the model. It is therefore possible that non-economic studies reporting this data in sources such as Medline have not been identified. The implications of this are unknown. However, the structure and driving forces of the model perhaps negate the effect of this omission. Bearing in mind the discussion in 5.4, it is possible that the identification of further studies may alter the input parameters stated above and this may alter the magnitude of the results slightly, however given the structure of the model it is unlikely to affect the direction of the results.

6 Additional work undertaken by the ERG

The only additional work undertaken by the ERG was a series of meta-analyses on the primary safety outcomes, Table 51, below. There was no difference between DBG and any of these outcomes.

The ERG requested the manufacturers to repeat the cost-effectiveness analysis with the inclusion of the RE-MOBILIZE study. The results of the meta-analysis of RE-MOBILIZE plus RE-MODEL and the results of the cost-effectiveness analysis based on this meta-analysis are shown in tables 52 and 53, below. The inclusion of the RE-MOBILIZE study reverses the results from DBG dominating to DBG being dominated for both dosages. However, the manufacturers do not believe that the RE-MOBILIZE study is generalisable to the England and Wales setting. It is their opinion that these analyses are therefore inappropriate for this submission. The ERGs clinical advisors agree with this opinion.

Table 51: Meta-analysis of principal safety outcomes for DBG versus enoxaparin (40mg o.d. or 30mg b.i.d)

	Major Bleed		**Major bleed / clinically-relevant bleed**		**Any bleed**	
Trials (and dose)	Relative risk (fixed effects, 95% CI)	Relative risk (random effects, 95% CI)	Relative risk (fixed effects, 95% CI)	Relative risk (random effects, 95% CI)	Relative risk (fixed effects, 95% CI)	Relative risk (random effects, 95% CI)
220mg o.d. DBG						
RE-NOVATE and RE-MODEL	1.24 (0.75, 2.05)	*1.24 (0.75, 2.05)*	1.18 (0.91, 1.52)	1.18 (0.91, 1.52)	1.03 (0.88, 1.21)	1.03 (0.87, 1.21)
RE-MODEL and RE-MOBILIZE	*0.73 (0.38, 1.30)*	*0.72 (0.27, 1.89)*	0.94 (0.69, 1.28)	0.92 (0.59, 1.42)	0.94 (0.78, 1.13)	0.94 (0.78, 1.14)
RE-NOVATE, RE-MODEL and RE-MOBILIZE	0.99 (0.63, 1.54)	1.04 (0.78, 1.40)	1.07 (0.85, 1.34)	1.04 (0.78, 1.40)	1.00 (0.86, 1.15)	1.00 (0.86, 1.15)
150mg o.d. DBG						
RE-NOVATE and RE-MODEL	0.88 (0.51, 1.52)	*0.88 (0.51, 1.52)*	1.21 (0.94, 1.55)	1.21 (0.94, 1.55)	0.99 (0.85, 1.17)	0.99 (0.85, 1.17)
RE-MODEL and RE-MOBILIZE	*0.66 (0.34, 1.30)*	*0.66 (0.28, 1.55)*	1.05 (0.78, 1.42)	1.03 (0.70, 1.53)	0.94 (0.78, 1.13)	0.94 (0.78, 1.13)
RE-NOVATE, RE-MODEL and RE-MOBILIZE	0.74 (0.46, 1.19)	0.75 (0.46, 1.21)	1.11 (0.89, 1.39)	1.12 (0.89, 1.40)	0.96 (0.83, 1.11)	0.96 (0.83, 1.11)

CI, confidence interval; DBG, dabigatran etexilate; data in *italics* provided by Addendum to MS, other data provided by ERG. For definitions of the bleeding events covered here: MS, p.49.

Table 52: Overall results utilising expanded set of meta-analyses (DBG 220mg)

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%**
Treatment effects						
RE-NOVATE + RE-MODEL (random)	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%	88%
RE-MOBILIZE + RE-MODEL (fixed)	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MNB: 1.04 (THR) 0.96 (TKR)	VTE: 1.08 MJB: 0.73 MNB: 0.97	N/A	DOMINATED	N/A	35%
RE-MOBILIZE + RE-MODEL (random)	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MNB: 1.04 (THR) 0.96 (TKR)	VTE: 1.09 MJB: 0.72 MNB: 0.97	N/A	DOMINATED	N/A	40%

CE, cost-effectiveness; DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; 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 53: Overall results utilising expanded set of meta-analyses (DBG 150mg)

Description of sensitivity analysis	Original value	New value	ICER (THR)	ICER (TKR)	Probability of CE (THR)	Probability of CE (TKR)
Base case	**-**	**-**	**DOMINANT**	**DOMINATED**	**76%**	**38%**
Treatment effects						
RE-NOVATE + RE-MODEL (fixed)	VTE: 1.28 (THR) 1.07 (TKR) MJB: 0.83 (THR) 0.99 (TKR) MNB: 1.11 (THR) 1.00 (TKR)	VTE: 1.12 MJB: 0.88 MNB: 1.05	DOMINANT	DOMINATED	99%	20%
RE-NOVATE + RE-MODEL (random)	VTE: 1.28 (THR) 1.07 (TKR) MJB: 0.83 (THR) 0.99 (TKR) MNB: 1.11 (THR) 1.00 (TKR)	VTE: 1.11 MJB: 0.88 MNB: 1.05	DOMINANT	DOMINATED	99%	22%
RE-MOBILIZE + RE-MODEL (fixed)	VTE: 1.07 MJB: 0.99 MNB: 1.00	VTE: 1.19 MJB: 0.66 MNB: 0.97	N/A	DOMINATED	N/A	4%
RE-MOBILIZE + RE-MODEL (random)	VTE: 1.07 MJB: 0.99 MNB: 1.00	VTE: 1.19 MJB: 0.66 MNB: 0.97	N/A	DOMINATED	N/A	11%

CE, cost-effectiveness; DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; 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

7 Discussion

7.1 Summary of clinical effectiveness issues

The review performed for the MS was adequate but there were a number of issues regarding the reporting and appraisal of studies and the description and presentation of analyses. The manufacturer's search strategy was adequately reported but limited, and the submission appears to contain all of the relevant head-to-head RCTs. Processes and validation of study screening and data extraction were not reported in full, and the validity assessment tool used was not entirely appropriate or adequate, although the application of a more appropriate tool did not greatly alter judgments on the overall quality of the included trials. The outcomes selected were relevant and appropriate. Statistical methods were explicitly described for the meta-analyses and all required meta-analyses were performed, including some not in the MS but produced at the request of the ERG. However, the pooling of data was not described fully and also appears to be inappropriate.

Overall the evidence from the two pivotal trials in the MS indicates that the 220mg o.d. dose of DBG is not inferior to the comparator enoxaparin, a LMWH, in terms of total VTE and all-cause mortality. LMWHs are the principal form of pharmacological anti-coagulant used in England in Wales. However, this is not the case for the supporting RE-MOBILIZE TKR trial, in which both the 220mg and 150mg o.d. doses are inferior to the comparator enoxaparin. The 220mg o.d. dose of DBG is not inferior to enoxaparin when combining both pivotal trials, and the supporting trial, in meta-analysis. However, there is greater uncertainty about the efficacy of the 150mg o.d. dose of DBG, which appears in meta-analysis to be inferior to enoxaparin in terms of the primary efficacy outcome of total VTE and all-cause mortality when the results of the RE-MOBILIZE trial are included in any analyses. Evidence from the sub-group analyses of the included trials also indicates that the 150mg o.d. dose may be less effective in terms of incidence of total VTE and all-cause mortality than the 220mg o.d. dose in the special populations indicated for this lower dose by the licence: the elderly (aged 75 years and older), and those with moderate renal impairment. Safety outcomes were not reported for these sub-groups. Both doses of DBG are also likely to be less effective than the other named comparator in the scope, fondaparinux, although the MTC reported does not demonstrate this particularly clearly.

However, both DBG doses were comparable to enoxaparin in terms of both the secondary efficacy outcome, major VTE and VTE-related death, and also the safety outcomes of major, clinically-relevant and minor bleeding. The intervention was also similar in terms of all other safety outcomes.

7.2 Summary of cost effectiveness issues

The ERG consider the structure of the model, the input parameters and the validity of the results to be satisfactory. The main concern in the comparison of DBG with LMWH is that the small incremental cost and health benefits are driven by the results of one trial in THR and one trial in TKR. In the comparison of DBG with fondaparinux in THR, it appears that fondaparinux is more cost-effective than DBG. However, these results are based on one study[25] and the RR used in the MS is different from that estimated by the ERG from this study.

The cost-effectiveness analysis based on a meta-analysis of Re-Model plus Re-Mobilize reverses the direction of the results, i.e. DBG is now dominated by LMWH for both doses. However it is the manufacturers opinion that the Re-Mobilize study is not generalisable to the England and Wales setting. The ERGs clinical advisors agree with this opinion.

7.3 Implications for research

Further trials of DBG compared to LMWH in both THR and TKR would serve to lessen the uncertainty surrounding the effectiveness and cost-effectiveness of these treatments. Follow up studies would be helpful to assess the effectiveness of DBG in an inpatient setting. Head to head trials of DBG versus fondaparinux would strengthen the evidence base for this comparison.

8. APPENDICES

Appendix 1: Quality Assessment using ScHARR-TAG economic modelling checklist

A statement of the problem

The problem is clearly defined.

A discussion of the need for modelling

There is no discussion surrounding any alternatives, although there is some justification for using the type of model employed.

A description of the relevant factors and outcomes

A clear description is provided.

A description of model including: type of model; time frame; perspective; and setting

All are clearly described.

A description of data sources, with description of respective strengths and weaknesses

All are clearly described.

Key assumptions relating to model structure and data stated

Key assumptions were clearly defined.

Disease specific factors included within modelling (Items to be specified in conjunction with expert clinical input)

All disease specific factors were clearly explained and verified by ERG clinical advisors.

Validation

The model was reviewed by the manufacturers' panel of experts. No internal, external or predictive validity was undertaken.

Results

The results are generalisable to the general population. No sub-group analysis was conducted.

Sensitivity analysis results

Both univariate and PSA was conducted. The methods and parameters included were satisfactory.

Appendix 2: Clarifications requested by the ERG to the manufacturers

Very Major

page	question / clarification / requirement
14	Please clarify why the RE-MOBILIZE study is included in effectiveness evaluation, if not appropriate for economic evaluation – inclusion and exclusion must be explained, as required
26	Please give complete list of the 15 excluded studies (please confirm that the 7 conference abstracts cited do report on trials subsequently published, i.e. the included RCTs or others)
26	Please provide a list of all citations identified by the search in BILIT and pre-BILIT; this will be required to validate the searches described in the submission. This is required because the search described in the submission has been rerun and only 10 items have been found, so it is assumed that 9 further unique citations were identified in BILIT and pre-BILIT. It is assumed that the RE-MOBILIZE trial was identified from this source as it was not found in the publicly accessible databases named.
26	Please highlight and explain that the RE-MOBILIZE trial is published as an abstract only – this is very important since a great deal of the data reported to be from this study in the submission are confidential and cannot be verified with reference to a published paper; this also affects the ERG's capacity to critically appraise this RCT
40	Please give baseline demographic and clinical characteristics of each study group in each trial, in accordance with point 14 on the CONSORT checklist, and highlight any differences between these within-trial groups, as required (presentation of overall trial demographic and clinical characteristics of all participants in a trial, Tables 13 and 14, was not required)
44, 45, 46	Please provide stages and numbers in complete accordance with the CONSORT flowchart, and point 13 on the CONSORT checklist *eg. please give numbers of eligible patients* *eg. please give reasons for withdrawals between randomization stage and treatment stage* *eg. please give numbers analyzed for both efficacy and safety endpoints, and numbers excluded from analysis with reasons*
59	Please provide tabulated responses (in a single table) to all critical appraisal questions, as required.
62, 64, 66	Please explain the modified ITT (mITT) analysis fully. It is presented here as the exact equivalent of the FAS, i.e. only those with evaluable venographs. It is presented as something different on p.60 Please report numbers of participants analyzed by FAS and analyzed by mITT. If they are not different, please state so explicitly Please also explain the rationale for exclusion of other treated patients from efficacy and safety analyses
70	Please provide random effects (RE) models for relative risk for the primary efficacy endpoint of the combined European trials (both FE and RE models are required for all analyses)
70	Please provide fixed and random effects models for relative risk for each dose for the combination of the two knee trials (RE-MODEL and RE-MOBILIZE). While it is appreciated that the combination of the European trials is

	valuable because it has high generalizability to the UK setting, there is also a case for combining the two knee trials as they concern the same population, with a much more similar risk of VTE (much higher and different from the hip population) and a more similar treatment duration. The inclusion of these analyses will provide NICE with all available information on which to base a decision, especially since there is otherwise only a single relevant RCT for each population to support the submission.
74	Please provide random effects models for relative risk for the secondary efficacy endpoint of the combined European trials (both FE and RE models are required for all analyses)
78	Please conduct meta-analyses of risk difference on both the primary and secondary endpoints, using both random and fixed effects models, as required.
78	Please conduct additional meta-analyses of risk difference on the combination of the RE-MODEL and RE-MOBILIZE trials
79	Currently, pooled analyses have only been performed on the secondary efficacy endpoint and no explanation has been given for the failure to perform this analysis on the primary efficacy endpoint (or safety endpoints). Also, the model used in the analysis that is provided is not described. Please perform such analyses, as required.
81 89	An MTC has been performed including fondaparinux, a specified comparator of the submission, but this included 5 fondaparinux trials, 2 of which arguably should not be included eg. hip fracture and abdominal surgery (I am assuming this is the case and this MTC has simply been copied from the NICE VTE guidance – although this is not made clear). If the MTC is to be retained: 1a) Please specify exactly the trials (references) that have been included in the MTC for each endpoint; the number and details of included trials relating to each intervention is completely unclear 1b) Please remove references to comparators not specified in the scope *eg. aspirin, stockings* 1c) Please explain the process of "estimation by adjusted indirect comparison" used to generate RRs for DBG and extended LMWH versus nil in the single intervention meta-analyses, and why no adjustment was possible for RE-NOVATE New analyses required: 2a) Please provide specific meta-analyses for an indirect comparison of relevant outcomes with fondaparinux, a specified comparator with DBG in this submission, in relevant combinations (*eg. possibly including but not restricted to 3 RCTs comparing fondaparinux with enoxaparin, the common comparator with DBG, 1 using the EU 40mg dose (elective hip), and 2 using the USA 30mg b.i.d dose (elective hip, and elective knee) eg. Lassen 2002, Bauer 2001, Turpie 2002). Alternatively, explain why these indirect comparisons with fondaparinux have not been performed (this does not include the comparison with placebo or nil*). 2b) Please perform a search for trials involving the submission's stated comparators (LMWH and fondaparinux) and report the results of that search (the current search for meta-analyses of all interventions is beyond the remit of this submission)

93	Please perform relevant meta-analyses (as above) using fixed and random effects models for bleeding outcomes, as required (*"if trials are designed to test significant differences between treatments with respect to an adverse effect, it should be reported in same detail as previous [efficacy] sections"*)

Major

page	question / clarification / requirement
Effectiveness Section	
2	Please provide a detailed and accurate contents list
3	Please note that the submission should not usually exceed 75 pages
8, 10, 13	Please justify both doses (220 mg and 150mg) – since the published RCTs do not distinguish between the populations receiving the 2 doses being evaluated, what is the evidence for the specified doses for the specific populations, *eg. the lower dose level for moderate renal impairment and elderly populations*?
14	Please clarify the comparator status of enoxaparin as a LMWH (*eg. what % of LMWH used is enoxaparin*)
14	Please clarify the statement that the rate of VTE and all-cause mortality in the comparator group in the RE-MOBILIZE trial was "uncharacteristically low"
16	Please include the results of the indirect comparisons (Section 5.6)
25	Please list the data sources searched, including any restrictions, as required by the QUORUM checklist. Please justify any restrictions of date
25	Please give information on supplementary methods used to identify studies (other than the searching of electronic databases), as required by the QUORUM checklist (*eg. handsearching of journals, reference and citation tracking*). If no such methods have been employed, please explain why
27	Please give the rationale behind the inclusion and exclusion criteria stated in 5.2.2, as required in 5.1, p.25
28	Please explain the processes by which data were extracted from the included studies, as required by the QUORUM checklist
30	Please explain the processes by which this trial was identified, and how any other studies were identified and excluded
38	Please provide, if possible, the dates defining the periods of recruitment and follow-up, in accordance with point 14 on the CONSORT checklist, as required
38	Please clarify any information given regarding points 9 and 10 on the CONSORT checklist, as required
39	Please clarify whether, and how the blinding process was evaluated, in accordance with point 11 on the CONSORT checklist, as required
44	Not all numbers are consistent with the published study, please check and revise flowchart or explain
61	Please justify the statement that VTE rates were "surprisingly low", and favouring the comparator
61	Please include median follow-up time of analysis, as required
66	Please justify statement that levels of VTE in comparator were "surprising"
68, 69	Please explain why secondary endpoints reported here do not correspond with the secondary endpoints as defined in Tables 15 and 16 previously
71-80	Please be consistent in using either trial names or trial numbers to identify trials, as required (p.3). Up to this point, trial names have been used, only to be replaced by trial numbers here.

80	Please give more detail on the sensitivity analyses *eg. numbers of missing events* *eg. highlight any significant differences between the therapies* *eg. explain why only the fixed effects model was chosen*
89, 92	Please clarify where the results are for the estimated pooled risk of HIT
94, 95	Please report absolute difference of DBG versus enoxaparin for major bleeding
94, 95	Please report absolute difference of DBG versus enoxaparin for clinically-relevant bleeding alone

Minor

page	**question / clarification / requirement**
12	Page number missing
23	Please check the dosing regimens and the differences between USA and EU according to the ACCP guidelines – the information given here differs from the information given on pp.36, 37
25, 215	Appendix 2, section 9.2: Please recheck the date ranges for the databases listed in Table 110 – are these correct?
25-26	It is stated that 2 reviewers screened all titles and abstracts "according to the inclusion and exclusion criteria as given below (section 5.2.2)". According to these criteria, only 3 RCTs would be included (the BISTRO II study would be excluded, for the reasons stated in 5.2.3). Please revise the numbers in 5.1, or explain the inclusion in 5.1 of the BISTRO II study according to the stated criteria
26	Please explain the inclusion of the BISTRO II trial in 5.2.1 (i.e. compares intervention with comparator, therefore included here, but excluded from included list by dose)
26	"The abstracts or papers . . . a further 15 were removed" – this sounds like a two-level screening process – please clarify exactly the process by which the 19 unique citations identified by the search were reduced to 4; also, does the generation of results not come BEFORE the selection by the 2 reviewers?
37	Please explain the differences, if any, between the populations receiving the different doses of DBG (Table 12)
39	Please explain why the justification of outcome measures appears under the section on trial methods (5.3.1), rather than Efficacy outcomes (5.3.4)
39	Please confirm the statement that all patients receiving twice daily subcutaneous injections is correct
40	Please explain the terms PK and PD
47	Please provide references for endpoints debate
48	Please provide references on stated associations of asymptomatic VTEs
79	Please explain the statement that the analyses "appear to favour enoxaparin" – they do favour enoxaparin, don't they?
83	Please explain how the Cochrane library differs from CENTRAL, is CENTRAL not a component of the Cochrane library? Please clarify which components of the Cochrane library were searched. Please explain why, if looking for meta-analyses only, a register of controlled trials was searched (CENTRAL)?
93	Please explain why extent of exposure is reported, it is not listed in the safety outcomes to be reported (p.49)
94, 95	Please explain the inclusion of a reference to the BISTRO II trial here (the

	trial was excluded, and there is no other reference to it in the submission)
103	Please provide references for endpoints debate
103	Please provide references on stated associations of asymptomatic VTEs
103	Please provide overview of results with reference to their critical appraisal
104	Please provide a reference(s) supporting the methodological approach adopted
Cost-effectiveness Section	
140	Table 57. Minor bleed = minor bleed + clinically relevant bleed. In the effectiveness section (pgs 94-95) major bleed is reported combined with clinically relevant bleed. Please provide a justification as to why minor bleed is combined with clinically relevant bleed in the cost-effectiveness section.
	Please repeat the cost-effectiveness analysis using estimates from a random effects model.
70	Please repeat the cost-effectiveness analysis using RRs from the fixed and random effects models for each dose for the combination of the two knee trials (RE-MODEL and RE-MOBILIZE), as requested above.

Appendix 3: Manufacturers response to clarification requests

Clinical effectiveness

A1. (incorporating B2 and B3)

A full list of the 15 excluded studies is provided below in **Table 1**, complete with reasons for exclusion.

Table 1 Papers excluded from the effectiveness evaluation

	Reference	Reason for exclusion
1	Caprini JA. 21st Cong of the International Society on Thrombosis and Haemostasis (ISTH), Geneva, 6 - 12 Jul 2007 J Thromb Haemost 5 (Suppl 2), (2007)	Abstract of pooled analysis of RE-MODEL, RE-NOVATE and RE-MOBILIZE. More detailed information from the pooled analysis is included Section 5.5 of the main submission and later in this document.
2	Eriksson BI. 21st Cong of the International Society on Thrombosis and Haemostasis (ISTH), Geneva, 6 - 12 Jul 2007 J Thromb Haemost 5 (Suppl 2), (2007)	Abstract - conference presentation of RE-NOVATE.
3	Kurth AA. 8th Cong of the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), Florence, 11 - 15 May 2007 (CD), (2007)	Abstract - conference presentation of RE-MODEL.
4	Troconiz IF. J Clin Pharmacol 47 (3), 371-382 (2007)	Not an RCT (pharmacokinetic study).
5	Eriksson BI. 48th Ann Mtg of the American Society of Hematology (ASH), Orlando, 9 - 12 Dec 2006 Blood 108, (2006)	Abstract - conference presentation of RE-MODEL.
6	Eriksson BI. 17th Int Cong on Thrombosis, Bologna, 26 - 30 Oct 2002 Pathophysiol Haemost Thromb 32 (Suppl 2), 69 (2002)	Not an RCT (dose-escalating study).
7	Stangier J. 18th Int Cong on Thrombosis, Ljubljana, 20 - 21 Jun 2004 Pathophysiol Haemost Thromb 33 (Suppl 2), 76-77 (2003)	Abstract of BISTRO-II - pharmacokinetic/pharmacodynamic data only, no clinical data presented.
8	Dahl OE. 18th Int Cong on Thrombosis, Ljubljana, 20 - 21 Jun 2004 Pathophysiol Haemost Thromb 33 (Suppl 2), 38-39 (2003)	Abstract – conference presentation of BISTRO-II (timing of initiation).
9	Eriksson BI. 18 Int Cong on Thrombosis, Ljubljana, 20 - 24 Jun 2004 J Thromb Haemost 3, 103-111 (2005)	Abstract – conference presentation of BISTRO-II (dose-response).
10	Eriksson BI. 17th Int Cong on Thrombosis, Bologna, 26 - 30 Oct 2002 J Thromb Haemost 2, 1573-1580 (2004)	Abstract of BISTRO-I (not an RCT).
11	Stangier J. Clin Pharmacokinet 47 (1), 47-59 (2008)	Not an RCT (pharmacokinetic study).
12	Stangier J. J Clin Pharmacol 45 (5), 555-563 (2005)	Not an RCT (pharmacokinetic study).
13	Pechlaner C. Lancet. 2007;370(9604):2002	Comment on RE-NOVATE.
14	National Horizon Scanning Centre, Year: 2006	Horizon scanning review.
15	N Ivanovic Centre for Reviews and Dissemination Year: 2007	Review.

The abstracts of the above records (where available) are provided in a separate document accompanying this written response.

The 7 conference abstracts referred to in point B2 of the clarification list are references 1, 2, 3, 5, 7, 8 and 9 in **Table 1**. We can confirm that these references report on clinical trials subsequently published in full (RE-NOVATE, RE-MODEL and BISTRO-II) with the exception of reference 1, which reports on the pre-specified pooled analysis of the phase-III trials detailed in section 5.5 of the main submission (and discussed later in this document).

A full list of the BILIT and pre-BILIT citations is provided in a separate document accompanying this written response. We can confirm that the 9 further unique citations referred to in point B3 of the clarification list were identified via this search, including the RE-MOBILIZE abstract.

A2. (incorporating B1 and B4)

In the main submission, it is stated that the RE-NOVATE and RE-MODEL clinical trials represent the pivotal evidence base for dabigatran etexilate (DBG) in the submission for regulatory approval in the EU. Further, the RE-MOBILIZE study provides supportive, as opposed to pivotal evidence. The differences between the designs of the studies, principally the different dosing regimens and treatment durations employed in the RE-MOBILIZE study, make it less applicable to the European/UK setting than the other two trials.

In the economic evaluation, we have attempted to ensure that the most appropriate evidence base is used for the UK setting, which clearly is the RE-NOVATE and RE-MODEL clinical trials.

Nevertheless, the submission template does not have the same criteria for study inclusion between the clinical effectiveness and cost-effectiveness sections. In the preamble to section 5 of the template, the instructions state the following:

"*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… 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).*"

Whilst the RE-MOBILIZE clinical trial is not a pivotal study, it is an active comparator phase-III RCT similar to RE-NOVATE and RE-MODEL. That is, the RE-MOBILIZE study provides additional evidence on the relative efficacy and safety of DBG, albeit under different study conditions. Although we believe the efficacy comparison in RE-MOBILIZE to be inappropriate for the UK setting, we would be reticent to exclude any data on the safety of DBG, irrespective of setting. In our opinion it is not for us to decide whether this evidence is appropriate and we believe it would be difficult to justify exclusion of the RE-MOBILIZE study from a general review of the clinical data on DBG. To do so would likely arouse suspicion. We would prefer to be transparent and present the data, allowing the reviewer to have access to all the evidence and draw their own conclusions.

However, importantly, this does not preclude the exclusion of RE-MOBILIZE from an economic evaluation applicable to a particular setting.

The RE-MOBILIZE study has been submitted and accepted for publication as a full manuscript but at the time of writing the timelines for publication are unknown. Consequently it is only currently available as an abstract as cited in the main submission.

A3. (incorporating B5-7)

Baseline demographics and clinical characteristics

Please find the baseline demographic and clinical characteristics for the three trials, stratified by treatment group presented in **Table 2** to **Table 4**.

Table 2 RE-NOVATE baseline demographics and clinical characteristics

	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Treated	1146 (100.0)	1163 (100.0)	1154 (100.0)	3463 (100.0)
Age [years]				
Mean (SD)	64.6 (10.4)	63.4 (11.1)	63.8 (10.8)	63.9 (10.8)
Median	65.0	65.0	65.0	65.0
Range	24 to 91	19 to 89	20 to 88	19 to 91
<65	536 (46.8)	578 (49.7)	572 (49.6)	1686 (48.7)
65-75	448 (39.1)	437 (37.6)	425 (36.8)	1310 (37.8)
>75	162 (14.1)	148 (12.7)	157 (13.6)	467 (13.5)
<70	770 (67.2)	785 (67.5)	777 (67.3)	2332 (67.3)
≥70	376 (32.8)	378 (32.5)	377 (32.7)	1131 (32.7)
Gender				
Male	510 (44.5)	496 (42.6)	503(43.6)	1509 (43.6)
Female	636 (55.5)	667 (57.4)	651(56.4)	1954 (56.4)
Race [N (%)]				
White	1137 (99.2)	1158 (99.6)	1146(99.3)	3441 (99.4)
Black	4 (0.3)	2 (0.2)	8 (0.7)	14 (0.4)
Asian	5 (0.4)	3 (0.3)	0 (0.0)	8 (0.2)
Height [cm]				
N	1146	1163	1151	3460
Mean (SD)	168 (9)	168 (9)	168 (10)	168 (9)
Median	168.0	168.0	168.0	168.0
Range	135 to 196	146 to 195	140 to 213	135 to 213
Weight [kg]				
Mean (SD)	78.6 (14.9)	79.1 (15.4)	77.8 (14.9)	78.5 (15.1)
Median	78.0	78.0	77.0	78.0
Range	36.5 to 140.0	44.0 to 142.0	40.0 to 142.0	36.5 to 142.0
Body Mass Index [kg/m²]				
N	1146	1163	1151	3460
Mean (SD)	27.7 (4.6)	27.8 (4.6)	27.5 (4.3)	27.7 (4.5)
Median	27.3	27.3	27.1	27.3
Range	16.4 to 50.8	17.1 to 48.2	16.2 to 48.9	16.2 to 50.8
CrCl at screening [mL/min]				
Missing	25 (2.2)	29 (2.5)	30 (2.6)	84 (2.4)
<30	4 (0.3)	0 (0.0)	7 (0.6)	11 (0.3)
30-50	76 (6.6)	60 (5.2)	71 (6.2)	207 (6.0)
50-80	384 (33.5)	402 (34.6)	395 (34.2)	1181 (34.1)
≥80	657 (57.3)	672 (57.8)	651 (56.4)	1980 (57.2)
Mean	88.6 (28.7)	90.3 (31.0)	88.9 (30.0)	89.3 (29.9)
Median	85.9	86.4	85.5	85.9
Range	26.4 to 231.0	30.2 to 295.7	22.4 to 238.7	22.4 to 295.7

In the RE-NOVATE trial, the demographic and baseline characteristics of the treated patients were similar in the three treatment groups. The median age was 65.0 years in all treatment groups; the percentages of patients in the age categories ≥70 years and >75 years were also similar in all treatment groups. The majority of patients were female in all treatment groups (55.5% for DBG 220 mg, 57.4% for DBG 150 mg and 56.4% for enoxaparin). Almost all patients were white (99.4%).

The median height was 168 cm in all treatment groups; median weight was 78.0 kg for both DBG groups and 77.0 kg in the enoxaparin group. The median BMI was 27.3 kg/m² in both DBG groups and 27.1 kg/m² in the enoxaparin group. The proportion of

obese patients, i.e. with a BMI >35kg/m², was 6.6% in the DBG 220 mg group, 7.8% in the DBG 150 mg group, and 4.4% in the enoxaparin group.

Creatinine clearance was determined at screening and was calculated using the Cockroft-Gault formula. The investigator was requested to calculate creatinine clearance only in cases where he suspected renal insufficiency. The median creatinine clearance was 85.9 mL/min in the DBG 220 mg group, 86.4 mL/min in the DBG 150 mg group, and 85.5 mL/min in the enoxaparin group. Four patients (0.3%) randomised to the DBG 220 mg group and 7 patients (0.6%) randomised to the enoxaparin group had a creatinine clearance below 30 mL/min. Overall 6.0% of patients had moderately impaired renal function (CrCl 30-50 mL/min) and 34.1% of all patients had mildly impaired renal function (CrCl 50-80 mL/min). However, the majority of patients (overall 57.2%) had normal kidney function (≥80 mL/min).

Table 3 RE-MODEL baseline demographics and clinical characteristics

	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Treated	679 (100.0)	703 (100.0)	694 (100.0)	2076 (100.0)
Age [years]				
Mean (SD)	67.3 (9.0)	67.5 (8.8)	68.3 (8.8)	67.7 (8.9)
Median	68.0	68.0	69.0	68.0
Age categories [years]				
<65	242 (35.6)	257 (36.6)	208 (30.0)	707 (34.1)
65-75	304 (44.8)	312 (44.4)	337 (48.6)	953 (45.9)
>75	133 (19.6)	134 (19.1)	149 (21.5)	416 (20.0)
<70	373 (54.9)	388 (55.2)	354 (51.0)	1115 (53.7)
≥70	306 (45.1)	315 (44.8)	340 (49.0)	961 (46.3)
Gender				
Male	238 (35.1)	252 (35.8)	216 (31.1)	706 (34.0)
Female	441 (64.9)	451 (64.2)	478 (68.9)	1370 (66.0)
Race				
White	671 (98.8)	690 (98.2)	689 (99.3)	2050 (98.7)
Black	5 (0.7)	8 (1.1)	4 (0.6)	17 (0.8)
Asian	3 (0.4)	5 (0.7)	1 (0.1)	9 (0.4)
Smoking history				
Missing	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Never smoked	488 (71.9)	502 (71.4)	518 (74.6)	1508 (72.6)
Ex-smoker	125 (18.4)	131 (18.6)	120 (17.3)	376 (18.1)
Smoker	65 (9.6)	70 (10.0)	56 (8.1)	191 (9.2)
Height, N	677	702	693	2072
Missing, N	2	1	1	4
Mean, (SD), [cm]	166 (10)	166 (10)	166 (10)	166 (10)
Median	165.0	165.0	165.0	165.0
Weight, N	679	703	693	2075
Missing, N	0	0	1	1
Mean (SD), [kg]	82.4 (14.6)	83.3 (15.0)	82.0 (15.3)	82.6 (15.0)
Median	81.0	82.0	80.0	81.0
Body Mass Index, N	677	702	692	2071
Missing, N	2	1	2	5
Mean (SD) [kg/m²]	29.9 (4.9)	30.1 (5.0)	29.8 (4.9)	29.9 (4.9)
Median	29.3	29.4	29.4	29.4
CrCl at screening [mL/min]				
N	653	677	677	2007
Missing	26	26	17	69
<30	1 (0.1)	1 (0.1)	2 (0.3)	4 (0.2)
30-50	37 (5.4)	36 (5.1)	57 (8.2)	130 (6.3)
50-80	234 (34.5)	235 (33.4)	256 (36.9)	725 (34.9)
≥80	381 (56.1)	405 (57.6)	362 (52.2)	1148 (55.3)
Mean (SD)	89.4 (28.7)	89.6 (28.1)	86.2 (28.5)	88.4 (28.4)
Median	86.6	87.2	82.4	85.1

In the RE-MODEL trial, the demographic characteristics were similar in all three treatment groups. The median age was 68.0 years (DBG 220 mg), 68.0 years (DBG 150 mg), and 69.0 years (enoxaparin); the percentage of patients of 70 years and older was 45.1% (DBG 220 mg), 44.8% (DBG 150 mg), and slightly higher at 49.0% in the enoxaparin group. The proportion of female patients was slightly lower in the DBG groups with 64.9% (DBG 220 mg), 64.2% (DBG 150 mg) than in the enoxaparin group with 68.9%. The mean BMI was also similar in all three treatment groups with 29.9, 30.1, and 29.8 kg/m^2, respectively. The vast majority of all patients were of white ethnic origin (overall 98.7%) with little differences between the three treatment groups. The majority of patients never smoked, and the proportion of non-smokers was slightly lower in the DBG groups (71.9% and 71.4%) than in the enoxaparin group (74.6%).

Only 4 patients, 1 patient in the DBG 220 mg group, 1 patient in the DBG 150 mg group, and 2 patients in the enoxaparin group had severely impaired renal function (creatinine clearance <30 mL/min). Moderately impaired kidney function (creatinine clearance 30 to 50 mL/min) was present in 5.4% (DBG 220 mg), 5.1% (DBG 150 mg), and 8.2% (enoxaparin) of patients. However, the majority of patients in all treatment groups had normal kidney function with creatinine clearance ≥80 mL/min (DBG 220 mg: 56.1%, DBG 150 mg: 57.6%, enoxaparin: 52.2%).

Table 4 RE-MOBILIZE baseline demographics and clinical characteristics

	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Treated	857 (100.0)	871 (100.0)	868 (100.0)	2596 (100.0)
Age [years]				
Mean (SD)	66.2 (9.5)	65.9 (9.5)	66.3 (9.6)	66.1 (9.5)
Median	67.0	66.0	67.0	67.0
Age categories [years]				
<65	350 (40.8)	358 (41.1)	340 (39.2)	1048 (40.4)
65-75	353 (41.2)	367 (42.1)	373 (43.0)	1093 (42.1)
>75	154 (18.0)	146 (16.8)	155 (17.9)	455 (17.5)
<70	526 (61.4)	535 (61.4)	519 (59.8)	1580 (60.9)
≥70	331 (38.6)	336 (38.6)	349 (40.2)	1016 (39.1)
Gender				
Male	371 (43.3)	364 (41.8)	364 (41.9)	1099 (42.3)
Female	486 (56.7)	507 (58.2)	504 (58.1)	1497 (57.7)
Race				
White	745 (86.9)	740 (85.0)	757 (87.2)	2242 (86.4)
Black	34 (4.0)	38 (4.4)	28 (3.2)	100 (3.9)
Asian	78 (9.1)	93 (10.7)	83 (9.6)	254 (9.8)
Height, N	857	871	868	2596
Mean, (SD), [cm]	167.2 (10.5)	166.8 (10.8)	167.3 (10.8)	167.1 (10.7)
Median	166.0	165.0	168.0	166.5.0
Weight				
Mean (SD), [kg]	88.4 (19.1)	87.6 (20.0)	88.0 (19.2)	88.0 (19.4)
Median	86.0	85.7	86.2	86.0
Body Mass Index				
Mean (SD) [kg/m²]	31.6 (6.0)	31.4 (6.1)	31.4 (6.0)	31.5 (6.0)
Median	30.6	30.3	30.5	30.5
CrCl at screening [mL/min]				
N	857	871	868	2596
Missing	13	15	9	37
<30	5 (0.6)	6 (0.7)	5 (0.6)	16 (0.6)
30-50	86 (10.0)	89 (10.2)	91 (10.5)	266 (10.2)
50-80	327 (38.2)	374 (42.9)	349 (40.2)	1050 (40.4)
≥80	426 (49.7)	387 (44.4)	414 (47.7)	1227 (47.3)
Mean (SD)	83.6 (30.1)	82.3 (30.0)	82.9 (29.5)	82.9 (29.9)
Median	80.3	77.3	78.6	78.3

In the RE-MOBILIZE trial, the demographic characteristics at baseline were similar for all treatment groups. The median age was 67.0 years (DBG 220 mg), 66.0 years (DBG 150 mg), and 67.0 years (enoxaparin); the percentage of patients 70 years and older was 38.6% (DBG 220 mg), 38.6% (DBG 150 mg), and 40.2% (enoxaparin). The proportion of female patients was 56.7% (DBG 220 mg), 58.2% (DBG 150 mg), and 58.1% (enoxaparin). The mean BMI was similar in all 3 treatment groups with 31.6, 31.4, and 31.4 kg/m^2 for DBG 220 mg, 150 mg and enoxaparin, respectively. Most patients were of white ethnic origin; 86.9% (DBG 220 mg), 85.0% (DBG 150 mg), and 87.2% (enoxaparin). Approximately half the patients from each treatment group had never smoked: 49.9% (DBG 220 mg), 50.2% (DBG 150 mg), and 52.9% (enoxaparin). The majority of the patients were from North America with 91.2%, 91.0% and 91.2% in the DBG 220 mg, DBG 150 mg, and enoxaparin treatment group, respectively.

A total of 16 patients (5 patients in the DBG 220 mg group, 6 in the DBG 150 mg group, and 5 in the enoxaparin group) had severely impaired renal function (creatinine clearance <30 mL/min) at baseline. Moderately impaired kidney function (creatinine clearance 30 to 50 mL/min) was present in 10.0% (DBG 220 mg), 10.2% (DBG 150 mg), and 10.5% (enoxaparin) of patients. The median creatinine clearance at baseline was 80.3 mL/min (DBG 220 mg), 77.3 mL/min (DBG 150 mg), and 78.6 mL/min (enoxaparin).

Participant involvement

In the RE-NOVATE study 3,613 patients were enrolled. One hundred and nineteen patients were not randomised since these patients did not meet some inclusion or exclusion criteria, withdrew informed consent, or experienced an adverse event prior to randomisation.

Therefore, 3,494 patients were randomised. Thirty-one randomised patients (DBG 220 mg: 12; DBG 150 mg: 11; enoxaparin: 8 patients) were not treated. Three patients did not receive any trial medication because of adverse events related to the surgery, 4 patients were not treated due to protocol violations, and 14 patients withdrew informed consent. Additionally, 10 patients were not treated because of “other reasons” including pre-dominantly re-scheduled surgery or patient’s unsuitable medical conditions.

Overall, 3,463 patients were treated (DBG 220 mg: 1,146; DBG 150 mg: 1,163; enoxaparin: 1,154). This group formed the largest analysis dataset (safety set/treated set) which comprised all treated patients (3,463). A patient was regarded as treated if he or she received at least 1 dose of trial medication, i.e. DBG, enoxaparin, or placebo.

The treated and operated population (FAS-op, n=3,435; DBG 220 mg: 1,137; DBG 150 mg: 1,156; enoxaparin: 1,142) was smaller than the treated population (n=3,463) since for most patients study drug (enoxaparin or matching placebo) was initiated the night before the planned surgery. Some patients received study drug, but then did not undergo the planned surgery. This analysis set was the basis for the analysis of bleeding events and symptomatic efficacy events.

Baseline diagnostic testing for the presence of VTEs by routine venography in patients scheduled for elective total hip replacement is neither feasible nor practical. Therefore, the trial protocol as well as the statistical analysis plan specified that the analysis populations for each efficacy endpoint be established on the basis of the inclusion of patients evaluable for that particular endpoint. To be included in the analyses of efficacy endpoints, the patients had to be randomised, had to receive treatement with study drug, had to undergo surgery, and had to have an evaluable venogram or an event that qualified for the primary endpoint (i.e. symptomatic VTE or death).

The largest analysis set for the analysis of efficacy endpoints was the treated and operated set (FAS-op). All other efficacy analysis sets were sub-sets of this population but were not necessarily nested within each other. The full analysis set (FAS) was defined as all patients who were treated, operated, and had venograms evaluable for distal and proximal DVT, or a symptomatic DVT, or pulmonary embolism confirmed by the central adjudication committee, or had died during the treatment period. The FAS consisted in total of 2651 patients overall (dabigatran 220 mg: 880 patients [77.4%], dabigatran 150 mg: 874 patients [75.6%], and enoxaparin:

897 patients [78.5%]); overall these were 77.2% of the patients belonging to the treated and operated set. Hence, the percentages of patients excluded from the FAS were similar in all treatment groups. In the trial protocol it was assumed that 35% of the patients would have non-evaluable venographies and hence only 65% of patients would have evaluable venographies. In fact, in this study, overall 76.5% of the treated and operated patients had an evaluable venography and were included in the FAS, further evidence that this study was conducted to a high standard.

In the RE-MODEL study a total of 2,183 patients were enrolled after informed consent. Of these 82 patients were not randomised to treatment, as either these patients did not meet the inclusion or exclusion criteria.

Overall, 2,101 patients were randomised to treatment, 25 patients were not treated because patients did not undergo surgery (n=19) and/or withdrew consent (n=9). Over all groups, 2,076 patients received treatment, 679 patients in the DBG 220 mg group, 703 patients in the DBG 150 mg group, and 694 patients in the enoxaparin group.

The largest analysis set was the safety set which comprised all patients who were randomised and received at least one oral dose or one subcutaneous injection (n=2,076). Of these, 4 patients (DBG 220 mg), 7 patients (DBG 150 mg), and 9 patients (enoxaparin) were not operated leaving 675 patients (DBG 220 mg), 696 patients (DBG 150 mg), and 685 patients (enoxaparin) who received treatment and underwent surgery; this population constituted the FAS-op analysis set.

The full-analysis set (FAS) was defined as all patients who received treatment and underwent surgery, had an evaluable venogram for distal and proximal DVT, or confirmed symptomatic DVT, PE, or had died. Overall, this population comprised 1,541 patients (75.0%) of all patients treated and operated. In all treatment groups, similar proportions of patients (DBG 220 mg: 25.5%, DBG 150 mg: 24.4%, enoxaparin: 25.3%) were excluded from the FAS-op to form the FAS. For almost all of these patients, the reason for the exclusion from FAS was the lack of an evaluable venogram. Only 2 patients in the DBG 150 mg group and 1 patient in the enoxaparin group had either a PE or had died prior to the venography. In the calculation of the sample size in the study protocol, a rate of 25% of non-evaluable venograms was assumed and hence the observed rate was very similar to the expected rate.

For the analysis of major VTE and VTE-related mortality, the FAS-major population was used that comprised 1,544 patients (75.1%). For the analysis of proximal DVT, FAS-pDVT was used comprising 1,541 (75.0%) patients; for the analysis of the total DVT, i.e. proximal and distal DVTs, the FAS-tDVT population was used (n=1,538, 74.8%). Finally the per-protocol set (PPS) comprised 1,439 (70.0%) patients without important protocol violations.

In the RE-MOBILIZE study a total of 3,016 patients were screened after informed consent. Of these 401 patients were not randomised to treatment as the patients did not meet the inclusion or exclusion criteria. It is not surprising that this number is much higher in RE-MOBILIZE than either RE-NOVATE or RE-MODEL. In RE-MOBILIZE, patients were randomised to treatment post-surgery, whereas randomisation took place pre-surgery in RE-NOVATE and RE-MODEL. Therefore any patient experiencing complications or events, either during surgery or in the immediate post-operative period, would be excluded. Overall, 2,615 patients were randomised to treatment, 19 patients were not treated. Over all groups, 2,596 patients received treatment, 857 patients in the DBG 220 mg group, 871 patients in the DBG 150 mg group, and 868 patients in the enoxaparin group.

This group formed the largest analysis set for this study (safety set). The full analysis set (FAS) was defined as all patients who had surgery and were randomised, received treatment, had an evaluable venogram for distal and proximal DVT, or had confirmed symptomatic DVT, PE, or had died. Overall, this population comprised 1,896 (73.0%) treated patients. Similar proportions of treated patients in the three arms were included in the FAS (DBG 220 mg: 70.5%, DBG150 mg: 74.5%, enoxaparin: 74.1%). The majority of patients who were excluded from the FAS did not have an evaluable venogram. A 25% non-evaluable venogram rate was assumed for calculating the sample size of the study; the observed rate of non-evaluable venograms was not unexpected. Four patients in the DBG 220 mg group, 1 in the DBg 150 mg group and 4 in the enoxaparin group had either a PE or died prior to the venography.

The FAS-major population was used for the analysis of major VTE and VTE-related mortality that comprised 1,942 patients (74.8%). The FAS-pDVT was used for the analysis of proximal DVT, including 1,934 (74.5%) patients. The FAS-tDVT population was used for the analysis of total DVT (proximal and distal DVTs; n=1,887, 72.7%). The PPS consisted of 1,811 (69.8%) patients without important protocol violations.

The analysis sets for each trial are summarised in **Table 5** to **Table 7**.

Table 5 RE-NOVATE analysis sets

	Dabigatran 220 mg N (%)	Dabigatran 150 mg N (%)	Enoxaparin N (%)	Total
Treated	1146	1163	1154	3463
Treated and operated	1137 (100.0)	1156 (100.0)	1142 (100.0)	3435 (100.0)
Total VTE and all-cause mortality (FAS)	880 (77.4)	874 (75.6)	897 (78.5)	2651 (77.2)
Major VTE and VTE related mortality (FAS-major)	909 (79.9)	888 (76.8)	917 (80.3)	2714 (79.0)
Proximal DVT (FAS-pDVT)	905 (79.6)	885 (76.6)	914 (80.0)	2704 (78.7)
Total DVT (FAS-tDVT)	874 (76.9)	871 (75.3)	894 (78.3)	2639 (76.8)
Symptomatic DVT (FAS-op)	1137 (100.0)	1156 (100.0)	1142 (100.0)	3435 (100.0)
PE (FAS-op)	1137 (100.0)	1156 (100.0)	1142 (100.0)	3435 (100.0)
Death (FAS-op)	1137 (100.0)	1156 (100.0)	1142 (100.0)	3435 (100.0)
Total VTE and all-cause mortality without major protocol violation (PPS)	816 (71.8)	812 (70.2)	824 (72.1)	2452 (71.4)

Table 6 RE-MODEL analysis sets

Analysis set *(criteria for inclusion)*	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Randomised, N	693**	708	699	2101
Safety set, N *(Randomised and treated*)*	679	703	694	2076
FAS-op, N (%) *(Treated and operated)*	675 (100.0)	696 (100.0)	685 (100.0)	2056 (100.0)
Full analysis set (FAS), N (%) *(evaluable venogram for distal and proximal DVT, or symptomatic DVT, PE, death)*	503 (74.5)	526 (75.6)	512 (74.7)	1541 (75.0)
FAS-major, N (%) *(evaluable venogram for proximal DVT, or confirmed symptomatic proximal DVT, PE, VTE-related death)*	506 (75.0)	527 (75.7)	511 (74.6)	1544 (75.1)
FAS-pDVT, N (%) *(evaluable venogram for proximal DVT or confirmed symptomatic proximal DVT)*	506 (75.0)	525 (75.4)	510 (74.5)	1541 (75.0)
FAS-tDVT, N (%) *(evaluable venogram for total VTE or confirmed symptomatic DVT)*	503 (74.5)	524 (75.3)	511 (74.6)	1538 (74.8)
Per-protocol set, N (%) *(Patients in FAS without relevant protocol deviations)*	475 (70.4)	494 (71.0)	470 (68.6)	1439 (70.0)

* Received at least one dose of oral study medication or at least one subcutaneous injection
** Patient 3693 was randomized to Dabigatran 220 mg (kit no 1915) but never received any treatment. The investigator reassigned the kit to patient 3689. Thus, 694 patients underwent randomisation to the dabigatran 220 mg group.

Table 7 RE-MOBILIZE analysis sets

Analysis set *(criteria for inclusion)*	Dabigatran 220 mg	Dabigatran 150 mg	Enoxaparin	Total
Randomised, N	862	877	876	2615
Safety set, N *(Randomised and treated*)*	857	871	868	2596
FAS-op, N (%) *(Treated and operated)*	857 (100.0)	871 (100.0)	868 (100.0)	2596 (100.0)
Full analysis set (FAS), N (%) *(evaluable venogram for distal and proximal DVT, or symptomatic DVT, PE, death)*	604 (70.5)	649 (74.5)	643 (74.1)	1896 (73.0)
FAS-major, N (%) *(evaluable venogram for proximal DVT, or confirmed symptomatic proximal DVT, PE, VTE-related death)*	618 (72.1)	656 (75.3)	668 (77.0)	1942 (74.8)
FAS-pDVT, N (%) *(evaluable venogram for proximal DVT or confirmed symptomatic proximal DVT)*	614 (71.6)	656 (75.3)	664 (76.5)	1934 (74.5)
FAS-tDVT, N (%) *(evaluable venogram or confirmed symptomatic DVT)*	600 (70.0)	648 (74.4)	639 (73.6)	1887 (72.7)
Per-protocol set, N (%) *(Patients in FAS without relevant protocol deviations)*	580 (67.7)	621 (71.4)	610 (70.3)	1811 (69.8)

* Received at least one dose of oral study medication or at least one subcutaneous injection

Critical appraisal of trials

Table 8 Critical appraisal of included clinical trials

Trial aspect	RE-NOVATE	RE-MODEL	RE-MOBILIZE
How was allocation concealed?	Each phase-III trial had a double blind, double dummy design. Randomisation was blinded to both investigators and patients. 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. Prior to database lock, procedures were in place to ensure that individuals associated with the conduct of the studies 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 teams nor were they entered into the trial databases until after database lock.		
What randomisation technique was used?	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.		
Was a justification of the sample size provided?	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. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.	Depending on the assumed incidence rates, sample sizes were calculated to achieve 90% power to state non-inferiority with a margin of 9.2% difference for total VTE and all-cause mortality. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.	Depending on the assumed incidence rates, sample sizes were calculated to achieve 90% power to state non-inferiority with a margin of 9.2% difference for total VTE and all-cause mortality. Preservation of 2/3 of the benefit of enoxaparin compared to placebo was acceptable to the FDA as an appropriate non-inferiority margin based on historical data.
Was follow-up adequate?	Yes. Follow up to 3 months. Mean duration of study 94 days. Haematology & clinical chemistry tests performed at 2 & 3months with focus on LFTs.	Yes. Follow up for 3 months. Haematology & clinical chemistry tests performed at 3 months with focus on LFTs.	Yes. Patients were followed up for 12-14 weeks.
Were the individuals undertaking the	No. The independent VTE endpoint adjudication committees performed their work blinded to randomised treatment		

outcomes assessment aware of allocation	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.		
Was the design parallel-group or crossover?	Parallel	Parallel	Parallel
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?	Multinational. No UK centres. European, Australian & S African populations. Similar to recommended UK practice, refer to NICE clinical guideline (reference 1 of the main submission).	Multinational. No UK centres. European, Australian & S African populations. Similar to recommended UK practice, refer to NICE clinical guideline (reference 1 of the main submission).	No, conducted in North America (with the exception of three UK patients). 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.	Population similar to UK population based on UK census data (please refer to tables 46 to 48 and accompanying text in the main submission).	Population similar to UK population (please refer to tables 46 to 48 and accompanying text in the main submission).	Broadly similar, though with a higher proportion of black patients, and slightly older age group (please refer to tables 46 to 48 and accompanying text in the main submission).
What dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	DBG: 220mg or 150mg od, starting with a half dose 1-4 hours after surgery Enoxaparin: 40mg od, starting the day before surgery. Both are in line with UK SPCs.	DBG: 220mg or 150mg od, starting with a half dose 1-4 hours after surgery Enoxaparin: 40mg od, starting the day before surgery Both are in line with UK SPCs.	DBG: 220mg or 150 mg od, starting 6-12 hours after surgery This is the same dose as UK SPC, but initiation is outside marketing authorisation. Enoxaparin: 30mg bd, starting 12-24 hours after surgery. This is a higher dose and later initiation than the UK SPC (but complies with the American label). Duration was 12-15 days for both

			treatments, which is outside the UK SPCs.
Were the study groups comparable?	Yes. Demographic and surgical characteristics were similar across treatment groups within each study.		
Were the statistical analyses used appropriate?	Yes. The endpoints considered and the non-inferiority design complies with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission).		
Was an intention-to-treat analysis undertaken?	The primary analysis was based on the Full Analysis Set (FAS) that was comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, and had an evaluable venogram or confirmed symptomatic DVT, PE, or death. This set is regarded as a modified intention to treat population in this type of study.		
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	The inclusion criteria were selected to allow entry of a representative yet homogeneous sample of patients undergoing primary elective total hip or knee replacement surgery. The exclusion criteria prevented entry of patients with significant co-morbidities or those whose participation might have represented a health risk for the patient. There is debate around the use of venographically confirmed VTE as the primary endpoint. It can be argued that symptomatic VTE and VTE-related mortality is a more clinically relevant outcome. However the problems associated with the use of this endpoint are well documented (i.e. the rarity of the event) and the primary endpoint adheres with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission).	The inclusion criteria were selected to allow entry of a representative yet homogeneous sample of patients undergoing primary elective total knee replacement surgery. The exclusion criteria prevented entry of patients with significant co-morbidities or those whose participation might have represented a health risk for the patient. There is debate around the use of venographically confirmed VTE as the primary endpoint. It can be argued that symptomatic VTE and VTE-related mortality is a more clinically relevant outcome. However the problems associated with the use of this endpoint are well documented (i.e. the rarity of the event) and the primary endpoint adheres with the EMEA guideline for study development in this therapeutic area (reference 29 in the main submission).

		As discussed, the dosing regimens, points of initiation and treatment durations in this study confound the results with respect to the UK setting.

DBG, dabigatran etexilate; DVT, deep vein thrombosis; LFT, liver function test; PE, pulmonary embolism; PK/PD, pharmacokinetic/pharmacodynamic; od, once daily dosing; SPC, summary of product characteristics; VTE, venous thromboembolism.

A4. (incorporating B9-13 and B16)

The full set of meta-analyses to cover all doses, endpoints and combination of trials is extensive. In the main submission, our intention was to present sufficient analyses to illustrate the trends in the results without overburdening the document. However, we acknowledge that the reasons for exclusion of the remaining analyses could have been made clearer.

The remaining analyses (for relative risk) are presented at the end of this document in **Figure 1** through **Figure 30**. The full set of analyses for risk difference is presented in a separate document accompanying this written response.

A5. (incorporating B14)

As stated in the main submission, the purpose of the pre-specified pooled analysis was to examine the secondary efficacy endpoint using a larger population than a single trial could permit. The EMEA guideline for development of studies in this therapeutic area (reference 29 in the main submission) advocates the use of the primary endpoint from the three DBG trials. It may be argued that the secondary endpoint (major VTE and VTE-related death) is more clinically relevant, however these events are rare and single trials powered to study this endpoint would need to be extremely large. This analysis was pre-specified for this particular purpose and should not be confused with a standard set of meta-analyses covering several endpoints.

Accordingly, no further analyses were performed as part of this study on other endpoints and therefore there is nothing additional for us to present.

This was a pooled analysis based on the summary statistics calculated for the three individual phase-III trials. The analysis used the overall absolute risk difference across the three studies and the 95% confidence interval for incidence of major VTE and VTE-related mortality during the treatment period, using a fixed effects model. As stated in the main submission, 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.

A6. (incorporating B8)

We apologise for any confusion caused by the use of the term “modified intention to treat analysis” (mITT) in the main submission. As presented in the response to A3, the analysis set used depends on the endpoint under consideration. In the main submission, we have used mITT as a catch-all term to represent the appropriate analysis set for each endpoint.

A7 and A8. (incorporating B15)

It is necessary to clarify the background and the rationale behind the choice of mixed treatment comparison (MTC).

In preparation for the potential submissions for health technology appraisal of DBG, it is not feasible to wait for a final scope to be issued by NICE before performing an indirect comparison that would exactly isolate a comparison of DBG with whichever indirect comparator is deemed appropriate. Such therapies (other than LMWH) differ significantly between countries, even within the UK (aspirin is an appropriate

comparator for Scotland), and therefore a comprehensive MTC that compared DBG with the full range of possible comparators was most desirable. Nevertheless, such an analysis must also be robust in terms of methodology and included studies.

Crucially, it must be clearly pointed out that the MTC presented in the main submission is based on that presented by the NCC-AC (reference 41 in the main submission), which formed the basis for the economic evaluation within the NICE clinical guideline on VTE prevention in surgical patients (reference 1 in the main submission). This analysis was selected following a systematic review of meta-analyses in this indication as the most robust and up-to-date study on which to base our MTC.

The methods and results of this study are outlined concisely in Section 12 of the NCC-AC report. The analysis included data from all relevant RCTs identified by the NCC-AC's clinical review. Full evidence tables for included studies are listed in Appendix D to the NCC-AC report.

In order to draw indirect comparisons between DBG and prophylactic interventions other than LMWH (including fondaparinux), the relative risks (RRs) for DBG versus enoxaparin were combined with RRs for LMWH versus Nil (estimated by the NCC-AC MTC), in order to estimate the RR for dabigatran versus Nil. Relative risks were combined using the adjusted indirect comparison method of Bucher *et al*., (1997) (reference 69 in the main submission) as follows:

> If DBG is represented as D; the comparator as C and the common agent (LMWH) as A; and
>
> Estimates of RR are represented as follows:
>
> - dabigatran vs the common agent: RR_{DA} and
> - the comparator vs the common agent: RR_{CA} (available from the NCC-AC meta-analysis).
>
> Then, using the method of Bucher, the RR for dabigatran vs the comparator (RR_{DC}) is given by:
>
> $$\ln RR_{DC} = \ln RR_{DA} - \ln RR_{CA}$$
>
> and the variance of RR_{DC} is given by:
>
> $$\text{Var}(\ln RR_{DC}) = \text{Var}(\ln RR_{DA}) + \text{Var}(\ln RR_{CA})$$
>
> Assuming that lnRR is normally distributed, then the upper 95% confidence interval (UCI) and lower 95% confidence interval (LCI) may be estimated as:
>
> $$\ln UCI_{DC} = \ln RR_{DC} + 1.96 \times \text{Var}(\ln RR_{DC})$$
> $$\ln LCI_{DC} = \ln RR_{DC} - 1.96 \times \text{Var}(\ln RR_{DC})$$

In reply to point 1c) of B15: This refers to the methods employed in the meta-analyses for accounting for the differing durations of treatment in the three DBG trials. In essence, it is assumed that the treatment effect is independent of the duration of treatment provided that the durations are the same for both agents. In this way, the meta-analyses give a measure of treatment effect for DBG versus enoxaparin that is not specific to any duration of treatment.

However, the RE-NOVATE study compared extended duration DBG with extended duration enoxaparin (28-35 days). Therefore the statement "No adjustment of meta-analysed RRs was possible for the extended regimen in trial 1160.48 (RE-NOVATE)" indicates that although RE-NOVATE data were included in the meta-analysis, no adjustment for the extended duration of treatment was made. In the analyses under question, all the RRs for DBG represent standard duration of treatment with the exception of the RR for RE-NOVATE only.

In reply to point B15, 2a):

We would like to make clear that we have made a similar assumption to that of NCC-AC that relative treatment effect of the various thromboprophylactic alternatives is independent of surgery type. Whilst developing this analysis, we contacted the authors of the NCC-AC report with the aim of confirming the quality of the analysis and, in particular, investigating the heterogeneity they may have discovered in their analysis. In their personal communication to us, the authors ("The NCC-AC Team", personal communication, February 2007) confirmed the following:

"Question: Section 3.10 mentions sub-group analysis by surgery type but I couldn't see any mention of this in the results section. Were analyses performed for individual surgery types, or sub-sets of surgery types?

Response: The subgroups were for each surgical speciality (i.e. general, gynaecological, orthopaedic, neurosurgery, cardiac, thoracic, neurosurgery, urology, vascular and mixed).

Question: To your knowledge, is there evidence that treatment effect varies by surgery type?

Response: We tested for heterogeneity within the subgroup analyses and found no convincing evidence of a difference between surgery types."

As such, we regard the MTC presented in the main submission as a robust analysis utilising all the available evidence and based on sound assumptions.

In your request, we are unsure whether you are asking us to (A) perform an indirect comparison within the meta-analysis (e.g. a meta-regression of the fondaparinux and DBG clinical trials) or (B) just a meta-analysis of the fondaparinux trials. If the analysis is to include the DBG trials, it is not clear which trials should be included.

If B is the request, the second analysis requested (US dose) has already been presented in Appendix E (Figure 147-150) to the NCC-AC report. In terms of the first analysis requested, this request seems to contradict point B10 which states: "*there is a case for combining the two knee trials as they concern the same population.*" Rather than mix the THR and TKR populations the NCC-AC included a sub-analysis of the 5 fondaparinux trials with a different approach, focussing on timing of initiation and different doses:

1) vs Pre-op LMWH: Agnelli (dalteparin, abdominal surgery); Eriksson (40mg enoxaparin, femoral fracture); Lassen (40mg enoxaparin, THR)
2) vs Post-op LMWH: Bauer (30mg enoxaparin, TKR); Turpie (30mg enoxaparin, THR)

It is likely that this choice of approach was a result of their findings relating to lack of evidence of differences between treatment effects across types of surgery.

Unfortunately there has been insufficient time to perform the extra analyses requested in point B15 2a). If these are absolutely required then they can be performed if extra time can be granted. However we believe that the analyses outlined above should be sufficient to address the concerns that have been raised.

In response to point B15 2b): We would like to express our concerns as to the validity of this request. Given that this submission concerns a single technology appraisal of dabigatran etexilate, we do not believe that it is required of us to complete full literature searches on clinical evidence for comparator medications. Nevertheless, a full literature search of both LMWH and fondaparinux was completed by the NCC-AC and we are confident that this search was of sufficient quality to satisfy the requirements of the indirect comparison.

We would also like to emphasise a general point regarding the indirect comparison with fondaparinux. We remain to be convinced that the comparison of DBG with fondaparinux is appropriate to practice in England and Wales. Whilst we acknowledge that fondaparinux is recommended as an alternative to LMWH in the NICE clinical guideline, this agent is very rarely used in standard practice as demonstrated by data from the National Joint Registry (reference 16 in the main submission). We would urge reviewers to place this comparison in context when critically assessing its methods and results.

A9.

We are concerned by this request which asks us to speculate on possible discounts or contract prices offered by competitors to hospitals, whilst ignoring any discounts that may be offered by ourselves. We have used the published NHS list prices of all the medications in our economic evaluation as recommended by the NICE Guide to Methods of Technology Appraisals. We acknowledge that the Methods Guide also states that any variations between public list price and actual price should be assessed in sensitivity analysis. However such prices that may be offered by our competitors are not in the public domain, and we have no evidence to suggest that any such discounts are of greater or lesser magnitude to discounts that we may offer following the launch of DBG.

Further, it should be noted that we have already reduced the price of LMWH in the base case from the list price of enoxaparin to a notional weighted average including the less expensive LMWH alternatives.

Cost-effectiveness

A10. (incorporating B17)

In the clinical effectiveness section, the bleeding rates from the DBG trials are presented in as disaggregated a form as possible with regards to definition of event. However in the economic evaluation, it was necessary to use a set of definitions that were as consistent as possible across all comparators. In our analyses, as it was feasible for a patient to have both a major and clinically relevant bleed, the categories “Major”, “Clinically Relevant” and “Minor” were based on the “worst” event data, and were therefore mutually exclusive. As an example, the data for the DBG 220mg treatment group of RE-MODEL were:

1. Major; 10/679
2. Clinically Relevant: 40/679

3. Clinically relevant and Minor combined: 100/679

Category 1 (Major) and 3 (Clinically relevant and Minor combined) were used in the economic evaluation. In our analysis of the NCC-AC trials for the minor bleed endpoint, minor bleed was defined as any bleed reported in the study that was not categorised as a major bleed (as defined in each individual study - there was no option but to rely on original study endpoint definitions). Unfortunately this was the closest we could get to equivalent definitions of major and minor bleed for the various possible interventions in the economic evaluation.

In the direct comparison, any difference between DBG and enoxaparin created by adjusting the definition of major and minor bleeding is unlikely to affect the overall results. In the indirect comparison, by categorising clinically relevant bleeding as minor bleed (which in the economic evaluation has minimal cost and quality of life impact), this approach is likely to favour fondaparinux which has a less favourable bleeding profile than DBG.

A11-12. (incorporating B18-19)

Table and Table present the overall results of the model utilising further meta-analysed estimates for the primary efficacy endpoint, major and minor bleed.

As would be expected, inclusion of the RE-MOBILZE data to the analysis shifts the results against DBG. However we would like to reiterate that we believe these analyses to be inappropriate to the England and Wales setting. Whilst the populations in RE-MODEL and RE-MOBILIZE may be similar, RE-MOBILIZE considers dosing regimens, treatment initiation and durations outside the UK marketing authorisations for both DBG and enoxaparin.

Table 9 Overall results utilising expanded set of meta-analyses (DBG 220mg)

	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%**
	Treatment effects						
B	RE-NOVATE + RE-MODEL (random)	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%	88%
C	RE-MOBILIZE + RE-MODEL (fixed)	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MNB: 1.04 (THR) 0.96 (TKR)	VTE: 1.08 MJB: 0.73 MNB: 0.97	N/A	DOMINATED	N/A	35%
D	RE-MOBILIZE + RE-MODEL (random)	VTE: 0.90 (THR) 0.97 (TKR) MJB: 1.29 (THR) 1.14 (TKR) MNB: 1.04 (THR) 0.96 (TKR)	VTE: 1.09 MJB: 0.72 MNB: 0.97	N/A	DOMINATED	N/A	40%

CE, cost-effectiveness; DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; 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 10 Overall results utilising expanded set of meta-analyses (DBG 150mg)

	Description of sensitivity analysis	Original value	New value	ICER (THR)	ICER (TKR)	Probability of CE (THR)	Probability of CE (TKR)
	Base case	**-**	**-**	**DOMINANT**	**DOMINATED**	**76%**	**38%**
	Treatment effects						
E	RE-NOVATE + RE-MODEL (fixed)	VTE: 1.28 (THR) 1.07 (TKR) MJB: 0.83 (THR) 0.99 (TKR) MNB: 1.11 (THR) 1.00 (TKR)	VTE: 1.12 MJB: 0.88 MNB: 1.05	DOMINANT	DOMINATED	99%	20%
F	RE-NOVATE + RE-MODEL (random)	VTE: 1.28 (THR) 1.07 (TKR) MJB: 0.83 (THR) 0.99 (TKR) MNB: 1.11 (THR) 1.00 (TKR)	VTE: 1.11 MJB: 0.88 MNB: 1.05	DOMINANT	DOMINATED	99%	22%
G	RE-MOBILIZE + RE-MODEL (fixed)	VTE: 1.07 MJB: 0.99 MNB: 1.00	VTE: 1.19 MJB: 0.66 MNB: 0.97	N/A	DOMINATED	N/A	4%
H	RE-MOBILIZE + RE-MODEL (random)	VTE: 1.07 MJB: 0.99 MNB: 1.00	VTE: 1.19 MJB: 0.66 MNB: 0.97	N/A	DOMINATED	N/A	11%

CE, cost-effectiveness; DBG, dabigatran etexilate; ICER, incremental cost-effectiveness ratio; 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

Requested meta-analyses:

Primary efficacy endpoint

Figure 1 RE-NOVATE plus RE-MODEL (random effects) – 220mg

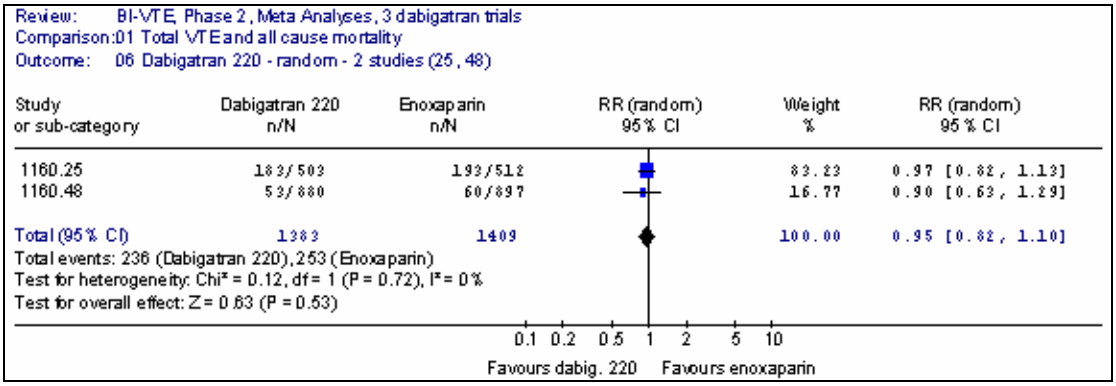


Figure 2 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

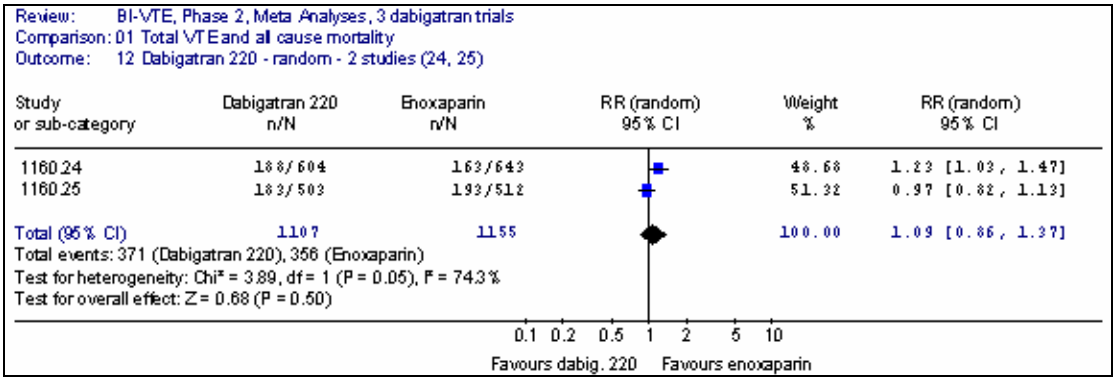


Figure 3 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

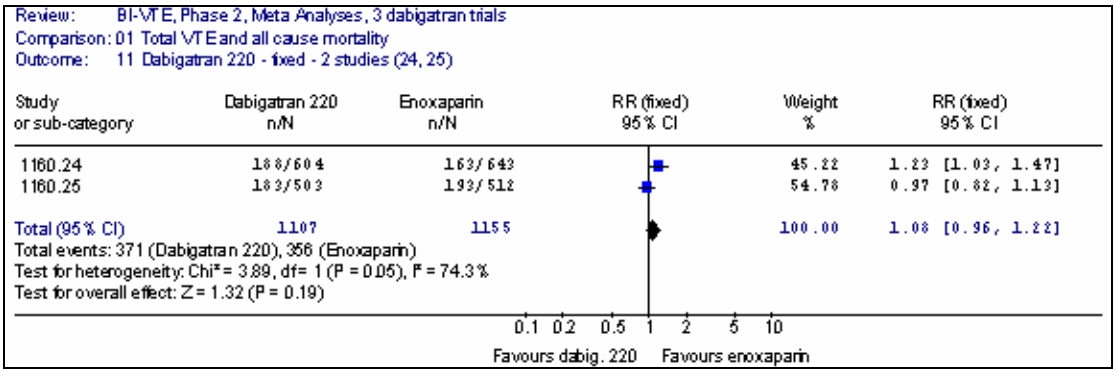


Figure 4 RE-NOVATE plus RE-MODEL (random effects) – 150mg

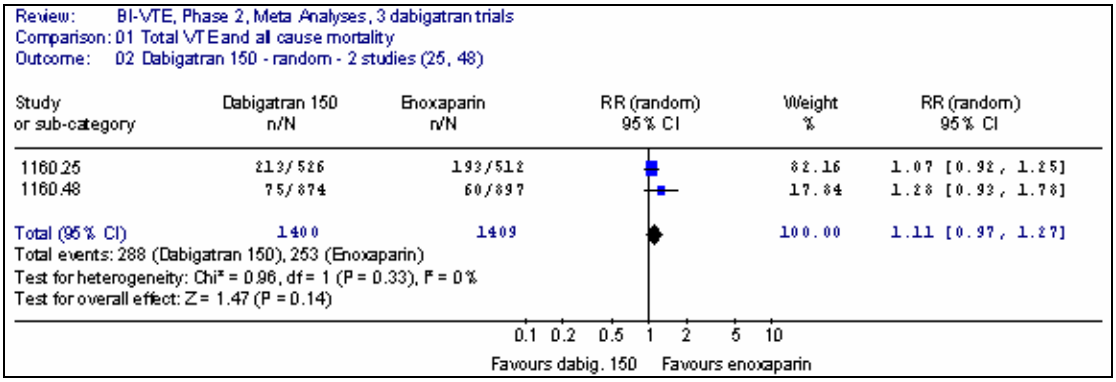


Figure 5 RE-MOBILIZE plus RE-MODEL (random effects) – 150mg

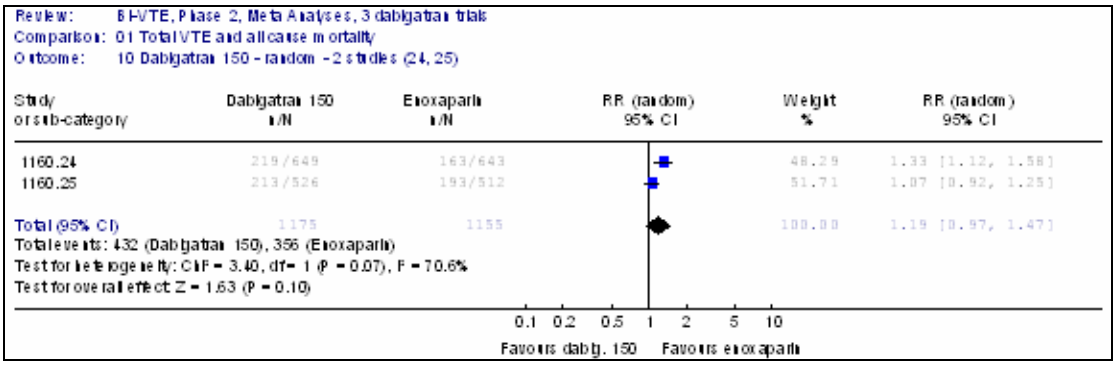
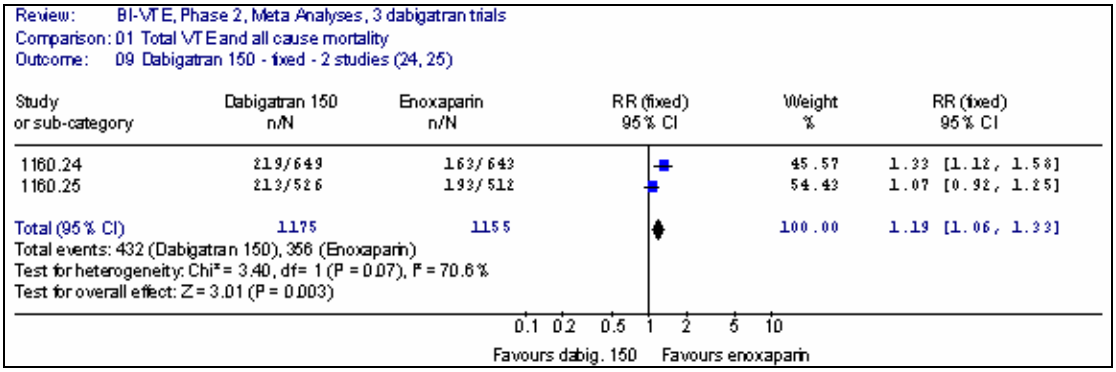


Figure 6 RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg



Secondary efficacy endpoint

Figure 7 RE-NOVATE plus RE-MODEL (random effects) – 220mg

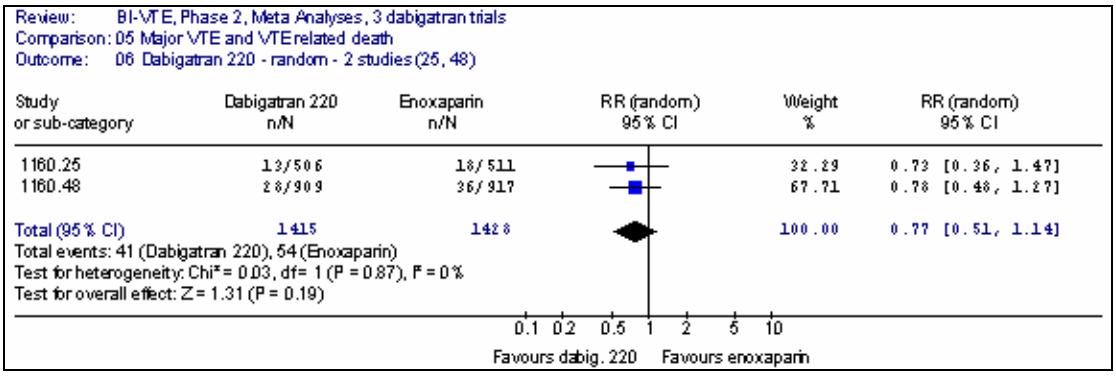


Figure 8 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

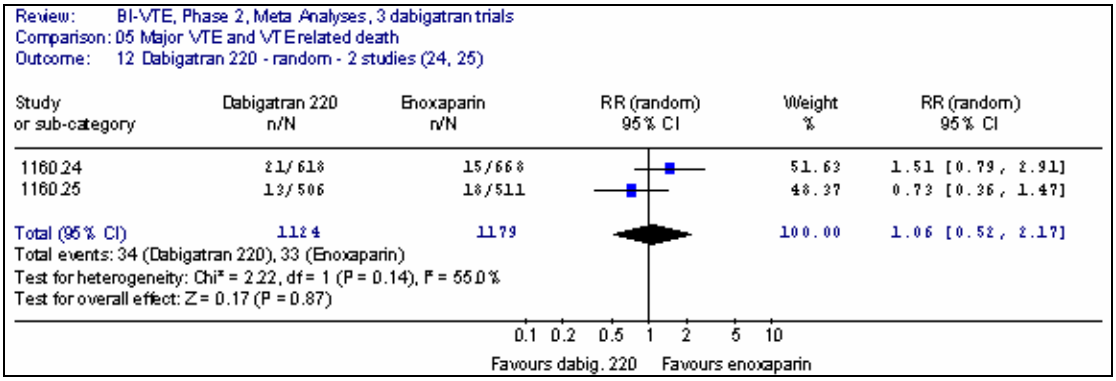


Figure 9 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

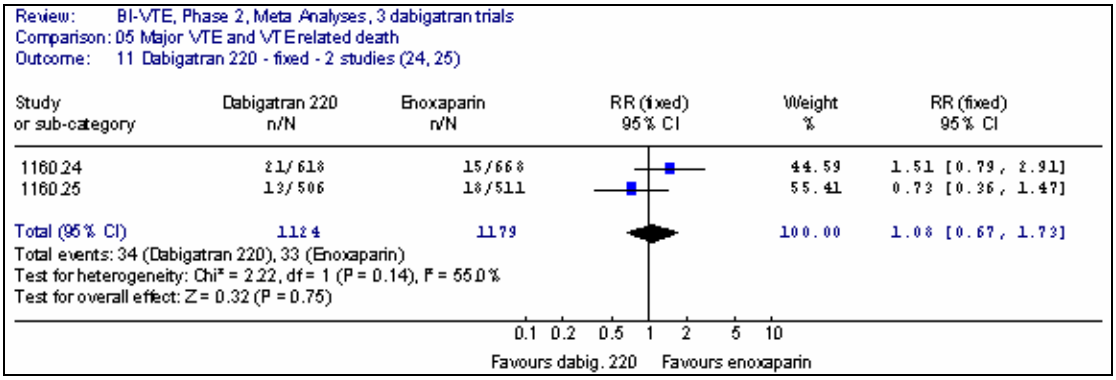


Figure 10 RE-NOVATE plus RE-MODEL (random effects) – 150mg

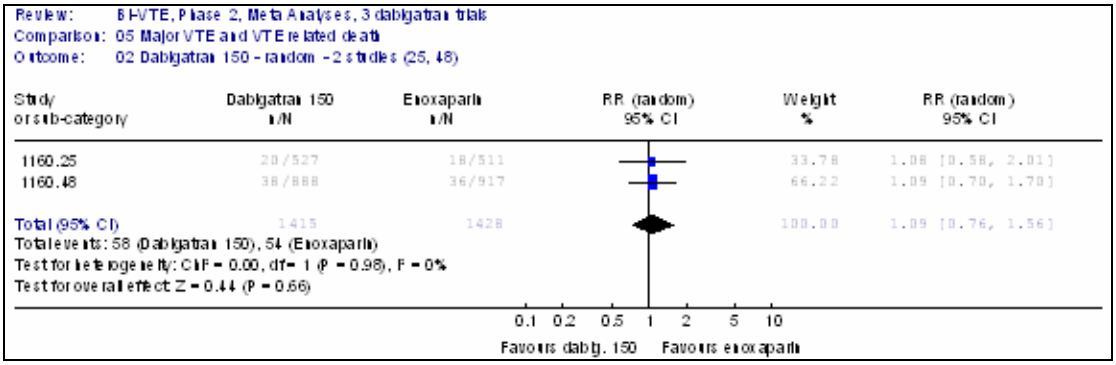


Figure 11 RE-MOBILIZE plus RE-MODEL (random effects) – 150mg

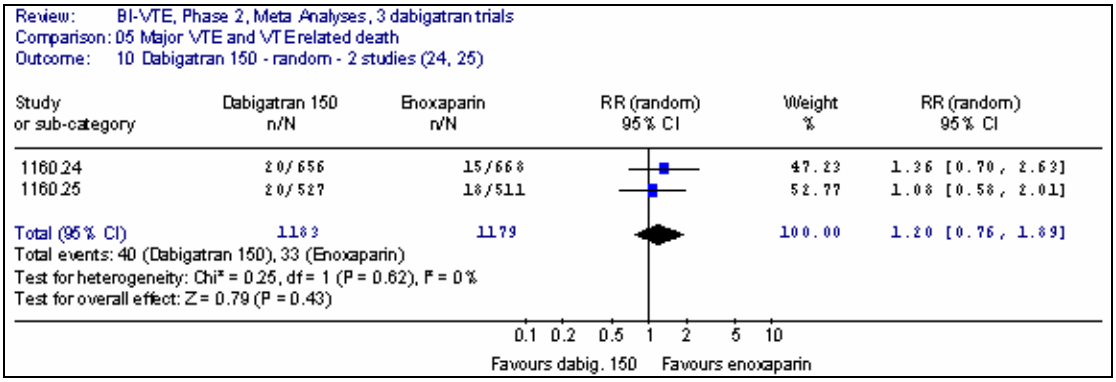
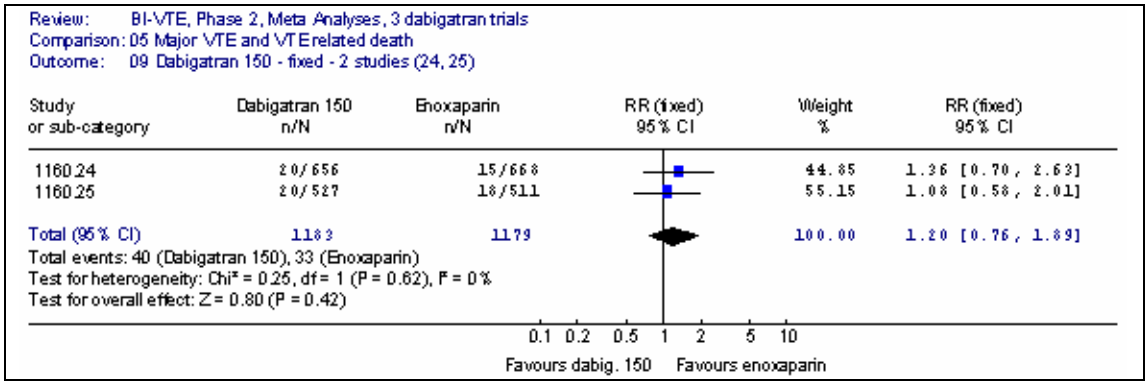


Figure 12 RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg



Major bleed

Figure 13 RE-NOVATE plus RE-MODEL (random effects) – 220mg

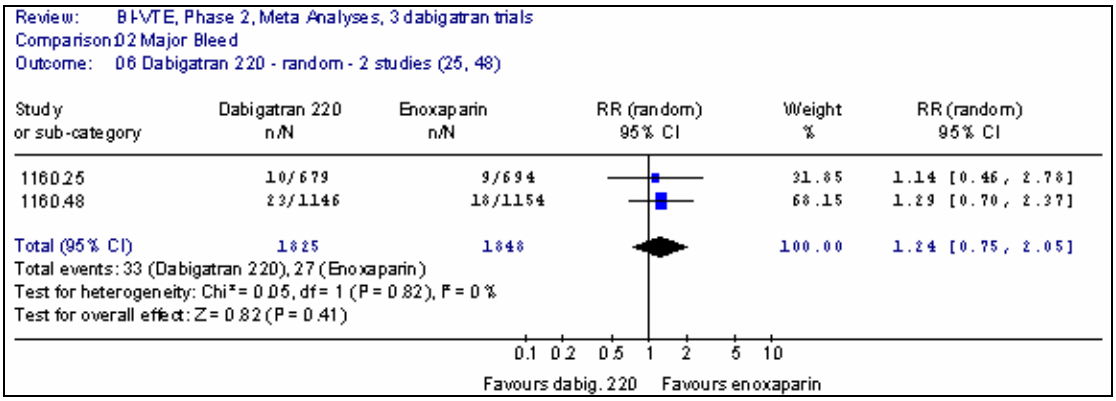


Figure 14 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

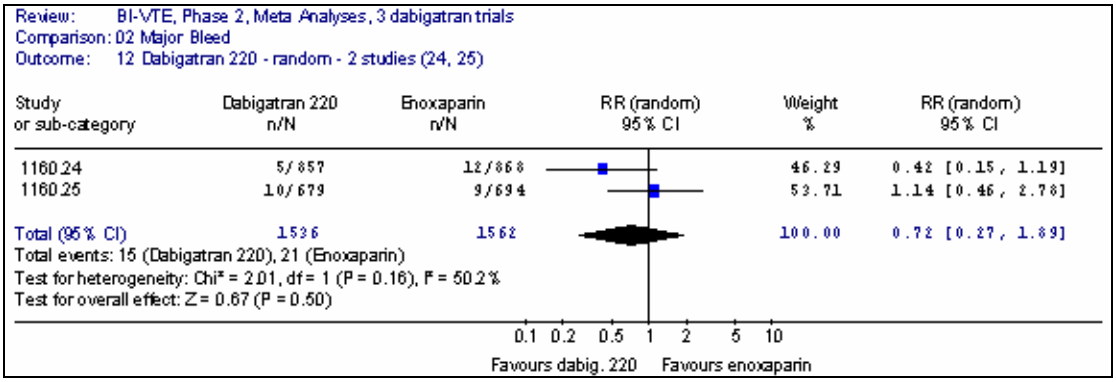


Figure 15 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

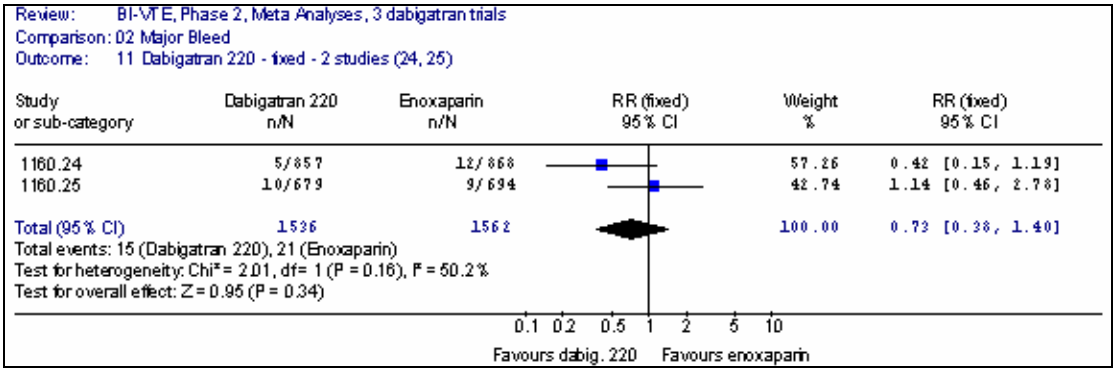


Figure 16 RE-NOVATE plus RE-MODEL (random effects) – 150mg

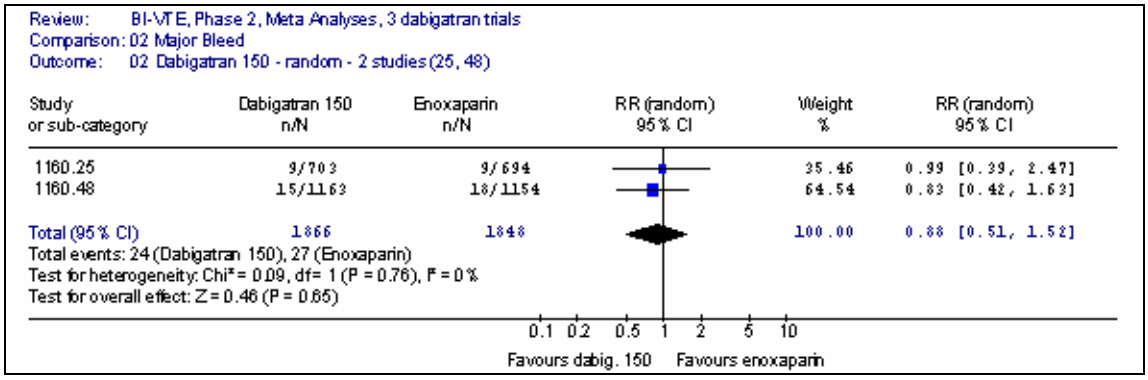


Figure 17 RE-MOBILIZE plus RE-MODEL (random effects) – 150mg

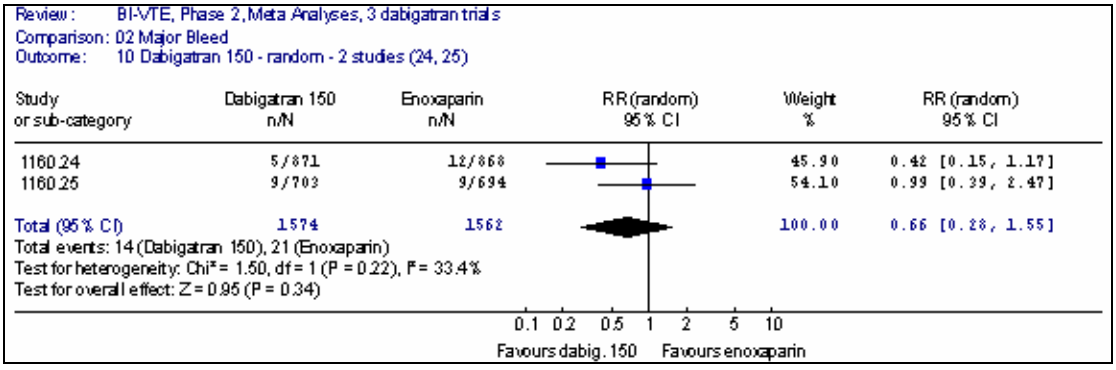
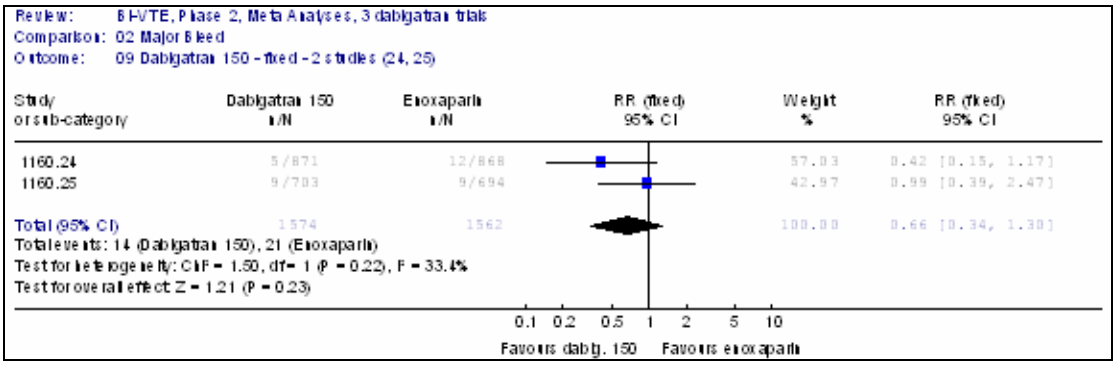


Figure 18 RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg



Clinically relevant bleed

Figure 19 RE-NOVATE plus RE-MODEL (random effects) – 220mg

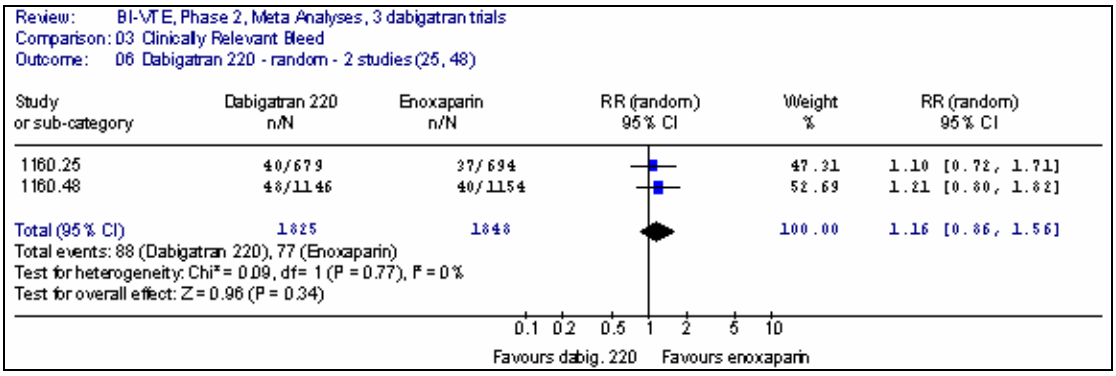


Figure 20 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

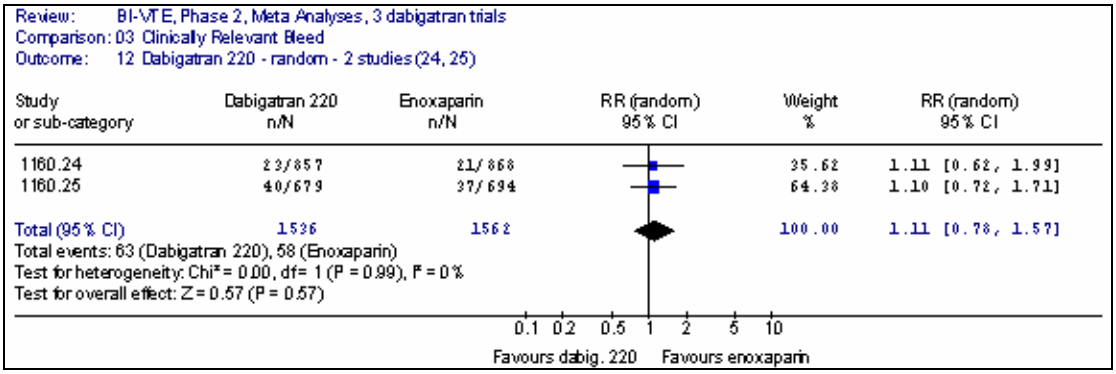


Figure 21 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

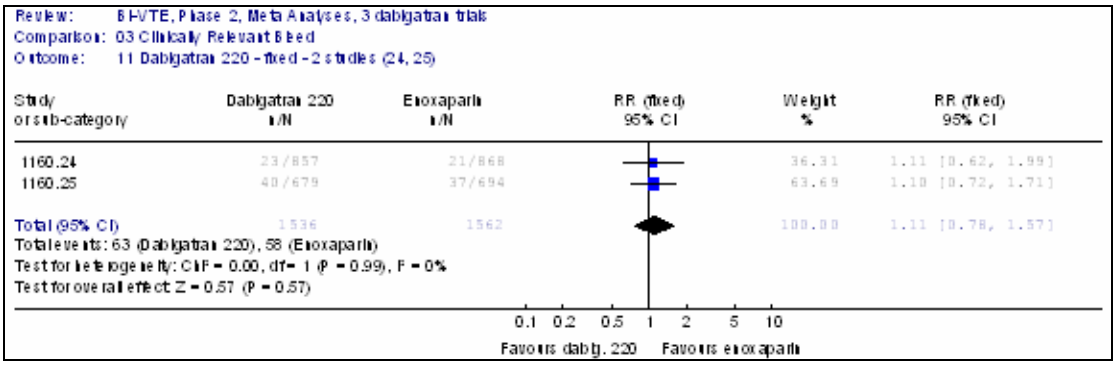


Figure 22 RE-NOVATE plus RE-MODEL (random effects) – 150mg

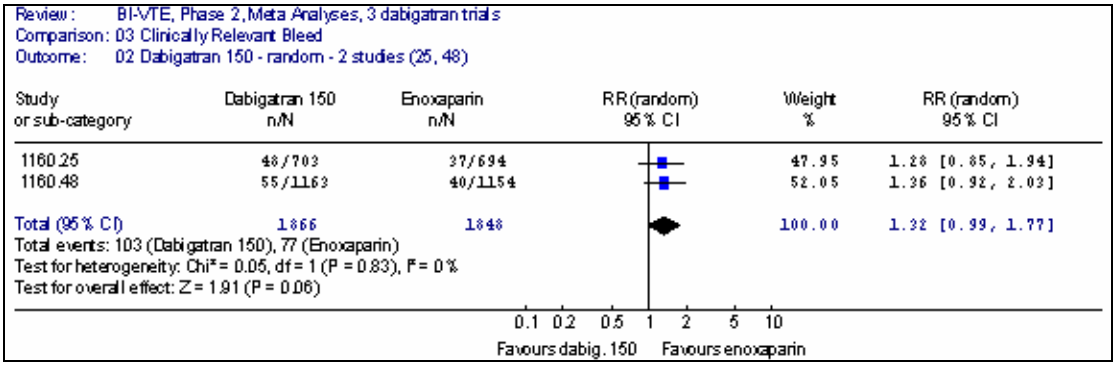


Figure 23 RE-MOBILIZE plus RE-MODEL (random effects) – 150mg

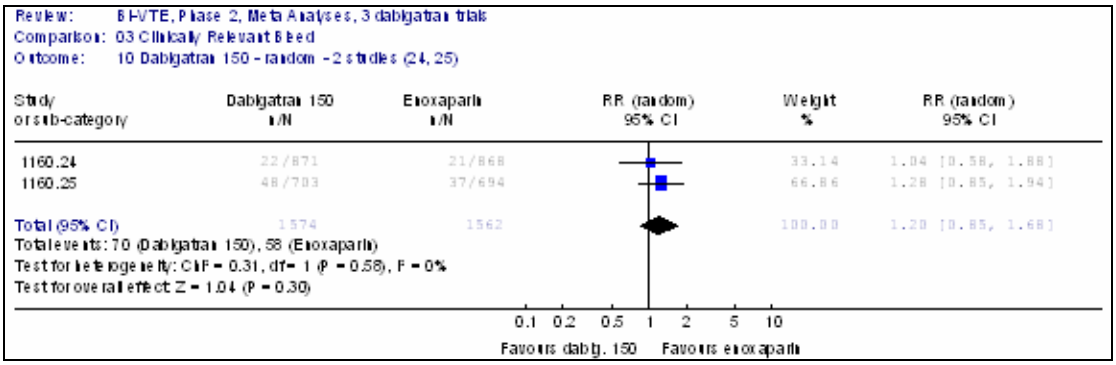
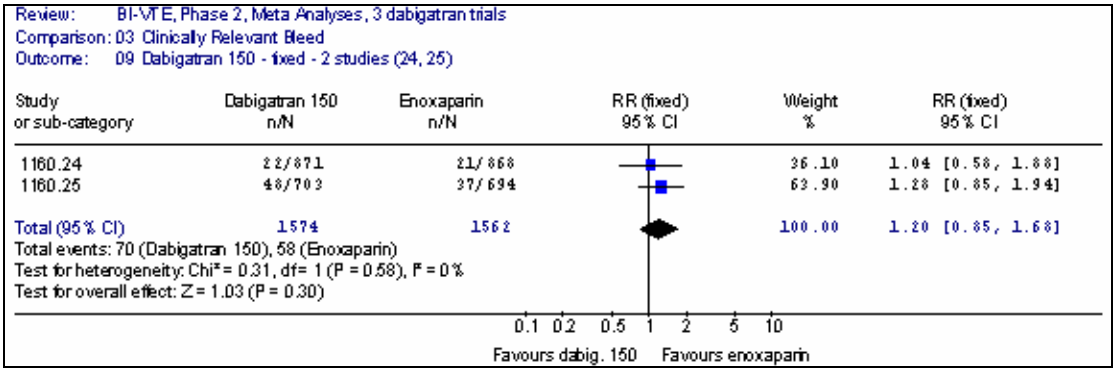


Figure 24 RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg



Clinically relevant/minor bleed

Figure 25 RE-NOVATE plus RE-MODEL (random effects) – 220mg

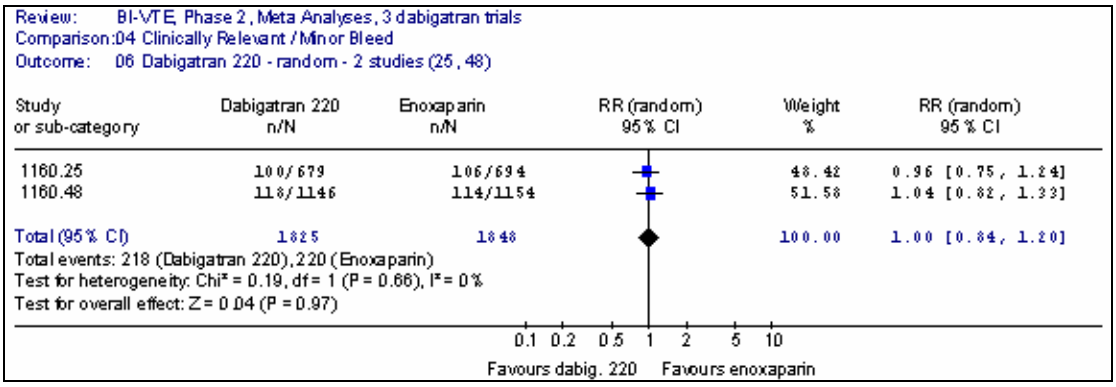


Figure 26 RE-MOBILIZE plus RE-MODEL (random effects) – 220mg

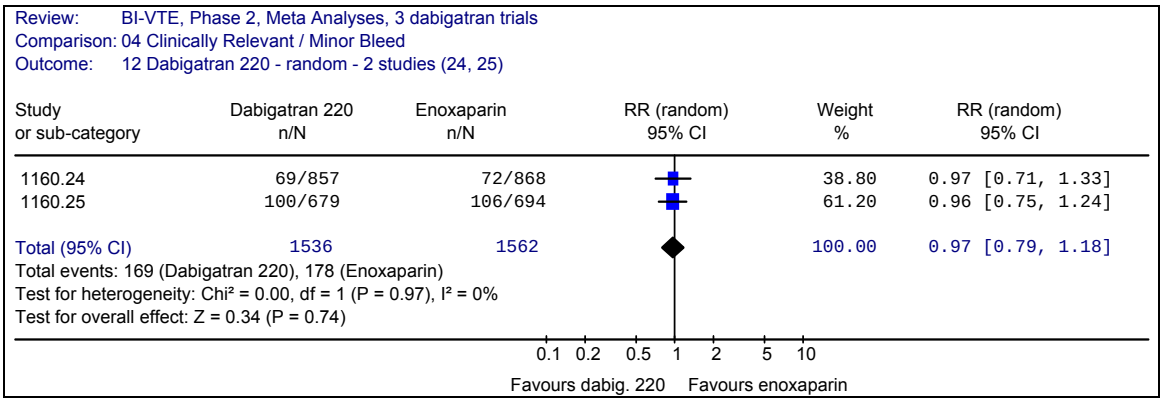


Figure 27 RE-MOBILIZE plus RE-MODEL (fixed effects) – 220mg

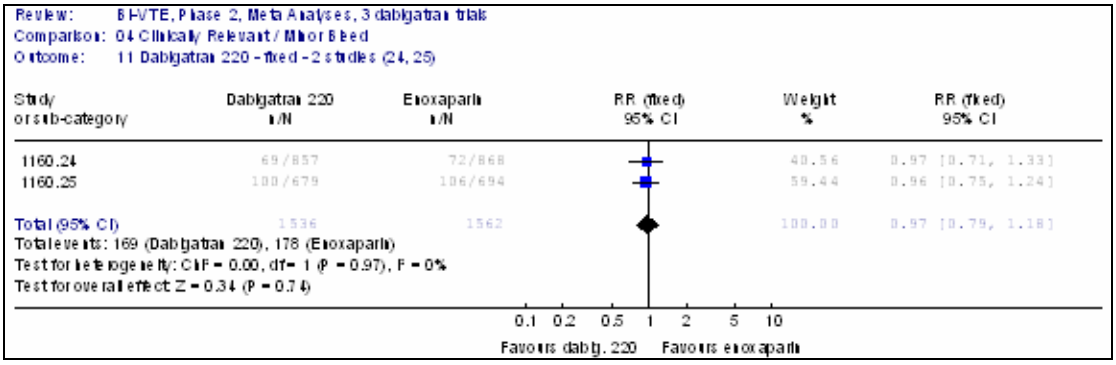


Figure 28 RE-NOVATE plus RE-MODEL (random effects) – 150mg

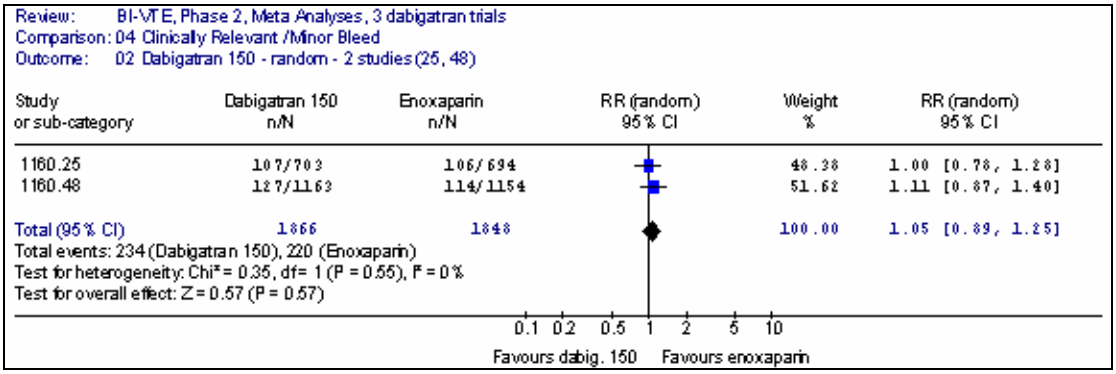


Figure 29 RE-MOBILIZE plus RE-MODEL (random effects) – 150mg

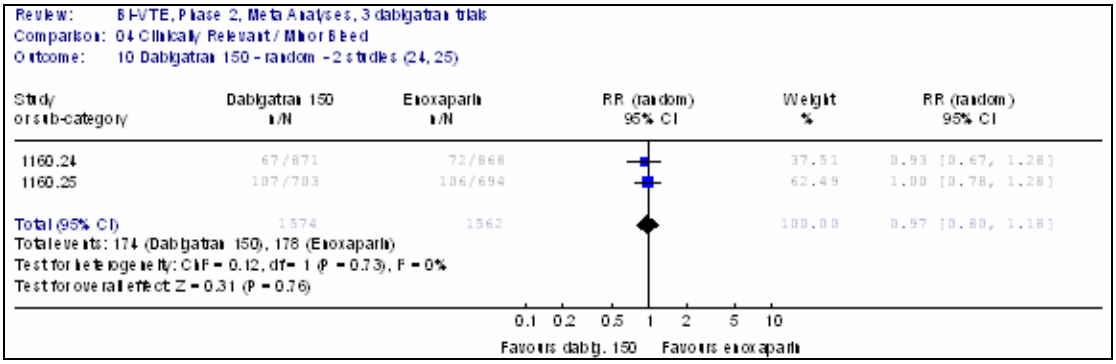
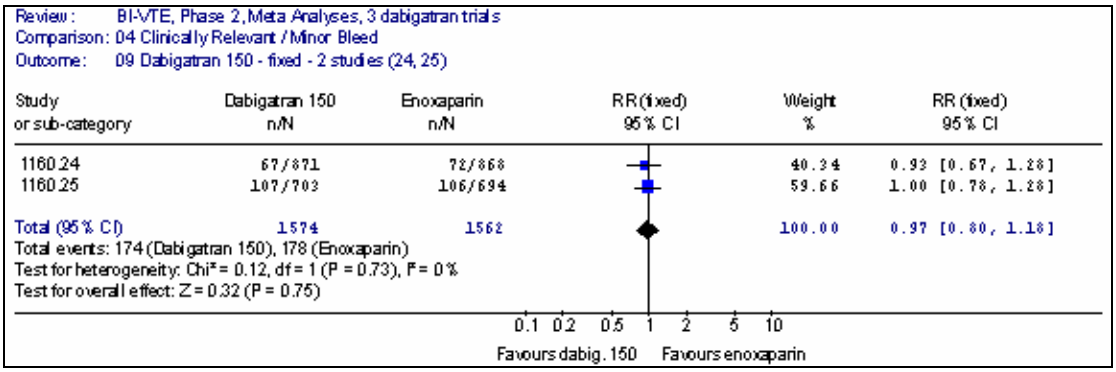


Figure 30 RE-MOBILIZE plus RE-MODEL (fixed effects) – 150mg



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