Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism

STA REPORT

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1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The manufacturer of dabigatran etexilate (Pradaxa®, Boehringer Ingelheim Ltd.) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). At the time of writing dabigatran etexilate (hereafter referred to as dabigatran) did not have marketing authorisation for the indication that is the focus of this single technology appraisal (STA). However marketing authorisation has been applied for and is anticipated to be for "treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults." In addition, on the 25th April 2014 the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion of the use of Pradaxa® (dabigatran) for this indication.

The final scope issued by NICE for this STA requested a population of "both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong)". The evidence review group (ERG) notes that the manufacturer presented disaggregated evidence for these populations specified in the NICE scope. The data for those who require long-term anticoagulation was presented for those who had received at least 3 months treatment for an acute DVT and/or PE. The ERG acknowledge that this is a reflection of the clinical trial data available and clinical experts advised the ERG that this is similar to the approach that would usually be taken in UK clinical practice, i.e. patients would receive 3–6 months acute treatment and then have an assessment to decided whether to continue treatment long term for secondary prevention of venous thromboembolism (VTE).

The clinical effectiveness trial data for dabigatran presented in the manufacturer's submission (MS) for long term secondary prevention of VTE are from two trials; RE-MEDY (dabigatran versus [vs] warfarin) and RE-SONATE (dabigatran vs placebo). RE-SONATE, the placebo-controlled dabigatran trial was conducted in patients who are at equipoise for the need for continued anticoagulation for secondary prevention of VTE. However, clinical experts advised the ERG that this population is difficult to define and would not be routinely anticoagulated for secondary prevention of VTE.

All of the clinical trial data for the use of dabigatran in VTE in the MS are based on trials of 150 mg BD of dabigatran. The ERG notes that the manufacturer anticipates that the license for dabigatran will recommend this dose with the exception of certain populations (i.e. patients aged 80 years or above and patients who receive concomitant verapamil are recommended 110 mg BD). The ERG also notes that the manufacturer does not present any trial data for the use of the 110 mg BD dose of dabigatran in VTE treatment and secondary prevention. The ERG is thus concerned about the lack of safety and

efficacy data for the lower dose (110mg BD) of dabigatran in the VTE population that are the focus of this STA.

Regarding comparators, the manufacturer presented data for:

- initial treatment with a low molecular weight heparin (LMWH) or fondaparinux and continued warfarin (vitamin K antagonist [VKA]);
- rivaroxaban; and
- LMWH for people with cancer.

The ERG notes that the data for initial treatment with LMWH or fondaparinux are aggregated and the manufacturer has assumed equal efficacy for these initial parenteral therapies. In addition, the only VKA for which the manufacturer has presented trial data versus dabigatran is warfarin. Clinical experts have advised the ERG that warfarin is the most commonly used VKA in the UK and so the ERG considers the manufacturer's approach to be reasonable.

The ERG is concerned about the manufacturer's definition of people with cancer being too broad compared to that used in clinical practice in the UK. In addition, there were small numbers of patients in the dabigatran clinical trials presented in the MS and no data from head-to-head trials of dabigatran versus rivaroxaban or LMWH. As a result, the ERG considers the data in the subgroup of people with cancer to be limited.

Regarding outcomes, the manufacturer excluded post thrombotic syndrome (PTS), heart failure and chronic thromboembolic pulmonary hypertension (CTEPH) from the clinical-effectiveness evidence submitted in the MS. The manufacturer informed the ERG that this was because data on PTS, heart failure and CTEPH were not collected in any of the key trials that informed the MS; RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE. Furthermore, health-related quality of life data (HRQoL) were collected in RE-COVER, RE-COVER II and RESONATE but not reported specifically in the clinical effectiveness section of the MS. In addition, the ERG notes that the HRQoL data for dabigatran is limited as there are no long-term data in secondary prevention of VTE.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The manufacturer presented clinical effectiveness evidence on dabigatran from four phase III trials: RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE. RE-COVER, RE-COVER II and RE-MEDY compared dabigatran with warfarin and RE-SONATE compared dabigatran with placebo. The ERG notes that the comparator (placebo) in RE-SONATE was not requested in the final scope issued by NICE. RE-COVER, RE-COVER II provide data following up to 6 months acute treatment of people with a DVT and/or PE. RE-MEDY and RE-SONATE provide longer-term secondary

prevention data. RE-MEDY was planned to be up to 36 months treatment in patients diagnosed with a symptomatic, proximal DVT or PE that had been successfully treated with standard doses of an approved anticoagulant for 3 to 12 months for confirmed acute symptomatic VTE or with dabigatran as part of the RE-COVER or RE-COVER II trials. RE-SONATE was 3 to 6 months treatment in patients who had completed 6 to 18 months of treatment with an oral anticoagulant treatment (VKA) for confirmed acute symptomatic VTE.

Patients randomised (1:1) to either dabigatran or warfarin were 2,564 in RE-COVER, 2,589 in RE-COVER II, and 2,866 in RE-MEDY. In RE-SONATE, at total of 1,353 patients were randomised (1:1) to dabigatran or placebo. The manufacturer reports data in the MS from two different analysis sets; the main efficacy analysis presented in the MS was the final analysis set (FAS). The FAS comprised of people who received at least one dose of study medication with patients assigned to their randomised treatment group regardless of actual drug taken. For the safety analyses, the treated set (TS) was used. This comprised of all randomised patients who received at least one dose of study medication with patients assigned to treatment group according to which drug they took (i.e. it may not have been the one they were randomised to). The ERG notes that both the FAS and TS populations were slightly smaller than the total randomised population that would usually be included in an intention-to-treat (ITT) analysis. However, given the small difference between FAS and ITT populations, the ERG considers that the use of non-standard ITT populations in the data analysis is unlikely to have had much impact on the resulting point estimates for dabigatran.

Time in therapeutic range (TTR) is a measure of warfarin control and not necessarily the same as treatment compliance but nonetheless important in assessing warfarin treatment efficacy. The target international normalised ratio (INR) for RE-COVER, RE-COVER II and RE-MEDY was an INR in the range of 2.0–3.0. The mean TTR for patients in the warfarin arm of RE-COVER, RE-COVER II and RE-MEDY was 59.9%, 56.9% and 61.5%, respectively.

Regarding discontinuations, less than 10% of people were lost to follow up in any one of the four dabigatran trials presented in the manufacturer's submission (RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE) with numbers well balanced between treatment groups.

The primary objective of RE-COVER and RE-COVER II was to prove the non-inferiority of dabigatran versus warfarin in the prevention of recurrent symptomatic VTE and deaths related to VTE at 6 months following an acute VTE event. Non-inferiority was proven based on the non-inferiority margin for the hazard ratio (HR) <2.75 in the FAS (RE-COVER: HR 1.05; 95% CI: 0.65 to 1.70, RE-COVER II: HR 1.13; 95% CI: 0.69 to1.85)) and per protocol populations (RE-COVER: HR 1.03; 95% CI: 0.63 to 1.69, RE-COVER II: HR 1.10, 95% CI: 0.67 to1.81). However, in the subsequent planned *a priori* analysis superiority was not reached. The ERG also consider it important to highlight

that the analyses were based on end of study data which included patients who completed 30 days follow-up after the end of the 6 month study drug treatment period.

The primary objective of RE-MEDY was to prove the non-inferiority of dabigatran versus warfarin in the prevention of recurrent symptomatic VTE and deaths related to VTE within 36 months. Non-inferiority was proven based on the non-inferiority margin for the HR <2.85 in the FAS (HR, 1.44; 95% CI, 0.78 to 2.64) and per protocol populations (HR, 1.42; 95% CI, 0.77 to 2.60). However, in the subsequent planned *a priori* analysis superiority was not reached. The ERG also considers it important to highlight that the analyses in RE-MEDY were based on the planned treatment period data i.e. did not include the 30 day follow-up period data.

The primary objective of RE-SONATE was to prove superiority of dabigatran versus placebo for the prevention of recurrent objectively confirmed symptomatic DVT or fatal or non-fatal PE, including unexplained death. Superiority was proven for this outcome in RE-SONATE (HR 0.08; 95% CI: 0.02 to 0.25).

The secondary efficacy outcomes of RE-COVER, RE-COVER II and RE-MEDY were the composite of recurrent symptomatic VTE and all deaths, the separate components of the primary efficacy outcome (recurrent symptomatic VTE and deaths related to VTE) and all deaths. Dabigatran was not associated with statistically significant differences for any of the primary or secondary efficacy outcomes in RE-COVER, RE-COVER II or RE-MEDY.

The secondary efficacy outcomes of RE-SONATE were the composite of symptomatic recurrent DVT, recurrent non-fatal PE and fatal PE (excluding unexplained death) and the separate components of the primary efficacy outcome. Results for all secondary efficacy outcomes were consistent with the primary endpoint in RE-SONATE, with fewer events with dabigatran compared with placebo.

The safety outcomes of RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE included bleeding events such as International Society on Thrombosis and Haemostasis (ISTH) major bleeding. There was no significant difference in major bleeding events between dabigatran and warfarin in RE-COVER, RE-COVER II or RE-MEDY, or between dabigatran and placebo in RE-SONATE.

The overall adverse event and safety profile of dabigatran was generally comparable when compared with warfarin for the outcomes reported in the MS. In terms of the comparison with placebo, the overall numbers of adverse events were similar for dabigatran and placebo (RE-SONATE). However, dabigatran was associated with statistically significantly more bleeding events (any bleeding event: HR 1.82; 95% CI: 1.23 to 2.68; p=0.0027).

[redacted].

As a result of the absence of head-to-head trials, the manufacturer carried out adjusted indirect comparisons (AICs) and network meta-analyses (NMAs). The aim of these AICs and NMAs was to compare dabigatran with rivaroxaban and LMWH, as specified in the final scope issued by NICE. The manufacturer chose to focus on the results of the AICs in the MS. The AICs reported in the MS comprised of the following comparisons:

Acute treatment:

- dabigatran versus rivaroxaban via warfarin (whole trial population);
- dabigatran versus LMWH via warfarin (people with active cancer).

Long-term secondary prevention of VTE:

- dabigatran versus rivaroxaban via warfarin (whole trial population).

The results of the AIC [redacted]

In terms of the acute treatment in the subgroup of patients with active cancer, the manufacturer reported that the results of the AIC suggested no significant differences in terms of efficacy and safety between dabigatran and LMWH monotherapy. However, numerical results were not reported in the MS.

The ERG notes that the results of the AICs were generally in keeping with those of the NMAs.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG considers that the inclusion and exclusion criteria for the four dabigatran trials were acceptable to address the trials' objectives. In addition, the ERG notes that the baseline characteristics of the randomised populations appeared to be well balanced between trial arms. However, the ERG notes that there is an absence of clinical trial data for the safety and efficacy of the 110mg BD dose of dabigatran in acute treatment and long term secondary prevention of VTE.

The ERG acknowledges that the outcome data reported from the trials in the MS appeared to be consistent with the data collected in the trial with the exception of the HRQoL data collected in the two RE-COVER trials and the RE-SONATE trial. However, the ERG notes that PTS, heart failure and CTEPH data requested in the NICE final scope were not specifically collected in any of the four trials. In terms of duration of follow-up and the statistical data analysis plan, the ERG considers that both were acceptable for the outcomes assessed in each of the four trials.

The results of RE-COVER and RE-COVER II demonstrated that dabigatran was non-inferior to warfarin in prevention of recurrent symptomatic VTE and deaths related to VTE in a 6 month acute treatment period for DVT and/or PE. However, superiority was not reached in either trial. The ERG considers that the overall adverse event and safety profile of dabigatran in the RE-COVER trials was generally comparable with warfarin for the outcomes reported in the MS. However, the ERG notes that there were numerically more retroperitoneal and GI bleeding events in the dabigatran group than in the warfarin group in both of the RE-COVER trials. The results of the subgroup analyses by cTTR suggested that the safety and efficacy of dabigatran compared with warfarin were independent of the level of warfarin control.

The results of RE-MEDY demonstrated that dabigatran was non-inferior to warfarin in prevention of recurrent symptomatic VTE and deaths related to VTE long-term treatment for secondary prevention of DVT and/or PE. However, superiority was not reached. The ERG considers that the overall adverse event and safety profile of dabigatran in RE-MEDY was generally comparable with warfarin for the outcomes reported in the MS. In addition, the results of the subgroup analyses by cTTR suggested that the safety and efficacy of dabigatran compared with warfarin were independent of the level of warfarin control, i.e. %TTR. Also, subgroup data according to index VTE event (i.e. PE or DVT) demonstrated no significant difference in the efficacy of dabigatran in relation to prevention of VTE and VTE-related mortality.

The results of RE-SONATE demonstrated that dabigatran was superior to placebo in prevention of recurrent symptomatic VTE and deaths related to VTE in long-term treatment for secondary prevention of DVT and/or PE. The ERG considers that the overall adverse event and safety profile of

dabigatran in RE-SONATE was generally comparable with placebo for the outcomes reported in the MS. However, the ERG does not consider RE-SONATE to meet the inclusion criteria for this STA based on the final scope issued by NICE as placebo/no treatment is not listed as a comparator of interest, and the population of 'equipoise' risk for recurrent VTE are not a population where routine anticoagulation would occur in UK clinical practice.

Regarding the AICs, the ERG considers it important to highlight the following potential issues:

- the definition of cancer used in the dabigatran trials was broader than the definition of cancer used in the other trials in the dabigatran versus LMWH analysis;
- the total number of people in the dabigatran trials with active cancer was small;
- the long-term secondary prevention data was based only on trials comprised of populations of people considered to be at equipoise for the need for long-term anticoagulation (RE-SONATE [dabigatran vs placebo] and EINSTEIN-extension [rivaroxaban vs placebo]).

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer developed a *de novo* Markov cost-utility model to investigate the cost-effectiveness of LMWH plus dabigatran (hereafter "dabigatran") compared with LMWH plus warfarin (hereafter "warfarin") and rivaroxaban in the full population, and LMWH monotherapy in a population with cancer, for:

- the acute treatment of people with a confirmed proximal DVT or PE (with or without proximal DVT); and
- the acute treatment and the secondary prevention of future DVTs or PEs.

The model developed by the manufacturer followed an average cohort through a lifetime time-horizon (60 years), with a model cycle length of one month (assumed to be 30 days). The manufacturer assumed that acute treatment would continue for 6 months, and secondary prevention would continue for 6 to 18 months, depending upon the comparator selected.

The manufacturer captured the costs and consequences of the initial and recurrent DVT or PE, and adverse bleeding events as a consequence of treatment. The probability of each event occurring was dependent upon whether the patient was on treatment or off treatment and, if the patient was on treatment, which treatment the patient was receiving. In addition, the manufacturer used co-existing health states to capture complications associated with DVT and PE events, specifically CTEPH and severe PTS. In sensitivity analysis, the manufacturer also captured the costs and consequences associated with treatment-related cardiovascular events (myocardial infarction and unstable angina) and dyspepsia.

Acute treatment of DVT and PE; manufacturer results

For the acute treatment of people with a confirmed proximal DVT or PE, the manufacturer estimated that the deterministic total cost per patient over the lifetime time horizon was £7,503 (dabigatran), £7,482 (warfarin) and £7,523 (rivaroxaban). The total quality-adjusted life years (QALYs) per patient were estimated to be 12.452 (dabigatran), 12.428 (warfarin) and 12.451 (rivaroxaban). Consequently, the deterministic incremental cost-effectiveness ratios (ICERs) were estimated in the base case to be:

- dabigatran versus warfarin, £862 per additional quality-adjusted life year (QALY) gained;
- dabigatran versus rivaroxaban, dabigatran dominant (less costly and more effective).

The probabilistic results were comparable, with the ICER for dabigatran versus warfarin estimated to be £1,016 per additional QALY gained, and dabigatran estimated to be dominant versus rivaroxaban (less costly and more effective). The manufacturer estimated the probability that dabigatran would be considered cost-effective at a willingness-to-pay threshold of £20,000 per additional QALY to be 93% (dabigatran versus warfarin), and 57% (dabigatran versus rivaroxaban).

The costs and QALYs estimated by the manufacturer for the full population analyses were very similar between interventions. Costs varied between all three treatment strategies by £40 in the deterministic analyses, and QALYs varied by approximately 0.02 per patient. In particular, for dabigatran versus rivaroxaban, the estimated total QALYs differed by 0.0003 over a lifetime for one patient. Therefore, whilst dabigatran was found to dominate rivaroxaban in the manufacturer's base case, the average total costs and QALYs estimated by the manufacturer imply that these treatments result in very similar costs and consequences.

For the analysis of dabigatran versus LMWH in the population with cancer, the manufacturer estimated for the deterministic analysis that the total cost per patient over the lifetime time horizon was £4,152 (dabigatran) and £5,522 (LMWH). The total QALYs per patient were estimated to be 5.805 (dabigatran), and 5.817 (LMWH). Consequently, the deterministic ICER was estimated in the base case to be £110,742, where dabigatran was less costly and less effective than LMWH.

The probabilistic results were comparable, with the ICER for dabigatran versus LMWH estimated to be £93,431, where dabigatran was estimated to be less costly and less effective than LMWH. The manufacturer estimated the probability that dabigatran would be considered cost-effective at a willingness-to-pay threshold of £20,000 per additional QALY versus LMWH to be 92%.

Acute treatment and secondary prevention of DVT and PE; manufacturer results

For the acute treatment and secondary prevention of DVT or PE, the manufacturer did not provide a fully incremental analysis. That is, the costs and QALYs associated with dabigatran differed for each head-to-head comparison as a consequence of differing model inputs for dabigatran in each analysis.

Specifically, the manufacturer used alternative estimates for dabigatran for: treatment duration; the probability of recurrent VTE; the probability of bleeding; and the probability of discontinuing treatment. The manufacturer estimated the following total cost per patient and total QALYs for the full population in the deterministic analysis:

- for dabigatran versus warfarin, £8,319 and 12.519 QALYs (dabigatran), £7,861 and 12.464 QALYs (warfarin);
- for dabigatran versus rivaroxaban, £7,785 and 12.480 QALYs (dabigatran), £7,852 12.478 QALYs (rivaroxaban).

Consequently, the deterministic ICERs were estimated in the base case to be:

- dabigatran versus warfarin, £8,319 per additional QALY gained;
- dabigatran versus rivaroxaban, dabigatran dominant (less costly and more effective).

The probabilistic results were comparable, with dabigatran versus warfarin estimated to result in an ICER of £8,848 per additional QALY gained, and dabigatran was found to be dominant versus rivaroxaban (less costly and more effective). The manufacturer estimated the probability that dabigatran would be considered cost-effective at a willingness-to-pay threshold of £20,000 per additional QALY to be 92% (dabigatran versus warfarin), and 81% (dabigatran versus rivaroxaban).

For the analysis of dabigatran versus LMWH in the population with cancer, the manufacturer estimated for the deterministic analysis that the total cost per patient for the lifetime time horizon was £7,821 (dabigatran) and £11,161 (LMWH). The total QALYs per patient were estimated to be 12.471 (dabigatran), 12.451 (LMWH). Consequently, dabigatran was found to dominate LMWH in the base case (less costly and more effective).

The probabilistic results were comparable, with the ICER for dabigatran versus LMWH estimated to also result in dabigatran dominance over LMWH. The manufacturer estimated the probability that dabigatran would be considered cost-effective at a willingness-to-pay threshold of £20,000 per additional QALY versus LMWH to be 100%.

As with acute treatment, the costs and QALYs estimated by the manufacturer for the full population analyses across the lifetime time-horizon were similar for the comparison of dabigatran versus rivaroxaban. The total lifetime cost difference per patient between dabigatran and rivaroxaban differed by £67 in the deterministic analysis. Moreover, the QALY differential between the two treatment strategies differed by less than 0.002 per patient over their lifetime. Therefore, the ERG considers that, whilst dabigatran dominates rivaroxaban in the base case, as with acute treatment, the average total costs and QALYs estimated by the manufacturer imply that these treatments are similar.

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

1.5.1 Strengths of the clinical analysis

The ERG considers the four dabigatran trials (RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE) presented in the MS for this STA, to be well conducted, international, double-blind, RCTs. The primary efficacy endpoint of the four key trials presented in the MS was the composite of recurrent symptomatic VTE and deaths related to VTE (RE-SONATE also included unexplained deaths as they were deemed to be a result of fatal PE). Dabigatran was proven to be non-inferior to warfarin (RE-COVER, RE-COVER II and RE-MEDY), and superior to placebo (RE-SONATE) for acute treatment and secondary prevention of VTE (DVT and PE).

The manufacturer conducted extensive subgroup analyses to demonstrate consistency of the treatment effect of dabigatran. In addition, the manufacturer submitted additional data for a comparator, placebo, which was not specified in the final scope issued by NICE.

AICs and NMAs were conducted by the manufacturer and enabled an indirect comparison of dabigatran with rivaroxaban and dabigatran with LMWH.

1.5.2 Strengths of the economic analysis

The ERG notes that the modelling approach adopted by the manufacturer was reasonable and consistent with previous economic evaluations in the acute treatment and secondary prevention of DVT and PE. The ERG notes that the model was generally well constructed and transparent, although the ERG identified a number of errors within the model, and several inconsistencies between the numbers reported in the manufacturer's submission and the model.

1.5.3 Weaknesses and areas of uncertainty in the clinical analysis

PTS, heart failure and CTEPH were listed as outcomes of interest in the final scope issued by NICE and were not presented as outcomes in the clinical effectiveness data of the MS. However, the ERG acknowledges that data for these outcomes were not specifically collected in RE-COVER, RE-COVER II, RE-MEDY or RE-SONATE. The effectiveness of dabigatran in reducing the VTE related adverse effects of PTS, heart failure and CTEPH is thus an area of uncertainty. In addition, there is an absence of long-term HRQoL data for dabigatran in acute treatment and secondary prevention of VTE.

The manufacturer did not present any clinical trial data for the safety or efficacy of the 110 mg BD dose of dabigatran which is likely to be the recommended dose for people aged over 80 years or those on concomitant verapamil. The ERG therefore considers the effectiveness of 110 mg BD dabigatran in VTE prevention is unknown.

The manufacturer has no direct head-to-head data for dabigatran versus rivaroxaban and so the ability to draw conclusions for this comparison is limited by the uncertainty around the indirect effect estimates generated from the AICs and NMAs. The ERG thus considers that the conclusions drawn from the AICs and/or NMAs would benefit from the addition of further head-to-head trials but acknowledges that no further data are currently available.

With respect to the subgroup of people with cancer, the ERG notes that the population of the dabigatran trials comprised only of a small number of people with active cancer. In addition, the definition of active cancer used in the dabigatran trials was broader than that used in UK clinical practice according to the ERGs clinical advisers. The ERG also notes that there are currently no head-to-head clinical trials for the comparison of dabigatran versus rivaroxaban or dabigatran versus LMWH in people with active cancer. The limited data provided within the MS is thus from indirect comparisons and associated with large amounts of uncertainty. The ERG thus considers that head-to-head trials are required to address the question of the effectiveness of dabigatran in VTE prevention in people with cancer.

The manufacturer used data from head-to-head trials for the comparison with warfarin and from AICs for comparison with rivaroxaban and LMWH. As no single analysis encapsulated all treatments of interest, this meant the manufacturer performed separate economic evaluations for each individual comparison rather than one analysis of all comparisons. This led to the results from the manufacturer's economic model not being comparable with one another and not presented as fully incremental results. The ERG conducted an exploratory NMA, which was used as the basis for a health economic scenario analysis.

1.5.4 Weaknesses and areas of uncertainty in the economic analysis

The ERGs main criticisms of the cost-effectiveness analyses were:

- a lack of a fully incremental analysis for the treatment and secondary prevention scenario;
- duration of secondary prevention set to 6-18 months rather than life-long for the treatment and secondary prevention analyses;
- a potential overestimate of cost associated with warfarin monitoring;
- uncertainty in model results arising as a consequence of:
    - lack of robust evidence supporting a utility decrement for warfarin treatment;
    - lack of clinical effectiveness and safety data for the reduced dose of dabigatran (110mg twice daily).

These concerns are described in more detail below. Other, more minor concerns were also identified and tested in scenario analyses.

Lack of a fully incremental analysis for the treatment and secondary prevention scenario

For the treatment and secondary prevention scenarios, the manufacturer used different data for dabigatran in the comparison with warfarin and rivaroxaban (for the full population), and LMWH (in the population with cancer). Specifically, the manufacturer assumed that the following model inputs would differ by comparison:

- the probability of recurrent VTE whilst receiving dabigatran;
- the type of recurrent VTE whilst receiving dabigatran (i.e. DVT, fatal PE, non-fatal PE);
- the probability of a major or clinically relevant non-major bleeding event whilst receiving dabigatran;
- the type of major or clinically relevant non-major bleeding event whilst receiving dabigatran (i.e. intra-cranial haemorrhage, other major bleed, fatal bleeding event, clinically relevant non-major bleeding event);
- the duration of treatment with dabigatran (6 months for the comparison with rivaroxaban and LMWH, and 18 months for the comparison with warfarin);
- the probability of discontinuing from dabigatran treatment.

The ERG acknowledges that, for the population with cancer versus the full population, it is plausible that parameters may differ; however, the ERG consulted with clinical experts and considers that there is no clinical basis from which to assume that the above parameters would differ for dabigatran when in comparison with warfarin or rivaroxaban in the full population.

The ERG notes that a key disadvantage of using alternative model parameters for dabigatran is that the results arising from each analysis cannot be compared, because the costs and QALYs associated with dabigatran will differ in each case.

Duration of secondary prevention set to 6-18 months rather than lifelong

The manufacturer modelled the duration of secondary prevention for the initial therapy as alternatively 6 months (dabigatran in comparison with rivaroxaban, and LMWH) and 18 months (dabigatran in comparison with warfarin).

The ERG sought clinical input around the duration of secondary prevention. The clinical experts asserted that in patients for whom the risk of recurrent VTE outweighed the risk of bleeding, secondary prevention would generally be life-long. The ERG is therefore concerned that the manufacturer has underestimated the likely treatment duration for dabigatran, warfarin, rivaroxaban and LMWH in clinical practice for secondary prevention.

A potential overestimate of cost associated with warfarin monitoring

The ERG notes that the manufacturer assumed that warfarin monitoring in the secondary prevention period would occur monthly, and that monitoring would be carried out as a mix of consultant-led and non-consultant led appointments.

Following clinical advice, the ERG considers that it is likely that appointments during secondary prevention would reduce to one every three months as patients become better controlled on warfarin. Moreover, the ERG understands that these appointments would generally be non-consultant led.

Uncertainty in model results arising from a lack of robust data for warfarin utility decrement

The ERG notes that the manufacturer has modelled a decrement in utility associated with warfarin treatment. This decrement was applied to reflect the burden upon HRQoL of warfarin treatment, because warfarin is associated with a number of factors which may negatively impact HRQoL, including the need for regular monitoring of INR, and a requirement of adjusting and monitoring diet and lifestyle.

To establish the HRQoL decrement associated with use of warfarin and LMWH, the manufacturer used data from an analysis of 48 patients who were receiving warfarin. The ERG is concerned that the data supporting the utility decrement for warfarin may not provide a robust estimate of disutility. This is due to a small sample size for the analysis which may limit generalisability of the results, the use of patient preferences to value the health states, and the lack of a similar analysis for dabigatran.

The ERG carried out a rapid and non-systematic search of the literature and was unable to identify any further appropriate estimates of warfarin disutility in the treatment and secondary prevention of VTE. Instead, the ERG identified a number of studies reviewing the impact of warfarin treatment on HRQoL in atrial fibrillation (AF). The ERG notes that a head-to-head comparison of warfarin and dabigatran from RE-LY, a trial for stroke prevention in AF, indicated that there was no long term difference in the EQ-5D scores for patients receiving warfarin and dabigatran.

The ERG considers that there is therefore uncertainty in what value is appropriate to model to reflect the HRQoL burden associated with warfarin treatment.

Uncertainty in model results arising from a lack of robust data for dabigatran 100mg twice daily

The draft summary of product characteristics (SmPC) for dabigatran for treatment and secondary prevention of DVT and PE states that the standard daily dose of dabigatran is 300mg per day, taken as one 150mg capsule twice daily. The draft SmPC also states that, for patients aged 80 years or above, or patients who receive concomitant verapamil, the daily dose shall be lowered to 220mg per day, taken as one 110mg capsule twice daily. By contrast, the clinical trials for dabigatran in DVT and PE

(RE-COVER I, RE-COVER II, RE-MEDY, RE-SONATE) considered only the dose of 300mg per day, and therefore no clinical data is available at the dose of 220mg per day.

Due to the lack of clinical data, the manufacturer assumed that efficacy and safety data for the 220mg dose would be equivalent to those associated with the 300mg dose within the economic analysis. Moreover, as the cost of a 220mg dose and a 300mg dose is identical, the cost data associated with the lower dose was also assumed to be equivalent.

The ERG is concerned that, without any clinical data at 220mg per day for the population of patients with DVT or PE, it is impossible to say whether the manufacturer's assumption of equivalence in efficacy is reasonable. The ERG notes that the dose of 220mg dabigatran has been studied in patients with atrial fibrillation (AF) in RE-LY; in those patients, efficacy data were not found to be equivalent to the 300mg dose. However, due to a lack of clinical data in the treatment and secondary prevention of VTE, the ERG considers it is not possible to infer what effect the dose of dabigatran will have on the model results.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG carried out a number of model corrections and scenario analyses to investigate alternative parameters and assumptions within the model structure. The ERG considered deterministic results only; this was for simplicity because the manufacturer's model results were consistent between deterministic and probabilistic results.

The ERG estimated a revised deterministic base case incremental cost-effectiveness ratio (ICER) for the comparisons of dabigatran and warfarin, and dabigatran and rivaroxaban, in both the acute treatment scenario and the treatment and secondary prevention scenario. The ERG did not attempt to estimate a base case ICER for dabigatran versus LMWH in the population with cancer. This is because the ERG has concerns over the reliability of the data in the population with cancer, and therefore the applicability of the findings for this comparison.

The ERG base case ICER incorporated all model corrections and the following scenarios:

- to enable a fully incremental comparison in the treatment and secondary prevention scenario:
    - ERG network meta-analysis (NMA) results for VTE recurrence;
    - consistent proportion of VTE event type across treatments (i.e. DVT, fatal PE and non-fatal PE);
    - ERG NMA results for bleeding events;

    - consistent proportion of bleeding event type across treatments (i.e. intra-cranial haemorrhage, other major bleeds, fatal bleeds, clinically relevant non-major bleeds);
    - the discontinuation rate for dabigatran set equal to the value in RE-MEDY rather than RE-SONATE in the comparison with rivaroxaban (secondary prevention only).
- secondary prevention following the initial event prescribed for life;
- changes in assumptions around warfarin monitoring, specifically:
    - initial anticoagulation appointment removed for warfarin (to reflect a potential error in the modelling methodology adopted by the manufacturer which overstated the number of warfarin appointments compared with other treatments);
    - warfarin monitoring in the secondary prevention period set to one appointment every three months;
    - non-consultant led follow-up visits for warfarin;
- a number of other more minor issues that were identified.

Acute treatment scenario

The deterministic ICERs for dabigatran versus warfarin and dabigatran versus rivaroxaban in the acute treatment scenario were estimated to be:

- £18,240 per additional QALY (dabigatran versus warfarin);
- dabigatran dominates rivaroxaban.

The results correspond to the manufacturer's results for the comparison of dabigatran versus rivaroxaban; the manufacturer also estimated that dabigatran was dominant (less costly and more effective) when compared with rivaroxaban. The ERG considers it important to note that the cost difference estimated through this analysis was £3 per patient over the lifetime of the model, with a QALY difference of 0.0018. Thus, the ERG notes that dabigatran and rivaroxaban are associated with very similar costs and consequences.

The estimate for dabigatran versus warfarin differs to the manufacturer's estimate of £862 per additional QALY. The ERG considers that the single largest driver of this difference was the reduction in cost associated with warfarin monitoring as a result of assuming that follow-up visits would be non-consultant led.

Treatment and secondary prevention scenario

The deterministic ICERs for dabigatran versus warfarin, and dabigatran versus rivaroxaban in the treatment and secondary prevention scenario were fully incremental, and estimated to be:

- rivaroxaban extendedly dominated by dabigatran;
- £35,768 per additional QALY (dabigatran versus warfarin).

The estimate for dabigatran versus warfarin differs to the manufacturer's estimate of £8,319 per additional QALY. The ERG considers that the largest drivers of this difference were: an increase in cost associated with dabigatran from lifelong secondary prevention for the initial event; a reduction in the cost associated with warfarin monitoring by assuming one appointment every three months rather than every month in the secondary prevention period; a reduction in cost associated with warfarin monitoring as a result of assuming that follow-up visits would be non-consultant led.

The ERGs revised base case ICER did not incorporate the removal of warfarin disutility in the secondary prevention period. This is because the ERG is not clear what value is most appropriate to capture the HRQoL impact of warfarin treatment. The ERG notes that this parameter is a key driver in the ERG base case result, and removal of the disutility associated with warfarin treatment in the secondary prevention period results in a large increase in the ICER associated with the comparison of dabigatran and warfarin, to approximately £90,000 per additional QALY. This is because the ERG analysis is increasingly sensitive to changes in incremental QALYs.

1.7 Key issues

In summary, the ERG believes the key issues to be as follows:

Clinical:

- dabigatran is non-inferior to warfarin for prevention of recurrent symptomatic VTE and deaths related to VTE, but dabigatran was not proven to be superior to warfarin;
- absence of direct comparative data from a randomised controlled trial comparing dabigatran with rivaroxaban;
- limited data on the safety and clinical benefit of dabigatran compared with rivaroxaban and LMWH in people with active cancer;
- lack of long term HRQoL data for people taking dabigatran for secondary prevention of VTE;
- absence of clinical trial data to assess the safety and efficacy of the 110mg BD dose of dabigatran in acute treatment and long-term secondary prevention of VTE.

Economic:

- the manufacturer provided a base case estimate of cost-effectiveness for acute treatment (deterministic results: dabigatran versus warfarin, £862 per additional QALY; dabigatran versus rivaroxaban, dabigatran dominates; dabigatran versus LMWH in the population with cancer, dabigatran is less costly and less effective);

- the manufacturer provided a base case estimate of cost-effectiveness for treatment and secondary prevention (deterministic results: dabigatran versus warfarin, £8,319 per additional QALY; dabigatran versus rivaroxaban, dabigatran dominates; dabigatran versus LMWH in the population with cancer, dabigatran dominates);
- the ERGs main criticisms of the economic analysis were:
    - the manufacturer did not provide a fully incremental economic analysis for the treatment and secondary prevention scenarios;
    - the manufacturer may have underestimated the duration of treatment in clinical practice, where life-long treatment is considered more likely;
    - the manufacturer may have overestimated the cost associated with warfarin monitoring in the base case analyses;
    - there is uncertainty in model results arising as a consequence of a lack of robust evidence supporting a utility decrement for warfarin treatment;
    - there is uncertainty in model results arising as a consequence of a lack of robust evidence for the 110mg twice daily dose of dabigatran.
- the ERG provided a base case estimate of cost-effectiveness for acute treatment (deterministic results: dabigatran versus warfarin, £18,240 per additional QALY; dabigatran versus rivaroxaban, dabigatran dominates);
- the ERG provided a base case estimate of cost-effectiveness for treatment and secondary prevention (deterministic results: dabigatran versus warfarin, £35,768 per additional QALY; dabigatran versus rivaroxaban, dabigatran extendedly dominates);
- a key driver in the difference between the manufacturer and ERG results was a reduction in the cost associated with warfarin monitoring for the ERG scenarios.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problems

The Evidence Review Group (ERG) notes that the focus of this single technology appraisal (STA) is on patients with deep vein thrombosis (hereafter referred to as DVT) or pulmonary embolism (hereafter referred to as PE). In the Context section of the manufacturer's submission (hereafter referred to as MS), the manufacturer provides an overview of the key aspects of venous thromboembolism (hereafter referred to as VTE) and dabigatran relevant to the decision problem (MS; Section 2). However, there is little discussion of the prevalence, risk factors and co-existing conditions associated with initial and recurrent DVT and PE events in the MS, which the ERG considers might have been beneficial. The ERG also notes that the majority of the published background data available, including that reported by the manufacturer, does not distinguish between initial or recurrent DVT or PE events.

All information presented in the following section in boxes is taken directly from the MS unless otherwise stated and the references have been renumbered.

The pathophysiology of VTE presented in the MS is summarised in Box 1.

Box 1. Pathophysiology of VTE (MS; pg 37 and 39)

Venous thromboembolism (VTE), the third most common cardiovascular disorder after coronary artery disease and stroke[1], includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is characterised by the formation of blood clots (thrombi) or emboli (broken-off clots) that block the blood vessels preventing blood flow, which may have serious consequences depending on the vessel involved and how extensive the blockage is.

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

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

The thrombi that form in the legs can extend. Fragments may break off and travel to the pulmonary artery in the lungs and cause PE with symptoms such as shortness of breath and chest pain. The risk of PE is greater with DVT in the large proximal veins than with distal DVT.[2]

Patients with venous thrombosis have a four-fold (95% CI 3.7-4.3) increased risk of death and hence a reduced median life expectancy compared with the general population.[3] The risk remains increased after the thrombotic event, even when no additional comorbidities are present.

Based on expert clinical advice, the ERG considers the manufacturer's overview of the underlying health problem to be accurate. However, the ERG considers the overview lacks important detail such as risk factors, incidence and prognosis of VTE. For this reason the ERG presents further details to supplement the manufacturer's overview of VTE.

It is widely accepted in clinical practice that certain risk factors increase the risk of VTE. The National Institute for Health and Care Excellence (NICE) Clinical Guideline on "Reducing the risk of venous thromboembolism in patients admitted to hospital" (CG 92) identifies the following risk factors for VTE:

- active cancer or cancer treatment;
- age over 60 years;
- critical care admission;
- dehydration;
- known thrombophilias;
- obesity (body mass index [BMI] over 30 kg/m2);
- one or more significant medical co-morbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions);
- personal history or first-degree relative with a history of VTE;
- use of hormone replacement therapy;
- use of oestrogen-containing contraceptive therapy;
- varicose veins with phlebitis;
- recent surgery;
- trauma;
- immobilisation.

Moreover, ethnicity is considered to be a major risk factor for VTE with significantly higher incidence among Caucasians and African Americans than among Hispanic persons and Pacific Islanders. White *et al.* reported an annual incidence of idiopathic VTE in persons over 18 years of 23 per 100,000 among Caucasians; 29 per 100,000 among African Americans; 14 per 100,000 among Hispanics; and 6 per 100,000 among Asian-Pacific Islanders.

The manufacturer also presented age-specific incidence rates of VTE (MS, Table 153) which show an exponential risk of developing VTE as age increases. The ERG believes these projections reflect the incidence rates witnessed in previous published cohort studies. For the general population, SIGN

Clinical Guideline 122 (Prevention and management of venous thromboembolism) reports that in the general population, the incidence of first VTE rises exponentially with increasing age:

- <40 years – annual incidence of 1/10,000;
- 60-69 years – annual incidence of 1/1,000;
- >80 years – annual incidence of 1/100.

The SIGN guideline suggests that this trend of VTE incidence with age may be related to immobility and coagulation activation.

Regardless of the risk factors highlighted above, the incidence of DVT is greater than PE with an approximate incidence of 124 per 100,000 for an initial DVT and 60 per 100,000 for an initial PE.[(4)]

Despite anticoagulation treatment for the treatment and / or prevention of VTE, patients remain at risk of recurrence of VTE for months or years depending on their underlying risk factors. For example, Prandoni *et al.* reported a cumulative incidence of recurrent VTE of 17% after 2 years, 24.3% after 5 years and 29.7% after 8 years of follow-up.[(5)]

VTE can be classified as provoked or unprovoked, depending on the presence or absence of associated risk factors. Provoked events are much less likely to result in a recurrence. Provoked events can include those occurring after surgery, recent long-haul air travel, pregnancy or use of oestrogen-containing contraceptive therapy. A study conducted by Martinez *et al.* reported that 18.6% of VTEs were active-cancer associated, 34.1% had a common risk factor (provoked), and that 47.2% VTEs were unprovoked VTEs (i.e. not associated with a risk factor such as recent immobilisation).

In terms of prognosis, DVT has a higher probability of recurrence compared with PE, but the recurrence is less likely to be a PE, which is the more serious event. In a study by Murin *et al*, 86% of recurrent events after DVT were DVT, whereas 66% of recurrent events after PE were PE.[(6)]

The manufacturer states “Dabigatran affects blood clotting, so most adverse reactions are related to bleeding” (MS; pg 42). In addition to bleeding, there are also complications associated with VTE events that the manufacturer accounts for within the economic model. These complications associated with VTE include recurrence of VTE, the development of post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).

CTEPH is a complication of PE and is associated with considerable morbidity and mortality. It is relatively rare after a first VTE, but the risk is significantly increased for patients who have experienced a recurrent PE. However, the risk of developing CTEPH is significantly reduced after two years of the PE event. In a prospective, long-term follow-up study Pengo et al., reported a 2 year

cumulative incidence of 3.8% after a first PE and 33% after a recurrent PE with no incident cases after 2 years.[7]

Patients experiencing an initial or recurrent DVT are at risk of developing PTS. Manifestations of PTS include chronic swelling and ulceration of the legs. The risk of developing PTS appears to remain highest for the first five years after the index DVT based on the eight-year cumulative incidence reported by Prandoni *et al*.[5] Prandoni *et al*. estimated that the cumulative incidence of PTS after two, five and eight years was 24.5, 29.6 and 29.8%, respectively.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer's overview of current service provision included an overview of the current NICE guideline for the management of VTE (CG144) (Box 2), along with a summary of the relevant NICE technology appraisals and other NICE recommendations (e.g. NICE guidelines and quality standards) (Box 5). In addition, the manufacturer outlined the factors relating to the estimated resource cost associated with dabigatran use in VTE (Box 6) and estimated the number of patients in England and Wales who would be eligible for treatment with dabigatran both in this new indication and the existing licensed indications (Box 7).

Box 2. Overview of CG144. (MS; pg 40-41)

NICE clinical guideline 144 depicts the pathway of pharmacological interventions for DVT or PE as follows:

- Offer a choice of LMWH or fondaparinux to patients with confirmed proximal DVT or PE taking into account comorbidities, contraindications and drug costs, with the following exceptions:
    - For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer UFH with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
    - For patients with an increased risk of bleeding consider UFH.
    - For patient with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy.

Start the LMWH, fondaparinux or UFH as soon as possible and continue it for at least 5 days or until the INR is 2 or above for at least 24 hours, whichever is longer.

- Offer LMWH to patients with active cancer and confirmed proximal DVT or PE, and continue LMWH for 6 months. At 6 months, assess the risks and benefits of continuing anticoagulation.

- Offer a VKA to patients with confirmed proximal DVT or PE within 24 hours of diagnosis and continue the VKA for 3 months. At 3 months, assess the risks and benefits of continuing VKA treatment.
    - Offer a VKA beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding.
    - Consider extending the VKA beyond 3 months for patients with unprovoked proximal DVT if their risk of VTE recurrence is high and there is no additional risk of major bleeding.

Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis and pulmonary embolism after a diagnosis of acute deep vein thrombosis in adults.[8]

Rivaroxaban is also recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.[9]

Abbreviations used in box: VTE venous thromboembolism, VKA, LMWH

The manufacturer reported that dabigatran can displace warfarin following initial low molecular weight heparin (LMWH) therapy (MS; pg 41). In addition, the manufacturer reported that dabigatran would not require a change to routine practice and existing services/protocols (MS; pg 41). The ERG requested further clarification from the manufacturer on their proposed positioning of dabigatran in the current treatment pathway, in particular relating to any requirement for initial LMWH therapy in the acute treatment of VTE with dabigatran. The manufacturer's response is presented in Box 3. The ERG notes that use of dabigatran in acute VTE requires an initial period of at least 5 days treatment with a parenteral anticoagulant prior to commencement of dabigatran. In contrast, treatment with the oral anticoagulant rivaroxaban can commence from day 1 of diagnosis of VTE and has no requirement for overlapping or prior parenteral anticoagulant administration. However, the advice from clinical experts to the ERG suggests that in clinical practice, patients are likely to receive LMWH during the work-up period prior to receiving a confirmed diagnosis of VTE. Patients will then go on to receive any of the currently licensed anti-coagulants.

Box 3. Initiation of dabigatran for treatment of acute VTE (Manufacturer's response to clarification question A1)

For the treatment of patients with DVT or PE, there will not be an overlap of dabigatran with LMWH treatment in clinical practice. The start of dabigatran treatment is following the cessation of the LMWH therapy. The Summary of Product Characteristics for dabigatran provides the following relevant guidance to healthcare professionals:

4.2 Posology and method of administration

The recommended daily dose of Pradaxa is 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days.
Switching (SPAF, DVT/PE)
Parenteral anticoagulants to Pradaxa
Discontinue the parenteral anticoagulant and start dabigatran etexilate 0-2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g. intravenous Unfractionated Heparin (UFH)).

The ERG requested clarification on the planned treatment duration for dabigatran in secondary prevention of VTE. The manufacturer's response regarding this included citing the British Committee for Standards in Haematology guidelines (Box 4). The clinical experts to the ERG agree with the manufacturer's response, in that after acute treatment of 3 to 6 months an assessment would take place in order to decide whether or not to continue long term anticoagulation as a preventative strategy.

Box 4. Treatment duration for VTE (Manufacturer's response to clarification question A1)

According to recommendations from the British Committee for Standards in Haematology, at least 3 months of anticoagulant treatment is required to prevent extension of thrombus and recurrence in patients with proximal DVT (i.e. involvement of popliteal vein or above) and/or PE:

- Patients with proximal DVT or PE should be treated for at least 3 months (1A)
- If a diagnostic strategy that identifies isolated calf vein DVT is employed, treatment of such clots can be restricted to 6 weeks (1A)
- Patients with cancer-associated VTE should initially be treated for 6 months with therapeutic dose LMWH rather than warfarin (1A).

The BCSH recommendations on long-term VKA therapy are as follows:

- Long-term anticoagulant therapy is not recommended in patients with VTE provoked by surgery (1B)
- Long-term anticoagulant therapy is not recommended in patients with VTE provoked by non-surgical transient trigger factors (1B)
- Patients with unprovoked proximal DVT or PE should be considered for long-term anticoagulation, taking into account information that may help predict risk of recurrence and risk of bleeding in the individual patient (2B)
- Long-term anticoagulant therapy is not recommended in patients with VTE confined to the calf (i.e. not extending into the popliteal vein) (1A).

Data from the VERITY registry conducted in the United Kingdom shows that the intended duration of warfarin treatment for treatment of DVT/PE was up to 6 months in 80% of patients, whilst 20% of

patients were intended to receive warfarin for more than 6 months.
The decision to continue long-term anticoagulation for secondary prevention of recurrent DVT and PE is a clinical decision taking into account the reduction in risk of venous thromboembolism versus the risk of bleeding.

The ERG note that the manufacturer reports that most adverse events with dabigatran are related to bleeding, a consequence relating to its mechanism of action in the interruption of the clotting cascade. The manufacturer reports that the pre-existing clinical protocols that exist for the emergency management of major or clinically relevant bleeding events would be all that is required for the management of such adverse events relating to dabigatran use. In addition, clinical experts highlighted to the ERG, that dabigatran is associated with gastrointestinal adverse events including GI bleeding and dyspepsia. The ERG notes that the manufacturer reports that there are no special requirements for co-therapy with dabigatran to specifically manage adverse events. Based on the advice of clinical experts the ERG agrees with this statement.

The ERG note that the manufacturer reported that use of dabigatran would not require INR monitoring and INR monitoring is associated with warfarin use. However, the ERG also notes rivaroxaban, which is already approved by NICE in this indication, does not require INR monitoring either. In addition, the summary of product characteristics for the use of dabigatran in other conditions states that in order to exclude patients with severe renal impairment (i.e. CrCL < 30 mL/min; a contraindication), renal function should be assessed by calculating the creatinine clearance (CrCL) prior to initiation of treatment with dabigatran. The ERG notes that renal impairment is not a contraindication for treatment with warfarin, whereas severe renal impairment is a contraindication for treatment with dabigatran and rivaroxaban. Clinical experts report that baseline assessment of renal function is usually conducted prior to commencement of treatment with warfarin as renal function is related to warfarin dosing. The ERG thus considers that assessment of renal function is already potentially a requirement in the treatment pathway.

Box 5. Summary of related NICE guidance. (MS; pg 39-40)

NICE clinical guideline 92: Reducing the risk of venous thromboembolism
NICE clinical guideline 144: Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing
NICE evidence update 55 (April 2014): A summary of selected new evidence relevant to NICE clinical guideline 144
NICE quality standard 29: Quality standard for diagnosis and management of venous thromboembolic diseases
NICE technology appraisal 261: Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism
NICE technology appraisal 287: Rivaroxaban for treating pulmonary embolism and preventing

recurrent venous thromboembolism.

NICE pathway: Venous thromboembolism

The ERG notes that there is one additional related NICE publication, NICE quality standard 3: Venous thromboembolism prevention, which was not reported in the MS. However, the ERG does not consider this to be a significant omission as it is covered within the NICE pathway: Venous thromboembolism.

Box 6. Factors relating to estimated resource cost associated with dabigatran use in VTE (MS; pg 42)

The main resource use associated with the use of dabigatran is its acquisition cost. There are no administration or monitoring costs specifically associated with the use of dabigatran. The unit costs of surgery consultations are taken from PSSRU[10] and of secondary care outpatient consultations from NHS reference costs 2012/2013[11] (inflated to 2014 values).

Dabigatran does not requiring INR testing. It has the potential to supersede the extensive infrastructure (along with its inherent costs) of hospital and clinical INR monitoring.

The ERG notes that the manufacturer does not explicitly report their estimated resource cost for the use of dabigatran in VTE in Section 2 of the MS. However, the manufacturer does highlight that the main cost likely to be associated with the integration of dabigatran in the treatment pathway for VTE is the acquisition cost of dabigatran. In addition, the manufacturer reports that there is a possibility that INR monitoring costs may be reduced as a result of the introduction of dabigatran. This is because dabigatran does not require INR monitoring and if fewer people are taking warfarin (which requires INR monitoring) then associated costs may be reduced.

The unit cost of dabigatran and dosing for different patient groups reported in the MS are presented in Table 1. The ERG considers it important to highlight that these costs relate to only the drug acquisition cost and do not include any associated resource use such as outpatient appointments. In addition, the ERG notes that the manufacturer reports that the average length of treatment for acute DVT or PE would be 6 months. However, for the prevention of recurrent DVT or PE the manufacturer suggests that the average length of a course of treatment would be 12 months to lifelong. The clinical advisers to the ERG reported that usually in UK clinical practice, acute treatment would be for 3 to 6 months and secondary VTE prevention would be planned as lifelong treatment unless the index VTE event was provoked and the risk is ongoing but not likely to be lifelong e.g. long haul flight related VTE. The ERG thus considers that the average treatment duration for secondary prevention would be expected to be life-long.

Table 1. Unit costs of technology being appraised (adapted from MS Table 18)

Pharmaceutical formulation	**Hard capsules**
Acquisition cost (excluding VAT)	£65.90 per 60 capsule pack (£2.20 per day)
Method of administration	Oral
Doses	150 mg, 110 mg
Dosing frequency	150 mg or 110 mg twice daily
Average length of a course of treatment	6 months for treatment of acute DVT and PE; 12 months (to lifelong) for the prevention of recurrent DVT and PE
Average cost of a course of treatment	Dependent on the patient's risk-benefit profile. A 6 months course of acute treatment would involve the outlay of £401.50 per patient (= (365/2)*£2.20 per day).
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	The standard daily dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. For the following groups the recommended daily dose of dabigatran is 220 mg taken as one 110 mg capsule twice daily: o Patients aged 80 years or above o Patients who receive concomitant verapamil For the following groups the daily dose of dabigatran of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding: o Patients between 75-80 years o Patients with moderate renal impairment o Patients with gastritis, esophagitis or gastroesophageal reflux o Other patients at increased risk of bleeding

Box 7. Manufacturer's estimates for the number of people in England and Wales eligible for dabigatran in each of its indications. (MS; pg 38-39)

It is estimated that there is in the region of 52,320 patients eligible for treatment with anticoagulation under the indication considered in this submission in England and Wales in 2014. This is projected to rise to 56,085 patients in 2018 due to growth and ageing of the population. These projections are based on the rates of incidence and recurrence of DVT and PE derived from a combined analysis of UK hospital and primary care databases (General Practice Research Database, Hospital Episode Statistics database)[12], which have been applied to the population projections for England and Wales from the Office of National Statistics[13].

For the second indication of dabigatran, the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF), 849,000 patients with AF have been registered,

according to the 2012/13 QOF database.

Finally, approximately 128,000 patients are eligible for dabigatran's third indication in primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery; (based on hip and knee procedures performed in the NHS England and Wales in 2013).[14]

The ERG consulted with clinical experts and considers the manufacturer's estimates for the number of people likely to be eligible for treatment with dabigatran for VTE to be reasonable.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

The manufacturer provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence[15] (NICE; MS, pg 47-48), together with the rationale for any deviation from the decision problem (Table 2).

Table 2. Summary of decision problem as outlined in the manufacturer's submission (adapted from MS; Section 5; pg 47-48)

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	People with deep vein thrombosis and/or pulmonary embolism	People with deep vein thrombosis and/or pulmonary embolism	N/A
Intervention	Dabigatran etexilate	Dabigatran etexilate	N/A
Comparator(s)	• Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • rivaroxaban <u>For people with cancer:</u> • low molecular weight heparin • rivaroxaban	• Initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist • rivaroxaban <u>For people with cancer:</u> • low molecular weight heparin • rivaroxaban	N/A
Outcomes	The outcome measures to be considered include: • mortality • venous thromboembolism recurrence • complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome, heart failure and chronic thromboembolic pulmonary hypertension. • adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding) • health-related quality of life	The outcome measures to be considered include: • mortality • venous thromboembolism recurrence • complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome and chronic thromboembolic pulmonary hypertension. • adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding) • health-related quality of life	The outcome 'heart failure' was not included in the clinical trials and could thus not be modelled either.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating	Cost utility analysis was performed, using a Markov Model in Microsoft Excel. The time horizon for both the 'treatment phase' and	N/A

	clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	'treatment + secondary prevention phase' is life time (60 years). The perspective is from an NHS & PSS perspective.	
Subgroups to be considered	If evidence allows, subgroups will be considered by type of venous thromboembolism (pulmonary embolism or deep vein thrombosis). The analysis should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). Guidance will only be issued in accordance with the marketing authorisation.	Various subgroup analyses have been conducted: • Type of index event: • DVT only • PE with/without DVT • Patient history of bleeding • Active cancer • Western European patients	N/A
Special considerations, including issues related to equity or equality		N/A	
Abbreviations used in the table: DVT, deep vein thrombosis; N/A, not applicable; PE, pulmonary embolism; PSS, personal social services			

The ERG noted that some of areas requested by the NICE scope were not covered within the MS although the manufacturer had indicated in their statement of the decision problem (MS; Section 5; pg 47-48) that they were addressed within the MS. The ERG requested further clarification from the manufacturer on these inconsistencies in the form of a revised table with full details on the rationale for any deviation from the NICE final scope. The manufacturer did not provide a revised table, but they responded to the ERG's questions regarding the comparison with fondaparinux and the comparison with rivaroxaban in people with cancer.

In terms of the comparison with fondaparinux (i.e. initial treatment with fondaparinux followed by treatment with a vitamin-K antagonist [VKA]), the manufacturer's response is presented in Box 8.

Box 8. Manufacturer's rationale for the absence of a separate comparison with fondaparinux (Manufacturer's response to clarification question A2)

As stated in Section 2.6 of the manufacturer's submission, fondaparinux is an alternative to LMWH or UFH for the initial treatment of DVT. However, it is not approved for long-term prophylaxis of VTE and therefore is not considered a relevant comparator for dabigatran for the treatment and long-term secondary prevention of VTE. For analyses of treatment of DVT and PE, fondaparinux is included as an option for initial parenteral treatment prior to adjusted-dose warfarin treatment.

The ERG consulted with clinical experts and agrees with the manufacturer that fondaparinux should not be routinely used for long term treatment or secondary prevention of VTE and do not consider this to be a comparison of interest in the NICE final scope. The ERG considers the comparison in the NICE final scope to be initial treatment with fondaparinux followed by continued treatment with a VKA. Clinical advisors to the ERG consider that use of fondaparinux in clinical practice is limited, with LMWH being the most commonly used initial treatment in the VKA VTE treatment pathway.

The ERG note that initial treatment with fondaparinux was included as an alternative to LMWH or unfractionated heparin (UFH) in the RE-COVER trials[16;17] and that 1 to 4% of people in each treatment group in the trials received fondaparinux. The ERG note that no subgroup analyses are presented by the manufacturer based on initial parenteral therapy, e.g. LMWH or fondaparinux. However, the ERG also note that the numbers of patients who received fondaparinux in the RE-COVER trials is small and so such analyses would be of limited value. The ERG therefore considers that the manufacturer's exclusion of the comparison of initial treatment with fondaparinux followed by treatment with a VKA in the MS was reasonable. The ERG also considers it important to highlight that conclusions thus cannot be made as to the different impact initial treatments (e.g. LMWH, fondaparinux) may have on the safety and efficacy of the subsequent treatment. This is because for the purposes of this review, all initial treatments have been assumed to have equal efficacy.

The ERG also requested clarification on why the manufacturer had not presented data in the MS for the comparison of dabigatran with rivaroxaban in relation to the subgroup of patients with active cancer. The manufacturer's response is presented in Box 9.

Box 9. Manufacturer's justification for omission of rivaroxaban comparison in people with cancer (Manufacturer's response to clarification question A2).

In a previous NICE Technology Appraisal of rivaroxaban for the treatment and secondary prevention of recurrent VTE (TA 261), the Appraisal Committee made the following conclusion in relation to the use of rivaroxaban in the subgroup of patients with active cancer:

"Given the lack of clinical evidence for this group of patients, the Committee was unable to make specific recommendations on the use of rivaroxaban in people with cancer but recognised the disadvantages of the currently available treatment, which involves regular injections, and which some patients might choose to decline."

Given this opinion from the Appraisal Committee, rivaroxaban was not considered to be a relevant treatment option in this subgroup and was therefore not included as a comparator to dabigatran for this subgroup in the submission.

Furthermore, LMWH monotherapy is considered to be standard treatment for DVT and PE in this subgroup. The British Committee for Standards in Haematology makes the following recommendation:

Patients with cancer-associated VTE should initially be treated for 6 months with therapeutic dose

LMWH rather than warfarin (1A).
It was therefore considered most appropriate to only include a comparison of dabigatran with LMWH monotherapy in the subgroup of patients with cancer.

The ERG agrees with the manufacturer that there is a lack of clinical data on the use of rivaroxaban in people with cancer. In addition, the ERG note that there are a lack of clinical evidence in publically available published sources for the safety and efficacy of rivaroxaban in people with cancer in both the acute and secondary prevention of VTE. The ERG have conducted an analysis using efficacy data identified on the use of rivaroxaban for acute treatment of VTE in people with cancer but were unable to source any data on safety or for its use in secondary prevention (see Section 4.9). The ERG also acknowledges that there are small numbers of both people and events in this subgroup data and so limited conclusions can be drawn from the results. For further details of this issue please see Section 3.1.

3.1 Population

The manufacturer presents data on dabigatran from four phase III trials in the MS; RE-COVER,[16] RE-COVER II,[17] RE-MEDY and RE-SONATE.[18] Within the MS the data is presented separately for people requiring acute treatment of VTE and for people requiring long term secondary prevention of VTE. The manufacturer presents data from two RCTs for each of the two populations. For the acute prevention of VTE, the manufacturer presents data from RE-COVER and RE-COVER II. These two RCTs were of identical design and had identical inclusion and exclusion criteria.

The two RCTs used to provide data for long term secondary prevention of VTE in the MS were RE-MEDY and RE-SONATE. The inclusion criteria for the secondary prevention trials differed compared to each other in terms of the duration of prior therapy. In RE-MEDY, 3 to 12 months of treatment for VTE were required at the time of screening whereas in RE-SONATE 6 to 18 months of treatment were required at the time of screening.

All four dabigatran trials limited inclusion to people over 18 years old, i.e. adults. No data are presented in the MS for the use of dabigatran in VTE in children. Clinical experts to the ERG note that the mean baseline age for each of trial populations is lower than what would be typically expected in the UK population for whom treatment with dabigatran in acute or secondary prevention of VTE would be indicated. The mean baseline age in the four dabigatran trials in the MS was between 53 and 56 years. The clinical experts to the ERG report that they would expect the majority of their equivalent VTE patients to be aged over 65 years and that a proportion of them would be over 80 years. The ERG considers this difference in age to be important as patients aged over 80 years are recommended a lower dose of dabigatran according to the draft SmPC. The baseline characteristics for the dabigatran trials would suggest that few, if any patients in the trials were aged over 80 years.

In addition, the trial protocols indicate that if any patients aged over 80 years were included in the trials then they would have received the same dose of dabigatran as those patients aged under 80 years. It can thus be concluded that if the dose reduction recommended in people aged over 80 years for the current licensed indications of dabigatran is also recommended in this new VTE indication, then there are no clinical trial data for this population presented in the MS. This issue will be discussed further in section 3.2.

In terms of baseline index event, the ERG considers the distribution within the dabigatran trials to reflect what would be expected in typical UK clinical practice, i.e. higher rates of DVT than PE.

RE-MEDY and RE-SONATE both allowed entry of patients from either of the RE-COVER trials. It should also be noted that less than 50% of patients in RE-MEDY and less than 10% in RE-SONATE were enrolled from the RE-COVER trials. There are thus limited data on people who are treated continuously with dabigatran starting from the acute phase of a VTE through to long term secondary prevention with dabigatran.

The manufacturer reports in the MS that the population in RE-SONATE were at lower risk for recurrence of VTE compared with the population of RE-MEDY. The manufacturer explains this as follows:

"RE-MEDY included patients considered to be at high-risk of recurrent VTE and thus indicated for further anticoagulation following acute VTE, while the remaining clinical trial, RE-SONATE, was a superiority study of dabigatran vs placebo in patients for whom there was considered to be clinical equipoise regarding the need for further anticoagulation."

The clinical advisers to the ERG consider the 'clinical equipoise' population in RE-SONATE to be difficult to define in clinical practice. However, it is thought that they would most likely be people whom currently would not receive ongoing treatment for secondary prevention of VTE. It could thus be considered that the population in RE-SONATE are a different population to that currently treated for secondary prevention of VTE in the UK.

In addition, it is reported by the manufacturer that active cancer was an exclusion criterion for RE-SONATE trial entry and so there are no data available for the subgroup of people with active cancer from this trial.

The ERG and their clinical advisors also have concerns about the definition of active cancer used in the RE-COVER, RE-COVER II and RE-MEDY trials potentially not being consistent with what would be considered active cancer in UK clinical practice. In the MS it is reported that the same definition for active cancer was used in RE-COVER, RE-COVER II and RE-MEDY. The definition

of active cancer was “a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within five years before enrolment; any treatment for cancer within five years before enrolment; or recurrent or metastatic cancer”. Clinical advisors to the ERG report that in UK clinical practice, the change in VTE treatment pathway for people with cancer would usually be based on a current diagnosis of active cancer at the time of assessment for VTE related therapy, or at most, cancer in remission for less than a year. The definition of active cancer in the dabigatran trials (RE-COVER, RE-COVER II and RE-MEDY) encompasses patients who may have been in remission for nearly 5 years and thus would not usually be considered in UK clinical practice to be active cancer patients.

The ERG requested clarification from the manufacturer in terms of the number of patients with cancer under active treatment or with ≤1year remission at baseline in RE-COVER I, RE-COVER II, and REMEDY for the randomised population. However, the manufacturer reported that they were unable to provide this data as the date of the “active cancer” event was not captured in the clinical trials. The ERG also notes that although patients with active cancer were included in three of the dabigatran trials and they were stratified by cancer status, the total number of patients was small and the event rates low. The ERG thus considers caution should be exercised when drawing any conclusions on the results of this review in the subgroup of people with cancer.

The ERG notes that the inclusion criteria for the four dabigatran trials limit inclusion of VTE events to proximal DVT and/or PE. This results in the exclusion of people with solely distal DVT. Clinical experts have advised the ERG that this is appropriate as the treatment pathway for proximal DVT would not necessarily be the same as that for proximal DVT. The ERG is thus unable to comment further on the safety or efficacy of dabigatran for treatment or prevention of distal DVT. In addition, henceforth the term DVT will be used to refer only to proximal DVT.

3.2 Intervention

The intervention that is the subject of this STA is dabigatran etexilate (Pradaxa®, hereafter referred to as dabigatran). Dabigatran is an orally administered pro-drug that is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a direct thrombin inhibitor. The result of the inhibition of thrombin is that conversion of fibrinogen into fibrin during the coagulation cascade is prevented and thus the development of thrombus is avoided. Dabigatran is administered in fixed doses with no current requirement for routine coagulation monitoring. It is principally excreted by the kidney and has a half-life of just 12–14 hours. However, the ERG note that the half-life is prolonged if renal function is impaired and in the draft summary of product characteristics (SmPC) is recommended that the dose of dabigatran in patients with moderate renal impairment is selected following an individual risk benefit assessment.

Dabigatran currently holds UK marketing authorisation for the use in:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.

The manufacturer reports that dabigatran was submitted to the European Medicines Agency (EMA) for regulatory approval use in treatment and prevention of recurrent VTE on 3 June 2013. CHMP positive opinion was adopted on 25 April 2014[19]. The manufacturer reports that they expected to receive marketing authorisation in the European Union at the end of June/beginning of July 2014.

The EMA positive opinion released on 25 April 2014[20] recommended the approval of dabigatran for following the indication, which is in line with that of this STA:

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The manufacturer also reported that dabigatran has already gained regulatory approval for use in this indication in Argentina, Chile, Russia, Philippines, Ecuador, Colombia, Mexico, Turkey (acute treatment only), and the USA. In addition, the manufacturer reported that they intend to make a full submission to the Scottish Medicines Consortium (SMC) for dabigatran use in this indication.

It is expected that the UK marketing authorisation for dabigatran in the acute treatment of VTE will include wording restricting its use to after treatment of at least 5 days with a parenteral anticoagulant. This treatment pathway was not explicitly stated in the NICE final scope, but it was reflected in the acute VTE treatment clinical trials data supplied within the MS (RE-COVER and RE-COVER II). The ERG thus considers the data provided by the manufacturer for acute treatment of VTE with dabigatran to reflect 'initial treatment with parenteral anticoagulant and continued dabigatran'. In terms of secondary prevention, this requirement for initial treatment is not applicable as it would usually be expected that the patient would already be on some form of anticoagulation following their primary VTE event.

The anticipated standard daily dose of dabigatran is 300 mg taken as one 150 mg capsule twice daily. A dose reduction to 220 mg daily taken as one 110 mg capsule twice daily is recommended for the following groups:

- patients aged 80 years or above;
- patients who receive concomitant verapamil.

In addition, individual assessment of the thromboembolic risk and the risk of bleeding to select the most suitable daily dose of dabigatran of 300 mg or 220 mg is recommended for the following groups:

- patients between 75-80 years
- patients with moderate renal impairment;
- patients with gastritis, esophagitis or gastroesophageal reflux;
- other patients at increased risk of bleeding.

Pharmacokinetic and pharmacodynamics analyses of dabigatran in both RE-LY (a study of dabigatran vs warfarin in people with NVAF and RE-COVER[16] (a study of dabigatran versus warfarin in people with acute VTE) studies have demonstrated that the pharmacodynamic responses (anticoagulation), as well as therapeutic response (bleeding and antithrombotic efficiency) are closely related to actual dabigatran exposure. The manufacturer reports (MS; pg 215) that "the existing data on the 110 mg BD dose from RE-LY together with the high consistency between the patient populations in terms of the pharmacokinetics, pharmacodynamics and exposure-response results seen in the RE-LY and RE-COVER studies, is sufficient evidence to consider the 110 mg BD dose for the same sub-populations in VTE as in NVAF, without further need of a dedicated clinical study." However, the ERG recommends exercising caution with this approach as it would entail extrapolation of the 110 mg BD dabigatran safety and efficacy findings from a study for a different patient population and clinical therapeutic indication to that under review in this technology appraisal. In addition, the ERG considers it inappropriate to draw conclusions on VTE events with the 110 mg BD dose when the VTE data in RE-LY were collected as either the composite of stroke and systemic embolism or as only PE. Data for DVT were not specifically collected and as a result it was not reported as a discrete outcome.

In addition, the ERG notes that there was a statistically significant difference in the efficacy of the higher (150 mg BD) and lower (110 mg BD) doses of dabigatran in the RE-LY study for the primary efficacy outcome of stroke or systemic embolism, favouring treatment with the higher dose (RR 0.73; 95% CI: 0.58 to 0.91, $p = 0.005$). In terms of the primary safety outcome, major bleeding, there was no statistically significant difference between the two doses of dabigatran although the results suggest a reduction in risk of major bleed with the 110 mg BD dose (150 mg BD vs 110 mg BD dabigatran RR 1.16; 95% CI: 1.00 to 1.34, $p = 0.052$). This suggests that there may be a reduction in efficacy but an improvement in safety with the 110 mg BD dose of dabigatran. The ERG also notes that the RE-LY study was looking at primary and/or secondary prevention of stroke and systemic embolism. RE-LY did not consider acute treatment of any VTE events and as such there is a lack of clinical data for dabigatran in this therapeutic indication. The ERG thus considers it particularly inappropriate to draw conclusions on the use of the 110 mg dose of dabigatran in the acute treatment phase of VTE.

To summarise, the ERG considers the intervention in the MS to be consistent with the anticipated licence and the NICE final scope for this STA. However, the ERG has concerns regarding the absence of clinical trial data for the 110 mg BD dose of dabigatran in patients requiring acute treatment or ongoing secondary prevention of VTE.

3.3 Comparators

The comparators for this STA listed in the final scope issued by NICE are:

- initial treatment with a low molecular weight heparin or fondaparinux and continued vitamin K antagonist; or
- rivaroxaban.

For people with cancer, the comparators are:

- low molecular weight heparin; or
- rivaroxaban.

The manufacturer presented data for acute parenteral treatment with heparin (either LMWH or unfractionated heparin [UFH]) or fondaparinux, followed by overlapping dose-adjusted warfarin that is continued without heparin therapy once a therapeutic INR level is reached. The therapeutic INR level was defined by the manufacturer as 2.0 to 3.0; based on clinical expert advice, the ERG consider this to be comparable with the target therapeutic INR level used in equivalent patients in the UK.

The manufacturer has assumed equal efficacy for the different parenteral drugs used within the initial treatment period. In addition, there was no stratification at baseline according to the parenteral therapy used. The ERG notes that the initial parenteral therapy used was similar at baseline between the dabigatran and warfarin groups in the RE-COVER trials.[16;17] However, clinical advisers to the ERG have suggested that the use of UFH and fondaparinux in the RE-COVER trials may be slightly higher than that in the UK, although the ERG has no audit data on their use in the UK. The ERG also acknowledges that the RE-COVER trials were multi-centre international trials and that the baseline parenteral therapies used are likely to reflect variations in clinical practice across the different trial centres.

The ERG is unsure of what effect, if any, the initial parenteral therapy would have on the overall safety and efficacy of dabigatran as no data for this is provided within the MS. In addition, the ERG acknowledges that the numbers for such an analysis would be small. It would also be a non-randomised subgroup thus making it difficult to draw any conclusions. It is thus assumed within this report that the drugs used for initial parenteral therapy (i.e. prior to dabigatran or warfarin therapy) have equal efficacy.

The manufacturer presented data for the comparison of dabigatran with rivaroxaban using an adjusted indirect comparison (AIC) within the MS. In addition, the ERG notes that the manufacturer has provided data in an additional report for rivaroxaban using a network meta-analysis (NMA). Based on the absence of head-to-head trial data, the ERG considers the manufacturer's decision to synthesise relative treatment effects using AIC and NMA methods to be appropriate. However, the ERG has concerns over the data sets used in the manufacturer's analyses. Please see section 4.9 for further details.

For the subgroup of people with cancer, the manufacturer presented data in the MS from clinical trials that compared acute parenteral treatment with heparin (either LMWH or UFH) or fondaparinux, followed by either dabigatran or overlapping and then continued dose-adjusted warfarin therapy rather than the continued LMWH requested in the NICE final scope. The ERG appreciates that this is a limitation of the available trial data for dabigatran in people with cancer; the RE-COVER trials protocols did not allow continued LMWH instead of warfarin in people with cancer. The manufacturer does report data from an AIC for the comparison of dabigatran with LMWH (via warfarin). In addition, within the supplementary meta-analysis report provided by the manufacturer, the ERG notes that data are presented for both acute treatment and secondary prevention of VTE in people with cancer using NMA. However, the ERG has concerns over both the comparability of the trials included in the networks and the trial population data sets used for the analyses. Further details on the ERG's critique of the manufacturer's AIC and NMA are provided in Section 4.8.

In terms of the comparison with rivaroxaban in people with cancer, the manufacturer presented no numerical data in Section 6, the clinical evidence section of the MS, or the additional meta-analysis report. The ERG requested further clarification from the manufacturer on this, as discussed above in Section 3. The ERG considers the manufacturer's decision to omit rivaroxaban as a comparator in people with cancer for secondary prevention of VTE to be appropriate based on the lack of available published data. However, the ERG considers there are some comparable data available for rivaroxaban in acute treatment of DVT and PE. Please see Section 4.9 for further details.

In summary, the ERG considers the manufacturer has included the key comparators requested in the NICE final scope within the MS. However, the ERG does not consider the comparison in the subgroup of people with cancer to be addressed fully within the MS for rivaroxaban.

3.4 Outcomes

The outcome measures to be considered according to the final scope issued by NICE are:

- mortality;
- venous thromboembolism recurrence;

- complications following deep vein thrombosis or pulmonary embolism, including post thrombotic syndrome (PTS), heart failure and chronic thromboembolic pulmonary hypertension (CTEPH);
- adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding); and
- health-related quality of life (HRQoL).

The primary efficacy endpoint of the four key trials presented in the MS was the composite of recurrent symptomatic VTE and deaths related to VTE (RE-SONATE also included unexplained deaths as they were deemed to be a result of fatal PE). Clinical advisors to the ERG indicate that this is suitable for addressing the outcome in the NICE final scope of venous thromboembolism recurrence.

The secondary efficacy endpoints of the four key trials presented in the MS were:

- composite of recurrent symptomatic VTE and all deaths (except for RE-SONATE where the composite of recurrent symptomatic VTE and deaths related to VTE was reported instead);
- symptomatic DVT;
- symptomatic PE (note two definitions used here and both not reported for all trials: non-fatal PE, or fatal and non-fatal PE);
- deaths related to VTE (fatal PE, except for in RE-SONATE where the outcome unexplained deaths was reported instead);
- all deaths (this was a safety endpoint in RE-SONATE).

The safety endpoints of the four trials included:

- incidence of bleeding events;
  - major bleeding events (MBEs);
  - MBEs or clinically relevant bleeding events (CRBEs);
- any bleeding events (MBEs, CRBEs, and nuisance bleeding events);
- adverse events (AEs; including findings in the physical examination).

In addition, the ERG notes that HRQoL data are discussed in the cost-effectiveness section of the MS (Section 7.4.3, pg 263). The manufacturer reports that during RE-COVER, RE-COVER II,[16;17] and RE-SONATE, patients were asked to complete the EQ-5D, a self-administered utility instrument assessing patients' health status. The results from this HRQoL assessment are not presented within the clinical effectiveness results in the MS. The ERG presents a summary of the EQ-5D findings from RE-COVER and RE-COVER II in Section 4.4.5.

The ERG also notes that the manufacturer does not report data specifically for the outcomes of PTS, heart failure and CTEPH within the MS. The ERG requested data on these during the clarification stage as the clinical advisors to the ERG reported that PTS and CTEPH in particular, were important outcomes. This is because both PTS and CTEPH are associated with significant morbidity and costs for both patients and the NHS. The manufacturer's response to the ERG's clarification request detailed that data for these outcomes could not be provided. The manufacturer's rationale for this included the information presented in Box 10.

Box 10. Manufacturer's rationale for exclusion of PTS and CTEPH data (Manufacturer's response to clarification question A14)

Patients with acute right heart failure were not enrolled in the clinical trials based on exclusion criteria: PE complicated with haemodynamic instability. PTS and CTPH constitute long-term complications of VTE. The dabigatran trials were of insufficient duration to collect meaningful comparative incidence data on these outcomes (6 months treatment duration for RE-COVER and RE-COVER II and up to 18 months treatment duration for RE-MEDY). It was therefore inappropriate to include these outcomes in the dabigatran trials.

The manufacturer also detailed that they had incorporated the long-term occurrence of these outcomes in the economic model using data from literature sources.

To summarise, given the available clinical data for dabigatran, the ERG considers that the outcome data presented in the MS by the manufacturer are appropriate.

3.5 Timeframe

The final scope issued by NICE specified that the analysis should consider both those who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (usually lifelong). The data presented for dabigatran in the MS for the acute treatment of VTE come from different clinical trials to the data presented for long term secondary prevention of VTE.

The data for the acute treatment are based on the RE-COVER[16] and RE-COVER II[17] clinical trials where the planned treatment duration was 6 months. The actual mean duration of exposure to study drug in the double dummy phase (i.e. during the period when both study drugs [warfarin and dabigatran placebo or warfarin placebo and dabigatran] were taken) when the trials were pooled for analysis was around 164 days in each treatment group.

The data for long-term anticoagulation (i.e. long-term secondary prevention of VTE) are based on the RE-MEDY and RE-SONATE clinical trials.[18] RE-MEDY included people whom had received between 3 and 12 months prior anticoagulation. Treatment duration in RE-MEDY was initially

planned to be 18 months although this was extended to 36 months following a protocol amendment. However, as a result of recruitment timing and participant refusal to the protocol amendment, the planned overall treatment duration ranged from 6 to 36 months. The mean treatment duration for the dabigatran group was 473 days, and for the warfarin group was 474 days. This equates to approximately 16 months treatment with a study drug.

RE-SONATE included people who had received 6 to 18 months of prior oral anticoagulant. The mean treatment duration for the dabigatran group was 165 days, and for the warfarin group was 162 days. This is roughly in keeping with the planned treatment duration in RE-SONATE which was 6 months.

Based on clinical expert advice, the ERG considers the 6 month duration of follow-up planned in RE-COVER and RE-COVER II to be suitable for assessing the safety and efficacy outcomes of treatment with dabigatran in people who require a limited period of anticoagulation. However, the ERG also acknowledges that no data are presented for people who require only 3 months treatment and so the ERG cannot comment specifically on this population.

In terms of the people requiring long-term anticoagulation for VTE, the ERG considers the data from RE-MEDY and RE-SONATE to address this population, although the long-term safety and efficacy data are limited by the trial durations.

3.6 Other relevant factors

The MS includes a section on equality issues where the manufacturer reports there are no equality issues (MS section 3.1). The clinical advisors to the ERG and the ERG agree with the manufacturer that there does not appear to be any major equality issues relating to dabigatran to be considered. In addition, the ERG is unaware of any ongoing Patient Access Scheme application.

The ERG notes that the final scope issued by NICE specified that evidence permitting, consideration should be given to the following subgroups:

- type of venous thromboembolism (pulmonary embolism [PE] or deep vein thrombosis [DVT]).

The manufacturer presented subgroup data in the MS based on the primary index event, i.e. PE or DVT and this was stratified for at randomisation. The ERG thus considers that the manufacturer has presented suitable subgroup data to address these subgroups within the MS.

4 CLINICAL EFFECTIVENESS

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

The manufacturer conducted a systematic review to identify published reports of trials relevant to the decision problem that is the focus of this STA. The aim of the systematic review was to identify evidence on the efficacy and safety of dabigatran etexilate (hereafter referred to as dabigatran) and relevant comparators for treatment and secondary prevention of VTE. The interventions of interest were dabigatran, rivaroxaban, edoxaban, apixaban, unfractionated heparin (UFH), low molecular-weight heparin (LMWH) (e.g., enoxaparin, dalteparin, tinzaparin, bemiparin and nadroparin), and fondaparinux. Trials comparing warfarin with placebo in the secondary prevention indication were also included. The ERG requested clarification from the manufacturer on the decision to limit the inclusion of warfarin to the secondary prevention review given that in the NICE scope it is a comparator in both the acute and secondary prevention phases. The manufacturer's response is presented in Box 11.

Box 11. Manufacturer's rationale for inclusion and exclusion of warfarin studies (Manufacturer's response to clarification question A21)

As dabigatran had been compared head-to-head with warfarin / VKA in two randomised trials in the treatment indication, it was considered that other trials investigating warfarin (but not also investigating any of the other listed treatments: dabigatran, rivaroxaban, edoxaban, apixaban, LMWH, UH and fondaparinux) would not add important information to the assessment of comparative effectiveness (principally as these warfarin trials were expected to be older). In the secondary prevention indication, dabigatran had been compared with warfarin and with placebo. It was therefore possible that trials comparing warfarin with placebo might add to the evidence for the effectiveness of dabigatran compared with warfarin or placebo (by adding indirect evidence to the direct head-to-head trial evidence). Therefore these trials were identified in order to assess the feasibility and utility of adding them to the evidence network.

The ERG considers that as parenteral therapy (UFH, LMWH or fondaparinux) followed by overlapping and continuing vitamin K antagonist (VKA) was a comparator in the final scope issued by NICE, the manufacturer's rationale is reasonable. However, the ERG considers there to be a possibility that further studies focusing on VKA therapy (i.e. warfarin) may exist in the literature and could potentially have been of relevance to any network meta-analysis (NMA) conducted for acute treatment. The ERG is unaware of any specific studies and, due to time constraints, was unable to conduct searches to identify such data. The ERG notes that the manufacturer did not use separate search strategies for the acute treatment and secondary prevention reviews and the search strategy used included terms for warfarin. The ERG expects that any warfarin studies in acute treatment not identified through the other drug search terms would have been identified by the manufacturer's

searches. However, these studies would then have been excluded during the study selection stages of the manufacturer's systematic review. The ERG is unable to comment further on the possibility of additional studies suitable for inclusion in the network meta-analysis for acute treatment.

4.1.1 Description and critique of manufacturer's search strategy

The manufacturer reports that the systematic review searches were performed in two phases. Phase 1 was to identify studies investigating dabigatran, rivaroxaban, edoxaban, and apixaban. Phase 2 comprised of searches for UFH, LMWH, and fondaparinux. The ERG requested further clarification on this decision. The manufacturer's response is presented in Box 12.

Box 12. Manufacturers rationale for conducting searches in 2 phases (Manufacturer's response to clarification question A20)

BI originally decided that UH, LMWH, and fondaparinux should not be included as comparators in the model, therefore the original searches omitted these interventions. Later, BI decided that UH, LMWH, and fondaparinux should be included; therefore the searches were performed for these interventions also.

In the MS it is reported that the following databases were searched during phase 1 and 2:

- MEDLINE and MEDLINE In-Process (using PubMed platform);
- Embase (using Dialog Platform);
- The Cochrane Library, including the following:
  - The Cochrane Database of Systematic Reviews;
  - The Cochrane Central Register of Controlled Trials;
  - Database of Abstracts of Reviews of Effectiveness;
- Biosciences Information Service (using the Dialog Platform).

The manufacturer reported that the phase 1 searches of electronic databases (for studies of dabigatran, rivaroxaban, edoxaban, and apixaban) were performed on 23 July 2012 and the phase 2 searches (for UFH, LMWH, and fondaparinux studies) were performed on 1 October 2012.

The manufacturer used a combination of free-text search terms and Medical Subject Heading (MESH) terms covering the following:

- population of interest: treatment and secondary prevention of DVT and PE;
- interventions of interest: dabigatran, rivaroxaban, edoxaban, apixaban, warfarin, UFH, LMWH (including enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin), and fondaparinux;

- study types: RCTs and non-randomised studies;
- exclusions: comments, editorials, letters, case reports, or studies in animals but not humans.

The ERG note that, according to the search strategies provided, search terms for phase 1 clinical trials were also used in the search strategies to exclude phase 1 trials from both the phase 1 and phase 2 searches. In addition, as highlighted by the manufacturer, the ERG notes that the phase 2 database searches included terms restricting the phase 2 search results to including only RCTs, i.e. observational data were excluded. The ERG considers this to be appropriate as any observational data identified through the phase 2 searches would not have been expected to provide any head-to-head data on the safety or efficacy of dabigatran. The ERG considers that observational data on dabigatran would have been identified in the phase 1 searches.

The manufacturer also conducted searches of internet websites and selected conference abstracts. The websites and conference abstracts that were searched included:

- International Society on Thrombosis and Haemostasis (http://www.isth.org/default/index.cfm/publications/abstracts/);
- Hematology Association (http://www.ehaweb.org/Congress/Previous-Congresses);
- ClinicalTrials.gov Web site (searched for ongoing trials);
- National Institute for Health and Care Excellence (http://www.nice.org.uk/);
- Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/index.php/en/home);
- German Institute for Quality and Efficiency in Healthcare (http://www.iqwig.de/projects-results.915.en.html);
- Pharmaceutical Benefits Advisory Committee, Australia (http://www.health.gov.au/internet/main/publishing.nsf/Content/health-publicat.htm);
- Scottish Medicines Consortium (http://www.scottishmedicines.org.uk/SMC_Advice/Advice_Directory/SMC_Advice_Directory).

The phase 1 internet searches were carried out on 19 and 20 July 2012, and the phase 2 internet searches between 11 and 13 October 2012. The ERG note that the searching of conference abstracts was limited to abstracts that were published between January 2010 and July 2012. There is a minor discrepancy in the MS text and the appendices regarding the end date for the phase 1 conference abstract searches: 23 July vs 19 July. The phase 2 searches were conducted on 13 October.

All of the searches were updated in 2014 with the electronic database searches being conducted on 28th April 2014 with date limitations of 9 July 2012 to present (phase 1) and 16 September 2012 to

present (phase 2). The internet searches were updated between 28th April and 1st May 2014 and limited to data published after 9 July 2012.

There was no restriction based on language applied in the database search strategies used by the manufacturer. In addition, the manufacturer reports that foreign-language sources that appeared relevant at the screening stage were extracted by linguists to determine their eligibility for inclusion.

The ERG considers the manufacturer to have conducted comprehensive searches using a variety of different sources including electronic medical databases and internet website pages. In addition, the manufacturer reports reviewing bibliographic reference lists of included studies, reviews, meta-analyses, and health technology assessment (HTA) documents. The ERG also considers the manufacturers search terms and restrictions to be appropriate for the systematic review.

4.1.2 Inclusion/exclusion criteria used in study selection

The manufacturer reports that the study selection process occurred in the following two phases:

- Level 1 screening: Titles and abstracts of studies identified from the electronic databases and from Internet searches were reviewed for eligibility by one researcher. A second researcher independently screened a random sample of 5% of the records. Any differences were resolved by consensus;
- Level 2 screening: Full texts of studies selected at level 1 were obtained and reviewed for eligibility by one researcher, using the same inclusion and exclusion criteria as used in level 1 screening. A second researcher independently screened a random sample of 5% of the records with any differences resolved by consensus.

In addition, the manufacturer reports that the second researcher reviewed all studies selected after the level 2 screening to confirm their eligibility. The MS suggests that foreign-language sources were excluded at the level 2 screening stage. The ERG are unsure as to why there were no language restrictions in the database searches and why linguists were involved in assessing foreign language publications during level 1 screening if they were subsequently excluded based on language of publication at level 2 screening. In addition, the ERG is unsure as to the impact excluding foreign language publications may have had.

The inclusion and exclusion criteria for the systematic review are detailed in Table 3.

Table 3. Inclusion and exclusion criteria for systematic review (adapted from MS table 20)

Criteria	Included	Excluded
Study Type	Randomised, controlled prospective clinical trials Non-randomised, controlled prospective clinical trials	Prospective observational studies (e.g., phase 4 studies) Preclinical studies Phase 1 studies

	Long-term follow-up studies (e.g., open-label follow-up studies)	Prognostic studies Retrospective studies Case reports Commentaries and letters (publication type) Consensus reports Reviews, systematic reviews, and meta-analyses (however, reference lists were reviewed for any relevant studies)
Patient Populations	Patients with DVT and/or PE receiving treatment or secondary prevention for recurrent DVT and/or PE	Patients receiving primary prophylaxis for prevention of a first DVT or PE event
Interventions	Dabigatran, rivaroxaban, edoxaban, and apixaban Warfarin (secondary prevention trials only) UFH or LMWH (all agents, including, but not limited to, enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin) given for more than 10 days, i.e., long-term or extended treatment only (trials investigating acute parenteral treatment with heparin, e.g., for 5-10 days followed by a vitamin K antagonist, were not included as heparin trials) Fondaparinux (given for 7 or more days)	Studies that do not include any of the interventions in the inclusion criteria list
Outcomes	Recurrent DVT or PE Bleeding Death	Regression rate of persistent echogenic masses
DVT, deep vein thrombosis; LMWH, low molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin.		

The ERG note that the study inclusion criteria included non-randomised, controlled prospective clinical trials and long-term follow-up studies (e.g., open-label follow-up studies) but one of the exclusion criteria is prospective observational studies (e.g., as phase 4 studies). The ERG is unsure as to which observational studies would be excluded or the definition of long-term used. The ERG notes that no observational studies were included in the manufacturer's review of clinical effectiveness and so the ERG is unable to comment further on this.

The ERG also notes that the manufacturer included edoxaban and apixaban as potential comparators of interest although they were not requested in the final scope issued by NICE. The manufacturer does not present data for these two drugs within the MS although the ERG notes that apixaban has been included in a NMA in the supplementary meta-analysis report supplied by the manufacturer.

4.1.3 Details of studies included in the review of clinical effectiveness

After deduplication, the manufacturer's searches resulted in 4,425 articles from the phase 1 searches, 4,944 from phase 2, and a total of 1,155 from the update searches of phase 1 and phase 2. Following abstract and full text screening, a total of 42 studies from 41 publications were included. Six of the studies were identified through the update search.

The manufacturer reported that 29 of the studies investigated acute treatment of DVT and/or PE and 13 of the studies investigated secondary prevention.

In terms of the 29 acute treatment studies, the manufacturer reported that four studies investigated dabigatran, three studies investigated rivaroxaban, 19 studies investigated LMWH, of which two also included UFH, two studies investigated apixaban and one study investigated edoxaban.

The manufacturer reported that of the 13 secondary prevention studies, two studies investigated dabigatran, one study investigated rivaroxaban, one study investigated LMWH, eight studies compared warfarin with no treatment or placebo or with alternative durations of warfarin therapy, and one study compared low-intensity warfarin with conventional-intensity warfarin. No studies investigating apixaban or edoxaban were identified.

The ERG concludes that based on the manufacturer's reported search results there should be six studies for dabigatran. However, only four studies are presented in the MS. The ERG considers the two dabigatran studies identified in the manufacturers update search may be duplicate publications of studies identified in the original search. The ERG is unable to verify this though as the manufacturer did not provide citations for the studies included from each of the searches.

The four dabigatran studies presented by the manufacturer in the MS are:

- RE-COVER (NCT00291330)(16) – designed to compare dabigatran (150 mg BD) and warfarin (target INR 2.0 – 3.0) for 6 months of treatment for acute symptomatic VTE
- RE-COVER II (NCT00680186)(17) – a second study but with duplicate methods of RE-COVER;
- RE-MEDY (NCT00329238)(18) – designed to compare the efficacy and safety of dabigatran (150 mg BD) and warfarin (target INR 2.0 – 3.0) in patients who had already completed 3 to 12 months of anticoagulation treatment and who were considered to be at risk for recurrent venous thromboembolism;
- RE-SONATE (NCT00558259)(18) – designed to evaluate whether dabigatran (150 mg BD) was superior to placebo in the prevention of recurrent symptomatic VTE in patients with confirmed symptomatic DVT or PE who had previously completed 6 to 18 months of anticoagulation treatment and were considered to be at equipoise for the need for continued anticoagulant therapy.

The ERG is not aware of any additional studies potentially relevant to this STA that have been omitted by the manufacturer.

4.1.4 Critique of data extraction

The manufacturer reported that the following data fields were included in the data extraction:

- trial acronym (if available);
- first author and year of the primary report;
- identity of any linked secondary reports;
- interventions (including dosages, duration of treatment, and type and duration of previous anticoagulation treatment) and associated patient numbers;
- patient population (key disease information, such as whether patients had DVT and/or PE; cause of DVT and/or PE; risk factors; time from onset of qualifying events or symptoms; previous DVT and/or PE; comorbidities; and key demographic information, such as age and percentage of the cohort that was female or male, and creatinine clearance);
- whether the trial was blinded (single blind, double blind);
- identification of the primary and key secondary outcome measures that were defined;
- duration of follow-up;
- results for the clinical outcomes of interest (if available), which could include the following:
    - number of patients with a recurrent DVT and/or PE;
    - hazard ratio for recurrent DVT and/or PE;
    - numbers of patients with a major bleed, a clinically relevant non-major bleed, or any bleed;
    - hazard ratio for bleeding;
    - treatment discontinuation due to adverse events;
    - death (DVT- or PE-related and all-cause);
    - patient-reported outcomes data.

In addition, the manufacturer reported that data were extracted from full-text versions of studies or clinical study reports, where available. The manufacturer also reported that quality-control procedures for the data extraction included verification of all extracted data with their original sources by a second researcher. The ERG considers this to be an acceptable method of data extraction.

4.1.5 Quality assessment

The manufacturer conducted a quality assessment for the trials included in the systematic review using what appears to be the Cochrane risk of bias tool. A summary of the manufacturer's quality assessment for the four key trials presented within the MS are presented in Table 4.

Table 4. Summary of manufacturers quality assessment for RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE (adapted from table 36 of the MS)

	RE-COVER	RE-COVER II	RE-MEDY	RE-SONATE
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
Did the analysis include an intention-to-treat analysis?	Yes	Yes	Yes	Yes
If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes

In general the ERG agrees with the manufacturer's quality assessment for each of the four trials. However, the ERG considers it important to highlight the manufacturer's response to "Did the analysis include an intention-to-treat analysis?". The studies utilised a modified intention-to-treat (mITT) approach with only patients receiving at least one dose of study medication being included in the analyses (referred to by the manufacturer as the final analysis set [FAS]). Supplementary intention-to-treat (ITT) data were provided to the ERG for the primary outcome at the clarification response stage. The ERG notes that the number of patients in the FAS was slightly lower than the number in the ITT population. However, as the difference in numbers between the ITT and FAS is small, the ERG does not consider it likely to have much impact on the overall results.

4.2 Summary and critique of submitted clinical effectiveness evidence

The manufacturer presented clinical effectiveness data on dabigatran from four phase III trials: RE-COVER,[16] RE-COVER II,[17] RE-MEDY[18] and RE-SONATE.[18] These four trials are discussed in further detail below.

4.3 Summary and critique of acute VTE treatment trials: RE-COVER and RE-COVER II

4.3.1 Description of RE-COVER and RE-COVER II trials

RE-COVER[16] and RE-COVER II[17] were phase III, double-blind, double-dummy, parallel-group, randomised, active controlled trials. They compared dabigatran 150 mg BD with adjusted-dose warfarin (target INR 2.0–3.0) in patients diagnosed with a confirmed acute symptomatic VTE and who had received initial treatment (for at least 5 days) with a parenteral anticoagulant approved for this indication. The aim of the RE-COVER studies was to demonstrate non-inferiority for dabigatran compared to warfarin based on the composite primary endpoint of recurrent symptomatic VTE and deaths related to VTE within 6 months.

RE-COVER and RE-COVER II were identical in terms of study design. RE-COVER was the first of the two trials to commence. However, the manufacturer reported that there was a low rate of recurrent VTE observed during recruitment to RE-COVER and so RE-COVER II was initiated to confirm the results of RE-COVER and to enable more precise subgroup analyses through use of pooled data from the two trials. The manufacturer did not provide further details in the MS on the specific subgroup analyses that this was aimed at.

RE-COVER and RE-COVER II are discussed together in the following sections of this report.

RE-COVER and RE-COVER II population

RE-COVER was conducted in 228 clinical centres in 29 different countries, and RE-COVER II was conducted in 208 centres in 31 countries. A total of 2,564 patients were included in RE-COVER and 2,589 in RE-COVER II. The patients in RE-COVER included those from seven UK centres and in RE-COVER II from five UK centres.

The inclusion and exclusion criteria for RE-COVER and RE-COVER II are presented in Table 5 and Table 6.

Table 5. Inclusion criteria for RE-COVER and RE-COVER II trials (adapted from MS Table 25)

Inclusion criteria
Patients could be included in the study if the following criteria were fulfilled:
1. Acute symptomatic unilateral or bilateral DVT of the leg involving proximal veins, and/or PE confirmed by definitive objective clinical test in patients for whom at least 6 months of anticoagulant therapy was considered appropriate by the investigator [proximal veins are: trifurcation area, popliteal, superficial femoral, deep femoral, common femoral, and iliac veins]
2. Male or female, being 18 years of age or older
3. Written informed consent for study participation

Table 6. Exclusion criteria for RE-COVER and RE-COVER II (adapted from MS table 26)

Exclusion criteria
If any of the following criteria applied (as defined in the original trial protocol) patients were barred from entering this study:
1. Overt symptoms of VTE for longer than 2 weeks prior to enrolment
2. PE satisfying at least one of the following criteria:
− Haemodynamic instability
− Embolectomy indicated or performed
− Thrombolytic therapy indicated or performed
− Suspected source of PE other than the legs
3. Actual or anticipated use of vena cava filter
4. Contraindications to anticoagulant therapy including contraindications to heparins or other alternate approved therapy used for initial treatment, and warfarin
5. Patients who in the investigator's opinion should not be treated with warfarin
6. Allergy to heparins (including history of heparin induced thrombocytopenia) or other alternate approved therapy used for initial treatment, warfarin or dabigatran, or to one of the excipients included in these medications
7. Patients who in the investigator's judgement were perceived as having an excessive risk of bleeding, for example because of:
− Haemorrhagic disorder or bleeding diathesis
− Trauma or major surgery within the last month or as long as an excessive risk of bleeding persisted after these events, or planned major surgery
− Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm
− History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intraarticular bleeding
− Gastrointestinal haemorrhage within the past 3 months
− Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
− Treatment with thrombolytic agents within 14 days before enrolment
− Anticipated need of restricted medication during the treatment period
− Known thrombocytopenia (platelet count <100·109/L)
8. Known anaemia (haemoglobin <100 g/L)
9. Need of anticoagulant treatment for disorders other than VTE
10. Recent unstable cardiovascular disease, such as uncontrolled hypertension at the time of enrolment (investigator's judgement), acute bacterial endocarditis, or history of myocardial infarction within the last 3 months
11. Elevated AST or ALT >2 x ULN (RE-COVER) or x3 ULN (RE-COVER II) based on the local laboratory results obtained at screening and prior to randomisation (or central screening laboratory results if available on time)
12. Liver disease expected to have any potential impact on survival (e.g. acute hepatitis, possibly active hepatitis B, hepatitis C or cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery)
13. Patients who had developed transaminase elevations upon exposure to ximelagatran (RE-COVER only)
14. Severe renal impairment (estimated creatinine clearance ≤30 ml/min)

15. Women who were pregnant, nursing, or of childbearing potential who refused to use a medically acceptable form of contraception throughout the study (A negative pregnancy test had to be obtained for any woman of childbearing potential prior to entry into the study.)

16. Participation in another clinical trial with an investigational drug during the last 30 days or previous participation in this study

17. Patients considered unsuitable for inclusion by the investigator, e.g. because considered unreliable to comply with the requirements for follow-up during the study and/or compliance with study drug administration, had a life expectancy less than the expected duration of the trial due to concomitant disease, or had any condition which in the opinion of the investigator would not allow safe participation in the study (e.g. drug addiction, alcohol abuse)

18. In case of anticipated study-related diagnostic procedures requiring contrast medium (e.g. contrast venography or pulmonary angiography):

− Elevated serum creatinine, which in the investigator's opinion contraindicated these examinations

− Known allergy to radio opaque contrast media or iodine, which in the investigator's opinion contraindicated these examinations

With Protocol Amendment 2 (dated 11 February 2008) it was added to the exclusion criteria that patients with an anticipated need of quinidine were barred from participation in this trial.

The ERG note that there were a large number of exclusion criteria but based on the advice of clinical experts the ERG considers them to be appropriate for the population and therapies under investigation.

The diagnosis of the VTE event at baseline in the RE-COVER trials was made with the use of compression ultrasonography or venography of leg veins and ventilation–perfusion lung scanning, angiography, or spiral computed tomography of pulmonary arteries.

Randomisation in the RE-COVER trials was performed following the confirmed diagnosis of a VTE. Randomisation was done using a computer-generated randomisation scheme with variable block sizes, stratified according to VTE event at presentation (PE or DVT without symptomatic PE) and the presence or absence of active cancer. In total there were four strata: 'active cancer and symptomatic PE', 'active cancer, no symptomatic PE', 'no active cancer, symptomatic PE', 'no active cancer, no symptomatic PE'. As discussed in section 3.1, the ERG has concerns about the definition of active cancer being too broad. The definition of active cancer in the Re-COVER trials was: a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within five years before enrolment; any treatment for cancer within five years before enrolment; or recurrent or metastatic cancer.

Randomisation took place between April 2006 and November 2008 in RE-COVER and between June 2008 and October 2010 in RE-COVER II.

The baseline characteristics of the patients included in the studies are reported in Table 7.

Table 7. Baseline characteristics of patients in the RE-COVER trials (adapted from MS table 27)

Characteristic	RE-COVER		RE-COVER II	
	Dabigatran (n = 1,273)	**Warfarin (n = 1,266)**	**Dabigatran (n = 1,280)**	**Warfarin (n = 1,288)**
Age – mean ± SD	55.0 ± 15.8	54.4 ± 16.2	54.7 ± 16.2	55.1 ± 16.3
Female sex – n (%)	535 (42.0)	520 (41.1)	499 (39.0)	512 (39.8)
Race – n (%)				
White	1,212 (95.2)	1,195 (94.4)	993 (77.6)	999 (77.6)
Black	36 (2.8)	31 (2.4)	19 (1.5)	19 (1.5)
Asian	25 (2.0)	40 (3.2)	267 (20.9)	270 (21.0)
BMI – mean ± SD	28.9 ± 5.7	28.4 ± 5.5	28.4 ± 5.8	28.4 ± 5.8
Type of index event				
DVT only	880 (69.1)	869 (68.6)	877 (68.5)	873 (67.8)
PE only	270 (21.2)	271 (21.4)	298 (23.3)	297 (23.1)
DVT and PE	121 (9.5)	124 (9.8)	104 (8.1)	117 (9.1)
Neither DVT or PE	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)
Cancer – n (%)	64 (5.0)	57 (4.5)	50 (3.9)	50 (3.9)
Previous VTE – n (%)	327 (25.7)	322 (25.4)	247 (19.3)	203 (15.8)
Abbreviations in table: BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; LMW, low-molecular-weight; ND, no data; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.				

The manufacturer reported that there were no significant differences between the dabigatran and warfarin treatment groups in the RE-COVER trials in terms of baseline characteristics. No measures of statistical significance were reported in the MS and so the ERG was unable to validate this statement. However, the ERG notes that based on the numerical data provided by the manufacturer, the treatment groups appear similar at baseline. The ERG considers it important to highlight that the majority of patients in the trials were white (95.2% in RE-COVER and 77.6% in RE-COVER II) and approximately 60% of patients were male. There were approximately 31% from Western Europe in RE-COVER and 17% from Western Europe in RE-COVER II. The average age of patients in the two trials was approximately 55 years old which, as discussed in Section 3.1, is younger than the population in the UK with VTE that would be expected to be eligible for treatment with dabigatran.

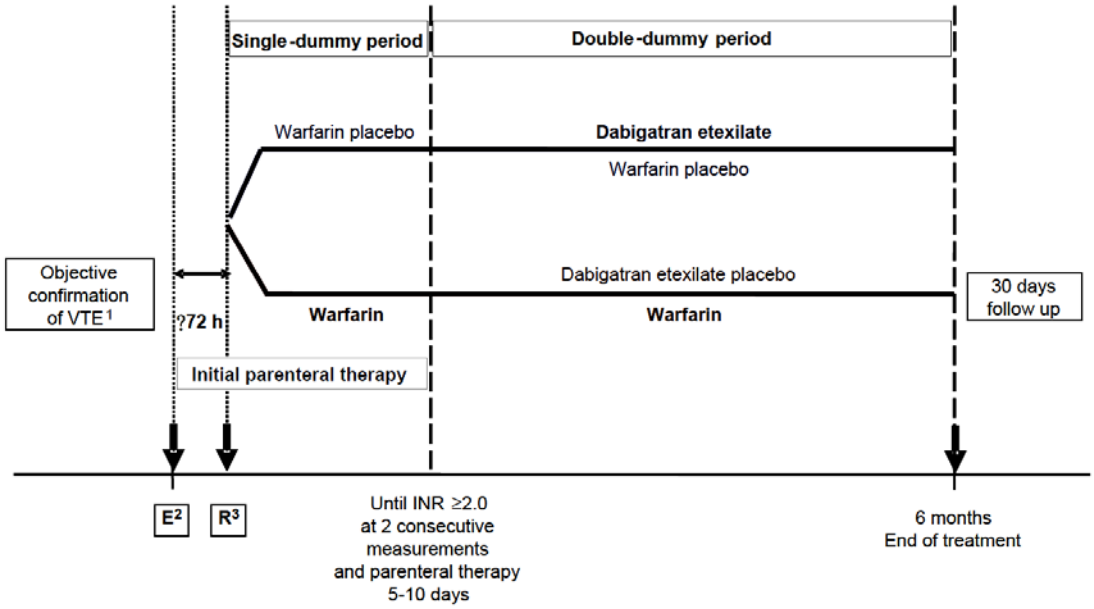
RE-COVER and RE-COVER II interventions and comparators

Patients in the RE-COVER trials were randomised in a 1:1 ratio to 6 months oral treatment with either dabigatran etexilate 150 mg BD and warfarin placebo or adjusted-dose warfarin (to maintain a target INR 2.0–3.0) and dabigatran placebo. The treatment-group a patient was assigned to was concealed from both the patient and the study personnel. In addition, treatments were administered in a double-blind manner with dabigatran-matching placebo capsules and warfarin-matching placebo tablets.

INR values were monitored to guide the warfarin therapy with a sham INR procedure used to prevent unintentional un-blinding. INR measurements were performed using a Point of Care (POC) device or alternative that provided an encrypted INR that was forwarded to an interactive voice response system (IVRS) in order to obtain an INR value to guide the clinician dosing of warfarin or warfarin placebo. The manufacturer reports that in some cases the use of the POC device was not feasible and so the INR was measured in a non-blinded manner by pre-specified individuals who then forwarded the non-blinded INR to the IVRS. These individuals were un-blinded, but had no other role during the conduct of the study and did not provide any INR values to personnel involved in the conduct of the study.

The 6 month treatment period of the RE-COVER studies comprised of an initial single dummy period where patients received warfarin or warfarin placebo until their INR (or sham INR) was ≥2.0 on at least 2 consecutive measurements. This single dummy period lasted around 5-10 days and was accompanied by use of non-randomised parenteral therapy. The single dummy period was followed by a double dummy period where the warfarin or warfarin placebo was continued, parenteral therapy discontinued, and dabigatran or dabigatran placebo initiated (Figure 1). The warfarin was administered as warfarin sodium 1mg, 3mg, and 5 mg tablets or matching placebo taken orally to target an INR of 2.0 to 3.0.

Figure 1: Study flow chart of the RE-COVER trials (reproduced from the MS)



Abbreviations: E, enrolment; INR, international normalised ratio; R, randomisation; VTE, venous thromboembolism.

The manufacturer reported that parenteral anticoagulation was given for a mean of 10 days in both treatment groups in RE-COVER and a mean of approximately 9 days in both treatment groups in RE-COVER II. Details of the drugs used as parenteral therapy and the duration of the single dummy phase are presented in Table 8.

Table 8. Duration and type of initial parenteral therapy in the RE-COVER studies (adapted from MS table 27)

	RE-COVER		RE-COVER II	
	Dabigatran (n = 1,273)	**Warfarin (n = 1,266)**	**Dabigatran (n = 1,280)**	**Warfarin (n = 1,288)**
Treatment after randomisation* (days)	median 6.0 IQR 5.0 - 8.0	median 6.0 IQR 5.0 - 8.0	6.8 ± 3.4 (mean +/- SD)	7.1 ± 3.7 (mean +/- SD)
Unfractionated heparin – n (%)	144 (11.3)	164 (13.0)	198 (15.5)	207 (16.1)
LMW heparin – n (%)	1,138 (89.4)	1,148 (90.7)	1133 (88.5)	1147 (89.1)
Fondaparinux – n (%)	50 (3.9)	36 (2.8)	32 (2.5)	21 (1.6)
*Treatment after randomisation in the single-dummy phase				

The ERG considers the treatment algorithm in the RE-COVER trials to be broadly consistent with the current UK treatment pathway for VTE and how dabigatran would be expected to be utilised in UK clinical practice. However, based on clinical expert opinion, the ERG considers that the planned duration of parenteral therapy in clinical practice may be lower than the median used in the RE-COVER trials as the dabigatran UK marketing authorisation is expected to require only 5 days of parenteral anticoagulation. The ERG is unsure whether this would affect the overall safety or efficacy of dabigatran.

RE-COVER and RE-COVER II outcomes

The primary efficacy endpoint in the RE-COVER trials was the composite of recurrent symptomatic VTE and deaths related to VTE. VTE was defined in the trials as the composite incidence of DVT (detected by venous compression ultrasonography or venography) and PE (detected by ventilation-perfusion lung scan, pulmonary angiography, or spiral [helical] CT).

The secondary efficacy endpoints and safety outcomes reported in the RE-COVER trials are presented in Table 9.

Table 9. Secondary outcomes and safety outcomes in the RE-COVER trials (adapted from MS table 29)

	Outcome
Secondary outcomes*	Composite of recurrent symptomatic VTE and all deaths Symptomatic DVT Symptomatic PE Deaths related to VTE All deaths
Safety outcomes#	Major Bleeding Events (MBEs) MBEs or Clinically Relevant Bleeding Events (CRBEs) Any bleeding events (MBEs, CRBEs, and nuisance bleeding events) Adverse Events (AEs; including findings in the physical examination) Discontinuation of study treatment due to AEs Laboratory measures, especially Liver Function Tests (LFTs) Acute Coronary Syndrome (ACS) ECG and vital signs
* All recurrent VTEs required objective verification by definitive diagnostic evaluation. All recurrent VTEs and all deaths were centrally adjudicated by an independent committee that was blinded to treatment allocation. Adjudicated results were used in the analysis. # All safety endpoints were assessed during treatment and the 6 days following the last intake of study medication. Any bleeding events and all suspected ACS were centrally adjudicated and all potentially liver-related safety issues were centrally reviewed by independent committees that were blinded with regards to the treatment allocation of patients. Adjudicated results were used in the analysis of bleeding events.	

The manufacturer reported that all VTE events were confirmed as follows:

- symptomatic DVT: confirmed by compression ultrasonography or venography;
- symptomatic PE: confirmed by spiral CT scan, pulmonary angiogram, or ventilation / perfusion lung scan;
- fatal VTE: confirmed by autopsy.

The safety outcome data collected in the RE-COVER trials were focused on bleeding related outcomes due to the nature of the interventions. The bleeding events were centrally adjudicated using pre-defined criteria. Bleeds were classified as major bleeding events (MBE), clinically relevant bleeding events (CRBE) and minor bleeds. Further details on the definitions of the bleeding events are provided in Table 10.

Table 10. Definitions of bleeding events in RE-COVER and RE-COVER II (adapted from MS table 30)

Bleeding event	**Definition**
Major bleeding event	International Society on Thrombosis and Haematosis criteria; i.e. one or more of: fatal bleeding symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome bleeding causing a fall in haemoglobin level of $20gL^{-1}$ ($1.24mmolL^{-1}$) or more, or leading to

	transfusion of ≥2 units of whole blood or red cells.
Clinically relevant bleeding event	One or more of: spontaneous skin haematoma ≥25cm^2 spontaneous nose bleed >5 minutes duration macroscopic haematuria, either spontaneous or, if associated with an intervention, lasting more than 24 hours spontaneous rectal bleeding (more than spotting on toilet paper) gingival bleeding >5 minutes bleeding leading to hospitalisation and/or requiring surgical treatment bleeding leading to a transfusion of <2 units of whole blood or red cells any other bleeding event considered clinically relevant by the investigator
Other bleeding events	All other bleeding events that did not fulfil the criteria for MBE or CRBE were classified as nuisance bleeds

In addition to the bleeding outcomes, hepatic function, coronary health and other adverse events (AEs) were routinely assessed. The liver function test (LFT) parameters measured included alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), and total bilirubin. Increases deemed to be of potential clinical significance were defined as: ≥3 x upper limit of normal (ULN) (AST, ALT), ≥2 x ULN (AP), and ≥2 mg/dL (total bilirubin).

The manufacturer also included data in the MS on two further composite outcomes referred to as net clinical benefit endpoints. The first comprised of the composite of non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause death and MBE. The second net clinical benefit endpoint also included MBEs and CRBEs. However, the ERG and their clinical advisers consider the outcome to be inappropriate as it comprises a post hoc analysis of both safety and efficacy outcomes. As a result, the ERG does not consider it appropriate to present the results of the analyses relating to these outcomes in this report.

The ERG notes that the primary safety and efficacy outcomes in the RE-COVER trials were centrally adjudicated by an independent committee. The committee were blinded to patients' study-group assignments and classified outcomes on the basis of pre-specified criteria. The ERG considers that this has reduced the risk of investigator bias affecting the results in terms of outcome assessment.

The ERG acknowledges that data on the outcome of HRQoL, specified in the final scope issued by NICE, were collected in the RE-COVER trials but not presented alongside the other clinical results in Section 2 of the MS. The HRQoL data was collected using the EQ-5D tool and are reported in a separate publication provided with the MS.[21] However, the ERG notes that chronic thromboembolic pulmonary hypertension (CTPH), post-thrombotic syndrome (PTS) and heart failure data were not specifically collected in the RE-COVER trials. The ERG considers that all other outcomes specified in the final scope issued by NICE were captured in the RE-COVER trials and reported appropriately in the MS for this STA.

RE-COVER and RE-COVER II subgroup analyses

The manufacturer reports in the MS that "pre-defined subgroup analyses of the primary endpoint were performed to evaluate the consistency of the treatment effect across a variety of patient groups". The subgroups that were analysed for the primary efficacy endpoint of the RE-COVER trials are presented in Table 11.

Table 11. Subgroup analyses for the primary endpoint in the RE-COVER trials (adapted from MS Table 33)

Subgroups	**Categories**
Drug-demographic interactions	Age (years): 18 to <40, 40 to <50, 50 to <65, 65 to <75, ≥ 75
	Sex: male, female
	Race: White, Asian, Black
	Ethnicity: Hispanic, non-Hispanic
	Body weight (kg): <50, 50 to <100, ≥100
	BMI (kg/m^2): <25, 25 to <30, 30 to <35, ≥35
Drug-disease interactions	Creatinine clearance (mL/min): <30, 30 to <50, 50 to <80, ≥80
	Active cancer at any time[1]: yes, no
Extrinsic factors	Geographical region: Western Europe[2], Central Europe[3], North America[4], Latin America[5], Asia[6], Other[7]
	Smoking history: never smoked, ex-smoker, current smoker
Risk factors for VTE	Previous VTE prior to the index event: yes, no
	Thrombophilia: yes, no
	History of venous insufficiency: yes, no
	Prolonged immobilisation: yes, no
	Long distance travel: yes, no
	Surgery/trauma: yes, no
	Recent use of oestrogens systematically[8]: yes, no
	Recent pregnancy[9]: yes, no
	Idiopathic VTE: non-idiopathic VTE, no risk factors identified/idiopathic VTE
Drug-drug interactions	Open-label parenteral therapy for the index event: UFH, LMWH, fondaparinux, any parenteral therapy[10]
	Extent of exposure to open-label parenteral therapy for the index event: ≤9 days, ≥9 days

	Use of concomitant therapies of special interest: platelet inhibitors, other antithrombotic agents, concomitant ASA use (categories: ASA daily dose ≤100 mg, ASA daily dose >100 mg, dose information missing, no ASA), NSAIDs, any anticoagulant

[1] Including active cancer at baseline and active cancer newly diagnosed during the study. Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment, any treatment for cancer within 5 years before enrolment, or recurrent or metastatic cancer. Active cancer diagnosed during the study was derived from AEs recorded during the trial (i.e. within 190 days after randomisation) by searching for AEs of the SOC 'neoplasms benign, malignant and unspecified (including cysts and polyps)', but excluding basal-cell or squamous-cell carcinoma of the skin.
[2] Austria, Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, UK
[3] Czech Republic, Hungary, Russia, Slovak Republic, Turkey, Ukraine
[4] Canada, USA
[5] Argentina, Brazil, Mexico
[6] India
[7] Australia, Israel, New Zealand, South Africa
[8] Defined as use within the last month
[9] Defined as within the last 3 months
[10] Including any of the following: UFH, LMWH, other heparin, fondaparinux.

The ERG acknowledges that there were a large number of subgroup analyses conducted in the RE-COVER trials. The ERG also notes that only results from selected subgroup analyses were reported by the manufacturer in the MS. The manufacturer reported that they presented the subgroups in which "the underlying risk of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran is expected to differ". These subgroups were reported as:

- type of index event;
- DVT only;
- PE with or without DVT;
- patient's with a history of bleeding;
- western European patient's.

In addition to the subgroup analyses described in Table 11, a subgroup analysis based on study centre INR control was conducted. Time in therapeutic range (TTR) was used as a measure of INR control and a study centre's INR control was approximated using the median of the centre's individual patients' TTR (cTTR). Five ranges of cTTR were considered for analysis in accordance with the quintiles of cTTR observed in RE-COVER and RE-COVER II. The manufacturer conducted an analysis based on quartiles of cTTR in response to a request by the ERG. The manufacturer's justification for their decision to use quintiles is presented in Box 13.

Box 13. Manufacturer's response to clarification on the use of cTTR quintiles (Manufacturer's response to clarification question A15)

We decided to focus on quintiles, since this provides more granularity in the assessment and the exclusion of the extreme categories allows still an assessment of a relevant spectrum of INR control reflecting the expected real world situation. Furthermore, using quintiles provide a balance between the number of events per category and the intended granularity.

The ERG consider both the analysis using quartiles and that using quintiles to be useful subgroup analyses to evaluate the effect of warfarin control in relation to dabigatran safety and efficacy.

RE-COVER and RE-COVER II follow-up

The RE-COVER trials were scheduled to end after patients had received 6 months treatment. Patients were randomised to a treatment group and commenced treatment with warfarin or warfarin placebo at visit 2. This was planned to occur within 72 hours of enrolment into either trial. After commencement of the double dummy treatment phase, patients were followed up approximately every 30 days until the end of the 6 months treatment (visit 9). Patients who completed the treatment period follow-up received an additional follow-up visit 30 days after completion of the study (visit 10), unless they had discontinued the study drug early. The full follow-up schedule for each of the RE-COVER trials is presented in Table 12.

Table 12. Follow-up visit schedule for RE-COVER and RE-COVER II (adapted from MS table 23)

RE-COVER	RE-COVER II
Visit schedule: 1. Screening a. Visit 1 (day -3 to 1) 2. Treatment period: single-dummy a. Visit 2 (day 1): initial parenteral therapy + trial medication (warfarin or warfarin placebo) 3. Treatment period: double-dummy a. Visit 3 (day 3 to 11): 1st oral dose of dabigatran or dabigatran placebo b. Visit 4 (day 30 [25-33]) c. Visit 5 (day 60 [±5]) d. Visit 6 (day 90 [±7]) e. Visit 7 (day 120 [±10]) f. Visit 8 (day 150 [±10]) g. Visit 9 (day 180 [±10]): last oral dose 4. Follow-up a. Visit 10 (day 210 [±14])	Visit schedule: 1. Screening a. Visit 1 (day -3 to 1) 2. Treatment period: single-dummy a. Visit 2 (day 1): initial parenteral therapy + trial medication (warfarin or warfarin placebo) 3. Treatment period: double-dummy a. Visit 3 (day 7 [±4]): 1st oral dose of dabigatran or dabigatran placebo b. Visit 4 (day 29 [±4]) c. Visit 5 (day 60 [±5]) d. Visit 6 (day 90 [±7]) e. Visit 7 (day 120 [±10]) f. Visit 8 (day 150 [±10]) g. Visit 9 (day 180 [±10]): last oral dose 4. Follow-up a. Visit 10 (day 210 [±14])

HRQoL data was collected at baseline, visit 6, visit 9 and end-of-treatment visit.

4.3.2 Description and critique of statistical approaches used in RE-COVER

RE-COVER[16] and RE-COVER II[17] were planned as non-inferiority studies to determine the efficacy and safety of dabigatran 150 mg BD compared with warfarin in patients with symptomatic VTE, using hazard ratios (HRs) and risk differences (RD). After achieving non-inferiority, it was planned for each trial to establish superiority (by means of hierarchical tests) of dabigatran 150 mg BD over adjusted-dose warfarin. The overall significance level was controlled by *a priori* ordering of hypotheses.

The HR in the RE-COVER studies was calculated based on the time to first occurrence of any component of the primary endpoint (recurrent symptomatic VTE and deaths related to VTE) using the Cox (regression) proportional hazard model. The RD was calculated using Kaplan-Meier estimates of the cumulative risk of an event at the end of 6 months of treatment.

The non-inferiority margins used in the RE-COVER studies were defined as 2.75 for the HR and 3.6% for the risk difference at month 6 (i.e. day 180). Both margins related to the lower boundary of the 95% confidence intervals (CIs) of the warfarin effect. This was to account for the variability in point estimates. It was planned so that if dabigatran was proven to be non-inferior to warfarin, dabigatran would preserve at least 57% of the warfarin effect vs placebo in HRs as well as at least 75% risk differences. The ERG is concerned that the threshold used for the lower boundary for non-inferiority is too low. However, the ERG acknowledges that the non-inferiority margin used in a similar technology appraisal[22] was 2.0 and the manufacturer also reports the results of RE-COVER and RE-COVER II in the MS in relation to this non-inferiority margin.

The ERG notes that it has been reported that the choice of non-inferiority margin and population used in the statistical analysis of non-inferiority trials can result in the introduction of bias in the results.[23] In addition, it has been reported previously that non-inferiority trials are often only considered positive if non-inferiority is demonstrated in both the ITT and per protocol populations.[24]

In total four data analysis sets were used for the RE-COVER trials; these were the full analysis set (FAS), the per-protocol set (PPS), the treated set (TS), and the pharmacokinetic set (PKS). The FAS was composed of all randomised patients who were documented to have taken at least one dose of study drug and patients were assigned to the randomised treatment groups regardless of the actual study drug taken. The TS comprised all randomised patients who were documented to have taken at least 1 dose of study drug. Patients in the TS were assigned to the treatment groups according to the treatment actually received. The PPS was a subset of the TS, restricted to patients without important protocol violations. The PKS included all randomised patients who were documented to have taken at least 1 dose of study drug and for whom at least 1 blood sample was available. The allocation of

patients to treatment groups in the PKS was based on the actual treatment received. The number of patients allocated to each treatment group for the FAS, TS and PPS data analysis sets are presented in Table 13.

Table 13. Number of patients in analysis sets for RE-COVER and RE-COVER II (adapted from MS table 31)

RE-COVER Analysis set	**Dabigatran**	**Warfarin**	**Total**
Randomised patients, n (%)	1,281 (100.0)	1,283 (100.0)	2,564 (100.0)
Full analysis set (FAS), n (%)	1,274 (99.5)	1,265 (98.6)	2,539 (99.0)
Treated patients (TS), n (%)	1,273 (100.0)	1,266 (100.0)	2,539 (100.0)
Per-protocol set (PPS), n (%)	1,222 (96.0)	1,192 (94.2)	2,414 (95.1)
PK set (PKS), n (%)	1,198 (94.1)	1,174 (92.7)	2,372 (93.4)
RE-COVER II Analysis set	**Dabigatran**	**Warfarin**	**Total**
Randomised patients, n (%)	1,293 (100.0)	1,296 (100.0)	2,589 (100.0)
Full analysis set (FAS), n (%)	1,279 (98.9)	1,289 (99.5)	2,568 (99.2)
Treated patients (TS), n (%)	1,280 (100.0)	1,288 (100.0)	2,568 (100.0)
Per-protocol set (PPS), n (%)	1,242 (97.0)	1,256 (97.5)	2,498 (97.3)

The differences in patient numbers by treatment arms for the FAS and TS in RE-COVER are due to one patient starting the study with a different treatment (warfarin) to the one allocated at randomisation (dabigatran). In RE-COVER II, three patients (one in the dabigatran group and two in the warfarin group) were dispensed incorrect medication kits at the randomisation visit. These three patients are assigned to their randomised treatment groups in the FAS and assigned to their received treatment group for the TS.

Analyses presented in the MS of the primary and secondary efficacy endpoints, and of HRQoL, in the RE-COVER trials, were based on the FAS and followed a mITT principle, because randomised patients that were not treated were excluded from the analysis.

The EQ-5D data were not imputed in cases of missing data.

The efficacy analyses for the acute VTE treatment studies included events that occurred between randomisation and the end of the 30 day post-treatment period:

- For patients who went on to the RE-MEDY[18] or RE-SONATE[18] trials this was the day after the last intake of the study drug.

- For patients who completed treatment (per investigator opinion) and did not roll over to RE-MEDY or RE-SONATE, the date of the last follow-up visit was considered the end of the post-treatment period.
- For patients who terminated treatment prematurely and did not roll over to RE-MEDY or RE-SONATE, the date of the last contact was considered the end of post-treatment period.

The ERG notes that the manufacturer's rationale for the 30-day follow-up period after the planned termination of study drug was "to observe for potential rebound effects or delayed adverse reactions" (manufacturer's response to clarification, pg 46). The ERG consider that data for the end of treatment (i.e. 6 months) rather than data following the additional 30 day study follow-up period, would be most beneficial in the assessment of the efficacy of dabigatran.

In general, the ERG considers the manufacturer's approach to the statistical analysis of the data in the RE-COVER trials to be appropriate. The ERG notes that an ITT population defined as 'analysed as randomised' was not presented in the MS, but data were provided at clarification for the primary efficacy outcome. In addition, the ERG considers the MS lacks details such as the PPS results for the primary outcome and details on the hierarchical superiority tests and results. The ERG also notes that the manufacturer presents data in the MS both separately for RE-COVER and RE-COVER II and from a pooled analysis of the two studies.

4.3.3 Summary statement

For this STA, two RCTs (RE-COVER and RE-COVER II) were included in the clinical effectiveness section of the MS to provide clinical data on dabigatran for the acute treatment of VTE.[16;17]

The ERG considers that the inclusion and exclusion criteria of the RE-COVER trials were acceptable to address the each trial's objectives. In addition, the ERG notes that the baseline characteristics of the randomised populations of the RE-COVER trials appeared to be well balanced between trial arms. The intervention was dabigatran, which is the focus of this STA, and the comparator warfarin.

The ERG considers that the outcome data reported from RE-COVER trials appeared to be broadly consistent with the data collected in the trial. However, the ERG notes that CTEPH, PTS and heart failure data requested in the NICE final scope were not specifically collected in the trials.

In terms of follow-up and statistical data analysis, the ERG considers that the duration of follow-up in the RE-COVER trials was acceptable for the outcomes assessed. The ERG also considers that the statistical analysis plan was suitable although the details reported in the MS were limited.

4.4 Summary of results of acute VTE treatment trials: RE-COVER and RE-COVER II

4.4.1 RE-COVER treatment compliance and discontinuations

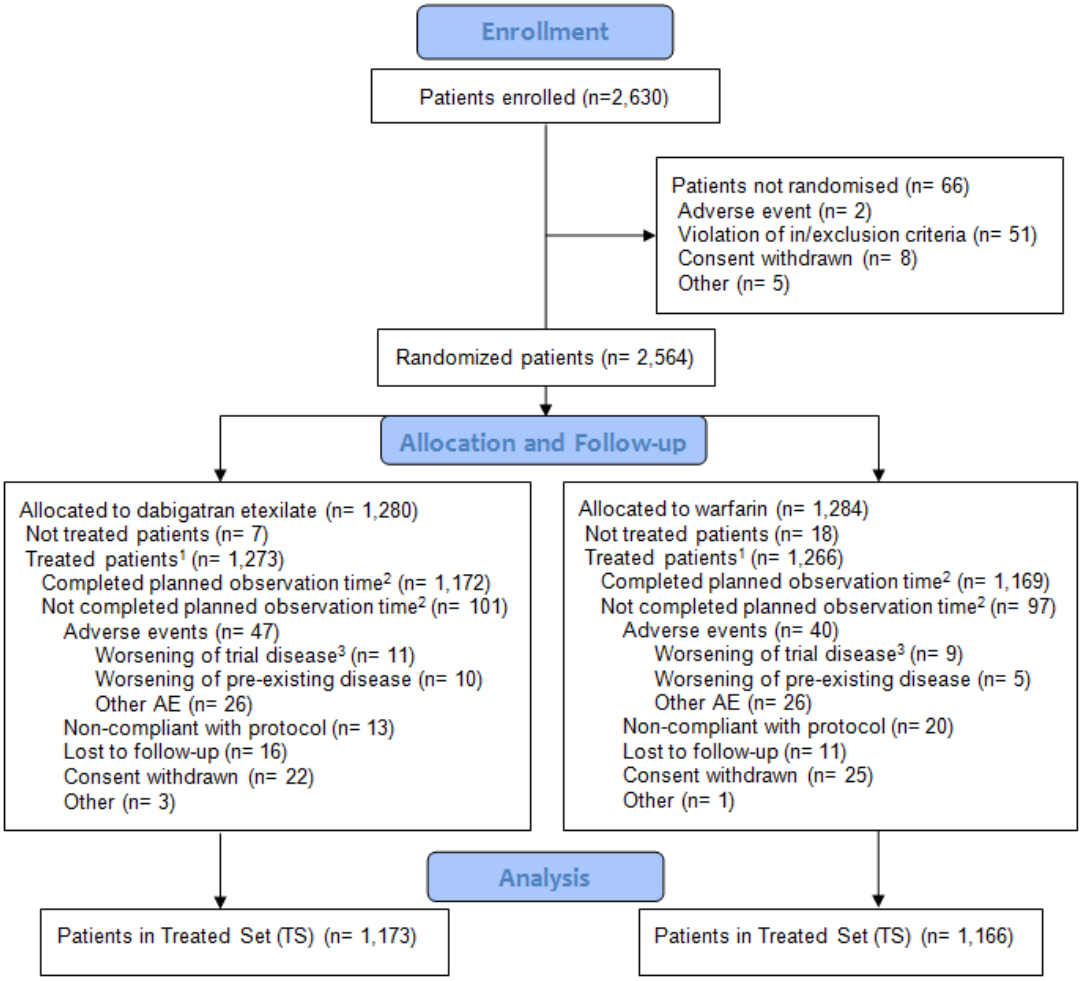
In total, 2,630 patients were enrolled in RE-COVER[16] with 2,564 patients randomised to either dabigatran (1,280 patients) or warfarin (1,284 patients). Only 25 of the randomised patients were not treated with their randomised study medication (dabigatran: 7, warfarin: 18).

Of the 2,630 patients enrolled, 66 patients (2.5%) were not randomised. The most common reason for non-randomisation was violation of the study protocol inclusion or exclusion criteria (n= 51; 1.9%). Two patients (0.1%) were not randomised due to AEs.

There were 2,539 patients who received at least one dose of study medication, and of these 92.2% completed the planned observation time, with no between group differences. The length of follow-up calculated as the time from randomisation of a patient to the end of study participation, was similar between the dabigatran and warfarin groups (mean: 191 vs 189 days, median: 193 vs 191 days).

There were 198 patients (7.8%) out of the 2539 who received treatment that ended up prematurely discontinuing trial medication, with slightly more discontinuations in the dabigatran group (7.9%) than in the warfarin group (7.6%). The reason for discontinuation of study medications was due to AEs in 3.8% of patients in the dabigatran group and 3.1% of patients in the warfarin group. The number of patients who completed the study was reasonably high with 1,173 and 1,166 patients in the dabigatran and warfarin groups, respectively. Full details on the flow of patients through the study period are presented in Figure 2.

Figure 2. Flow chart of participants in RE-COVER (reproduced from MS Figure 6)



[1] Patients who received at least 1 dose of study medication (active study medication or placebo)
[2] The investigator was to record on the 'Trial completion' page of the CRF if the patient had completed the planned observation time or the reason for non-completion, which was to be selected from a list of pre-defined reasons on this CRF page.
[3] Symptomatic DVT or PE as based on the assessment of the investigator, including an extension of the existing thrombus or a new suspected event.

TTR is a measure of warfarin control and not necessarily the same as treatment compliance but nonetheless important in assessing warfarin treatment efficacy. The target INR for RE-COVER was an INR in the range of 2.0–3.0. The mean TTR over the 6 month treatment period for patients in the warfarin arm of RE-COVER was 59.9% (standard deviation [SD] ±22.9%). The ERG notes the standard deviation is large and suggests there was a wide range of variability around the TTR. However, based on the advice of clinicians the mean TTR is lower than the mean TTR expected in a UK centre. The clinical experts consulted reported INR control of 60% to 80% in their clinical experience. Furthermore, the ERG notes that, the TTR increased throughout the duration of RE-COVER to an average of 65.7% after 6 months of treatment (CSR; pg 158).

4.4.2 RE-COVER II treatment compliance and discontinuations

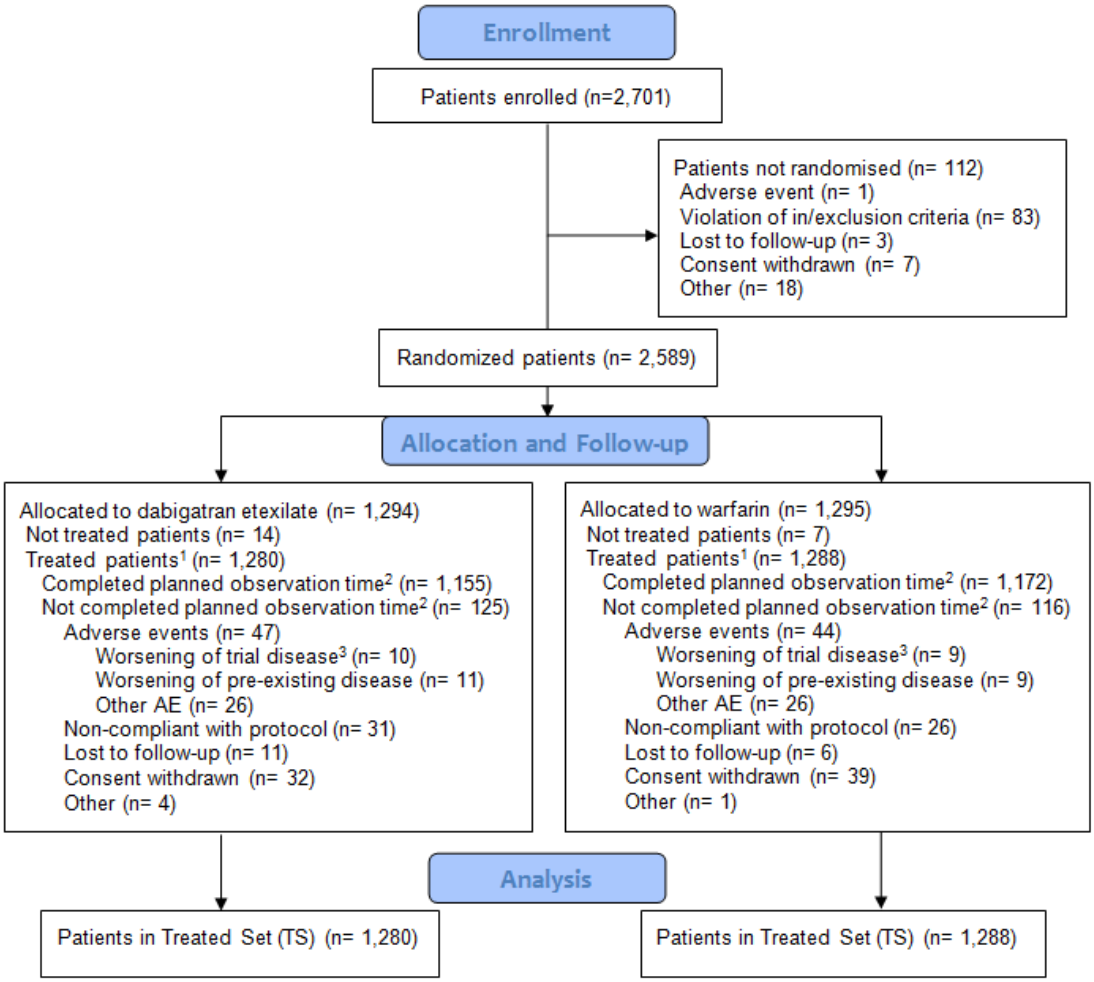
RE-COVER II[17] enrolled 2,701 patients with 2,589 of these patients randomised and 112 patients (4.1%) not randomised. The most common reason for non-randomisation was a violation of the

inclusion or exclusion criteria (3.1%). The 2,589 patients randomised were randomised to either dabigatran (1,294 patients) or warfarin (1,295 patients). There were 21 randomised patients who were not treated with study medication (dabigatran: 14, warfarin: 7): 9 of these patients refused to take study medication or withdrew consent; 10 of these patients were non-compliant with the study protocol; 2 of these patients had an AE.

In addition, there were 241 randomised patients (9.3%) who prematurely discontinued study medication. The proportions discontinuing in RE-COVER II were similar in both treatment groups (dabigatran: 9.7%, warfarin: 9.0%). Reasons for study drug discontinuation included AEs in 3.6% of patients in the dabigatran group and 3.4% of patients in the warfarin group.

A total of the 2,568 patients received treatment and 90.6% of these completed the planned follow-up, with no between-group differences for those patients who did not. Full details on the flow of patients through the study period are presented in Figure 3.

Figure 3. Flow chart of participants in RE-COVER II (reproduced from MS Figure 7)



[1] Patients who received at least 1 dose of study medication (active study medication or placebo)

[2] The investigator was to record on the 'Trial completion' page of the CRF if the patient had completed the planned observation time or the reason for non-completion, which was to be selected from a list of pre-defined reasons on this CRF page.
[3] Symptomatic DVT or PE as based on the assessment of the investigator, including an extension of the existing thrombus or a new suspected event.

In terms of treatment compliance, TTR is a measure of warfarin control. The mean TTR over the 6 month treatment period for patients in the warfarin arm of RE-COVER II was 56.9% (SD ±21.9). The ERG notes the standard deviation is large and suggests there was a wide range of variability around the TTR. However, based on the advice of clinicians the mean TTR is lower than the mean TTR expected in a UK centre. The clinical experts consulted reported INR control of 60% to 80% in their clinical experience. Furthermore, the ERG notes that, the TTR increased throughout the duration of RE- COVER II to an average of 58.9% after 6 months of treatment, with a peak in month 5 of 62.2% (MS CSR; pg 133).

4.4.3 RE-COVER treatment effectiveness results

The results of RE-COVER[16] with respect to the primary and secondary efficacy endpoints are presented in Table 14. The ERG notes that the manufacturer reports that dabigatran 150 mg BD demonstrated non-inferiority to adjusted-dose warfarin for the primary efficacy outcome (hazard ratio, 1.10; 95% CI, 0.65, 1.84, p < 0.001) at both the non-inferiority margin of 2.75 and that of 2.0. The ERG notes that it is reported in the CSR that non-inferiority was also proven based on the non-inferiority margin for the hazard ratio (HR) <2.75 in the per protocol population (HR 1.03; 95% CI 0.63 to 1.69). However, following the attainment of non-inferiority, superiority was tested for, but was not reached.

Table 14. RE-COVER efficacy outcome results (adapted from MS Table 37 and 39)

Outcome	**Population**	**Dabigatran**		**Warfarin**		**Hazard ratio (95% CI)**	***p*-value**
		N	**N**	**n**	**N**		
During treatment period (at 6 months)							
VTE and VTE related deaths, *n* (%)	FAS population	30 (2.4)	1,274	27 (2.1)	1,265	1.10 (0.65, 1.84)	<0.0001 (for non-inferiority)
	ITT population	30 (2.4)	1,281	27 (2.2)	1,283	NR	<0.0001 (for non-inferiority) 0.4984 (for superiority)
Symptomatic DVT*	FAS	16	1,274	18	1,265	NR	NR
Symptomatic PE‡*	FAS	13	1,274	6	1,265	NR	NR
VTE-related deaths#*	FAS	1	1,274	3	1,265	NR	NR
Up to the end of the post-treatment period*							

VTE and VTE related deaths, n (%)	FAS population	34 (2.7)	1,274	32 (2.5)	1,265	1.05 (0.65, 1.70)	<0.0001 (for non-inferiority) 0.8508 (for superiority)
	ITT population	34 (2.7)	1,281	32 (2.5)	1283	1.05 (0.65, 1.70) ~	<0.0001 (for non-inferiority) 0.8372 (for superiority)
Symptomatic DVT*	FAS	17	1,274	22	1,265	NR	NR
Symptomatic PE‡*	FAS	16	1,274	7	1,265	NR	NR
VTE-related deaths#*	FAS	1	1,274	3	1,265	NR	NR

*Patients with at least one event

‡Symptomatic, non-fatal PE.

#Fatal PE with or without previous symptomatic non-fatal PE.

~Obtained from the Cox model with factors treatment, active cancer at baseline, PE symptomatic at baseline, and the interaction between active cancer at baseline and symptomatic PE at baseline. Missing cancer information coded as no for 1 patient.

Abbreviations used in table: CI, confidence interval; DVT, deep vein thrombosis; FAS, full analysis set; ITT, intention-to-treat; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

The manufacturer reported in the MS that there was no statistically significant difference by treatment group in the rate of any of the secondary endpoints. The results for the assessment of statistical significance were not reported in the MS and so the ERG is unable to comment further on the manufacturer's assessment.

4.4.4 RE-COVER II treatment effectiveness results

The results of RE-COVER II[17] with respect to the primary and secondary efficacy endpoints are presented in Table 15. The ERG notes that the manufacturer reports that dabigatran 150 mg BD demonstrated non-inferiority to adjusted-dose warfarin for the primary efficacy outcome of VTE and VTE related deaths (hazard ratio 1.08; 95% CI 0.64 to 1.80, $p < 0.001$) at both the non-inferiority margin of 2.75 and that of 2.0. The ERG notes that it is reported in the CSR that non-inferiority was also proven based on the non-inferiority margin for the hazard ratio (HR) <2.75 in the per protocol population (HR 1.10, 95% CI 0.67 to1.81). However, following the attainment of non-inferiority, superiority was tested for, but like in the RE-COVER trial, superiority was not reached.

Table 15. RE-COVER II efficacy outcome results (adapted from MS Table 38 and 41)

Outcome	**Population**	**Dabigatran**		**Warfarin**		**Hazard ratio (95% CI)**	***p*-value**
		n	**N**	**N**	**N**		
During treatment period (at 6 months)*							
VTE and VTE related deaths, *n* (%)	FAS population	30 (2.3)	1,279	28 (2.2)	1,289	1.08 (0.64,	<0.0001 (for non-

						1.80)	inferiority) 0.7756 (for superiority)
	ITT population	30 (2.4)	1,293	28 (2.2)	1,296	NR	<0.0001 (for non-inferiority) 0.7736 (for superiority)
Symptomatic DVT*	FAS	24	1,279	16	1,289	NR	NR
Symptomatic PE‡*	FAS	5	1,279	12	1,289	NR	NR
VTE-related deaths#*	FAS	1	1,279	0	1,289	NR	NR
Up to the end of the post-treatment period *^							
VTE and VTE related deaths, n (%)	FAS population	34 (2.7)	1,279	30 (2.3)	1,289	1.13 (0.69, 1.85)	0.0002 (for non-inferiority) 0.6159 (for superiority)
	ITT population	34 (2.6)	1,293	30 (2.3)	1,296	1.13 (0.69, 1.85)~	0.0002 (for non-inferiority) 0.6158 (for superiority)
Symptomatic DVT*	FAS	26	1,279	16	1,289	NR	NR
Symptomatic PE‡*	FAS	7	1,279	14	1,289	NR	NR
VTE-related deaths#*	FAS	3	1,279	0	1,289	NR	NR
All deaths	FAS	29	1,279	26	1,289	NR	NR

*Patients with at least one event

^Definition of the end of post-treatment period: For patients who completed the trial as planned and did not roll-over to RE-MEDY, the end of the post-treatment period was the date of trial completion collected at the follow-up visit. For patients who rolled over to RE-MEDY the end of the post-treatment period was the day after the last intake of warfarin / warfarin placebo of the RE-COVER II study medication

‡Symptomatic, non-fatal PE

#Fatal PE with or without previous symptomatic non-fatal PE; note numerical discrepancy in table of MS compared with text and references cited. ERG have used number from CSR here.

~Obtained from the Cox model with factors treatment, active cancer at baseline, PE symptomatic at baseline, and the interaction between active cancer at baseline and symptomatic PE at baseline.

Abbreviations used in table: CI, confidence interval; DVT, deep vein thrombosis; FAS, full analysis set; ITT, intention-to-treat; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

The manufacturer reported in the MS that there was no statistically significant difference by treatment group in the rate of any of the primary or secondary efficacy endpoints. The results for the assessment of statistical significance were not reported in the MS and so the ERG is unable to comment further on the manufacturer's assessment. The ERG note that there was numerically fewer symptomatic non-fatal PEs but more symptomatic DVTs in the dabigatran group than in the warfarin group. However, it should also be noted that the number of events in each group was small.

In terms of the all-cause mortality, the most frequent cause of death was cancer (15 patients in each treatment group). Four patients died of a bleeding event (1 dabigatran, 3 warfarin) and three patients died of a fatal PE (all in the dabigatran group). One of the patients who died of a fatal PE had a symptomatic PE (without cancer) at baseline. The ERG also note that two of the patient's with fatal PE's died during the single dummy phase of the trial and thus never received dabigatran.

4.4.5 Pooled RE-COVER and RE-COVER II analyses

A pooled analysis of the RE-COVER[16] and RE-COVER II[17] studies supported data from the individual trials; with dabigatran 150 mg BD shown to be comparable to warfarin for the primary endpoint (symptomatic recurrent VTE and VTE related death). Pooled event rates for the primary and secondary efficacy outcomes are presented in Table 16.

Table 16. Efficacy outcomes in pooled analysis of RE-COVER and RE-COVER II on treatment of acute VTE (adapted from MS table 43)

Outcome	**Dabigatran n = 2,553**	**Warfarin n = 2,554**	**Hazard ratio* (95% CI)**
Primary endpoint of VTE and VTE related deaths, n (%)			
During 6 months	60 (2.4)	55 (2.2)	1.09 (0.76, 1.57)
During the study period plus an additional 30 day follow up	68 (2.7)	62 (2.4)	1.09 (0.77, 1.54)
Secondary endpoints, n (%)			
Symptomatic DVT#	40 (1.6)	34 (1.3)	ND
Symptomatic non-fatal PE#	18 (0.7)	18 (0.7)	ND
Death related to PE#	2 (0.1)	3 (0.1)	ND
All deaths	46 (1.8)	46 (1.8)	1.0 (0.67, 1.51)

*The hazard ratio was estimated with the use of the Cox model with factor treatment stratified by study, assuming different baseline hazards per study.

#These are the events contributing to the primary endpoint. In the case of a patient suffering 2 different events, the first event is counted.

Abbreviations used in table: CI, confidence interval; ND, no data.

Quality of life (QoL) data were captured in both of the RE-COVER trials using EQ-5D although no QoL data were presented in the clinical section of the MS. However a pooled analysis of EQ-5D data from the RE-COVER trials was supplied in a separate report.[21]

Table 17 presents the number of patients with EQ-5D data (i.e. who completed at least one EQ-5D item or the visual analogue scale [VAS]) at each visit.

Table 17. Number of patients with EQ-5D data (at least one item or the VAS completed) at each visit Number of patients with EQ-5D data (adapted from ref 75 MAPI)

Trial	Visit	Dabigatran	Warfarin	Total
RE-COVER	Baseline	1263	1248	2511
	Visit 6	1113	1117	2230
	Visit 9	1049	1063	2112
	End-of-treatment visit	100	89	189
RE-COVER II	Baseline	1264	1270	2534
	Visit 6	1130	1124	2254
	Visit 9	1076	1087	2163
	End-of-treatment visit	88	91	179

The change in EQ-VAS score from baseline to 6 months by treatment group, and type of index event experienced by patients, is presented in Table 18. The mean improvements in EQ- VAS from baseline to 6 months were similar in the dabigatran group and in the warfarin group, although no summary estimates of the difference between the treatment groups were presented.

Table 18. Change from baseline to 6 months in EQ-VAS score in pooled analysis of RE-COVER and RE-COVER II on treatment of acute VTE (adapted from ref 75 MAPI)

EQ-5D		Symptomatic index DVT		Symptomatic index PE		Symptomatic index PE and symptomatic index DVT	
		Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Warfarin
Change from baseline to visit 9 (6 months)	n	1458	1460	457	471	194	199
	Mean (SD)	15.49 (19.76)	14.94 (19.61)	16.91 (21.22)	19.79 (21.97)	17.21 (20.07)	16.85 (20.55)
Abbreviations used in table: SD, standard deviation							

4.4.6 RE-COVER and RE-COVER II safety and adverse events

Adverse events

An overview of the number of adverse events (AEs) that occurred during the RE-COVER studies is presented in Table 19.[16;17]

Table 19. Summary of adverse events in RE-COVER and RE-COVER II (reproduced from MS Table 61)

Outcome	RE-COVER		RE-COVER II	

	Dabigatran n = 1273	Warfarin n = 1266	Dabigatran n = 1280	Warfarin n = 1288
Patients with any AE – n (%)	844 (66.3)	856 (67.6)	852 (66.6)	916 (71.1)
Patients with severe AEs – n (%)	96 (7.5)	101 (8.0)	156 (12.2)	153 (11.9)
Drug-related AEs* – n (%)	195 (15.3)	229 (18.1)	194 (15.2)	282 (21.9)
AEs leading to discontinuation – n (%)	115 (9.0)	86 (6.8)	100 (7.8)	100 (7.8)
*Relationship as assessed by the investigator Abbreviations used in table: AE, adverse event.				

The ERG notes that in RE-COVER, 115 (9.0%) patients in the dabigatran group had an AE that led to treatment discontinuation, compared to 86 (6.8%) patients in the warfarin group (hazard ratio, 1.33; 95% CI 1.01, 1.76; p = 0.05). However, there was no significant difference in the number of patients in each treatment group that discontinued treatment due to AEs during the treatment period in RE-COVER II (7.8% of patients in each treatment group).

The manufacturer reported in the MS that the most frequently recorded AEs in RE-COVER were gastrointestinal (GI) disorders. These were more frequent in the dabigatran group (25.1% of patients) than in the warfarin group (19.2%). The most frequent GI AE was nausea (3.8% vs 4.6%, dabigatran vs warfarin respectively), although there were greater between treatment group differences in the incidence of diarrhoea (4.5% vs 3.0%, dabigatran vs warfarin respectively) and dyspepsia (3.1% vs 0.7%, dabigatran vs warfarin respectively). In terms of cardiac disorders, there were similar numbers of AEs reported by both dabigatran and warfarin patients (3.5% vs 3.6%). Overall, the only significant difference between the two treatment groups in the frequency of any AE was for dyspepsia (p<0.001).

The AEs most frequently assessed as drug-related by the investigator's in RE-COVER were bleeding events (dabigatran vs warfarin): epistaxis (1.7% vs 3.8%), haematuria (1.5% vs 2.1%), rectal haemorrhage (1.4% vs 1.2%), contusion (0.9% vs 1.5%), gingival bleeding (0.7% vs 1.4%), and headache (1.1% vs 1.0%). The ERG also noted from

In RE-COVER II, the most frequent AEs in both treatment groups were 'gastrointestinal disorders' (22.9% vs 22.8%, dabigatran vs warfarin respectively) followed by 'infections and infestations' (19.4% vs 20.3%, dabigatran vs warfarin respectively). The ERG examined the clinical study report (CSR) for further details on the 'gastrointestinal disorders' as no further details were provided in the MS. The most frequent GI AE in RE-COVER II was diarrhoea (4.3% vs 4.4%, dabigatran vs warfarin respectively). In terms of dyspepsia and rectal bleeding, there were numerically more events of both in the dabigatran group compared with the warfarin group (dyspepsia: 2.9% dabigatran vs 1.2% warfarin; rectal bleeding: 2.7% dabigatran vs 1.1% warfarin). No assessment of statistical significance was reported. The manufacturer reported that the only between group differences in any adverse events were for 'investigations' (7.6% vs 11%, dabigatran vs warfarin respectively) and 'renal and urinary disorders' (4.4% vs 7.1%, dabigatran vs warfarin respectively). The difference in

‘investigations’ was mainly due to raised INRs in the warfarin group (0.2% dabigatran vs 3.0% warfarin) and the difference in ‘renal and urinary disorders’ mainly due to haematuria (1.3% dabigatran vs 3.9% warfarin).

Investigator assessed drug-related AEs in RE-COVER II were not discussed in the MS. The ERG reviewed the CSR to obtain details on the investigator assessed drug-related AEs in RE-COVER II that occurred more frequently with dabigatran compared with warfarin. In the CSR, it was reported that the only AEs assessed by the investigator’s that occurred more often with dabigatran than warfarin were dyspepsia (1% dabigatran vs 0.2% warfarin) and rectal haemorrhage (1.2% dabigatran vs 0.9% warfarin).

Bleeding events

Table 20 presents a summary of the bleeding events reported in RE-COVER and RE-COVER II.

Table 20. Summary of bleeding events in RE-COVER and RE-COVER II (adapted from MS table 62)

Outcome	**RE-COVER**		**RE-COVER II**	
	Dabigatran n = 1,274	**Warfarin n = 1,265**	**Dabigatran n = 1,280**	**Warfarin n = 1,288**
MBE – n (%)	20 (1.6)	24 (1.9)	15 (1.2)	22 (1.7)
Hazard ratio (95% CI)	0.82 (0.45, 1.48)		0.69 (0.36, 1.32)	
Fatal event – no. of events	1	1	0	1
Bleeding into critical organ – no. of events	1	9	6	4
Event resulting in fall in Hb level or need for BT* – n (%)	20 (1.6)	18 (1.4)	13	19
MBE or CRBE – n (%)	71 (5.6)	111 (8.8)	64 (5.0)	102 (7.9)
Hazard ratio (95% CI)	0.63 (0.47, 0.84)		0.62 (0.45, 0.84)	
Any bleeding event – n (%)	205 (16.1)	277 (21.9)	200 (15.6)	285 (22.1)
Hazard ratio (95% CI)	0.71 (0.59, 0.85)		0.67 (0.56, 0.81)	
Site of bleeding – no. of events				
Intracranial	0	3	2	6
Intraocular	8	9	5	14
Retroperitoneal	4	1	3	1
Intraarticular/ intramuscular	8	27	9	20
GI	53	35	48	33
Urogenital	53	95	51	75
Nasal	40	107	43	76

Other	137	205	160	255
*Included in this category were patients in whom there was a reduction in haemoglobin level of at least 20 g/L or who required a transfusion of at least 2 units of whole blood or red cells. Abbreviations used in table: BT, blood transfusion; CRBE, clinically relevant bleeding event; GI, gastrointestinal; Hb, haemoglobin; MBE, major bleeding event.				

In both RE-COVER and RE-COVER II, fewer patients in the dabigatran group had MBEs compared to the warfarin group although this difference was statistically non-significant. In RE-COVER, gastrointestinal and urogenital bleeding were the most common sites of bleeding in patients treated with dabigatran, while nasal bleeding was most common in warfarin patients.

In RE-COVER II, significantly fewer patients in the dabigatran group (5.6%) compared with the warfarin group (8.8%) had major or clinically relevant non-major bleeding events (HR 0.63; 95% CI: 0.47 to 0.84; p = 0.002). However, the ERG notes that there were numerically more retroperitoneal and GI bleeding events in the dabigatran group than in the warfarin group in both of the RE-COVER trials (Table 20), although there was no assessment of statistical significance reported in the MS.

Coronary events

The ERG note that there were numerically more acute coronary syndrome (ACS) events in the dabigatran group than the warfarin group in both of the RE-COVER trials, and most of the ACS events were related to myocardial infarction (MI) events (Table 21).

Table 21. ACS events in RE-COVER and RE-COVER II (reproduced from MS Table 63)

Outcome	**RE-COVER**		**RE-COVER II**	
	Dabigatran n = 1,274	**Warfarin n = 1,265**	**Dabigatran n = 1,280**	**Warfarin n = 1,288**
ACS – n (%)				
All	5 (0.4)	3 (0.2)	4 (0.3)	2 (0.2)
Myocardial infarction	4 (0.3)	2 (0.2)	4 (0.3)	2 (0.2)
Abbreviations used in table: ACS, Acute coronary syndrome.				

Hepatic events

LFTs were closely monitored during both RE-COVER trials in order to record any changes of potential clinical significance. There were numerically more abnormalities in LFTs in the warfarin group compared to the dabigatran group (Table 22). However, there was no report of an assessment of statistical significance in the MS so the ERG are unsure whether any of the between group differences were statistically significant.

Table 22. Patients with possibly clinically significant abnormalities for LFT parameters in RE-COVER and RE-COVER II (adapted from MS table 64)

Parameter	RE-COVER		RE-COVER II	
	Dabigatran n/N* (%)	**Warfarin n/N* (%)**	**Dabigatran n/N* (%)**	**Warfarin n/N* (%)**
ALT	26/1,204 (2.2)	38/1,198 (3.2)	31/1,238 (2.5)	40/1,248 (3.2)
AST	21/1,204 (1.7)	22/1,198 (1.8)	29/1,238 (2.3)	27/1,248 (2.2)
AP	16/1,202 (1.3)	20 (/1,197 (1.7)	8/1,238 (0.6)	6/1,248 (0.5)
Total bilirubin	7/1,204 (0.6)	13/1,198 (1.1)	13/1,238 (1.1)	19/1,248 (1.5)

*n is the number of patients with abnormalities of possible clinical significance, N is the number of patients with at least 1 post-baseline assessment of the respective parameter.

Abbreviations in table: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase.

Abnormalities in the ALT and AST values were further categorised in the MS by multiples of the ULN. The manufacturer reported that there was no difference between treatment groups within either of the RE-COVER studies in terms of these analyses of LFT abnormalities. The results of the analyses are presented in Table 23.

Table 23. Abnormal LFTs in RE-COVER and RE-COVER II (reproduced from MS Table 22)

Parameter	RE-COVER		RE-COVER II	
	Dabigatran n/N* (%)	**Warfarin n/N* (%)**	**Dabigatran n/N* (%)**	**Warfarin n/N* (%)**
AST >3 x ULN	38/1,220 (3.1)	25/1,199 (2.1)	24/1,238 (1.9)	25/1,248 (2.0)
ALT >3 x ULN	42/1,220 (3.4)	46/1,199 (3.8)	30/1,238 (2.4)	43/1,248 (3.4)
ALT >3 x ULN + bilirubin >2 x ULN	2/1,055 (0.2)	4/1,106 (0.4)	1/1,238 (0.1)	2/1,248 (0.2)

*n is the number of patients with abnormalities of possible clinical significance, N is the number of patients with at least 1 post-baseline assessment of the respective parameter.

Abbreviations in table: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ND, no data; ULN, upper limit of normal.

4.4.7 Pooled RE-COVER and RE-COVER II safety and adverse events

The manufacturer reported that two safety comparisons were made using pooled data from the two RE-COVER trials:[16;17]

- from the start of any drug (from single-dummy period);
- from the start of oral drug only (double-dummy period, after warfarin had reached therapeutic levels and parenteral therapy was discontinued).

The manufacturer also reported that, irrespective of the dataset used (single or double dummy), the pooled data from RE-COVER and RE-COVER II demonstrated a trend towards fewer bleeding events with dabigatran than with warfarin, with the exception of MBEs (Table 24).

Table 24. Safety outcomes in pooled analysis of RE-COVER and RE-COVER II on treatment of acute VTE (reproduced from MS Table 23)

Outcome	**Dabigatran (n = 2,553)**	**Warfarin (n = 2,554)**
From the start of any study drug (single and double-dummy periods)		
MBEs, n (%)	37 (1.4)	51 (2.0)
Hazard ratio (95% CI)*	0.73 (0.48, 1.11)	
Intracranial bleeding	2 (0.1)	5 (0.2)
MBEs or CRBEs, n (%)	136 (5.3)	217 (8.5)
Hazard ratio (95% CI)*	0.62 (0.50, 0.76)	
Any bleeding events, n (%)	411 (16.1)	567 (22.2)
Hazard ratio (95% CI)*	0.70 (0.61, 0.79)	
From the start of the oral drug only (double dummy period only)		
MBEs, n (%)	24 (1.0)	40 (1.6)
Hazard ratio (95% CI)*	0.60 (0.36, 0.99)	
Intracranial bleeding	2 (0.1)	4 (0.2)
MBEs or CRBEs, n (%)	109 (4.4)	189 (7.7)
Hazard ratio (95% CI)*	0.56 (0.45, 0.71)	
Any bleeding events, n (%)	354 (14.4)	503 (20.4)
Hazard ratio (95% CI)*	0.67 (0.59, 0.77)	
Acute coronary syndrome, n (%)		
Any	9 (0.4)	5 (0.2)
Myocardial infarction	8 (0.3)	4 (0.2)
*The hazard ratio was estimated with the use of the Cox model with factor treatment stratified by study, assuming different baseline hazards per study. Abbreviations in table: CRBE, clinically relevant bleeding event; MBE, major bleeding event.		

4.4.8 RE-COVER and RE-COVER II subgroup analyses

The manufacturer reported in the MS that they conducted subgroup analyses for subgroups in which the underlying risks of recurrent DVT, PE, or bleeding, or the treatment effect for dabigatran was expected to differ. These subgroups included separate analyses of the four stratification factors accounted for during randomisation in the RE-COVER trials.[16;17] The efficacy outcomes for each strata in RE-COVER and RE-COVER II are presented in Table 25 and Table 26, respectively.

Table 25. RE-COVER efficacy outcomes by stratification factor subgroups_(adapted from Manufacturer's response to clarification question A3)

Outcome	Population	Baseline stratification factor / subgroup	Dabigatran		Warfarin		Hazard ratio (95% CI)	*p*-value
			n	N	N	N		
During treatment period (at 6 months)^								
VTE and VTE related deaths, *n* (%)	ITT	Whole population	30 (2.4)	1281	27 (2.2)	1283	NR	<0.0001 (for non-inferiority) 0.4984 (for superiority)
	ITT	No symptomatic PE	19 (2.2)	887	14 (1.6)	887	NR	NR
	ITT	Symptomatic PE	11 (2.9)	394	13 (3.3)	396	NR	NR
	ITT	No cancer	28 (2.4)	1217	24 (2.0)	1225	NR	NR
	ITT	Cancer	2 (3.4)	64	3 (5.3)	58	NR	NR
	ITT	Symptomatic PE with cancer	1 (5.9)	19	1 (6.3)	16	NR	NR
	ITT	Symptomatic PE without cancer	10 (2.7)	375	12 (3.2)	380	NR	NR
	ITT	No symptomatic PE with cancer	1 (2.4)	45	2 (5.0)	42	NR	NR
	ITT	No symptomatic PE without cancer	18 (2.2)	842	12 (1.5)	845	NR	NR
Up to the end of the post-treatment period*								
VTE and VTE related deaths, n (%)	FAS	Whole population	34 (2.7)	1,274	32 (2.5)	1,265	1.05 (0.65, 1.70)	<0.0001 (for non-inferiority) 0.8508 (for superiority)
	FAS	No symptomatic PE	19 (2.2)	882	14 (1.7)	871	NR	NR
	FAS	Symptomatic PE	11 (2.9)	392	13 (3.3)	394	NR	NR
	FAS	No cancer	28 (2.4)	1210	24 (2.0)	1,208	NR	NR
	FAS	Cancer	2 (3.4)	64	3 (5.4)	57	NR	NR
	FAS	Symptomatic PE with cancer	1 (5.9)	19	1 (6.3)	16	NR	NR
	FAS	Symptomatic PE without cancer	10 (2.7)	373	12 (3.2)	378	NR	NR
	FAS	No symptomatic PE with cancer	1 (2.5)	45	2 (5.1)	41	NR	NR
	FAS	No symptomatic PE without cancer	18 (2.2)	837	12 (1.5)	830	NR	NR

^ Number of patients and cumulative risk computed at day 180,

*Patients with at least one event who were considered in the primary analysis

Abbreviations used in table: CI, confidence interval; DVT, deep vein thrombosis; FAS, full analysis set; ITT, intention-to-treat; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism .

Table 26. RE-COVER II outcomes by stratification factor subgroups_adapted from Manufacturer's response to clarification question A3)

Outcome	**Population**	**Baseline stratification factor / subgroup**	**Dabigatran**		**Warfarin**		**Hazard ratio (95% CI)**	***p*-value**
			n	**N**	**N**	**N**		
During treatment period (at 6 months)*								
VTE and VTE related deaths, *n* (%)	ITT	Whole population	30 (2.4)	1,293	28 (2.2)	1,296	NR	<0.0001 (for non-inferiority) 0.7736 (for superiority)
	ITT	No symptomatic PE	23 (2.7)	887	20 (2.3)	881	NR	NR
	ITT	Symptomatic PE	7 (1.8)	406	8 (2.0)	415	NR	NR
	ITT	No cancer	28 (2.3)	1,242	26 (2.1)	1,246	NR	NR
	ITT	Cancer	2 (5.2)	51	2 (4.4)	50	NR	NR
	ITT	Symptomatic PE with cancer	0 (0.0)	10	0 (0.0)	12	NR	NR
	ITT	Symptomatic PE without cancer	7 (1.8)	396	8 (2.0)	403	NR	NR
	ITT	No symptomatic PE with cancer	2 (6.7)	41	2 (5.8)	38	NR	NR
	ITT	No symptomatic PE without cancer	21 (2.5)	846	18 (2.2)	843	NR	NR
Up to the end of the post-treatment period**								
VTE and VTE related deaths, n (%)	FAS	Whole population	34 (2.7)	1,279	30 (2.3)	1,289	1.13 (0.69, 1.85)	0.0002 (for non-inferiority) 0.6159 (for superiority)
	FAS	No symptomatic PE	23 (2.7)	876	20 (2.3)	876	NR	NR
	FAS	Symptomatic PE	7 (1.8)	403	8 (2.0)	413	NR	NR
	FAS	No cancer	28 (2.3)	1,229	26 (2.1)	1,239	NR	NR
	FAS	Cancer	2 (5.2)	50	2 (4.4)	50	NR	NR
	FAS	Symptomatic PE with cancer	0 (0.0)	10	0 (0.0)	12	NR	NR
	FAS	Symptomatic PE without cancer	7 (1.8)	393	8 (2.0)	401	NR	NR
	FAS	No symptomatic PE with cancer	2 (6.7)	40	2 (5.8)	38	NR	NR
	FAS	No symptomatic PE without cancer	21 (2.5)	836	18 (2.2)	838	NR	NR

*Number of patients and cumulative risk computed at day 180

**Patients with at least one event who were considered in the primary analysis

Abbreviations used in table: CI, confidence interval; DVT, deep vein thrombosis; FAS, full analysis set; ITT, intention-to-treat; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism .

The manufacturer reported that for all four strata the 95% confidence intervals for the HRs included 1, indicating that the observed numerical differences between treatment groups were not statistically significant. The manufacturer did not present numerical data for all the analyses to support this statement and so the ERG is unable to verify the manufacturer's findings.

The ERG notes that, although not statistically significant, the direction of effect is reversed to favour dabigatran in the subgroup with cancer compared with the whole trial populations in the RE-COVER trials. The HR for the primary endpoint in RE-COVER was 0.62 (95% CI: 0.10 to 3.71) in patients with cancer and 1.09 (95% CI: 0.66 to 1.80) in patients without cancer at baseline. The HRs for dabigatran vs warfarin for the same outcome in RE-COVER II were 0.95 (95% CI: 0.13 to 6.76) in patients with cancer and 1.15 (95% CI: 0.69 to 1.91) in patients without cancer at baseline.

The manufacturer also presented data from pooled analyses of RE-COVER and RE-COVER II for specific subgroups including non-stratified subgroups for the efficacy outcome of VTE and VTE related deaths, and the safety outcomes MBE, and MBE and CRBE (Table 27, Table 28 and Table 29, respectively).

Table 27. VTE and VTE related deaths for specific subgroups in pooled analysis of RE-COVER and RE-COVER II until the end of post-treatment period (adapted from MS Table 44)

	Dabigatran		**Warfarin**		
	Total N	**Event n (%)**	**Total N**	**Event n (%)**	**Hazard ratio (95% CI)**
Total	2553	68	2554	62	-
Symptomatic PE as index event					
No	1758	45 (2.6)	1747	37 (2.1)	1.20 (0.78, 1.86)
Yes	795	23 (2.9)	807	25 (3.1)	0.93 (0.53, 1.63)
Active cancer					
Yes	173	10 (5.8)	162	12 (7.4)	0.76 (0.33, 1.76)
History of bleedings					
Yes	123	6 (4.9)	129	5 (3.9)	1.28 (0.39, 4.21)
Geographical region					
Western Europe	613	13 (2.1)	626	18 (2.9)	0.74 (0.36, 1.50)
Abbreviations: PE, pulmonary embolism.					

Table 28. Incidence of MBE in specific subgroups for pooled RE-COVER and RE-COVER II analyses from the start of the oral drug only (double dummy period only) (adapted from MS Table 67)

	Dabigatran		**Warfarin**		
	Total N	**Event n (%)**	**Total N**	**Event n (%)**	**Hazard ratio (95% CI)**
Total	2456	24	2462	40	-
Symptomatic PE as index event					
No	1697	20 (1.2)	1694	32 (1.9)	0.62 (0.35, 1.08)
Yes	759	4 (0.5)	768	8 (1.0)	0.50 (0.15, 1.67)
Active cancer					
Yes	159	6 (3.8)	152	7 (4.6)	0.78 (0.26, 2.32)
History of bleedings					
Yes	117	1 (0.9)	124	4 (3.2)	0.29 (0.03, 2.61)
Geographical region					
Western Europe	588	8 (1.4)	604	8 (1.3)	1.02 (0.38, 2.71)
Abbreviations in table: PE, pulmonary embolism.					

Table 29. Incidence of MBE or CRBE in specific subgroups for pooled RE-COVER and RE-COVER II analyses from the start of the oral drug only (double dummy period only) (adapted from MS Table 68)

	Dabigatran		**Warfarin**		
	Total N	**Event n (%)**	**Total N**	**Event n (%)**	**Hazard ratio (95% CI)**
Symptomatic PE as index event					
No	1697	73 (4.3)	1694	134 (7.9)	0.53 (0.40, 0.70)
Yes	759	36 (4.7)	768	55 (7.2)	0.65 (0.43, 0.99)
Active cancer					
Yes	159	23 (14.5)	152	20 (13.2)	NR
History of bleedings					
Yes	117	13 (11.1)	124	17 (13.7)	NR
Geographical region					
Western Europe	588	30 (5.1)	604	57 (9.4)	NR
Abbreviations in table: NR, not reported; PE, pulmonary embolism					

The ERG note that further subgroup data for the primary efficacy outcome are reported in the Schulman *et al*. 2014 publication[17] and that the p value for interaction was statistically significant for the subgroups of smoking history (p = 0.04) and history of prior coronary artery disease (p = 0.02).

However, the ERG considers that these differences should be interpreted with caution as they relate to non-stratified subgroups.

Warfarin control

[redacted]

The ERG also requested the manufacturer provide data for centres with TTR <60% and those with TTR≥60%. This request was based on clinical expert advice that the expected %TTR in UK centres treating patients with VTE would be at least 60%. The safety and efficacy findings (Table 30 and Table 31) are generally in keeping with the results of the whole trial population analyses reported above (Table 14 and Table 15).

Table 30. Hazard ratios for composite of recurrent symptomatic VTE and deaths related to VTE including components in centres with TTR < 60% and ≥60% for RE-COVER and RE-COVER II combined (FAS) (adapted from Manufacturer's response to clarification question A4)

Outcome	Centres with TTR <60%		Centres with TTR ≥60%	
	HR (95% CI)	P value^	HR (95% CI)	P value^
VTE and VTE related deaths	1.33 (0.76, 2.35)	0.3188	0.99 (0.64, 1.53)	0.9542
Symptomatic PE#	0.99 (0.39, 2.51)	0.9906	1.06 (0.54, 2.06)	0.8681
Symptomatic DVT	1.62 (0.81, 3.24)	0.1710	0.93 (0.54, 1.63)	0.8063
Death related to VTE	2.00 (0.18, 22.03)	0.5720	1.02 (0.14, 7.25)	0.9829
All death	0.89 (0.55, 1.44)	0.6385	1.25 (0.65, 2.41)	0.5075

Symptomatic PE includes fatal PE

^ Obtained from Cox Model with factor treatment, stratified by study

Abbreviations used in the table: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; VTE, venous thromboembolism

Table 31. Hazard ratio for **bleeding** events since start of any treatment in centres with **TTR** <60% and ≥60% for RE-COVER and RE-COVER II combined (treated set) (adapted from Manufacturer's response to clarification question A4)

Outcome	**Centres with TTR <60%**		**Centres with TTR ≥60%**	
	HR (95% CI)	P value^	HR (95% CI)	P value^
MBE	0.68 (0.38, 1.21)	0.1869	0.81 (0.44, 1.50)	0.4984
CRBE	0.43 (0.29, 0.64)	<0.0001	0.74 (0.54, 1.02)	0.0676
MBE or CRBE	0.50 (0.36, 0.69)	<0.0001	0.75 (0.56, 1.00)	0.0494
Any bleeding	0.60 (0.50, 0.74)	<0.0001	0.75 (0.56, 1.00)	0.0023
Any intracranial bleeding	1.00 (0.14, 7.10)	0.9994	NR	NR
Any GI bleeding	1.23 (0.73, 2.09)	0.4391	1.31 (0.85, 2.02)	0.2150

^ Obtained from Cox Model with factor treatment, stratified by study

Abbreviations used in the table: CI, confidence interval; CRBE, clinically relevant bleeding event; DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; MBE, major bleeding event; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism

Age

In both RE-COVER and RE-COVER II the manufacturer reported in the MS that there appeared to be a tendency for dabigatran to have better efficacy with increasing age although the p values for interaction were not statistically significant at any age. The manufacturer also reported that "in all studies, when age was analysed as a continuous variable, compared with warfarin, the efficacy of dabigatran was somewhat lower in younger patients and higher in older patients, with equal efficacy at about age 60". No further details were provided on this analysis. In addition, there were no results reported in the MS for the impact of age on any of the bleeding or other safety outcomes. The ERG notes there are small numbers of people in some of the age subgroups, but are unable to comment further on this issue of age related treatment interaction.

Cancer

Only 4.5% of patients across the two RE-COVER trials (when pooled) met the definition for active cancer at baseline. As discussed in Section 3, the ERG has concerns about the applicability of these subgroup data to the UK population due to the differing definition of active cancer used in UK clinical practice compared with the trials' definitions.

The results from both RE-COVER and RE-COVER II for the subgroup of people with cancer suggest that there is a significantly higher frequency of recurrent VTE or VTE-related mortality among patients who had cancer compared to patients who did not have cancer Efficacy and safety endpoints in cancer patients in RE-COVER and RE-COVER II (adapted from MS Table 92). This was independent of the anticoagulation treatment received. In terms of the safety and efficacy of dabigatran amongst the cancer patients, the results were similar for both the dabigatran and warfarin

groups. However, the absence of a statistically significant difference between the treatment groups for all the outcomes reported is not specifically mentioned in the MS.

Table 32. Efficacy and safety endpoints in cancer patients in RE-COVER and RE-COVER II (adapted from MS Table 92)

Cancer at any time during study	**VTE or VTE-related death[1] Patients, n/N (%)**		**MBEs[2] Patients, n/N (%)**		**MBEs or CRBEs[2.] Patients, n/N (%)**		**Any Bleeds[2] Patients, n/N (%)**	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Warfarin
Pooled data from RE-COVER and RE-COVER II								
No	58/2380 (2.4)	50/2392 (2.1)	18/2297 (0.8)	33/2310 (1.4)	86/2297 (3.7)	169/2310 (7.3)	315/2297 (13.7)	468/2310 (20.3)
Yes	10/173 (5.8)	12/162 (7.4)	6/159 (3.8)	7/152 (4.6)	23/159 (14.5)	20/152 (13.2)	39/159 (24.5)	35/152 (23.0)

[1]Measured from randomization (i.e. start of parenteral therapy plus either warfarin or warfarin placebo) up to the end of the pre-specified post-treatment follow-up

[2]Measured from the start of the double-dummy period (i.e. oral dabigatran or warfarin alone) to the end of the 6-month study period.

4.4.9 Summary of RE-COVER and RE-COVER II results

- Dabigatran demonstrated non-inferiority vs adjusted-dose warfarin in terms of prevention of recurrent VTE and VTE-related mortality. In pooled analysis, the hazard ratio for dabigatran vs warfarin for this composite endpoint was 1.09 (95% CI: 0.77 to 1.54).
- There were no statistically significant differences between dabigatran and warfarin in any of the secondary endpoints in the two RE-COVER studies (i.e. composite of recurrent symptomatic VTE and all deaths; symptomatic DVT; symptomatic non-fatal PE; death related to VTE; and all deaths).
- There was no significant difference in major bleeding events between dabigatran and warfarin in RE-COVER or RE-COVER II.
- The overall incidence of treatment-emergent reported AEs were generally similar between dabigatran and warfarin, although the ERG notes that numerically more episodes of dyspepsia and rectal bleeding were noted with dabigatran in RE-COVER and RE-COVER II.
- There was a slightly higher incidence of acute coronary syndrome events in the dabigatran groups compared with the warfarin groups.
- The safety and efficacy data in cancer patients suggests no significant difference between dabigatran and warfarin but the ERG recommend caution in drawing conclusions as there were few patients with active cancer in RE-COVER or RE-COVER II.
- There was no statistically significant difference between group difference in recurrent VTE and VTE-related mortality based on index event (i.e. symptomatic PE or no symptomatic PE) in the pooled analysis of RE-COVER and RE-COVER II ($p = 0.38$).

4.5 Summary and critique of secondary prevention VTE trials: RE-MEDY

4.5.1 Description of RE-MEDY trial

RE-MEDY[18] was a phase III, double-blind, double-dummy, parallel-group, randomised, active controlled trial. In RE-MEDY, the efficacy and safety of dabigatran 150 mg BD was compared with adjusted-dose warfarin (target INR 2.0–3.0) in patients diagnosed with a symptomatic, proximal DVT or PE that had been successfully treated with standard doses of an approved anticoagulant for 3 to 12 months for confirmed acute symptomatic VTE or with dabigatran as part of the RE-COVER or RE-COVER II trials.[16;17] RE-MEDY aimed to evaluate the efficacy and safety of dabigatran for long-term prophylaxis after VTE.

RE-MEDY was designed to demonstrate non-inferiority based on the composite primary endpoint of recurrent symptomatic VTE and deaths related to VTE within 36 months. The primary composite endpoint for RE-MEDY was the same as that in the RE-COVER trials, although it was assessed at 36 months (i.e. 39–48 months after initial treatment for VTE) rather than 6 months.

RE-MEDY population

RE-MEDY was conducted at 264 sites in 33 countries. Patients were recruited and randomised between July 2006 and July 2010. In total, 2,866 patients were included and underwent randomisation in RE-MEDY. The patients randomised in RE-MEDY included those from 5 UK centres and made up 1.6% of the population of RE-MEDY.

The inclusion and exclusion criteria for RE-MEDY are presented in Table 33 and Table 34.

Table 33. Inclusion criteria for RE-MEDY (adapted from MS Table 25)

1. Objectively confirmed symptomatic uni- or bilateral DVT of the leg involving proximal veins or PE, treated with approved anticoagulant therapy, or with study drug (in RE-SONATE previous study drug was introduced as an amendment), taken for (RE-MEDY) 3 to 12 months or (RE-SONATE) 6 to 18 months at the time of screening,.
2. Male or female, being 18 years of age or older (the age criterion was turned around as an exclusion criterion in RE-SONATE)
3. Written informed consent for study participation.

Table 34. Exclusion criteria for RE-MEDY (adapted from MS Table 26)

1. Symptomatic DVT or PE at screening
2. Patients with primary PE with suspected origin other than leg limbs (e.g. upper limbs, right heart).
3. Actual or anticipated use of vena cava filter
4. Interruption of anticoagulant therapy for 2 or more weeks during the 3-6 months of treatment for the prior VTE (changed from 3 to 6 months to 3 to 12 months treatment following Protocol Amendment 2, dates 15 March 2007)

5. Patients who in the investigator's opinion should not be treated with warfarin
6. Allergy to warfarin or dabigatran, or to one of the excipients included in these medications
7. Patients who in the investigator's judgement are perceived as having an excessive risk of bleeding.
    a. Haemorrhagic disorder or bleeding diathesis
    b. Trauma or major surgery within the last month or as long as an excessive risk of bleeding persists after these events, or planned major surgery
    c. Any of the following intracranial pathologies: neoplasm, arteriovenous malformation or aneurysm
    d. History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding
    e. Gastrointestinal haemorrhage within the past 3 months
    f. Symptomatic or endoscopically documented gastro-duodenal ulcer disease in the previous 30 days
    g. Treatment with thrombolytic agents within 14 days before enrolment
    h. Anticipated need of restricted medication during the treatment period
    i. Known thrombocytopenia (platelet count $<100*10^9$/L)
8. Known anaemia (haemoglobin <100 g/L)
9. Need of anticoagulant treatment for disorders other than VTE
10. Recent unstable cardiovascular disease, such as uncontrolled hypertension at the time of enrolment (investigator's judgement), acute bacterial endocarditis or history of myocardial infarction within the last 3 months
11. Elevated AST or ALT >2x ULN based on the local lab results obtained at screening and prior to randomisation (or central screening lab if available on time)
12. Liver disease expected to have any potential impact on survival (e.g. acute hepatitis, or possibly active hepatitis B, hepatitis C or cirrhosis, but not Gilbert's syndrome or hepatitis A with complete recovery)
13. Patients who have developed transaminase elevations upon exposure to ximelagatran
14. Severe renal impairment (estimated creatinine clearance ≤30 ml/min)
15. Women who are pregnant, nursing or of childbearing potential who refuse to use a medically acceptable form of contraception throughout the study.
16. Participation in another clinical trial with an investigational drug during the last 30 days, except for the RE-COVER, or previous participation in this study. Following Protocol Amendment 6, dates 12 December 2008, patients who had completed the RE-COVER II trial were allowed to enter into RE-MEDY
17. Patients considered unsuitable for inclusion by the investigator, e.g. because considered unreliable to comply with the requirements for follow-up during the study or compliance with study drug administration, had a life expectancy less than the expected duration of the trial due to concomitant disease, or had any condition which in the opinion of the investigator did not allow safe participation in the study (e.g., drug addiction, alcohol abuse)
18. In case of anticipated study related diagnostic procedures requiring contrast medium (e.g., contrast venography or pulmonary angiography):
    a. Elevated serum creatinine, which in the investigator's opinion contraindicates these examinations
    b. Known allergy to radio opaque contrast media or iodine, which in the investigator's opinion contraindicated these examinations

Following Protocol Amendment 4, dated 14 February 2008, patients with an anticipated need for quinidine treatment were excluded.

The ERG notes that there were a large number of exclusion criteria but based on the advice of clinical experts the ERG considers them to be appropriate for the population and therapies under investigation.

Patients in RE-MEDY were randomised in a 1:1 ratio to receive active dabigatran (150 mg BD) and a warfarin-like placebo or active warfarin and a dabigatran-like placebo in a double-dummy design. Prior to randomisation, patients were required to have taken 3 to 12 months of anticoagulant for treatment of an acute VTE.

Randomisation was stratified into four groups resulting from the combination of two stratification factors: active cancer (yes/no) and symptomatic PE (yes/no). To prevent unequal treatment allocation, blocks of 4 were used and the blocks were assigned to strata. The strata were the same as those used in the RE-COVER trials. In addition, the definition of active cancer was the same as that used in the RE-COVER trials: "a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before the enrolment; any treatment for cancer within 5 years; or recurrent or metastatic cancer." As discussed in Section 3.1, the ERG have concerns that the definition of active cancer in RE-MEDY may be too broad as it encompasses patients who may have been in remission for nearly 5 years and thus would not usually be considered in UK clinical practice to be active cancer patients.

The baseline characteristics of the patients included in RE-MEDY are reported in Table 35.

Table 35. Baseline characteristics of patients in the RE-MEDY trial (adapted from MS Table 28)

Characteristic	**RE-MEDY**	
	Dabigatran (n = 1,430)	**Warfarin (n =1,426)**
Age – mean ± SD	55.4 ± 15.0	53.9 ± 15.3
Female sex – n (%)	559 (39.1)	555 (38.9)
Race – n (%)		
White	1,288 (90.1)	1,284 (90.0)
Black	29 (2.0)	28 (2.0)
Asian	113 (7.9)	114 (8.0)
American Indian	0	0
Weight (kg) – mean ± SD	86.1 ± 19.3	86.0 ± 18.9
Type of index event		
DVT only	938 (65.6)	922 (64.7)
PE only	324 (22.7)	335 (23.5)
DVT and PE	167 (11.7)	168 (11.8)
Neither DVT or PE	1 (0.1)	1 (0.1)
Cancer – n (%)	60 (4.2)	59 (4.1)
Treatment duration before randomisation – days	198 ± 157	200 ± 117

Enrolled from either RE-COVER or RE-COVER II	589(41.2)	552(38.7)
Enrolled from RE-COVER study - n (%) Dabigatran group Warfarin group	519(36.3) 236 (16.5) 283 (19.8)	497(34.9) 254 (17.8) 243 (17.0)
Enrolled from RE-COVER II study - n (%)	70 (4.9)	55 (3.9)
Exposure to study drug – days	473 ± 211	474 ± 206

The manufacturer reported that there were no significant differences between the dabigatran and warfarin treatment groups in RE-MEDY in terms of baseline characteristics. No measures of statistical significance were reported in the MS and so the ERG was unable to validate this statement. However, the ERG notes that based on the numerical data provided by the manufacturer, the treatment groups appear similar at baseline. The ERG considers it important to highlight that in keeping with the RE-COVER trials, the majority of patients in RE-MEDY were white (90%) and male (approximately 60%). In addition, the ERG notes that 40% of the patients in RE-MEDY were recruited from the RE-COVER trials. There were 27.5% of people in RE-MEDY at study centres in Western Europe. The average age of patients in RE-MEDY was approximately 55 years, which is similar to the average age in the RE-COVER trials, and as discussed in Section 3.1, is younger than the population in the UK with VTE that would be expected to be eligible for treatment with dabigatran.

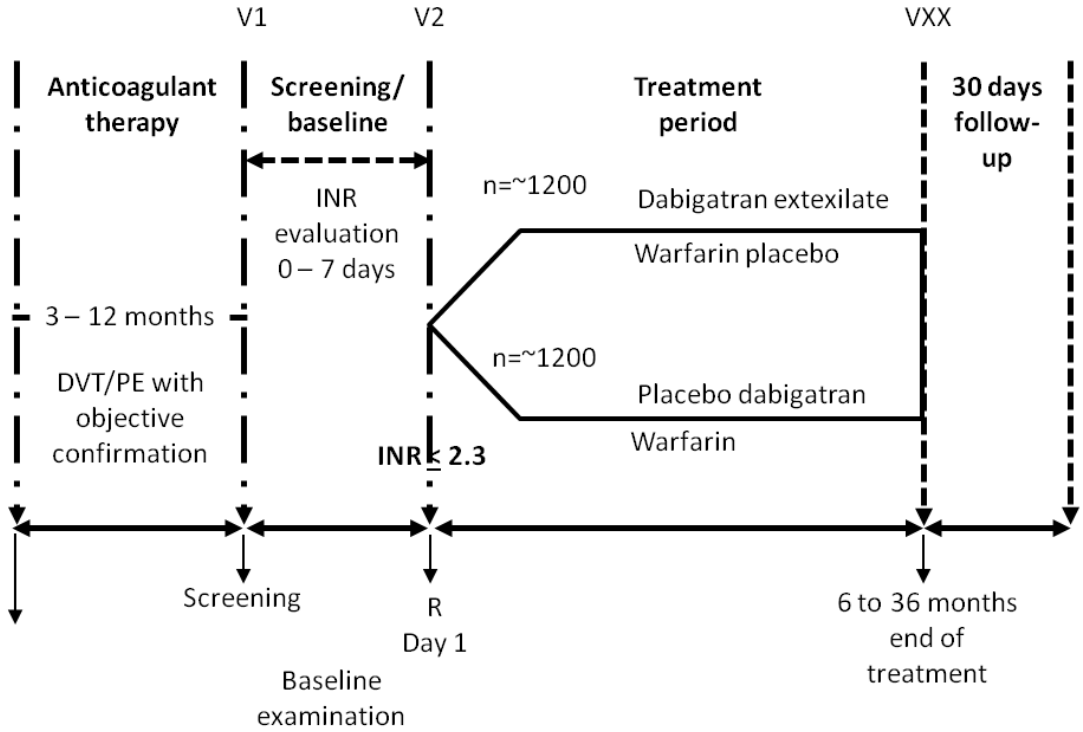
Interventions and Comparators

The randomisation methods, blinding and study interventions in RE-MEDY were the same as in the RE-COVER trials described in Section 4.3.1. A key difference in RE-MEDY in terms of the interventions compared to the RE-COVER trials was that the intended treatment duration was 6 to 36 months (following acute treatment of VTE of 3-12 months) in RE-MEDY compared with a maximum of 6 months treatment for an acute VTE in the RE-COVER trials. This is related to the difference in treatment goals between the trials. The aim of REMEDY was to assess the use of dabigatran in secondary prevention of VTE, whereas the RE-COVER trials were designed to assess the initial 6 month treatment of a VTE. In RE-MEDY there was no requirement for parenteral anticoagulation prior to commencement of randomised study drug. This again is related to the fact that RE-MEDY is looking at secondary prevention of VTE. In order to enter RE-MEDY, patients were required to have taken 3–12 months of anticoagulation treatment prior to commencing their randomised study drugs. RE-MEDY was thus double dummy from the point of randomisation, whereas the RE-COVER trials had an initial single dummy period where non-randomised parenteral therapy was given alongside warfarin/warfarin placebo.

In summary, patients in RE-MEDY were randomised in a 1:1 ratio to receive oral dabigatran 150 mg BD and an oral warfarin-like placebo (1,430 patients) or oral warfarin and an oral dabigatran-like placebo (1,426) (Figure 4). The warfarin was administered as warfarin sodium 1mg, 3mg, and 5 mg

tablets taken orally to target an INR of 2.0 to 3.0. A sham INR procedure was used in the dabigatran group to maintain blinding.

Figure 4. Study flow chart for RE-MEDY treatment schedule (reproduced from MS Figure 5)



Abbreviations: CUS, compression ultrasonography; DVT, deep vein thrombosis; INR, international normalised ratio; PE, pulmonary embolism; R, randomisation.

The ERG notes that some of the outcome data in RE-MEDY includes data collected after the 30 days follow-up at which point patients may have been off randomised anticoagulant treatment for 30 days. Clinical advisers to the ERG consider that patients requiring anticoagulation beyond the 3–6 month initial treatment period would remain on lifelong treatment. As a result, the ERG does not consider the data from RE-COVER at the 30 day follow-up visit to be applicable to the standard UK population whom would be treated for secondary prevention of VTE. The ERG thus focuses on the RE-MEDY end of treatment results in the following sections.

Outcomes

The primary efficacy endpoint in RE-MEDY was the composite of recurrent symptomatic VTE and deaths related to VTE. VTE was defined as in the RE-COVER trials as the composite incidence of DVT (detected by venous compression ultrasonography or venography) and PE (detected by ventilation-perfusion lung scan, pulmonary angiography, or spiral [helical] CT).

The secondary efficacy endpoints and safety outcomes reported in RE-MEDY are presented in Table 36.

Table 36. Secondary outcomes and safety outcomes in the RE-MEDY trial (adapted from MS table 29)

	Outcome
Secondary outcomes*	Composite of recurrent symptomatic VTE (fatal and non-fatal) and all deaths Symptomatic DVT Symptomatic PE (fatal or non-fatal) Deaths related to VTE (i.e. fatal PE) All deaths
Safety outcomes#	Major Bleeding Events (MBEs) MBEs and Clinically Relevant Bleeding Events (CRBEs) Any bleeding event (MBEs, CRBEs, and nuisance bleeds) Adverse Events (AEs) Discontinuation of study treatment due to AEs Laboratory measures, especially Liver Function Tests (LFTs) Acute Coronary Syndrome (ACS) ECG and vital signs
* All recurrent VTEs required objective verification by definitive diagnostic evaluation. All recurrent VTEs and all deaths were centrally adjudicated by an independent committee that was blinded to treatment allocation. Adjudicated results were used in the analysis. # All safety endpoints were assessed during treatment and the 6 days following the last intake of study medication. Any bleeding events and all suspected ACS were centrally adjudicated and all potentially liver-related safety issues were centrally reviewed by independent committees that were blinded with regards to the treatment allocation of patients.	

The definitions of the bleeding events were the same as those used in the RE-COVER trials and are described in detail in Section 4.3.1. The manufacturer also included data in the MS for RE-MEDY on the two composite outcomes referred to as net clinical benefit endpoints described in Section 4. However, the ERG and their clinical advisers consider the outcome to be inappropriate as it comprises a *post hoc* analysis of both safety and efficacy outcomes. As a result, the ERG does not consider it appropriate to present the results of the analyses relating to these outcomes in this report.

The ERG notes that the primary safety and efficacy outcomes in RE-MEDY were centrally adjudicated by an independent committee. The committee were blinded to patients' study-group assignments and classified outcomes on the basis of pre-specified criteria. The ERG considers that this has reduced the risk of investigator bias affecting the results in terms of outcome assessment.

The ERG notes that CTEPH, PTS, heart failure and HRQoL data were not specifically collected in RE-MEDY. The ERG considers that all other outcomes specified in the final scope issued by NICE were captured in RE-MEDY and reported appropriately in the MS for this STA.

Subgroup analyses

The manufacturer reports in the MS that "pre-defined subgroup analyses of the primary endpoint were performed to evaluate the consistency of the treatment effect across a variety of patient groups". The

subgroups that were analysed for the primary efficacy endpoint of RE-MEDY are presented in Table 37.

Table 37. Subgroup analyses for the primary endpoint in RE-MEDY (adapted from MS Table 34)

Factors	Subgroups (categories)
Demographics	Age (years): 18 to <40, 40 to <50, 50 to <65, 65 to <75, ≥ 75
	Sex: male, female
	Race: White, Asian, Black
	Ethnicity: Hispanic, non-Hispanic
	Body weight (kg): <50, 50 to <100, ≥100
	BMI (kg/m^2): <25, 25 to <30, 30 to <35, ≥35
	Creatinine clearance (mL/min): <30, 30 to <50, 50 to <80, ≥80
	Smoking history: never smoked, ex-smoker, current smoker
	Geographical region: Asia[1], Eastern Europe[2], Latin America[3], North America[4], Western Europe[5], Other[6]
Baseline risk factors for VTE and medical history	More than 1 previous VTE: yes, no
	Symptomatic PE as primary VTE event: yes, no
	Time from the qualifying VTE to randomisation (months): <3, 3 to <6, 6 to <9, 9 to <12, ≥12 months
	Active cancer[7]: yes, no
	History of non-haemorrhagic stroke: yes, no
	History of coronary artery disease: yes, no
	Additional medical history/baseline conditions as recorded on the CRF
Trial conduct	Participation in RE-COVER/RE-COVER II (not rolled over from RE-COVER or RE-COVER II, roll-over patients who took dabigatran in RE-COVER, roll-over patients who took Warfarin in RE-COVER, rolled over from RE-COVER II[8])

[1] China, India
[2] Bulgaria, Czech Republic, Hungary, Poland, Russia, Slovakia, Turkey, Ukraine
[3] Argentina, Brazil, Mexico
[4] Canada, USA
[5] Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, UK
[6] Australia, Israel, New Zealand, South Africa

The ERG acknowledges that there were a large number of subgroup analyses conducted in RE-MEDY. The ERG also notes that only results from selected subgroup analyses were reported by the

manufacturer in the MS. In addition, as for the RE-COVER studies, subgroup analyses based on cTTR quartiles and quintiles were also provided for RE-MEDY by the manufacturer.

RE-MEDY follow-up

Follow-up in RE-MEDY was originally planned to be 18 months. However, Protocol Amendment 6 (dated 12 December 2008) extended the treatment duration of ongoing patients who consented to extend study participation to up to 36 months. The resulting follow-up duration of patients in RE-MEDY varied from 6 to 36 months.

The full follow-up schedule for RE-MEDY is presented in Table 38.

Table 38. Follow-up visit schedule for RE-MEDY (adapted from MS table 24)

Follow-up visit schedule
1. Screening and baseline period a. Visit 1 (day -7 to 1) 2. Randomisation a. Visit 2 (day 1) 3. Treatment and follow-up a. Visit 3 (day 15 [±3]) b. Visit 4 (day 30 [±7]) c. Visit 5 (day 60 [±7]) d. Visit 6 (day 90 [±7]) e. Visit 7 (day 120 [±7]) f. Visit 8 (day 150 [±7]) g. Visit 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 (day 180, 270, 360, 450, 540, 630, 720, 810, 900, 990 [±14])

4.5.2 Description and critique of statistical approaches used in RE-MEDY

RE-MEDY[18] was planned as a non-inferiority study to determine the efficacy and safety of dabigatran 150 mg BD compared with warfarin in patients with symptomatic VTE, using HRs and RDs. The ERG notes that the non-inferiority margin's in RE-MEDY were different to those used in the RE-COVER studies.[25;26] The non-interiority margin's in RE-MEDY were defined as 2.85 for the HR and 2.8% for the risk difference at month 18. The non-inferiority margins in the RE-COVER trials were 2.75 for the HR and 3.6% for the risk difference.

The manufacturer reported that in RE-MEDY if both margins (HR and RD) were met then dabigatran would preserve "at least 70% of the warfarin effect vs. placebo in HRs (based on the point estimates) as well as at least two thirds in risk differences (based on the lower bounds of 95% CI) if proven to be non-inferior to warfarin" (MS pg 87). The ERG is concerned that the threshold used for the lower boundary of the non-inferiority margin in RE-MEDY was too low compared with other similar trials.

The ERG had similar concerns about the non-inferiority margin used in the RE-COVER trials (described in Section 4.3.2).

The planned sample size (at least 1,200 patients per treatment group) and treatment duration (up to 36 months) in RE-MEDY was intended to have at least 80% power to claim non-inferiority with one-sided alpha=0.025 (after Protocol Amendment 6, dated 12 December 2008). The calculation assumed a discontinuation rate of 20% within the 18-month treatment period. In the original protocol, the planned sample size was 1,000 patients per group for a total of 36 expected events from combined groups, to have at least 85% power to claim non-inferiority with one-sided alpha=0.025. This calculation assumed an equal hazard rate of 2.0% for both groups for the primary endpoint and a discontinuation rate of 20% over 18 months.

Protocol amendment six was a result of a lower than projected event rate. The protocol was thus amended to increase the sample and extend the planned treatment period for patients already enrolled who consented to the extension, with the resulting planned study treatment period ranging from six to 36 months.

This protocol amendment resulted in three cohorts of patients in RE-MEDY:

1. Patients who had completed the trial prior to implementation of this amendment or who were not willing to consent to the amendment. These patients had a planned treatment duration of 18 months.
2. Patients who had been randomised prior to implementation of this amendment and re-consented to trial participation as per this amendment. These patients had a planned treatment duration of between 18 and 36 months. The actual treatment period was shorter than 18 to 36 months if a primary outcome event occurred or trial discontinuation was required due to adverse events or other reasons.
3. Patients randomised after implementation of the protocol amendment but enrolled within 18 months of the planned study close-out (i.e. June 2010). These patients had a planned treatment duration of 6 to <18 months.

For the primary analysis, the overall hazard ratio (from a Cox model) and the risk difference (from Kaplan-Meier [KM] estimates) were reported. For the evaluation of the data, 3 analysis sets were used; these were the randomised set (RS), the FAS, and the PPS. The RS included all randomised patients, whether treated or not. The FAS and PPS used the same definitions as the RE-COVER trials (Section 4.3.2). All efficacy analyses were based on the FAS, with the exception of the PPS analysis of the primary endpoint. For the efficacy analyses, patients were allocated to the treatment groups as randomised, regardless of the actual medication taken ('FAS as randomised'). An on-treatment

analysis was performed as a sensitivity analysis for the primary endpoint (using the ‘FAS as treated’ population, which was the FAS set in the RE-COVER trials). The analysis of the safety endpoints was based on the 'FAS as treated'. The number of patients allocated to each treatment group for the different analysis sets are presented in Table 39.

Table 39. Number of patients in analysis sets for RE-MEDY (adapted from MS table 31

RE-MEDY Analysis set	Dabigatran	Warfarin	Total
Randomised set (RS), n (%)	1,435 (100.0)	1,431 (100.0)	2,866 (100.0)
Full analysis set (FAS), n (%)			
as randomised	1,430 (99.7)	1,426 (99.7)	2,856 (99.7)
as treated	1,430 (99.7)	1,426 (99.7)	2,856 (99.7)
Per-protocol set (PPS)	1,400 (97.6)	1,400 (97.8)	2,800 (97.7)

The 'FAS as randomised' and the 'FAS as treated' had the same number of patients per treatment group. However, they were not composed of precisely the same patients: 1 patient in each treatment group was dispensed an incorrect medication kit (wrong treatment) at the randomisation visit and continued on this treatment throughout the study.

In general, the ERG considers the manufacturer’s approach to the statistical analysis of the data in the RE-MEDY to be appropriate as the number of patients in the FAS and RS were similar.

4.5.3 Summary statement

RE-MEDY was included in the clinical effectiveness section of the MS to provide clinical data on dabigatran versus placebo for long term secondary prevention of VTE.

The ERG considers the inclusion and exclusion criteria of RE-MEDY to be acceptable to address the trial’s objectives. In addition, the ERG notes that the baseline characteristics of the randomised populations of RE-MEDY appeared to be well balanced between trial arms. The intervention was dabigatran, which is the focus of this STA, and the comparator warfarin.

The ERG considers that the outcome data reported from RE-MEDY appeared to be broadly consistent with the data collected in the trial. However, the ERG notes that CTEPH, PTS and heart failure data requested in the NICE final scope were not specifically collected in the trials.

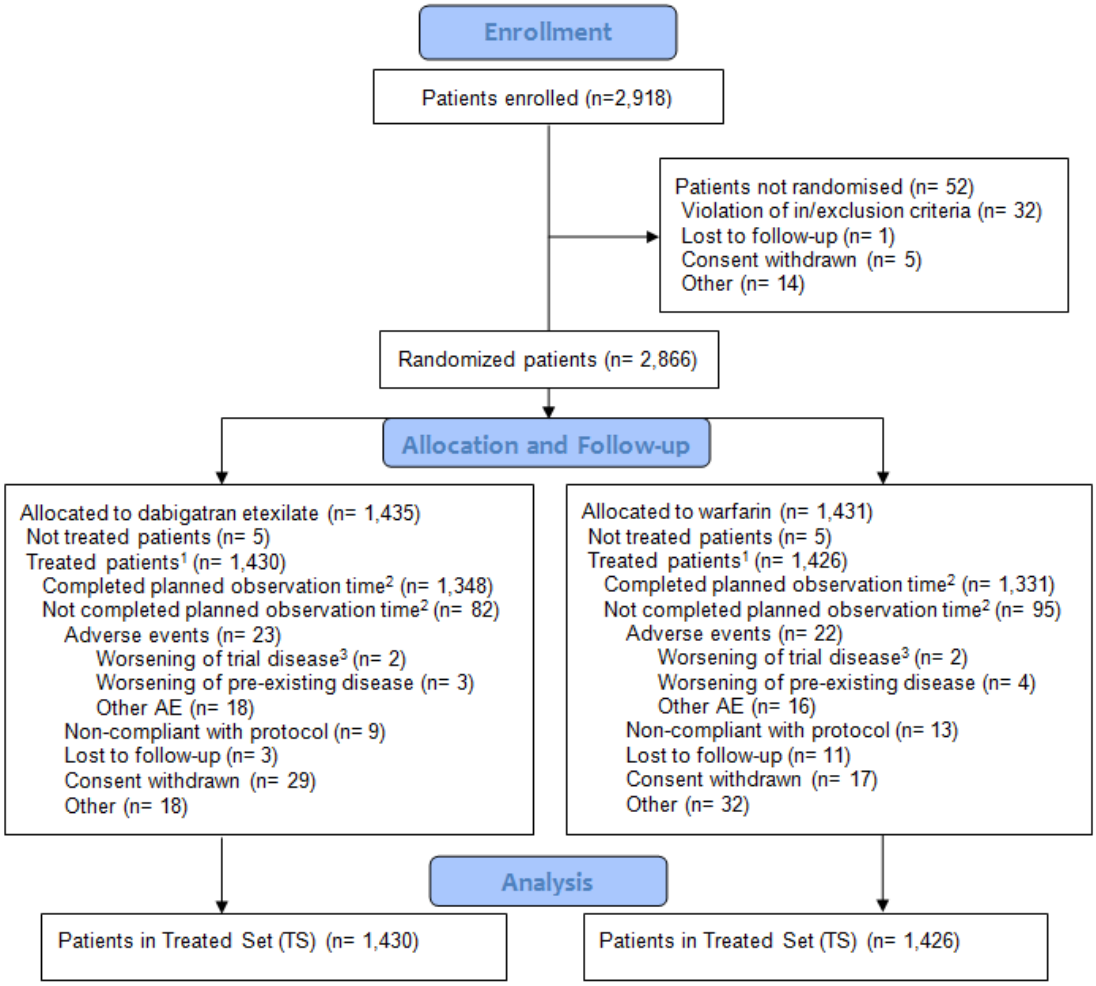
In terms of follow-up and statistical data analysis, the ERG considers that the duration of follow-up in RE-MEDY was acceptable for the outcomes assessed and the statistical analysis plan was suitable.

4.6 Summary of results of secondary prevention VTE trials: RE-MEDY

4.6.1 RE-MEDY treatment compliance and discontinuations

There were 2,918 patients enrolled in RE-MEDY[18] and 52 (1.8%) of these were not randomised. The most frequent reason for non-randomisation was a violation of the inclusion or exclusion criteria (1.1%). This resulted in a total of 2,866 patients who were randomised to either dabigatran (1,435 patients) or warfarin (1,431 patients). Of the randomised patients, 10 patients were not treated with study medication (5 patients of each treatment group): 5 patients refused to take study medication, 1 patient was non-compliant with the study protocol (they took part in a different clinical trial) and 4 patients were reported with 'other' reasons (3 were not compliant with eligibility criteria and 1 refused to participate in the study). This resulted in 2,856 treated patients, of which 93.8% completed the planned observation time, and there were no between-group differences for those patients who did not (dabigatran: 5.7%, warfarin: 6.6%). The reasons for discontinuation of study medication were due to AEs in 1.6% of patients in the dabigatran group and 1.5% of patients in the warfarin group. Full details on the flow of patients through the study period are presented in Figure 5.

Figure 5. Flow chart of participants in RE-MEDY (reproduced from MS Figure 8)



[1] Patients who received at least 1 dose of study medication (active study medication or placebo)
[2] The investigator was to record on the 'Trial completion' page of the CRF if the patient had completed the planned observation time or the reason for non-completion, which was to be selected from a list of pre-defined reasons on this CRF page.
[3] Symptomatic DVT or PE as based on the assessment of the investigator, including an extension of the existing thrombus or a new suspected event.

In RE-MEDY, over the 3-year treatment period, patients in the warfarin group had a mean of 22.9 INR tests, and the INR was in the therapeutic range 61.5% of the time. This mean TTR is slightly higher than that seen in the RE-COVER trials and based on the advice of clinicians the ERG consider it to be a closer reflection of the TTR expected in a UK centre. The clinical experts consulted reported INR control of 60% to 80% in their clinical experience. Furthermore, the ERG notes that, the TTR in RE-MEDY had increased to a mean of 69.8% at months 31-33 after first warfarin dose (MS CSR; pg 14).

4.6.2 REMEDY treatment effectiveness results

The results of RE-MEDY[18] with respect to the primary and secondary efficacy endpoints are presented in Table 40. The ERG notes that dabigatran 150 mg BD demonstrated non-inferiority to

adjusted-dose warfarin for the primary efficacy outcome based on the non-inferiority margin of 2.85 (HR, 1.44; 95% CI, 0.78 to 2.64, p < 0.001). The ERG notes that it is reported in the CSR that non-inferiority was also proven based on the non-inferiority margin for the hazard ratio (HR) <2.85 in the per protocol population (HR, 1.42; 95% CI, 0.77 to 2.60). However, superiority was not reached.

Table 40. RE-MEDY efficacy outcome results at 18 months (adapted from MS table 45 and 46, and MS response to clarification question A3)

Outcome	**Population**	**Dabigatran**		**Warfarin**		**Hazard ratio (95% CI)**	***p*-value**
		n	**N**	**n**	**N**		
VTE and VTE-related death (excl. Unexplained death)	FAS*	26 (1.8)	1,430	18 (1.3)	1,426	1.44 (0.78, 2.64)	0.01 (for non-inferiority) 0.2424 (for superiority)
	ITT	26 (1.8)	1,435	18 (1.3)	1,431	1.43 (0.78, 2.63) ~	0.0134 (for non-inferiority) 0.2457 (for superiority)
Patients with event; VTE, VTE-related and unexplained death	FAS*	27 (1.9)	1,430	20 (1.4)	1,426	1.33 (0.74, 2.40)	0.0055 (for non-inferiority) 0.3349 (for superiority)
	ITT**	22 (1.7)	1,435	17 (1.4)	1,431	NR	<0.0001 (for non-inferiority) 0.4052 (for superiority)
Recurrent symptomatic VTE and all deaths	FAS*	42	1,430	36	1,426	1.18 (0.75 to 1.84)	NR
Symptomatic DVT	FAS*	17 (1.2)	1,430	13 (0.9)	1,426	1.32 (0.64, 2.71)	NR
Symptomatic non-fatal PE	FAS*	10 (0.7)	1,430	5 (0.4)	1,426	2.04 (0.70, 5.98)	NR
Deaths related to VTE	FAS*	1 (0.1)	1,430	1 (0.1)	1,426	1.01 (0.06, 16.22)	NR
All deaths	FAS*	17 (1.2)	1,430	19 (1.3)	1,426	0.90 (0.47, 1.72)	NR

*Analysis was based on data for the planned treatment period, regardless of whether the study drug was discontinued early.

**Number of patients with event and number of patients and cumulative risk computed at Day 540.

~The hazard ratio was estimated using a meta−analysis approach: first hazard ratios were estimated within each cohort using a Cox regression model adjusted for the factors treatment and baseline stratification factor (symptomatic PE as qualifying event). The overall hazard ratio was calculated by pooling the hazard ratios across the cohorts with inverse variance weighting of by−cohort hazard ratios.

Abbreviations used in table: CI, confidence interval; DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

The ERG notes that there were no statistically significant differences by treatment group in the rate of any of the secondary endpoints.

The ERG notes that the number of patients who died during the planned treatment period was similar between the treatment groups (dabigatran: 17 patients; warfarin: 19 patients). The manufacturer reported that the most frequent adjudicated cause of death was cancer (dabigatran: 7 patients, warfarin: 9 patients). In terms of the VTE related mortality, one patient in the dabigatran group and one patient in the warfarin group died from PE.

4.6.3 REMEDY safety and adverse events

Adverse events

An overview of the number of AEs that occurred during RE-MEDY[18] is presented in Table 41.

Table 41. Summary of adverse events in RE-MEDY (reproduced from MS Table 69)

Outcome	**Dabigatran** **n = 1,430**	**Warfarin** **n = 1,426**
Patients with any AE – n (%)	1,029 (72.0)	1,010 (70.8)
Patients with severe AEs – n (%)	143 (10.0)	151 (10.6)
Drug-related AEs* – n (%)	229 (16.0)	280 (19.6)
AEs leading to discontinuation – n (%)	145 (10.1)	126 (8.8)
* Relationship as assessed by the investigator. AE, adverse event.		

The ERG notes that the overall number of AEs was similar between the treatment groups. The most common AEs were infections and infestations (dabigatran: 29.7%, warfarin: 34.4%), gastrointestinal disorders (26.3% vs 22.2%), and musculoskeletal and connective tissue disorders (25.7% vs 26.0%). AEs assessed by the investigator as drug-related were less frequent in the dabigatran treatment group (16.0%) than the warfarin group (19.6%). However, the percentage of patients who discontinued study drug due to AEs was higher in the dabigatran group than in the warfarin group (10.1% vs 8.8%). The manufacturer reported that the most frequent AEs that led to discontinuation of study drug were DVT (0.8% vs 1.1%) and haematuria (0.5% in both treatment groups). The most common serious AEs were DVT (0.7% vs 0.4%), PE (0.6% vs 0.2%), chest pain (0.3% vs 0.6%), abdominal pain (0.3% vs 0.6%), and prostate cancer (0.3% vs 0.5%). The ERG reviewed the CSR for further details on the most frequent drug-related AEs as assessed by the investigator and notes that these were ‘gastrointestinal disorders’ (7.2% dabigatran vs 4.9% warfarin). The most frequently reported drug-related ‘gastrointestinal disorders’ with dabigatran were (dabigatran vs warfarin): rectal haemorrhage (1.1% vs 0.9%, respectively), nausea (1.0% vs 0.2%, respectively) and dyspepsia (1.2% vs 0.4%, respectively).

Bleeding events

Table 42 presents a summary of the bleeding events reported in RE-MEDY and Table 43 presents a breakdown of the sites of the MBE.

Table 42. Summary of bleeding events in RE-MEDY (reproduced from MS table 70)

Outcome	**Dabigatran n = 1,430**	**Warfarin n = 1,426**
MBE, n (%)	13 (0.9)	25 (1.8)
Hazard ratio (95% CI)	0.52 (0.27, 1.02)	
MCRB, n (%)	80 (5.6)	145 (10.2)
Hazard ratio (95% CI)	0.54 (0.41, 0.71)	
Fatal event	0	1
Bleeding into critical organ	8	13
Event resulting in fall in Hb level or need for BT	9	18
Abbreviations: BT, blood transfusion; CI, confidence interval; MBE, major bleeding event; MCRB, major or clinically relevant bleeding.		

Table 43. Sites of MBE in RE-MEDY (reproduced from MS table 71)

Preferred term*	**Dabigatran**	**Warfarin**
Intracranial (total)	2	4
Cerebral	2	3
Subdural	0	1
Eye haemorrhage	4	3
Gastrointestinal haemorrhage	5	8
Peritoneal/retroperitoneal hematoma	1	2
Haemarthrosis	0	3
Muscle haematoma	0	3
Other	3	4
*MedDRA – Medical dictionary for regular activities. The MedDRA preferred terms differ in some cases from the reports from the investigators to the sponsors but are more correct since in 7 cases the investigators only described the location as “other”.		

Any bleeding event was reported in 277 patients in the dabigatran group (19.4%) and 373 patients in the warfarin group (26.2%) after adjudication. The hazard ratio for dabigatran vs warfarin was 0.71 (95% CI 0.61, 0.83), with a p-value of <0.001. The ERG notes that in the breakdown of bleeding events, there was no significant difference in MBE between dabigatran and warfarin. However, in terms of MCRB, dabigatran was associated with significantly fewer events compared with warfarin (5.6% vs 10.2%, respectively; HR 0.54, 95% CI 0.41 to 0.71, p < 0.001).

Coronary events

There were 59 suspected ACS events during the study that triggered central adjudication, 20 were classified as 'definite' ACS events and three as 'likely' events by the ACS adjudication committee. Statistically significantly more patients in the dabigatran group (0.9%) compared with the warfarin group (0.2%) were reported with ACS events during the on-treatment period that were adjudicated as definite events (HR 4.35; 95% CI 1.24, 15.27. p-value 0.0217). The most common definite ACS event during treatment was MI, with nine events in the dabigatran group and one event in the warfarin group (Table 44).

Table 44. ACS events during the on treatment period in RE-MEDY (reproduced MS table 72)

Outcome	**Dabigatran** **n = 1,430**	**Warfarin** **n = 1,426**
ACS		
During treatment – n (%)	13 (0.9)	3 (0.2)
Post-treatment – n	1	5
Cardiac death – n	0	0
Myocardial infarction – n	9	1
Ischaemia/unstable angina – n	3	1
*Includes events that occurred from the day after last intake of study drug until trial termination. Abbreviations: ACS, acute coronary syndrome.		

During the post-treatment period (starting on the day after last intake of study drug), one patient in the dabigatran group and five patients in the warfarin group were reported with ACS events adjudicated as definite. MI was reported by the dabigatran patient (onset of the event was one day after last intake of study drug) and three of the warfarin patients (all events started more than 14 days after last intake of study drug).

The ERG also note that the manufacturer reports there was a slightly higher baseline prevalence of cardiac risk factors in the dabigatran treatment group than in the warfarin treatment group. A history of coronary artery disease was reported for 8.4% vs 6.1% of patients, heart failure for 4.0% vs 2.9% of patients, hypertension for 40.7% vs 36.5% of patients, and diabetes mellitus for 10.5% vs 7.6% of patients, respectively. However, the manufacturer has not presented a further breakdown of the risk factors in relation to the patients who had ACS events in RE-MEDY. The ERG is thus unsure whether these small differences in the baseline characteristics are linked to the overall incidence of ACS events in RE-MEDY.

Hepatic events

There were numerically more abnormalities in LFTs in the warfarin group compared to the dabigatran group (Table 45). However, there was no report of an assessment of statistical significance in the MS so the ERG are unsure whether any of the between group differences were statistically significant.

Table 45. Patients with potentially clinically significant abnormalities for LFT parameters in RE-MEDY (adapted from MS table 73)

Parameter	**Dabigatran n/N* (%)**	**Warfarin n/N* (%)**
ALT	26/1,411 (1.8)	30/1,402 (2.1)
AST	23/1,411 (1.6)	23/1,402 (1.6)
AP	9/1,411 (0.6)	14/1,401 (1.0)
Total bilirubin	9/1,411 (0.6)	8/1,402 (0.6)

* n is the number of patients with abnormalities of possible clinical significance, N is the number of patients with at least 1 post-baseline assessment of the respective parameter.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase.

Abnormalities in the ALT and AST values were further categorised in the MS by multiples of the ULN. The manufacturer reported that there was no significant difference between treatment groups in terms of these analyses of LFT abnormalities. In addition, the manufacturer reported that extreme LFT values (above 20 x ULN) occurred only in one patient (dabigatran group). The results of the analyses are presented in Table 46.

Table 46. Abnormal LFTs in RE-MEDY (reproduced from table 22 in the MS)

Parameter	**Dabigatran n (%)**	**Warfarin n (%)**
AST >3 x ULN	15 (1.0)	18 (1.3)
ALT >3 x ULN	24 (1.7)	26 (1.8)
ALT >3 x ULN + total bilirubin >2 x ULN	2 (0.1)	1 (0.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Dyspepsia

Details of the number of patients experiencing dyspepsia in RE-MEDY weren't provided in the MS. The ERG thus obtained further details from the CSR on the number of patients reporting dyspepsia as dabigatran has previously been associated with dyspepsia. The results reveal that there were more episodes of dyspepsia with dabigatran compared to warfarin (4.1% vs 1.9%, respectively) although there was no report of an assessment of statistical significance testing. In terms of episodes of

dyspepsia that were attributed by the investigator as drug-related, 1.2% were with dabigatran compared with 0.4% with warfarin.

4.6.4 RE-MEDY subgroup analyses

The efficacy outcomes for each strata and each of the different follow-up duration cohorts in RE-MEDY[18] are presented in Table 47. However, the manufacturer didn't provide details of the number of people in each group or any assessment of statistical significance in the MS. The results for all the cohorts and strata apart from 'no symptomatic PE without cancer' demonstrate a trend to more VTE events in the dabigatran group compared with the warfarin group.

Table 47. RE-MEDY subgroup analyses for primary efficacy outcome (VTE and VTE deaths) [FAS data set] (adapted from MS table 45 CSR table 15.2.1.1.1:2)

Subgroup	**Dabigatran**		**Warfarin**		**Hazard ratio (95% CI)**	***p*-value**
	n (%)	**N**	**n (%)**	**N**		
Cohort 1 (Planned treatment duration 18 months)	18 (2.3)	778	14 (1.8)	794	1.32 (0.66, 2.65)	NR
Cohort 2 (Planned treatment duration >18 months)	4 (1.4)	285	3 (1.1)	268	1.34 (0.30, 5.98)	NR
Cohort 3 (Planned treatment duration <18 months)	4 (1.1)	367	1 (0.3)	364	3.96 (0.44, 35.39)	NR
Symptomatic PE with cancer*	4 (16.0)	NR	2 (8.7)	NR	NR	NR
Symptomatic PE without cancer*	14 (3.0)	NR	9 (1.9)	NR	NR	NR
No symptomatic PE with cancer*	4 (11.4)	NR	3 (8.3)	NR	NR	NR
No symptomatic PE without cancer*	14 (1.5)	NR	18 (2.0)	NR	NR	NR

* Analysis for first adjudicated recurrent VTE or VTE death by baseline strata

Abbreviations used: CI, confidence interval; DVT, deep vein thrombosis; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism.

In terms of the other pre-defined subgroup analyses, the manufacturer reports that there was no significant difference in efficacy in the predefined subgroup analyses. However, no numerical results were presented in the MS. The ERG note that further subgroup data for the primary efficacy outcome are reported in the supplementary appendix to Schulman *et al*. 2013[18] and that the p value for interaction was not statistically significant for any of the subgroups reported.

Warfarin control

[redacted]

As for the RE-COVER studies, the ERG also requested the manufacturer provide data for centres with TTR <60% and those with TTR≥60%. The safety and efficacy findings (Table 48 and Table 49) are generally in keeping with the results of the whole trial population analyses reported above (Table 40). The results of this subgroup analysis suggest a trend favouring dabigatran for efficacy in centres with TTR<60% (i.e. centres with poor warfarin control have fewer VTE events with dabigatran compared with warfarin), whereas the centres with better warfarin control (TTR>60%) have fewer VTE events with warfarin compared with dabigatran.

Table 48. Hazard ratios for composite of recurrent symptomatic VTE and deaths related to VTE including components in centres with TTR < 60% and ≥60% for RE -MEDY (FAS) (MS response to clarification question A4)

Outcome	**Centres with TTR <60%**		**Centres with TTR ≥60%**	
	HR (95% CI)	P value~	HR (95% CI)	P value~
VTE and VTE related deaths	1.10 (0.42, 2.86)	0.8422	1.72 (0.79, 3.75)	0.1750
Symptomatic PE#	3.02 (0.31, 29.04)	0.3384	1.77 (0.52, 6.03)	0.3644
Symptomatic DVT	0.83 (0.28, 2.48)	0.7411	1.85 (0.68, 5.00)	0.2258
Death related to VTE	NR	NR	NR	NR
All death	0.87 (0.32, 2.40)	0.7903	0.93 (0.39, 2.19)	0.8641

Symptomatic PE includes fatal PE

~ Obtained from Cox Model with factor treatment

Abbreviations used in the table: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism

Table 49. Hazard ratio for **bleeding** events since start of any treatment in centres with **TTR** <60% and ≥60% for RE-MEDY (treated set) (MS response to clarification question A4)

Outcome	**Centres with TTR <60%**		**Centres with TTR ≥60%**	
	HR (95% CI)	P value~	HR (95% CI)	P value~
MBE	0.54 (0.18, 1.62)	0.2734	0.45 (0.19, 1.10)	0.0793
CRBE	0.44 (0.27, 0.71)	0.0007	0.67 (0.46, 0.96)	0.0310
MBE or CRBE	0.45 (0.29, 0.70)	0.0005	0.61 (0.43, 0.87	0.0058
Any bleeding	0.65 (0.50, 0.84)	0.0009	0.76 (0.62, 0.92)	0.0060
Any intracranial bleeding	0.49 (0.04, 5.39)	0.5589	0.51 (0.05, 5.68)	0.5876
Any GI bleeding	1.51 (0.71, 3.23)	0.2869	1.34 (0.76, 2.37)	0.3121

~ Obtained from Cox Model with factor treatment

Abbreviations used in the table: CI, confidence interval; CRBE, clinically relevant bleeding event; DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; MBE, major bleeding event; PE, pulmonary embolism; VTE, venous thromboembolism

Cancer

Less than 5% of patients in RE-MEDY met the definition for active cancer at baseline. Also, as discussed in Section 3.1, the ERG have concerns about the applicability of these subgroup data to the

UK population due to the differing definition of active cancer used in UK clinical practice compared with the trials' definitions.

The results suggest that there is a significantly higher frequency of recurrent VTE or VTE-related mortality among patients who had cancer compared to patients who did not have cancer. However, this was independent of the anticoagulation treatment received. In terms of the safety and efficacy of dabigatran amongst the cancer patients, the results were similar for both the dabigatran and warfarin groups (Table 50). However, the absence of a statistically significant difference between the treatment groups for all the outcomes reported is not specifically mentioned in the MS.

Table 50. Efficacy and safety endpoints in cancer patients in RE-MEDY (adapted from MS Table 92)

Cancer at any time during study	**VTE or VTE-related death[1] Patients, n/N (%)**		**MBEs[2] Patients, n/N (%)**		**MBEs or CRBEs[2.] Patients, n/N (%)**		**Any Bleeds[2] Patients, n/N (%)**	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Warfarin
No	23/1342 (1.7)	15/132 1 (1.1)	9/1342 (0.7)	21/1321 (1.6)	68/1342 (5.1)	125/1321 (9.5)	257/1342 (19.2)	332/1321 (25.1)
Yes	3/88 (3.4)	3/105 (2.9)	4/88 (4.5)	4/105 (3.8)	12/88 (13.6)	20/105 (19.0)	21/88 (23.9)	41/105 (39.0)

[1] Measured from the randomization to the end of the planned treatment period (6-36 months)
[2]Measured from the first dose of the study drug until 3 days after receipt of the last dose.

4.6.5 Summary of REMEDY results

- Dabigatran was proven non-inferior to warfarin in a population intended for long-term treatment and secondary prevention of symptomatic VTE following anticoagulant treatment for 3 to 12 months after the index acute VTE (HR, 1.44; 95% CI, 0.78 to 2.64).
- There were no statistically significant between-treatment differences for the primary or secondary efficacy endpoints in RE-MEDY.
- The overall incidence of treatment-emergent reported AEs were generally similar between dabigatran and warfarin in RE-MEDY, although the ERG note that there were numerically more episodes of dyspepsia and acute coronary syndrome events with dabigatran compared with warfarin.
- There was no significant difference in major bleeding events between dabigatran and warfarin in RE-MEDY.
- The safety and efficacy data in cancer patients suggest no significant difference between dabigatran and warfarin but the ERG recommend caution in drawing conclusions as there were few patients with active cancer in RE-MEDY.
- There was no statistically significant difference between group difference in recurrent VTE and VTE-related mortality based on index event (i.e. symptomatic PE or no

symptomatic PE; p = 0.275) in RE-MEDY.Summary and critique of secondary prevention VTE trials: RE-SONATE

4.6.1 Description of RE-SONATE trial

RE-SONATE[18] was a phase III, double-blind, randomised controlled trial comparing dabigatran 150 mg BD with placebo in patients who had completed 6 to 18 months of treatment with an oral anticoagulant treatment (VKA) for confirmed acute symptomatic VTE. The primary objective of RE-SONATE was to demonstrate superiority of dabigatran over placebo based for the composite primary endpoint of recurrent DVT or fatal or non-fatal PE (including unexplained death) during the treatment period.

RE-SONATE population

Patients were recruited for RE-SONATE from 147 sites in 21 countries. At clarification stage, the manufacturer confirmed that there were no centres or participants from the UK included in this trial. Patients were eligible if they were at least 18 years of age and had objectively confirmed, symptomatic, proximal DVT or PE that had already been treated with an approved anticoagulant or if they had received dabigatran in one of the two previous clinical trials of short-term treatment of VTE (RE-COVER or RE-COVER II)[16;17] and if they were considered to be at equipoise for the need for continued anticoagulant therapy.

In response to a clarification request the manufacturer supplied the definition used for “equipoise” in the trial: equipoise is a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. Equipoise as used in RE-SONATE refers to the fact that there is uncertainty with respect to the need for continued anticoagulation, indicating that the risk/benefit of extended treatment is not clear. The manufacturer specified two exclusion criteria which specifically relate to the equipoise criteria:

- Indication for VKA other than DVT and/or PE.
- Patients in whom anticoagulation treatment for their index PE or DVT should have been continued.

As discussed in Section 3, it is thought that the equivalent of this equipoise population in the UK would most likely be people whom currently would not receive ongoing treatment for secondary prevention of VTE. It could thus be considered that the population in RE-SONATE are a different population to that currently treated for secondary prevention of VTE in the UK.

The inclusion and exclusion criteria for RE-SONATE are listed in Table 51. In RE-SONATE the required duration of initial treatment before trial enrolment was 6 to 18 months. For patients enrolled

from RE-COVER and RE-COVER II, a point-of-care coagulometer with encrypted INR results was used to guide the transition between the studies so that the patients and investigators would remain unaware of the initial treatment.

Table 51. Inclusion/exclusion criteria of RE-SONATE (adapted from MS Table 25 and 26)

Inclusion criteria	Exclusion criteria
Objectively confirmed symptomatic uni- or bilateral DVT of the leg involving proximal veins or PE, treated with approved anticoagulant therapy, or with study drug (in RE-SONATE previous study drug was introduced as an amendment), taken for (RE-MEDY) 3 to 12 months or (RE-SONATE) 6 to 18 months at the time of screening,. Male or female, being 18 years of age or older (the age criterion was turned around as an exclusion criterion in RE-SONATE) Written informed consent for study participation.	Younger than 18 years of age Indication for VKA other than DVT and/or PE Patients in whom anticoagulant treatment for their index PE or DVT should be continued Active liver disease or liver disease decreasing survival (e.g. acute hepatitis, chronic active hepatitis, cirrhosis) or ALT >3 x ULN Creatinine clearance <30 ml/min Acute bacterial endocarditis Patients who in the investigator's judgement were perceived as having an excessive risk of bleeding, for example because of anticipated need for quinidine or other restricted medication during the treatment period. Uncontrolled hypertension (investigator's judgement) Intake of another experimental drug within the 30 days prior to randomisation into the study, with the exception of patients participating in RE-COVER trials. Life expectancy <6 months Childbearing potential without proper contraceptive measures, pregnancy or breast feeding Patients with known hypersensitivity to dabigatran or any other component of the investigational product or the placebo capsules Patients deemed unsuitable for inclusion by the investigator, because considered unreliable to comply with the requirements of the study and/or compliance with study drug administration, or because having any condition or disease which in the opinion of the investigator would not allow safe participation in the study. Patients with known active cancer

The baseline characteristics of the randomised trial population in RE-SONATE are reported in Table 52. The ERG agrees with the manufacturer's assessment that the treatment groups in RE-SONATE appear well balanced in terms of their baseline characteristics.

Table 52. Characteristics of participants in RE-SONATE across randomised groups (adapted from MS Table 28)

Characteristic	Dabigatran (n = 681)	Warfarin (n = 662)
Age – mean ± SD	56.1 ± 15.5	55.5 ± 15.1
Female sex – n (%)	300 (44.1)	298 (45.0)

Race – n (%) White Black Asian American Indian	 610 (89.6) 9 (1.3) 58 (8.5) 4 (0.6)	 585 (88.4) 14 (2.1) 60 (9.1) 3 (0.5)
Weight (kg) – mean ± SD	83.7 ± 18.0	84.0 ± 18.6
Type of index event DVT only PE only DVT and PE Neither DVT or PE	 431 (63.3) 183 (26.9) 47 (6.9) 20 (2.9)	 441 (66.6) 178 (26.9) 35 (5.3) 8 (1.2)
Cancer – n (%)	1*	2*
Treatment duration before randomisation – days	293 ± 107	299 ± 110
Enrolled from RE-COVER study - n (%) Dabigatran group Warfarin group	 7 (1.0) 8 (1.2)	 8 (1.2) 4 (0.6)
Enrolled from RE-COVER II study - n (%)	NA	NA
Exposure to study drug – days	165 ± 45	162 ± 47
*Active cancer was an exclusion criterion, and the numbers represent protocol violations. Abbreviations: DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; SD, standard deviation.		

RE-SONATE intervention and comparator

Patients in RE-SONATE were randomised 1:1 to treatment with fixed dose dabigatran or placebo via IVRS. Randomisation was stratified by centre in blocks of 4 and also within centres according to previous participation in RE-COVER. The study medications were administered using a double blind design with placebo tablets matched to the active treatments. In the MS, the manufacturer reported that “neither the patient nor the investigator was informed about the allocated treatment. Individuals involved in the conduct and assessments of the study remained blinded to the randomisation schedule until the database was locked.” (MS pages 68–69, Table 24).

The intervention under investigation in RE-SONATE was dabigatran capsules 150 mg taken orally BD and the comparator in was placebo capsules taken orally BD. Prior anticoagulant therapy was discontinued, and the study drug was started when the INR was 2.3 or lower.

RE-SONATE outcomes

The primary endpoint in RE-SONATE was a composite of objectively confirmed symptomatic recurrent DVT, fatal or non-fatal PE, and unexplained death. Secondary and safety endpoints captured in RE-SONATE are listed in Table 53, and definitions of endpoints are listed in Table 54.

At the clarification stage the manufacturer supplied some data on GI bleeds, as per NICE final scope. GI bleeding events were defined as any bleeding event with a GI bleeding site, including MBEs, clinically relevant non-major bleeding events (CRNMBE) and minor GI bleeds.

The ERG notes that the manufacturer did not report data from RE-SONATE in the MS on HRQoL or complications following deep vein thrombosis or pulmonary embolism, including PTS, heart failure and CTEPH.

The ERG considers that all other outcomes specified in the final scope issued by NICE[15] were captured in RE-SONATE and reported appropriately in the MS for this STA.

Table 53. Outcomes in RE-SONATE (adapted from MS Table 29)

	RE-SONATE
Primary endpoint	• Composite of objectively confirmed symptomatic recurrent DVT or fatal or non-fatal PE (including unexplained death)
Secondary endpoints	• Composite of recurrent DVT, recurrent non-fatal PE and fatal PE (including unexplained death) • Separate components of primary efficacy outcome
Safety endpoints	• Bleeding events • Major bleeding events (MBE) • MBE or clinically relevant bleeding events (CRBE) • Any bleeding event (major, clinically relevant and nuisance bleeds) • All deaths • Cardiovascular events (ACS, ischaemic stroke, transient ischaemic attack, non-CNS systemic embolism, vascular death) • Adverse events • Laboratory measures (especially liver function tests)
Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism	

Table 54. Definitions of bleeding events in RE-SONATE (adapted from MS Table 30)

	RE-SONATE
Major bleeding event	International Society on Thrombosis and Haematosis criteria; i.e. one or more of: • fatal bleeding • symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome • bleeding causing a fall in haemoglobin level of 20gL-1 (1.24mmolL-1) or more, or leading to transfusion of ≥2 units of whole blood or red cells.
Clinically relevant bleeding	Overt bleeding not meeting criteria for MBE but associated with medical

event	intervention, unscheduled contact with a physician, (temporary) cessation of study treatment, or associated with discomfort such as pain, or impairment of activities of daily life. Examples: • epistaxis >5 minutes duration or if repetitive or leads to an intervention • gingival bleeding if spontaneous or >5 minutes duration • macroscopic haematuria, either spontaneous or, if associated with an intervention, lasting more than 24 hours • macroscopic gastro-intestinal haemorrhage • haemoptysis, if more than a few speckled in the sputum • intramuscular haematoma • subcutaneous haematoma if >25cm2, or >100cm2 if provoked • multiple source bleeding
Other bleeding events	All other bleeding events that did not fulfil the criteria for MBE or CRBE were classified as trivial bleeds
Abbreviations: MBE, major bleeding events; CRBE, MBE or clinically relevant bleeding events	

RE-SONATE subgroup analyses

A large number of subgroup analyses were specified *a priori* and carried out on the RE-SONATE trial data (Table 55). The ERG notes that the subgroup analyses in RE-SONATE were limited to the primary efficacy outcome. In addition, the ERG notes that patients were not stratified at randomisation for any of the characteristics assessed within the subgroup analyses.

Table 55. Subgroup analyses for the primary endpoint in RE-SONATE (reproduced from MS Table 35)

Subgroups (categories)
Participation in RE-COVER study: yes, no
Age (years): <65, 65 to <75, ≥75
Gender: male, female
Race: American Indian/Alaskan National, Asia, Black/African American, Hawaiian/Pacific Isle, White
Ethnicity: Non-Hispanic/Latino, Hispanic/Latino, Missing
Geographical region: Western Europe, Central Europe, North America, Asia, Other
Qualifying event: confirmed symptomatic DVT only, confirmed symptomatic PE only, confirmed symptomatic DVT and PE, no confirmed symptomatic DVT or PE
History of multiple VTEs: 1, >1
Baseline creatinine clearance (mL/min): <30, 30 to <50, 50 to <80, ≥80, missing
Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism

RE-SONATE follow-up

The planned treatment duration was 6 months for both dabigatran and placebo. However, if 36 confirmed VTE events had occurred before all patients had completed the intended study duration, either the 3 or 6 month visit would be the final study treatment visit for all patients still treated. Therefore, the last included patients would be treated for at least 3 months. However, RE-SONATE included an extended follow-up period, after the end of treatment, of 1 year.

4.6.2 Summary statement

RE-SONATE[18] was included in the clinical effectiveness section of the MS to provide clinical data on dabigatran versus placebo for long term secondary prevention of VTE. The ERG does not consider RE-SONATE to meet the inclusion criteria for this STA based on the final scope issued by NICE as placebo/no treatment is not listed as a comparator of interest, and the population of 'equipoise' risk for recurrent VTE are not a population where routine anticoagulation would occur in UK clinical practice.

The ERG considers the inclusion and exclusion criteria for RE-SONATE to be acceptable for addressing the trial's objectives. In addition, the ERG considers the baseline characteristics of the randomised populations in RE-SONATE appear well balanced between trial arms. The intervention was dabigatran which is the focus of this STA, and the comparator placebo. The ERG considers that dabigatran vs placebo was not a comparison of interest specified in the NICE final scope.

The ERG considers that the outcome data reported from RE-SONATE appears to be consistent with the data collected in the trial. However, the ERG note that data for listed subgroup analyses were not reported in the MS.

In terms of follow-up and the statistical analysis of the data from the RE-SONATE, the ERG consider the duration of follow-up to be acceptable for the outcomes assessed and the statistical analysis plan to be suitable.

4.6.3 Description and critique of statistical approaches used in RE-SONATE

The objective of RE-SONATE[18] was to determine whether dabigatran was superior to placebo in the prevention of the composite outcome of recurrent DVT, fatal or non-fatal PE and unexplained death. According to the manufacturer's power calculation 36 primary outcome events would be required for the study to have 95% power to detect a 70% risk reduction in the dabigatran group compared to placebo (two-sided type I error = 0.05). The manufacturer did not state what the calculated treatment/follow up time would need to be or the expected % loss to follow-up. However, it was

stated that assuming a 3% frequency of primary events in the placebo group, approximately 900 people per group would be needed. In accordance with the protocol, after 36 centrally confirmed recurrent symptomatic VTE events had been reached, recruitment into the trial was stopped. At this point the number of people randomised to each group was around 600.

Results were calculated and presented as hazard ratios with a 95% CI. Results were also presented as Kaplan-Meier plots for which patients who did not experience an event were censored. The primary efficacy endpoint was also analysed as time to first event using a Cox proportional hazards model. 95% CIs were calculated using the Clopper- Pearson method, and Fisher's exact test was used to compare the 2 treatment groups.

The primary analysis in RE-SONATE was not based on the ITT population, but the FAS population, i.e. randomised patients who had taken at least one dose of study medication. In total 98.3% of the randomised population continues into the extended follow-up period. Safety analyses of patients in the extended follow-up period were conducted on the population of treated-subjects, with patients assigned according to the study medication to which they were exposed the longest.

The ERG considers the manufacturer's approach to the statistical analysis of the data in RE-SONATE to be appropriate.

4.7 Summary of results of secondary prevention VTE trials: RE-SONATE

4.7.1 RE-SONATE treatment compliance and discontinuations

A total of 1,366 patients were enrolled in RE-SONATE[18] and of these 1,353 were randomised; 685 patients to treatment with dabigatran and 668 patients to placebo. Of the randomised patients, 681 patients in the dabigatran group and 662 patients in the placebo group received at least one dose of study treatment, constituting the FAS population used for analysis. Of these 669 and 651 patients respectively completed the double-blind phase, which included the treatment period and 30-day follow-up visit. Thus, the number of patients who did not complete the double-blind phase was relatively low and even between the treatment arms (1.8% in the dabigatran group and 1.7% in the placebo group). However, according to the manufacturer's response to clarification questions 10.4% of patients in the dabigatran group compared to 15.0% of patients on placebo discontinued treatment prematurely.

The vast majority of patients completed the 6 months study duration in both groups; 91.3% and 94.6% for dabigatran and placebo respectively. However a small percentage had their last follow-up visit at 3

months (8.7% on dabigatran and 5.4% on placebo) because the pre-defined number of primary efficacy events was reached before all patients had completed the intended study duration.

1,330 patients (treated and untreated) continued into the extended follow-up period, comprising 1,323 (98.5%) of the 1,343 patients in the FAS population (dabigatran: 98.7%; placebo: 98.3%) and 7 of the 10 patients who were randomised but not treated. The manufacturer did not state how many of these patients were followed up for the full duration of the extended follow-up period.

4.7.2 RE-SONATE treatment effectiveness results

Dabigatran demonstrated superiority to placebo (p<0.001) for the prevention of recurrent objectively confirmed symptomatic DVT or fatal or non-fatal PE, including unexplained death (HR 0.08; 95% CI: 0.02 to 0.25).[18] The result of RE-SONATE for the composite primary efficacy outcome is presented in Table 56. At the end of the extended follow-up of 12 months dabigatran still showed a statistically significant reduction in recurrent VTE and unexplained death (HR 0.61; 95% CI: 0.42 to 0.88).

Table 56. RE-SONATE primary efficacy outcome (reproduced from MS Table 47)

	Dabigatran **n = 681**	**Placebo** **n = 662**
Patients with event*, n (%)	3 (0.4)	37 (5.6)
Hazard ratio (95% CI)	0.08 (0.02, 0.25)	
p-value for superiority	<0.001	
*One subject (placebo group) had a symptomatic centrally confirmed DVT and PE on the same day Abbreviations: CI, confidence interval.		

Results for all secondary efficacy outcomes were consistent with the primary endpoint in RE-SONATE (Table 57). For all component events, the frequency was consistently lower in the dabigatran arm than the placebo arm.

Table 57. RE-SONATE secondary efficacy outcomes (adapted from MS Table 48)

Outcome	**Dabigatran** **n = 681**	**Placebo** **n = 662**	**Hazard ratio (95% CI), p-value**

Recurrent VTE excluding unexplained deaths, n (%)	3 (0.4)	35 (5.3)	0.08 (0.03, 0.27)
Symptomatic DVT, n (%)	2 (0.3)	23 (3.5)	p < 0.0001
Symptomatic non-fatal PE, n (%)	1 (0.1)	14 (2.1)	NR
Unexplained deaths, n (%)	0 (0.0)	2 (0.3)	NR
Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; NR, not reported.			

4.7.3 RE-SONATE safety and adverse events

The AE data for RE-SONATE[18] were reported for the treated population. The overall incidence of AEs (which included bleeding events and efficacy outcome events) was comparable between dabigatran and placebo, though the incidence of serious AEs and AEs leading to discontinuations were lower in the group treated with dabigatran than for the placebo group (Table 58).

The most frequently reported AE for patients in the dabigatran treatment group were GI disorders, which were reported by 16.5% of patients receiving on dabigatran and by 8.8% of patients receiving placebo. The most frequently reported serious AEs were respiratory, thoracic and mediastinal disorders (dabigatran: 1.0%; placebo: 3.5%) and vascular disorders (dabigatran: 0.4%; placebo: 2.6%).

Table 58. Summary of adverse events in RE-SONATE (reproduced from MS Table 75)

Outcome	**Dabigatran** **n = 681**	**Placebo** **n = 662**
Patients with any AE – n (%)	346 (50.6)	324 (49.2)
Patients with serious AEs – n (%)	47 (6.9)	60 (9.1)
AEs leading to discontinuation – n (%)	50 (7.3)	81 (12.3)
Abbreviations: AE, adverse event.		

Bleeding events

All bleeding events were adjudicated by an independent committee that was blinded to the treatment allocation of patients. Bleeding events were classified as MBE, CRBE, or trivial bleeding events. The definitions of MBE and CRBE were consistent with the definitions used in the active-controlled trials: RE-COVER, RE-COVER II and RE-MEDY.

The incidence of any bleeding event, including MBEs, CRBEs and trivial bleeding events, was significantly higher in the dabigatran group (10.5%) than in the placebo group (5.9%) (HR 1.82; 95% CI: 1.23 to 2.68; p=0.003). There were significantly more major or clinically relevant non major bleeds (MCRBs) in the dabigatran group than in the placebo group (HR 2.92; 95% CI: 1.52 to 5.60, p = 0.001). The ERG noted that there was a slight discrepancy in the number of MCRBs reported in the

text and table presented in the MS and the resulting HR (one patient in the placebo group; HR remains statistically significant); the ERG have used the data reported in the Schulman publication as these correlate with the end of treatment (i.e. last day of study drug intake).The results for bleeding events in RE-SONATE are presented in Table 59. MBE during the treatment period in RE-SONATE (adapted from MS Table 76)

Table 59. MBE during the treatment period in RE-SONATE (adapted from MS Table 76)

Bleeding event	**Dabigatran n = 684**	**Placebo n = 659**	**Hazard ratio (95% CI)**	**p value**
MBE – n (%)	2 (0.3)	0 (0.0)	Clopper-Pearson/Fisher's exact test p = 0.4998	
MCRB – n (%)	36 (5.3)	12 (1.8)	2.92 (1.52, 2.68)	0.001
Any bleeding event – n (%)	72 (10.5)	39 (5.9%)	1.82 (1.23-2.68)	0.003
Abbreviations: CI, confidence interval; MBE, major bleeding event; MCRB, major or clinically relevant non major bleeding				

According to the MS the most frequently reported CRBEs were rectal bleeds for patients receiving dabigatran (1.9%). For placebo, the most common CRBE sites were urogenital (0.5%) (Table 60). In terms of any bleeding event, it is reported in the MS and by Schulman *et al.*[18] that rectal bleeding occurred in 19 patients (2.8%) in the dabigatran group and in five patients (0.8%) in the placebo group. Schulman *et al.* reported that the occurrence of 'any bleeding events' at other sites were similar between the dabigatran and placebo treatment groups. No further numerical data were reported in the MS or Schulman *et al.* publication.

Table 60. CRBEs during the treatment period in RE-SONATE (reproduced from MS Table 77)

Bleeding site	**Dabigatran n = 684**	**Placebo n = 659**
Rectal	13 (1.9)	2 (0.3)
Urogenital	5 (0.7)	3 (0.5)
Gastrointestinal	5 (0.7)	2 (0.3)
Nasal	4 (0.6)	2 (0.3)
Pulmonary	3 (0.4)	2 (0.3)
Gingival	2 (0.3)	0 (0.0)
Uterus	2 (0.3)	1 (0.2)
Skin	2 (0.3)	1 (0.2)
Intramuscular	1 (0.1)	0 (0.0)

At the clarification stage the manufacturer provided data on GI bleeding events for which there was no statistically significant difference between patients in the dabigatran and placebo groups (Table 61).

Table 61. Hazard ratios until end of treatment for gastrointestinal bleed since start of any treatment in RE-SONATE (MS response to clarification question A5)

Outcome	Dabigatran vs placebo HR (95% CI)	P value*
GI bleed	2.38 (0.46, 12.27)	0.3000
*P value for superiority Abbreviations used in the table: CI, confidence interval; HR, hazard ratio		

Cardiovascular events

The overall incidence of cardiovascular events during the treatment period was low and comparable between the dabigatran and the placebo groups (Table 62).

Table 62. Summary of cardiovascular events during the treatment period in RE-SONATE (reproduced from MS Table 78)

Parameter	Dabigatran n = 684	Placebo n = 659
Patients with CV events – n (%) [number of events]	3 (0.4)	2 (0.3)
NSTEMI	0 (0.0)	1 (0.2)
STEMI	1 (0.1)	0 (0.0)
UA	0 (0.0)	0 (0.0)
TIA	2 (0.3)	0 (0.0)
Ischaemic stroke	0 (0.0)	1 (0.2)
Non-CNS systemic embolism	0 (0.0)	0 (0.0)
Abbreviations: CV, cardiovascular; CNS, central nervous system; NSTEMI: non ST−segment elevation myocardial infarction; STEMI: ST−segment elevation myocardial infarction; UA: unstable angina; TIA: transient ischaemic attack.		

Hepatic events

The two treatment groups were comparable with regard to the incidence of elevated LFT values on treatment (Table 63).

Table 63. Summary of hepatic events during the treatment period in RE-SONATE (reproduced from MS Table 79)

Parameter	Dabigatran n = 684	Placebo n = 659*
ALT		

≤ 2 x ULN	650 (95.0)	625 (98.9)
> 2 x ULN	14 (2.0)	5 (0.8)
> 3 x ULN	4 (0.6)	0 (0.0)
AST		
≤ 2 x ULN	657 (96.1)	630 (95.7)
> 2 x ULN	7 (1.0)	6 (0.9)
> 3 x ULN	2 (0.3)	2 (0.3)
Total bilirubin		
≤ 2 x ULN	664 (97.1)	634 (96.5)
> 2 x ULN	1 (0.1)	1 (0.2)
> 3 x ULN	0 (0.0)	0 (0.0)
*n = 658 for AST measurements. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.		

4.7.4 RE-SONATE subgroup analyses

In the MS, the manufacturer listed several pre-specified subgroup analyses for the primary outcome in RE-SONATE.[18] However, no results from subgroup analyses were presented in the MS. At the clarification stage the manufacturer provided results for the subgroup of geographical region (Western Europe) for the primary outcome and for bleeding events.

No patients in the dabigatran group had recurrent symptomatic VTE or a VTE related death in the Western Europe subgroup compared to 24 patients in the placebo group (Table 64).

Table 64. Frequency for composite of recurrent symptomatic VTE and deaths related to VTE, including components, in Western Europe for RE-SONATE (adapted MS response to clarification question A4)

Outcome	Dabigatran	Placebo
N	374	367
VTE and VTE related deaths	0	24
Symptomatic PE*	0	11
Symptomatic DVT	0	15
Death related to VTE	0	0
All death	0	0
* Symptomatic PE includes fatal PE.		

In the subgroup of patients in Western Europe, there incidence of MBEs and CRBEs as well as any bleed was statistically significant between the treatment groups, with more bleeds in patients treated with dabigatran than in patients on placebo (Table 65).

Table 65. Frequency, yearly event rate and hazard ratio for bleeding events since start of any treatment in Western Europe from RE-SONATE(MS response to clarification question A4)

Outcome	Dabigatran vs placebo HR (95% CI)	P value~
MBE	NR	NR
CRBE	2.45 (1.08, 5.57)	0.0319
MBE or CRBE	2.45 (1.08, 5.57)	0.0319
Any bleeding	1.82 (1.11, 3.00)	0.0179
Any intracranial bleeding	NR	NR
Any GI bleeding	0.96 (0.13, 6.79)	0.9649
~ Obtained from Cox Model with factor treatment Abbreviations used in the table: CI, confidence interval; CRBE, clinically relevant bleeding event; DVT, deep vein thrombosis; GI, gastrointestinal; HR, hazard ratio; MBE, major bleeding event; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism		

The ERG note that the results for the Western Europe subgroup are in keeping with the whole trial population for RE-SONATE. The ERG also notes that this was a non-randomised subgroup and results should thus be interpreted with caution.

4.7.5 Summary of RE-SONATE results

- Dabigatran demonstrated superiority compared with placebo for the prevention of recurrent objectively confirmed symptomatic DVT or fatal or non-fatal PE, including unexplained death in RE-SONATE (HR 0.08; 95% CI: 0.02 to 0.25).
- The results for all secondary efficacy outcomes were consistent with the primary endpoint in RE-SONATE, with fewer events with dabigatran compared with placebo.
- The overall numbers of adverse events were similar for dabigatran and placebo (RE-SONATE). However, dabigatran was associated with statistically significantly more bleeding events (any bleeding event: HR 1.82; 95% CI: 1.23 to 2.68; p=0.0027).

4.8 Description and critique of the indirect comparisons and network meta-analyses

4.8.1 Methods

The manufacturer conducted both adjusted indirect comparisons (AICs) and network meta analyses (NMAs) to provide relative treatment effect estimates between dabigatran and rivaroxaban for efficacy and safety endpoints. The same searches used to identify trials were used as those described above in Section 4.1.1. However, the inclusion/exclusion criteria differed. The inclusion/exclusion criteria for the AIC and NMA are detailed in Table 66.

Table 66. Inclusion and exclusion criteria (adapted from MS table 57)

	Inclusion	Exclusion

Population	Patients with DVT and PE receiving treatment or secondary prevention for recurrent DVT and PE	Patients receiving primary prophylaxis for prevention of a first DVT or PE event
Intervention	Dabigatran, rivaroxaban Warfarin (secondary prevention trials only) UFH or LMWH (all agents, including, but not limited to, enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin) given for more than 10 days, i.e., long-term or extended treatment only (trials investigating acute parenteral treatment with heparin, e.g., for 5-10 days followed by a VKA, were not included as heparin trials) Fondaparinux (given for 7 or more days)	Studies that do not include any of the interventions in the inclusion criteria list
Comparator	Dabigatran Rivaroxaban Warfarin UFH LMWH (including enoxaparin, dalteparin, tinzaparin, bemiparin, and nadroparin) Fondaparinux	Other comparators
Outcomes	Recurrent DVT or PE Bleeding Death	Regression rate of persistent echogenic masses
Study design	Randomised, controlled prospective clinical trials Non-randomised, controlled prospective clinical trials Long-term follow-up studies (e.g., open-label follow-up studies)	Prospective observational studies (e.g., phase 4 studies) Preclinical studies Phase 1 studies Prognostic studies Retrospective studies Case reports Commentaries and letters (publication type) Consensus reports Reviews, systematic reviews, and meta-analyses (however, reference lists were reviewed for any relevant studies)

The methods used for abstract appraisal, study inclusion, data extraction and quality assessment were the same as those reported in Section 4.1.

There were no head-to-head trials identified comparing dabigatran to rivaroxaban and so the manufacturer conducted an indirect comparison using the available trial data. There are several different methods commonly used to compare treatments that have not been investigated in head-to-head trials. The manufacturer chose to use two different approaches, AIC and NMA (also known as mixed treatment comparison [MTC]). The manufacturer reported only the results of the AIC in the

MS. However they also provided the data and results used in the NMA in a separate report. The manufacturer's rationale for presenting the AIC results was: ".... a mixed-treatment comparison of all trials was performed. However, the results of this approach were not used further since the evidence network did not include mixed evidence from head-to-head trials and indirect evidence and hence did not add additional information." The ERG does not consider this to be a justification for using AIC over NMA as there were more than 2 interventions of interest in each NMA and so using an AIC methodology limits the ability to compare outcomes between the different treatments. This is because the resulting point estimates from multiple AICs, despite using the same baseline treatment, are not directly comparable. In contrast, the resulting point estimates for different treatments from an NMA are comparable. The ERG thus considers the results of the manufacturers NMA to be of potential importance and has discussed them further in Section 4.8.

The ERG agrees with the manufacturer's description of an AIC: "Adjusted indirect comparison (AIC) is a simple and transparent method that requires an identical common comparator across trials to compare the treatments of interest. This method can be used to form indirect comparisons between treatments for different types of effect estimates, for example, RR, HR, and mean difference." And that: "The AIC provides an estimate of the relative efficacy and safety of competing interventions that have not been compared directly, whilst preserving randomisation and retaining the strengths of the underlying RCTs."

The manufacturer used the Bucher method[27] to conduct their AICs. Where applicable the manufacturer used random effects meta-analyses to generate pooled estimates for head-to-head trials comparing the same treatments and then used these data in the AIC.

In terms of the NMA, the manufacturer used a frequentist approach with mixed effects regression models developed in SAS to perform the NMA. The manufacturer reported that the models were flexible in the sense that if confronted with insufficient data, they would fail to estimate the random interaction term and automatically resolve to a fixed effects model.

AIC and NMA were performed by the manufacturer to provide safety and efficacy comparative effect estimates for dabigatran versus rivaroxaban for acute VTE treatment, and also separately for secondary prevention of VTE. In addition, the manufacturer conducted subgroup analyses based on index event (DVT or PE), risk of recurrent VTE (high risk/equipoise risk for secondary prevention trials only) and presence of active cancer at baseline.

4.8.2 Outcomes reported in the AICs and NMAs

The outcomes of interest reported in the AICs and NMAs were:

- recurrent VTE, defined as the composite of recurrent VTE and VTE-related mortality;

- major bleeding;
- composite bleeding endpoint consisting of major or clinically relevant bleeding (MCRB).

Bleeding that was not clinically relevant (minor or nuisance bleeds) was not included as an outcome in these analyses.

4.8.3 Studies included in the analyses

Table 67 provides a summary of the key trials that were included in the analyses. The manufacturer also conducted quality assessments for each of the trials. The quality assessments were reported in the MS, but due to time constraints the ERG was unable to validate all of them. However, the ERG notes that in general the manufacturer assessed the trials to be of reasonable or unclear quality.

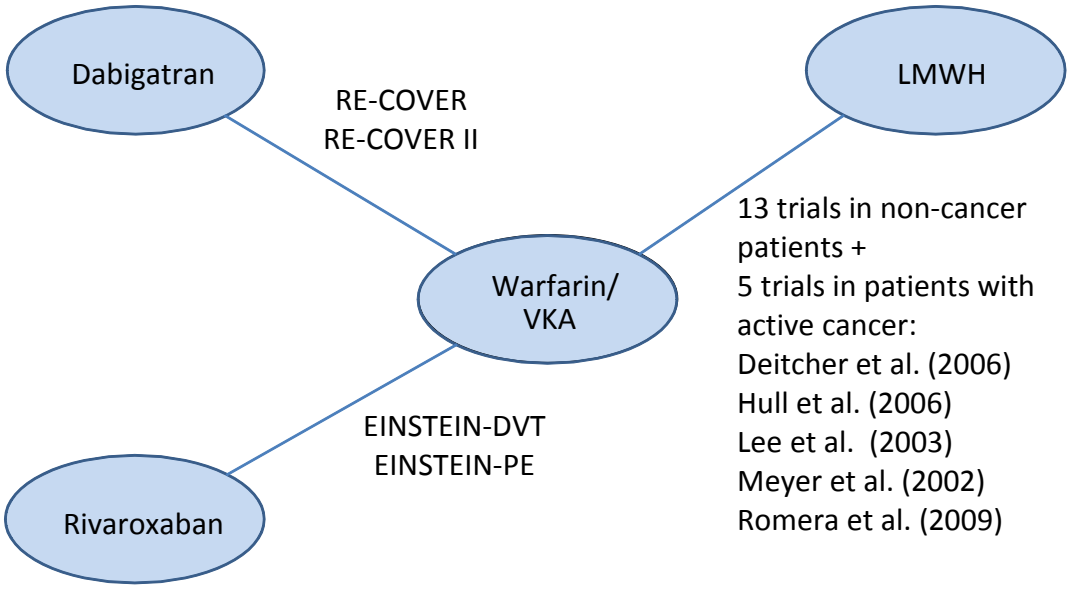
Table 67. Summary of trials included in analyses

	Treatments of Interest					**Endpoints of Interest**		
Trial	Dabigatran	Rivaroxaban	Warfarin	Placebo	Low Molecular-Weight	Recurrent VTE	Clinically Relevant Bleeds	Major Bleeds
VTE Treatment								
RE-COVER[16]	✓		✓			✓	✓	✓
RE-COVER II[17]	✓		✓			✓	✓	✓
EINSTEIN-DVT[28]		✓	✓			✓	✓	✓
EINSTEIN-PE[29]		✓	✓			✓	✓	✓
Deitcher et al. (2006)[30]			✓		✓	✓		✓
Hull et al. (2006)[31]			✓		✓	✓		✓
Lee et al. (2003)[32]			✓		✓	✓		✓
Meyer et al. (2002)[33]			✓		✓	✓		✓
Romera et al. (2009)[34]			✓		✓	✓		✓
VTE Secondary Prevention								
RE-SONATE[18]	✓			✓		✓	✓	✓
RE-MEDY[18]	✓		✓			✓	✓	✓
EINSTEIN-Extension[35]		✓		✓		✓	✓	✓
Cancer DACUS[36]				✓	✓	✓		✓
Kearon et al. (1999)[37]			✓	✓		✓		✓
WODIT (Agneli 2001)[38]			✓	✓		✓		✓
WODIT-PE (Agneli 2003)[39]			✓	✓		✓	✓	✓
DURAC (Schulman 1997)[40]			✓	✓		✓		✓
Faraj et al. (2004)[41]			✓	✓		✓		✓

Acute treatment

The network diagram for trials investigating acute treatment of DVT and PE is presented in Figure 6.

Figure 6. Network diagram: acute treatment of DVT and PE



LMWH = Low molecular-weight heparin; VKA = vitamin K antagonist
[a] Patients received acute parenteral treatment (e.g., 5-10 days of LMWH or UFH) prior to the named intervention.

The key AICs presented by the manufacturer to address the NICE final scope for acute treatment of VTE were:

- dabigatran vs rivaroxaban via warfarin; and
- dabigatran vs LMWH via warfarin in cancer patients.

The data for dabigatran vs warfarin in the AIC for dabigatran vs rivaroxaban (whole population) was from a pooled analysis of the RE-COVER and RE-COVER II studies (discussed in Section 4.4).

In terms of the rivaroxaban trials included in the analysis for acute treatment of DVT and PE, Einstein-DVT[28] and Einstein-PE[29], they were both open-label phase III trials that randomised patients to either rivaroxaban (15mg twice daily for the first 3 week, followed by 20mg once daily) or subcutaneous (SC) body-weight-adjusted enoxaparin (1mg/kg twice daily) for at least 5 days plus a VKA, either warfarin or acenocoumarol, for the treatment of recurrent acute symptomatic DVT or PE. Treatment duration was 3, 6 or 12 months.

As the Einstein studies included a mix of VKAs with no subgroup data reported for warfarin, it was assumed that all VKAs were therapeutically equivalent in the analyses. In addition, as discussed in Section 3, all initial parenteral treatments (e.g. LMWH) were assumed to have equal efficacy in the AICs and MTCs.

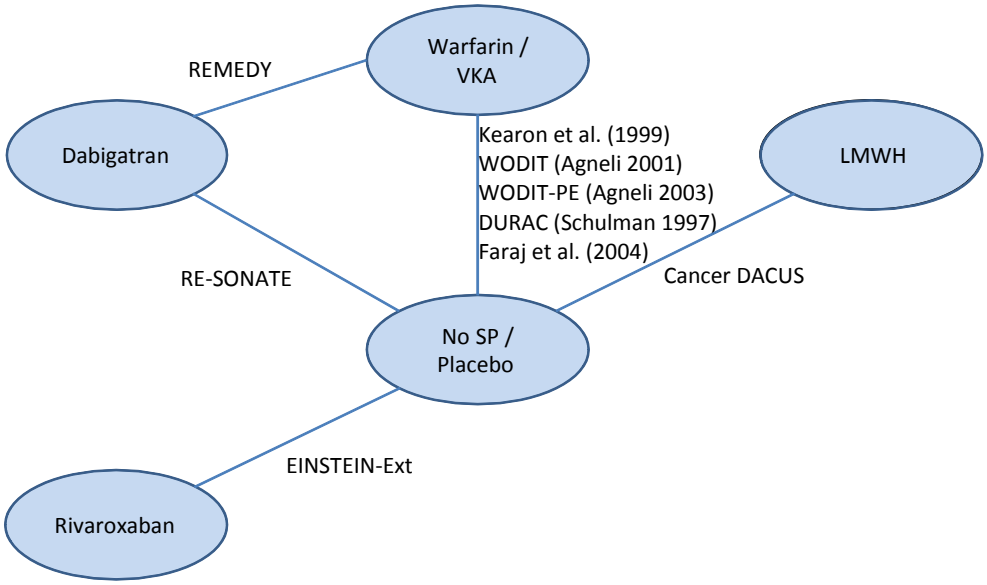
In terms of the subgroup of people with cancer requested in the NICE final scope for acute treatment of DVT and PE, the manufacturer conducted AICs of dabigatran with LMWH monotherapy using adjusted-dose warfarin as the common comparator for the treatment of DVT and PE. The treatment effect estimates for LMWH monotherapy versus warfarin were obtained by meta-analysis of 5 trials in which LMWH monotherapy was compared to warfarin in patients with active cancer.[30-34] The treatment effect estimates for dabigatran versus warfarin were obtained from a meta-analysis of the cancer subgroup data from RE-COVER and RE-COVER II. However, the comparison of dabigatran versus rivaroxaban via warfarin in cancer patients requested in the NICE final scope was not reported. The ERG requested further clarification from the manufacturer on this, as discussed in Section 3. The ERG disagrees with the manufacturer's response to clarification and considers that there are sufficient data to enable a comparison of dabigatran vs rivaroxaban for the acute treatment of VTE in cancer patients.

In terms of the differences between the comparators in the manufacturer's AICs and NMAs for acute treatment of VTE, 13 additional trials were included for warfarin vs LMWH in non-cancer patients to provide data for LMWH. However, the ERG do not consider these essential as LMWH in non-cancer patients was not a comparator of interest in the NICE final scope for this STA.

Secondary prevention of VTE

The network diagram for trials investigating secondary prevention of DVT and PE is presented in Figure 7.

Figure 7. Network diagram: secondary prevention of DVT and PE



Ext = extension; LMWH = low molecular-weight heparin; SP = secondary prevention; VKA = vitamin K antagonist

The key AICs presented by the manufacturer to address the NICE final scope for long term secondary prevention of VTE were:

- dabigatran vs rivaroxaban via placebo; and
- dabigatran vs LMWH via placebo in cancer patients.

Einstein-Extension[35] was the only rivaroxaban study included in the analyses to provide data on the secondary prevention of recurrent DVT and PE. It was a phase III, randomised, placebo-controlled, double-blind trial designed to assess the relative efficacy and safety of rivaroxaban 20mg in the prevention of recurrent symptomatic DVT or PE in patients who had completed 6 to 12 months of rivaroxaban or VKA treatment for an acute episode of VTE.

For the secondary prevention of recurrent VTE indication in patients with active cancer, AIC of dabigatran with LMWH monotherapy was performed using placebo as the common comparator. There was one trial identified and included for the comparison of LMWH monotherapy versus placebo in patients with active cancer, the Cancer DACUS trial.[36] The dabigatran versus placebo data from RE-SONATE trial was included in the analysis rather than any long-term follow-up data from RE-MEDY. The ERG considers this to be a flaw in the analysis as cancer patients were actively

excluded from RE-SONATE. In addition, as discussed in Section3.1, the ERG have concerns that the definition of active cancer used in the dabigatran trials was too broad compared with standard UK clinical practice and that used in Cancer Dacus. This would thus likely bias the efficacy results in favour of dabigatran as they are a lower risk population for VTE events. In addition, as discussed in Section3, the manufacturer did not perform an AIC or MTC for dabigatran vs rivaroxaban in long-term secondary prevention of VTE in people with active cancer. The ERG considers the manufacturer's decision to omit rivaroxaban as a comparator in people with cancer for secondary prevention of VTE to be appropriate based on the lack of available published data.

In terms of the differences between the comparators in the manufacturer's AICs and NMAs for secondary prevention of VTE, 6 additional trials were included for 2 additional comparisons. These comprised of 5 warfarin vs placebo trials in non-cancer patients and the dabigatran vs warfarin data from RE-MEDY.

4.8.4 Heterogeneity

The manufacturer performed the following tests and analyses of the data to assess and account for heterogeneity:

- compared study design of the trials included in the meta-analyses;
- assessed [NMA] model fit using the "reduced chi-squared" statistic, i.e. the Pearson chi-square divided by the degrees of freedom. Estimates of the reduced chi-squared statistic close to 1.0 indicate a well-fitting model. Values much greater than 1 indicate persisting heterogeneity within the data. Values considerably less than 1 indicate a saturated model;
- examined heterogeneity within the direct meta-analysis using the I2 and chi2 tests of heterogeneity and by inspection of the Forest plots;
- compared meta-analysis results with results from head-to-head comparison trials.

The manufacturer reported that the main sources of heterogeneity among the trials were:

- type of index VTE (DVT and PE) (acute prevention trials only);
- presence of risk factors for recurrent VTE (e.g. the LMWH trials studies patients with active cancer);
- duration of treatment and/or follow-up;
- time in the target INR range for the warfarin/VKA arm.

The manufacturer reported that the primary analyses included trials without adjustment for between-trial heterogeneity, despite their differences in things such as those mentioned above. The reasons that the manufacturer did not adjust for between-trial heterogeneity using covariates were as follows:

- some important sources of heterogeneity could not be reliably represented numerically (e.g., underlying risk);
- lack of variability within covariates to capture heterogeneity would generate unreliable model estimates (e.g., prior VTE history, proportion of cancer patients);
- due to paucity of trial data, the model could not support multiple covariates to adjust for multiple sources of heterogeneity.

However, the manufacturer reports that sensitivity/subgroup analyses were performed to explore the impact/importance of trial heterogeneity. These analyses included:

- type of index VTE, i.e. DVT, PE or both (acute treatment analyses);
- cancer patient population, i.e. trials with cancer only patients (acute treatment and secondary prevention analyses).

The ERG notes that these subgroups are consistent with the subgroups requested in the NICE final scope for this STA. However, the ERG notes that the manufacturer presents no results for dabigatran versus rivaroxaban in the cancer patient population.

4.8.5 Results for acute treatment

The meta-analysis data used in the manufacturers AIC for acute treatment of VTE are presented in Table 68 and the results of the AIC are presented in Table 69.

The results of the equivalent NMA analysis are presented in Table 70. The ERG notes that the results of both the AIC and NMA are similar. The results are all statistically non-significant. However, they suggest a trend towards fewer VTE events and fewer major bleeds with rivaroxaban compared with dabigatran. The results of both the AIC and NMA for dabigatran versus warfarin were consistent with the results of the RE-COVER trials.

Table 68. Trial data and meta-analysis results used in the AIC for acute treatment (adapted from MS table 58)

	Treatment	**Recurrent VTE**		**Clinically Relevant Bleeds**		**Major Bleeds**	
Trial	Comparison	Hazard Ratio (95% CI)	Relative Risk (95% CI)	**Hazard Ratio (95% CI)**	**Relative Risk (95% CI)**	**Hazard Ratio (95% CI)**	**Relative Risk (95% CI)**
RE-COVER	Dabigatran vs Warfarin	1.05 (0.65, 1.70)	1.05 (0.66, 1.70)	0.63 (0.47, 0.84)	0.64 (0.48, 0.85)	0.82 (0.45, 1.48)	0.83 (0.46, 1.49)
RE-COVER II	Dabigatran vs Warfarin	1.13 (0.69, 1.85)	1.14 (0.70, 1.85)	0.62 (0.45, 0.84)	0.63 (0.47, 0.85)	0.69 (0.36, 1.32)	0.69 (0.36, 1.32)
RE-COVER meta-analysis		1.09 (0.77, 1.54)	1.10 (0.78, 1.54)	0.63 (0.51, 0.77)	0.63 (0.51, 0.78)	0.76 (0.49, 1.18)	0.76 (0.49, 1.18)

Heterogeneity P-value (I^2)		0.83 (0%)	0.82 (0%)	0.94 (0%)	0.97 (0%)	0.70 (0%)	0.67 (0%)
EINSTEIN-DVT	Rivaroxaban vs Warfarin	0.68 (0.44, 1.04)	0.70 (0.46, 1.07)	0.97 (0.76, 1.22)	1.00 (0.80, 1.26)	0.65 (0.33, 1.30)	0.70 (0.35, 1.38)
EINSTEIN-PE	Rivaroxaban vs Warfarin	1.12 (0.75, 1.68)	1.13 (0.76, 1.69)	0.9 (0.76, 1.07)	0.91 (0.77, 1.07)	0.49 (0.31, 0.79)	0.50 (0.31, 0.80)
EINSTEIN meta-analysis		0.88 (0.54, 1.43)	0.90 (0.56, 1.43)	0.92 (0.80, 1.06)	0.94 (0.82, 1.07)	0.54 (0.36, 0.79)	0.56 (0.38, 0.82)
Heterogeneity P-value (I^2)		0.10 (63.7%)	0.11 (61.9%)	0.62 (0%)	0.47 (0%)	0.50 (0%)	0.43 (0%)

VTE = venous thromboembolism; Clinically relevant bleeds = major bleeds and non-major clinically-relevant bleeds; CI = Confidence Interval.

If a cell count is 0 (i.e. 0 events), 0.5 is added to both cell counts (outcome risk in a given treatment arm)- this adjustment is only applied to relative risk data.

Table 69. AIC estimates for dabigatran versus rivaroxaban for the acute treatment of DVT and PE (adapted from MS table 59)

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
				[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]		[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

[redacted]

Table 70. NMA estimates of relative treatment effects acute analysis (data from MS ref 33, meta-analysis report)

Outcome (treatment analysis)	Population	Dabigatran vs Rivaroxaban		Dabigatran vs Warfarin		Dabigatran vs LMWH	
		RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
Recurrent VTE	Whole population	1.22 (0.59, 2.52)	0.485	1.10 (0.66, 1.81)	0.655	1.83 (1.03, 3.26)	0.042
	Active cancer	NA	NA	0.75 (0.00, 3246.0)	0.738	1.54 (0.00, 9232.7)	0.641
Major Bleeds	Whole population	1.36 (0.39, 4.74)	0.449	0.76 (0.36, 1.61)	0.336	0.96 (0.43, 2.16)	0.912
	Active cancer	NA	NA	1.62 (0.23, 11.21)	0.525	1.52 (0.18, 13.06)	0.616
Clinically Relevant Bleeds*	Whole population	0.68 (0.14, 3.36)	0.198	0.63 (0.16, 2.46)	0.146	NA	NA

*NMA estimates for clinically relevant bleeds not reported for the active cancer subgroup

Abbreviations used in table: CI, confidence interval; LMWH, low molecular weight heparin; NA, not applicable; RR relative risk; VTE, venous thromboembolism

4.8.6 Results for secondary prevention of DVT and PE

The results of the AIC for secondary prevention of VTE are presented in Table 71 and the results of the equivalent NMA analysis are presented in Table 72. The manufacturer used only RE-SONATE[18] in the AIC rather than both RE-MEDY[18] and RE-SONATE. In the NMA reported in a separate report provided by the manufacturer, an analysis using both RE-MEDY and RE-SONATE was conducted (whole population) and an analysis with just RE-SONATE (low risk/equipoise). The ERG considers the population of RE-SONATE to be most similar to the population of EINSTEIN-ext,[35] the rivaroxaban trial in the analyses. However, the ERG consider RE-MEDY to be most representative of the UK population for whom secondary prevention of VTE with oral anticoagulants would be required.

[redacted]

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[redacted] 71 [redacted]

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		[redacted]		[redacted]		
[redacted]						

Table 72. NMA estimates of relative treatment effects in secondary prevention analysis (data from MS reference 33, meta-analysis report)

Outcome (prevention analysis)	Population	Dabigatran vs Rivaroxaban		Dabigatran vs Warfarin		Dabigatran vs LMWH	
		RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
Recurrent VTE	Whole population	0.93 (0.02, 45.47)	0.964	0.69 (0.07, 7.07)	0.697	0.27 (0.01, 13.45)	0.412
	Equipoise/low risk	0.39 (0.00, 46.35)	0.610	0.25 (0.01, 10.40)	0.357	NA	NA
	Equipoise/Low Risk + No Extended Follow Up*	0.39 (0.00, 4580.4)	0.426	0.68 (0.00, 12676)	0.710	NA	NA
Major Bleeds	Whole population	0.19 (0.00, 1.1E8)	0.487	0.55 (0.01, 47.51)	0.339	0.59 (0.00, 145782)	0.681
	Equipoise/low risk	0.49 (0.00, 566E9)	0.798	1.52 (0.00, 1.63E9)	0.840	NA	NA
	Equipoise/Low Risk + No Extended Follow Up*	0.49 (0.00, 522E9)	0.798	1.45 (0.00, 1.98E9)	0.860	NA	NA
Clinically Relevant Bleeds	Whole population	0.42 (0.00, 17414)	0.486	0.70 (0.00, 736.56)	0.629	NA	NA
	Equipoise/low risk	0.57 (0.00,	0.457	1.69 (0.00,	0.569	NA	NA

		291.51)		6875.0)			
	Equipoise/Low Risk + No Extended Follow Up*	0.57 (0.00, 250.98)	0.449	NA	NA	NA	NA
* No extended follow up = follow up does not exceed study treatment period by more than 30 days. Abbreviations used in table: CI, confidence interval; LMWH, low molecular weight heparin; NA, not applicable; RR relative risk; VTE, venous thromboembolism							

4.8.7 Dabigatran versus LMWH monotherapy in patients with active cancer

For acute treatment, the manufacturer reported that the results of the AIC suggested no significant differences in terms of efficacy and safety between dabigatran and LMWH monotherapy in the subgroup of patients with active cancer. However, numerical results were not reported in the MS. As mentioned previously, the number of patients with active cancer at baseline or during follow-up in the RE-COVER and RE-COVER II trials was small (approximately 5% of randomised patients).[25;26] In addition, as discussed in section 3.1, the ERG has concerns about the definition of active cancer being too broad in the RE-COVER trials and thus recommends caution in drawing any conclusions from these data.

The manufacturer did not present the results from either an AIC or NMA for dabigatran versus LMWH in secondary prevention of VTE in cancer patients.

In addition, no data were presented in the MS for dabigatran versus rivaroxaban in cancer patients.

4.9 Additional work on clinical effectiveness undertaken by the ERG

As part of the evaluation, the ERG carried out an exploratory NMA of the acute treatment and secondary prevention of VTE based on the trials presented in the MS. In addition, for the population of people with cancer, the ERG identified trials using the manufacturer's submissions and ERG reports for the rivaroxaban STAs in DVT and PE acute treatment and secondary prevention (TA 261 and TA 287). The ERG's exploratory work focused on those outcomes that inform the health economic analysis (i.e. VTE recurrence, major bleed, clinically relevant non-major bleed). The ERG's approach differed from the manufacturer's approach in that all outcomes were assessed at the end of treatment rather than the end of the observed period in the trial. Incorporating dissimilar trial data has been shown to have a profound impact on the results of a NMA.[42] This was particularly important in the assessment of secondary prevention of VTE, where our clinical experts advised that continuous treatment would occur rather than treatment merely being extended to one-year.

In addition, where possible the ERG used ITT data in the analyses. In terms of the dabigatran trials, ITT data was also used where possible as opposed to the FAS data that was used in the manufacturer's NMA.

The ERG's analyses were conducted using WinBUGS and a Bayesian MCMC simulation[43] rather than the frequentist approach using SAS undertaken by the manufacturer. Fixed and random effects models were explored and the model that had the lowest Deviance Information Criterion (DIC) was selected when reporting results. DIC measures the fit of the model while penalising for the number of effective parameters.[44] The odds ratio (OR) was used as a summary statistic for all analyses as it has been shown to be associated with less heterogeneity in meta-analysis than risk difference or relative risk.[45] As Bayesian statistical inference provides the probability that an estimate will take a particular value, results are presented with a 95% Credible Interval (CrI) rather than a 95% Confidence Interval (CI).

In all cases, in the ERGs NMAs the fixed effects model was preferred over the random effects model (i.e. DIC fixed effects was always found to be lower than the DIC random effects). Similarly the residual deviance for the each fixed effects model was very similar to the number of unconstrained data points for each outcome indicating good fitting models.[46]

4.9.1 Acute treatment of VTE

The trial network created by the ERG for the acute treatment of VTE is depicted in Figure 8; this is a linear "network", in which warfarin is the treatment that links dabigatran to rivaroxaban. The results from the NMA for the acute treatment of VTE are presented in Figure 8.

Figure 8. Network of four randomised controlled trials[25;26;28;29] informing the NMA conducted by the ERG for the acute treatment of VTE

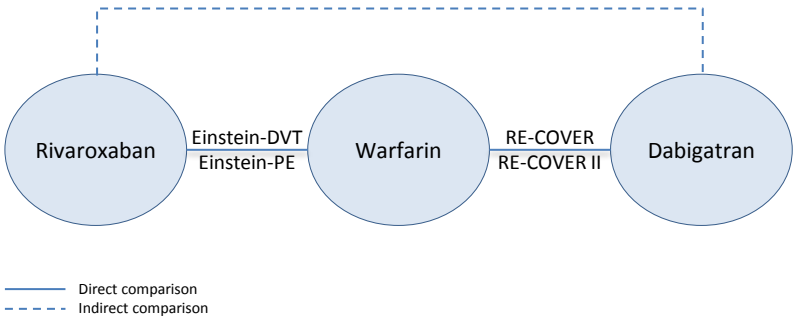


Table 73. Results from the NMA conducted by the ERG for the acute treatment of VTE using dabigatran as a baseline (OR <1 favours comparator; OR >1 favours dabigatran)

Outcome	Mean Odds Ratio	95% Credible Interval	
		Lower	Upper
VTE			
Warfarin vs dabigatran	0.921	0.636	1.281
Rivaroxaban vs dabigatran	0.837	0.516	1.299
Major bleed			
Warfarin vs dabigatran	1.369	0.860	2.061
Rivaroxaban vs dabigatran	0.763	0.402	1.320
CRNMB			
Warfarin vs dabigatran*	1.647	1.310	2.035
Rivaroxaban vs dabigatran*	1.647	1.234	2.114

*Statistically significant at the 5% level.

Abbreviations used in table: CRNMB, clinically relevant non-major bleed; VTE, venous thromboembolism; vs, versus.

The trial network created by the ERG for the acute treatment of VTE in the cancer subpopulation indicated in the NICE scope[15] is depicted in Figure 9; this is a "radiating star" shaped network, in which warfarin is the treatment that links dabigatran, rivaroxaban, and low molecular weight heparin (LMWH). The results from the NMA for the acute treatment of VTE in the cancer subpopulation are presented in Figure 9.

Figure 9. Network of nine randomised controlled trials[25;26;28-34] informing the NMA conducted by the Evidence Review Group for the acute treatment of VTE in the cancer subpopulation

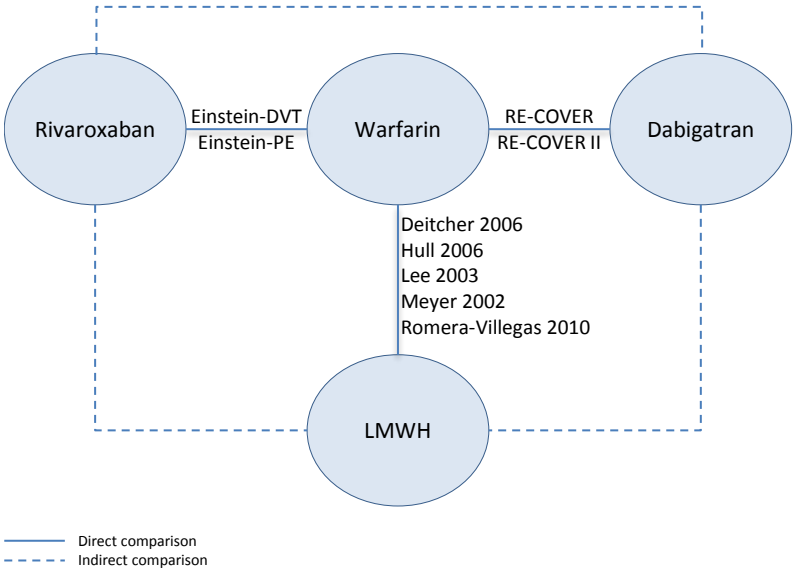


Table 74. Results from the NMA conducted by the ERG for the acute treatment of VTE in the cancer subpopulation using dabigatran as a baseline (OR <1 favours comparator; OR >1 favours dabigatran)

Outcome	Mean Odds Ratio	95% Credible Interval	
		Lower	Upper
VTE			
Warfarin vs dabigatran	1.871	0.308	6.452
Rivaroxaban vs dabigatran	1.294	0.122	5.421
LMWH vs dabigatran	0.958	0.146	3.365
Major bleed			
Warfarin vs dabigatran	0.741	0.149	2.149
Rivaroxaban vs dabigatran	ND	ND	ND
LMWH vs dabigatran	0.852	0.154	2.666
CRNMB			
Warfarin vs dabigatran	ND	ND	ND
Rivaroxaban vs dabigatran	ND	ND	ND
LMWH vs dabigatran	ND	ND	ND
Abbreviations used in table: CRNMB, clinically relevant non-major bleed; LMWH, low molecular weight heparin; ND, no data available for analysis; VTE, venous thromboembolism; vs, versus.			

In summary, the results of the NMA indicate a non-significant reduction in recurrent VTE and a non-significant increase in major bleed with warfarin compared to dabigatran. There is a non-significant reduction in risk of recurrent VTE and major bleed with rivaroxaban compared to dabigatran. Warfarin and rivaroxaban are associated with a statistically significant increased risk of CRNMB compared to dabigatran.

The ERG was initially concerned about the small size of the cancer subpopulation within the trials comparing dabigatran and rivaroxaban with warfarin. However, while this is a limitation of the analysis, the size of the subpopulations is very similar to most of the trials comparing LMWH with warfarin, which were specifically conducted in patients with active cancer. Only the trial conducted by Lee *et al.*[32] was noticeable larger with 672 participants.

While still non-significant, the results for cancer patients appear to be reversed for warfarin compared to dabigatran when considered alongside the whole population. Warfarin is associated with a non-significant increase in risk of recurrent VTE and a decrease in major bleed. Rivaroxaban has a non-significant increase in risk of recurrent VTE when compared to dabigatran with no data available to assess major bleed. LMWH is associated with a non-significant reduction in recurrent VTE and major bleed. No data were available to assess CRNMB in patients with active cancer.

4.9.2 Secondary prevention of VTE

The trial network created by the ERG for the secondary prevention of VTE is depicted in Figure 10; this network has a “loop” connecting dabigatran with warfarin and placebo directly and indirectly.

However the link for dabigatran with rivaroxaban is indirectly via placebo only. The Agneli 2003 trial that was included in the manufacturer's NMA was omitted from the ERG's NMA because there were no comparable end of treatment data available. The data in Agneli 2003 used in the manufacturer's NMA included an extended 'off treatment' follow-up period which the ERG consider to be a potential source of heterogeneity. The results from the ERG's NMA for the secondary prevention of VTE are presented in Table 75.

Figure 10. Network of seven RCTs[28;37;38;40;41;47;48] informing the NMA conducted by the ERG for the secondary prevention of VTE

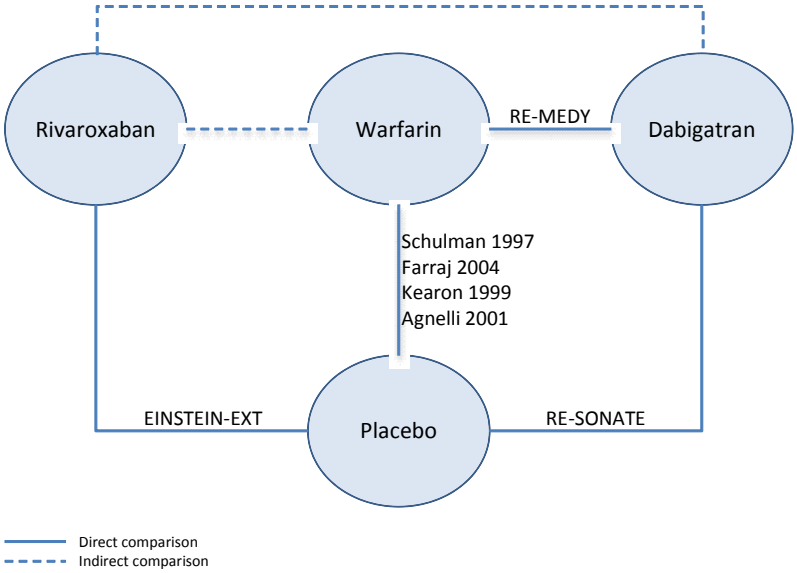


Table 75. Results from the NMA conducted by the ERG for the secondary prevention of VTE using dabigatran as a baseline (OR <1 favours comparator; OR >1 favours dabigatran)

Outcome	Mean Odds Ratio	95% Credible Interval	
		Lower	Upper
VTE			
Warfarin vs dabigatran	0.948	0.509	1.616
Rivaroxaban vs dabigatran	1.744	0.510	4.388
Placebo vs dabigatran*	9.670	4.469	19.140
Major bleed†			
Warfarin vs dabigatran*	2.039	1.007	3.759
Rivaroxaban vs dabigatran	42	0.329	113
Placebo vs dabigatran	0.726	0.232	1.704
CRNMB			
Warfarin vs dabigatran*	1.849	1.358	2.472
Rivaroxaban vs dabigatran	2.133	0.681	5.303
Placebo vs dabigatran*	0.387	0.205	0.643

*As zero events occurred for placebo in EINSTIEN-EXT[28] and RE-SONATE[48], a single major bleed had to be added to placebo to establish a link between dabigatran and rivaroxaban using these studies. This may result in an underestimate of risk of major bleed in for these two treatments.

†Statistically significant at the 5% level.

Abbreviations used in table: CRNMB, clinically relevant non-major bleed; VTE, venous thromboembolism; vs, versus.

The manufacturer raised concerns about the comparability of the studies RE-MEDY and RE-SONATE. However, after careful inspection of the inclusion/exclusion criteria of each study and the available demographics for both patient populations, the ERG considered them similar enough to be included in the same network. This assumption is conditional on the relative treatment effect being consistent in patient populations at different baseline risk; i.e. if RE-MEDY is considered to be patients at high risk of a subsequent VTE and patients in RE-SONATE considered to be at perfect "equipoise".

The ERG did compare the results for prevention of VTE from the individual studies and the results from the NMA for the head-to-head treatment options. For warfarin vs dabigatran this was OR 0.775, 95% CI: 0.410 to 1.465 (RE-MEDY) compared with OR 0.948, 95% CrI: 0.509 to 1.616 (NMA). For placebo vs dabigatran this was OR 12.647, 95% CI: 3.881 to 41.217 (RE-SONATE) compared with OR 9.670, 95% CrI: 4.469 to 19.140 (NMA). The ERG doesn't consider these results to be inconsistent.

Overall, the results from the NMA for the secondary prevention of VTE demonstrate a non-significant reduction in risk of recurrent VTE, and a significant increase in risk of major bleed and CRNMB with warfarin compared to dabigatran. While the results for rivaroxaban compared to dabigatran are all non-significant, the trend is in favour of dabigatran for each outcome. As might be expected, there is a significant increase in risk of recurrent VTE and a significant decrease in CRNMB with placebo

compared with dabigatran. However, the reduction in risk of major bleed for placebo is non-significant when compared to dabigatran. This is likely to be due to the imputed event in RE-SONATE and EINSTEIN-EXT, which was required to link a comparison of dabigatran and rivaroxaban for major bleed as this comparison was deemed a higher priority than the assessment of either treatment to placebo.

The two studies presented by the manufacturer for secondary prevention of VTE in patients with active cancer were the subpopulation from RE-SONATE[48] and Cancer DACUS.[36] The ERG notes there is a discrepancy between the manufacturer's report for RE-SONATE and the meta-analysis report provided with the MS. The MS describes that active cancer was an exclusion criterion for RE-SONATE and that only 3 patients with active were enrolled in RE-SONATE. The meta-analysis report details that data from the subgroup of people with active cancer in RE-SONATE were used in analyses with Cancer DACUS for secondary prevention effect estimates of dabigatran vs LMWH in people with cancer. The number of people in this cancer subgroup of RE-SONATE in the meta-analysis report is higher than 3. However, as the numbers of patients and numbers of events presented by the manufacturer were small, and the ERG could not validate the results extracted from the published abstract of Cancer DACUS or those from RE-SONATE, the ERG believes there are insufficient data to perform an analysis of secondary prevention of VTE in patients with active cancer.

4.10 Conclusions of the clinical effectiveness section

4.10.1 Summary of clinical results

Acute treatment of VTE

- Dabigatran demonstrated non-inferiority vs adjusted-dose warfarin in terms of prevention of recurrent VTE and VTE-related mortality in a pooled analysis of RE-COVER and RE-COVER II (HR 1.09; 95% CI: 0.77 to 1.54).
- There were no statistically significant differences between dabigatran and warfarin in any of the secondary endpoints in the two RE-COVER studies (i.e. composite of recurrent symptomatic VTE and all deaths; symptomatic DVT; symptomatic non-fatal PE; death related to VTE; and all deaths).
- There was no significant difference in major bleeding events between dabigatran and warfarin in RE-COVER or RE-COVER II.
- The overall incidence of treatment-emergent reported AEs were generally similar between dabigatran and warfarin, although the ERG notes that numerically more episodes of dyspepsia and rectal bleeding were noted with dabigatran in RE-COVER and RE-COVER II.
- There was a slightly higher incidence of acute coronary syndrome events in the dabigatran groups compared with the warfarin groups.

- The results of the AIC [redacted]
- The safety and efficacy data in cancer patients suggests no significant difference between dabigatran and warfarin but the ERG recommend caution in drawing conclusions as there were few patients with active cancer in RE-COVER or RE-COVER II.

Long-term secondary prevention of VTE

- Dabigatran was proven non-inferior to warfarin in a population intended for long-term treatment and secondary prevention of symptomatic VTE following anticoagulant treatment for 3 to 12 months after the index acute VTE event.
- There were no statistically significant between-treatment differences for the primary or secondary efficacy endpoints in RE-MEDY.
- The overall incidence of treatment-emergent reported AEs were generally similar between dabigatran and warfarin in RE-MEDY, although the ERG note that there were numerically more episodes of dyspepsia and acute coronary syndrome events with dabigatran compared with warfarin.
- There was no significant difference in major bleeding events between dabigatran and warfarin in RE-MEDY.
- Dabigatran demonstrated superiority compared with placebo for the prevention of recurrent objectively confirmed symptomatic DVT or fatal or non-fatal PE, including unexplained death in RE-SONATE (HR 0.08; 95% CI: 0.02 to 0.25).
- The results for all secondary efficacy outcomes were consistent with the primary endpoint in RE-SONATE, with fewer events with dabigatran compared with placebo.
- The overall numbers of adverse events were similar for dabigatran and placebo (RE-SONATE). However, dabigatran was associated with statistically significantly more bleeding events (any bleeding event: HR 1.82; 95% CI: 1.23 to 2.68; p=0.0027).
- [redacted]
- The safety and efficacy data in cancer patients suggest no significant difference between dabigatran and warfarin but the ERG recommend caution in drawing conclusions as there were few patients with active cancer in RE-MEDY.

4.10.2 Clinical issues

- UK marketing authorisation is not currently held for the use of dabigatran; although, positive opinion from the EMA has been adopted.
- Absence of clinical trial data to assess the safety and efficacy of the 110mg BD dose of dabigatran in acute treatment and long-term secondary prevention of VTE.

- Lack of long term QoL data for people taking dabigatran for secondary prevention of VTE;
- PTS, heart failure and CTEPH were listed as outcomes of interest in the final scope issued by NICE and were not presented as outcomes in the clinical effectiveness data of the MS. However, data on PTS, heart failure or CTEPH were not collected in the dabigatran trials.
- Dabigatran is non-inferior to warfarin for prevention of recurrent symptomatic VTE and deaths related to VTE, but dabigatran was not proven to be superior to warfarin;
- Absence of direct comparative data from a randomised controlled trial comparing dabigatran with rivaroxaban;
- The definition of cancer used in the dabigatran trials was broader than the definition of cancer used in UK clinical practice and the total number of people in the dabigatran trials with active cancer was small;
- Extremely limited data on the safety and clinical benefit of dabigatran compared with rivaroxaban and LMWH in people with active cancer.

5 COST EFFECTIVENESS

5.1 Introduction

The manufacturer developed a *de novo* Markov cost-utility model to evaluate the cost-effectiveness of dabigatran etexilate (hereafter referred to as dabigatran) for the treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE), and the secondary prevention of recurrent DVT and PE in adults. In addition to the economic evidence provided in the manufacturer's submission (MS) (Table 76), the manufacturer submitted a Microsoft© EXCEL-based economic model. The following sections (Section 5.3 and Section 5.4) provide a summary and critique of the economic evidence submitted by the manufacturer in support of this Single Technology Appraisal (STA).

Table 76. Summary of key information within the manufacturer's submission

Information	Section (MS)
Details of the systematic review of the economic literature	7.1
Population	7.2
Model structure	7.3
Technology	7.2.7
Treatment continuation rules	7.2.8
Clinical parameters and variables	7.3
Measurement and valuation of health effects and adverse events	7.4
Resource identification, valuation and measurement	7.5
Sensitivity analysis	7.6
Results	7.7
Validation	7.8
Subgroup analysis	7.9
Interpretation of economic evidence	7.10
Strengths and weaknesses of economic evaluation	7.10.3
Abbreviation used in table: MS, manufacturer's submission.	

5.2 Summary of the manufacturers' key results

The manufacturer presented deterministic and probabilistic results for the comparisons for dabigatran versus warfarin, rivaroxaban and LMWH (in the population with cancer) for acute treatment only, and treatment and secondary prevention within the MS. A summary of the ICERs presented by the manufacturer is provided in Table 77, for ease of reference.

Table 77. A summary of the ICERs presented by the manufacturer for acute treatment and treatment and secondary prevention

Dabigatran versus >>	Warfarin (full population)	Rivaroxaban (full population)	LMWH (population with cancer)
Acute treatment only (deterministic)			
ICER	£862	Dabigatran dominant (less costly, more effective)	£110,742 (SW quadrant; dabigatran less costly and less effective)
Acute treatment only (probabilistic)			
ICER	£1,016*	Dabigatran dominant (less costly, more effective)	£93,431 (SW quadrant; dabigatran less costly and less effective)
Probability of dabigatran being considered cost-effective at a threshold of £20,000 versus selected comparator	93%	57%	92%
Treatment and secondary prevention (deterministic)			
ICER	£8,319	Dabigatran dominant (less costly, more effective)	Dabigatran dominant (less costly, more effective)
Treatment and secondary prevention (probabilistic)			
ICER	£8,848**	Dabigatran dominant (less costly, more effective)	Dabigatran dominant (less costly, more effective)
Probability of dabigatran being considered cost-effective at a threshold of £20,000 versus selected comparator	92%	81%	100%

* Note, reported as £1,016 (MS pg 26, pg 356) but alternatively reported as £1,061 (MS pg 364)

** Note, reported as £8,465 (MS, pg 356)

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin, MS, manufacturer's submission; SW, south-west.

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

The manufacturer carried out a systematic review of the economic literature to identify cost-effectiveness publications relevant to the use of dabigatran for the acute treatment and secondary prevention of DVT and PE. Details of the search strategy, inclusion and exclusion criteria, data extraction tables, and study quality assessment were provided within the submission (MS; pgs 219-228, Appendix 10).

The following electronic databases were searched: MEDLINE; MEDLINE In-Process; Embase; EconLit; BIOSIS; the Cochrane Library. The search was carried out in February 2013 and updated in April 2014. Search terms captured the condition of interest (DVT / PE), a range of interventions, and economic evaluation studies. Publications dated from the year 2000 were included in the review; the

restriction on date was justified by the manufacturer "because economic data published before that time were unlikely to be relevant to current treatment practices, resource patterns, and costs" (MS; pg 454).

In addition to database searches, a number of internet searches were carried out to identify conference abstracts (MS; Appendix 10) and published health technology assessments (HTAs). The internet searches were carried out in February 2013, and updated during April and May 2014. Conference abstracts were limited to those published from January 2011; the restriction on date was justified by the manufacturer "as high-quality studies reported in abstract form before 2011 were expected to have been published in a peer-reviewed journal" (MS; pgs 220-221). No date restriction was applied for HTA documentation. Reference lists of included cost-effectiveness studies were also reviewed.

A total of 12 cost-effectiveness analyses were identified from the original search (5 studies) and the updated search (7 studies). Of the 12 studies, three were carried out from the perspective of the UK. One of these studies related to a manufacturer submission for NICE TA261; an STA appraising the use of rivaroxaban for the treatment of acute DVT and secondary prevention of DVT and PE.[(49)] The remaining two UK studies were conference abstracts; McLeod *et al.* and Wolowacz *et al.*; the manufacturer reported that both studies were published in 2013. The manufacturer did not provide the full references for these studies and the ERG was unable to identify these papers. The manufacturer reported that McLeod *et al*. described a Markov model developed using data from EINSTEIN-PE, a head-to-head clinical trial comparing acute treatment of PE with rivaroxaban versus low-molecular-weight heparin (LMWH) plus a vitamin-K antagonist (VKA) in patients with an initial PE. The manufacturer further reported that Wolowacz *et al*. described a Markov model populated with data from RE-SONATE (Section 4.7), to compare the use of dabigatran with placebo for the secondary prevention of future DVT and PE, for people who had completed 6 to 18 months prior treatment with a VKA.

The ERG considers that the search terms used by the manufacturer to identify economic evaluations were comprehensive and appropriate; however, the ERG notes that searches were limited by date, which may have resulted in the omission of relevant publications. To assess the impact of this restriction, the ERG reviewed economic evaluation studies included within the systematic review for two related STAs, TA261 (an STA appraising the use of rivaroxaban for the treatment of acute DVT and secondary prevention of DVT and PE) and TA287 (an STA appraising the use of rivaroxaban for the treatment of acute PE and secondary prevention of DVT and PE). The ERG notes that no economic evaluation studies were identified within these STAs that were published before the year 2000; therefore, the ERG considers that the restriction by date is unlikely to have resulted in the omission of key evidence.

The inclusion and exclusion criteria applied are considered to be reasonable, with the exception of the choice of included interventions. The manufacturer elected to restrict included studies to those which evaluated at least one of the following treatments: apixaban, dabigatran, edoxaban and rivaroxaban. Economic analyses and cost studies comparing LMWH, unfractionated heparin (UFH), warfarin and fondaparinux, that did not evaluate apixaban, dabigatran, edoxaban or rivaroxaban were identified but not formally included in the review. The justification for limiting by intervention was not stated within the submission; therefore, the ERG asked for further rationale at the clarification stage. The manufacturer stated: "at the time that this systematic review was designed, BI [Boehringer Ingelheim] had identified these as the interventions of interest in the economic model" (manufacturer response to clarification; pg 58). As a consequence of this limit, the manufacturer omitted data from a number of studies which considered only warfarin, LMWH or UFH, and which were included in TA261 and TA287.[50-55] Despite this limitation applied by the manufacturer, the ERG notes that Marchetti *et al.* was identified and included in the review; this study reports a decision tree analysis comparing LMWH with warfarin over 3-months for the prevention of DVT recurrence.[56] It is unclear why this study was identified and included in the analysis.

Although the search strategy adopted by the manufacturer appears generally appropriate, the ERG considers that a number of relevant cost-effectiveness analyses were omitted from the manufacturer's included studies. In particular, the manufacturer did not include HTA reports pertaining to NICE TA287, despite reviewing HTA publications.[57] In addition, NICE clinical guideline CG144, a guideline relating to the management of venous thromboembolic diseases, was not identified or included.[58] The ERG considers that cost-effectiveness evidence within TA287 and CG144 are of relevance for this STA; therefore the ERG summarised the data within these studies in Table 78 for completeness, along with a summary of TA261.

Table 78. Summary of cost-effectiveness evidence contained within TA261, TA287 and CG144

Intervention and comparators	Model overview	Costs	Benefits	ICER
TA287 Rivaroxaban for treating PE and preventing recurrent VTE, 2013				
• Rivaroxaban (15mg twice a day for 21 days followed by 20mg daily). • Initial treatment with LMWH (enoxaparin 1.5mg/kg daily) with continued treatment as follows: VKA (warfarin); LMWH for people for whom a VKA is not considered appropriate.	• 40 year (lifetime) Markov model from the NHS/PSS perspective, with 3-month cycle length; • cost-utility analysis (for the full population); • cost-minimisation (for the active cancer subgroup); • 13 health states: on-treatment for index event; off-treatment post index PE; off-treatment post index DVT; recurrent DVT; recurrent PE; recurrent PE post DVT; major EC; major IC; CRNM bleed; CTEPH; long term CTEPH; post-IC bleed (an absorbing state for all patients who experience an IC bleed); death; • the incidence of PTS applied as costs and HRQoL payoffs to the whole surviving cohort.	Costs included: • daily drug acquisition costs; • INR monitoring; • costs of VTE events; • cost of bleeding; • management of PTS and CTEPH. Unit costs were taken from the NHSRC 2010/11(59), the Unit costs for Health and Social care 2011(60) and the BNF 64(61). Costs were discounted at 3.5% per annum after year one.	HRQoL was modelled relative to a baseline for DVT, PE, IC bleed, EC bleed and PTS. Estimates were taken from a systematic review of the literature. Treatment related utilities were taken from Marchetti et al., 2001.(56) Benefits were discounted at 3.5% per annum after year one.	**Full population** Rivaroxaban versus LMWH and VKA: • rivaroxaban was dominant at 3, 6 and 12 months of treatment; • ICER (QALY) of £13,252 for life long treatment. Appraisal Committee most plausible ICER: £17,900 - £22,900. **Cost minimisation of rivaroxaban vs LMWH in the population with cancer** Over the 6 month period rivaroxaban was associated with a cost saving of £903.
TA261 Rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE, 2012				
• Rivaroxaban (15mg twice a day for 21 days followed by 20mg daily). • Initial treatment with LMWH (enoxaparin 1.5mg/kg daily) with continued VKA treatment (warfarin).	• 40 year (lifetime) Markov model from the perspective of the NHS/PSS, with 3-month cycle length; • cost-utility analysis (for the full population); • cost-minimisation (for the active cancer subgroup); • 10 health states: on treatment for	Costs included: • daily drug acquisition costs; • INR monitoring; • costs of VTE events; • cost of bleeding; • management of PTS and CTEPH. Unit costs were taken from the	HRQoL was modelled relative to a baseline for DVT, PE, IC bleed, EC bleed and PTS. Estimates were taken from a systematic review of the literature. Treatment related utilities were obtained from Marchetti et al.[56]	**Full population** Rivaroxaban versus LMWH/VKA: rivaroxaban was dominant at 3, 6 and 12 months of treatment. Appraisal Committee most plausible ICER: £19,400. **Population with cancer**

• For cancer patients, LMWH treatment (dalteparin) at UK licensed dose.	index event; off treatment; recurrent DVT; recurrent PE; CRNM bleed; IC bleed; major EC bleed; CTEPH (operable and inoperable); post-stroke (an absorbing state for all patients who experience an IC bleed); death; • the incidence of PTS applied as costs and HRQoL payoffs to the whole surviving cohort.	NHSRC 2009/10[62], the Unit costs for Health and Social care 2010[63], and MIMS. Costs were discounted at 3.5% per annum after year one.	Benefits were discounted at 3.5% per annum after year one.	Over the 6 month period rivaroxaban was associated with a cost saving of £903.
CG144 Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing, 2012				
All patients receive 3 months of initial anticoagulant treatment. **Intervention:** warfarin as long-term anticoagulant. Patients are treated indefinitely unless they have an episode of major bleeding. **Comparator:** No long-term treatment.	• lifetime cost-utility analysis (45 years) with a 1-year cycle length, using a Markov model structure, carried out from the perspective of the UK NHS/PSS; • health states modelled: No event; major bleed; off treatment; recurrent VTE; stroke; death.	Costs included: • daily drug acquisition costs; • INR monitoring; • cost of stroke; • cost of bleeding. Costs were discounted at 3.5% per annum after year one.	Disutilities applied for: • PE; • MBE; • stroke. Disutility was applied for one month for recurrent PE and major bleeding events, No disutility was applied for a recurrent DVT.	No long-term strategy versus long-term strategy: probabilistic ICER (QALY): £9,601 (initial PE), and £79,758 (initial DVT). At a WTP threshold of £20,000 per additional QALY, long-term treatment in patients with an initial DVT was estimated to have a 13% probability of being the optimal strategy, increasing to 80% in patients with an initial PE.
Abbreviations used in table: BNF British National Formulary; CG, clinical guideline; CRNM, clinically relevant non-major; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; EC, extra cranial; HRG, Healthcare Resource Group; HRQoL, health-related quality of life; HTA, health technology assessment; IC, intracranial; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; INR, international normalised ratio; LMWH, low-molecular-weight heparin; LY, life year; MBE, major bleeding event; MIMS, Monthly Index of Medical Specialities; NHSRC, NHS Reference Costs; PE, pulmonary embolism; PEA, pulmonary endarterectomy; PTS, post-thrombotic syndrome; QALY, quality-adjusted life year; VKA, vitamin-K antagonist; VTE, venous thromboembolism; WTP, willingness-to-pay.				

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

5.4.1 NICE reference case checklist

Table 79 and Table 80 summarise the ERGs quality assessment of the manufacturer's economic evaluation. Table 79 summarises the ERGs appraisal of the manufacturer's economic evaluation against the requirements set out in the NICE reference case checklist for a base case analysis, with reference to the NICE scope outlined in Section 3; Table 80 summarises the ERGs appraisal of the quality of the manufacturer's *de novo* economic model using the Philips checklist.[64]

The ERGs main criticisms of the cost-effectiveness analysis were:

- a lack of a fully incremental analysis for the treatment and secondary prevention scenario;
- duration of secondary prevention set to 6-18 months rather than life-long for the treatment and secondary prevention analyses;
- a potential overestimate of cost associated with warfarin monitoring;
- uncertainty in model results arising as a consequence of:
    - lack of robust evidence supporting a utility decrement for warfarin treatment;
    - lack of clinical effectiveness and safety data for the reduced dose of dabigatran (110mg twice daily).

These criticisms are described in greater detail in the subsequent sections.

Table 79. NICE reference case checklist for a base case analysis

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Broadly yes, although the ERG notes: • the scope requested consideration of long-term anticoagulation (usually lifelong); whereas the manufacturer modelled 6-18 months secondary prevention; • the manufacturer did not compare the use of dabigatran versus initial treatment with fondaparinux and continued VKA (for the full population); • the manufacturer did not did not compare the use of dabigatran versus rivaroxaban (for the population with cancer); • the manufacturer limited consideration of DVT to proximal DVT.
Comparator(s)	Alternative therapies routinely used in the NHS	Broadly, yes. The manufacturer addressed three of five comparators listed within the scope: • initial treatment with a low-molecular-weight heparin or fondaparinux and continued vitamin K antagonist • rivaroxaban

		• for people with cancer, low-molecular-weight heparin However, the manufacturer did not consider the remaining two comparators outlined in the scope: • initial treatment with fondaparinux and continued VKA (for the full population); • rivaroxaban (for the population with cancer).
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes; the ERG notes that the time horizon selected (60 years) may be longer than necessary to capture the costs and consequences associated with treatment. This is described in more detail in Section 5.4.5, and relates to concerns around the average age of patients entering the model potentially being underestimated by the manufacturer, which the ERG believes may have resulted in a longer time-horizon than necessary.
Synthesis of evidence on outcomes	Systematic review	Yes, a systematic review was carried out. However, the ERG notes that the synthesis of this data was not carried out using network meta-analysis; instead, the manufacturer used a series of head-to-head and indirect comparisons. The limitation of this approach for the secondary prevention analyses was that data for dabigatran varied in each comparison, resulting in a lack of comparability across assessed scenarios.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D.
Benefit valuation	Time-trade off or standard gamble	Yes, TTO.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes, UK sample.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes.

Table 80. Philips checklist[64]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Clearly stated (UK NHS).
S3: Rationale for structure	Clearly stated.
S4: Structural assumptions	The ERG has concerns with the following structural assumptions: • patients experiencing a recurrent VTE do not receive secondary prevention; • patients experiencing a major bleeding event stop treatment permanently; • dyspepsia was not included in the base case analysis. The ERG explored the impact of varying each of these assumptions (Section 5.5).
S5: Strategies/ comparators	The manufacturer considered acute treatment (6-months) and acute treatment followed by secondary prevention (6 months acute treatment followed by a further 6-18 months treatment, depending upon the comparator) as separate scenarios. The manufacturer considered LMWH plus dabigatran, LMWH plus warfarin, and rivaroxaban (for the full population), and LMWH monotherapy (for the population with cancer). The following comparators were not included in the analysis: • initial treatment with fondaparinux and continued vitamin-K antagonist (for the full population); • rivaroxaban (for the population with cancer). The ERG considers the omission of comparison with fondaparinux was reasonable given the limited use of this treatment in clinical practice. The ERG considers the omission of comparison with rivaroxaban for the population with cancer as reasonable due to a lack of relevant rivaroxaban clinical data (Section 5.4.4.1). In addition, the ERG is concerned that the manufacturer has underestimated the duration of secondary prevention in clinical practice. The ERG notes that the manufacturer modelled a duration of between 6 and 18 months, depending upon the selected comparator. The ERG considers it is more likely that secondary prevention will be lifelong. The ERG explored the impact of this in sensitivity analysis (Section 5.5).
S6: Model type	Appropriate; cost-utility analysis.
S7: Time horizon	Appropriate: a lifetime horizon was applied within the model. The ERG notes that the time horizon selected (60 years) may be longer than necessary to capture the costs and consequences associated with treatment. This is described in more detail in Section 5.4.5, and relates to concerns around the average age of patients entering the model potentially being underestimated by the manufacturer, which the ERG believes may have resulted in a longer time-horizon than necessary. The ERG explored the impact of reducing the time horizon in sensitivity analysis (Section 5.5).
S8: Disease states/pathways	Largely appropriate. The ERG notes that the health state of dyspepsia, an adverse event of treatment, was excluded from the base case analysis; the ERG explored the impact of including dyspepsia within the base case (Section 5.5).
S9: Cycle length	Appropriate; the ERG considers one month to be a reasonable cycle length to capture the consequences of modelled events.
Data	
D1: Data identification	The manufacturer's literature searches for cost-effectiveness analyses, resource use and cost, and utilities were clearly described. However, the ERG notes the following:

	• the rationale for selecting identified data sources for the model were not consistently described; • where data sources for the model were not identified from the literature search, description of how studies used were identified and selected was not provided; • previous NICE technology appraisals were not identified from the literature searches despite review of published health technology assessments.
D2: Pre-model data analysis	The manufacturer carried out the following pre-model data analysis: • the manufacturer estimated the impact of the initial and recurrent VTE events on HRQoL using EQ-5D data collected within RE-COVER I and II and analysed prior to inclusion within the model. The ERG considers that these data represent the largest source of HRQoL data available for the impact of VTE (Section 5.4.12.3); • in a sensitivity analysis, the manufacturer used analysis carried out using data from the General Practice Research Database to investigate the impact of INR control on rates of recurrence and bleeding. The purpose of the sensitivity analysis was to quantify the possible differences in recurrence and bleeding that might be seen in clinical practice compared with those seen in clinical trials; with differences arising as a consequence of differences in INR control. The ERG has concerns about the validity of the results from this analysis (Section 5.4.11).
D2a: Baseline data	Baseline data were taken from clinical trials. For secondary prevention, the manufacturer applied baseline data such that data for dabigatran differed for each comparison. Consequently, a fully incremental analysis across all comparators is not possible; each comparison must be interpreted as a standalone head-to-head analysis. The ERG carried out a sensitivity analysis using the same data for dabigatran for each comparator to facilitate comparison between interventions (Section 5.5.2).
D2b: Treatment effects	The key measure of efficacy modelled by the manufacturer was the probability of recurrent VTE. The manufacturer estimated the incidence of recurrent VTE for each treatment, before applying the proportion of people who experienced a DVT (proximal), PE (fatal), and PE (non-fatal). Similarly, the key measure of safety modelled by the manufacturer was the probability of major and clinically relevant non-major bleeding. The manufacturer estimated the incidence of major or clinically relevant non-major bleeding for each treatment, before applying the proportion of people who experienced an intra-cranial MBE, an extra cranial MBE, or a CRNMBE. The ERG notes that, by using combined clinical endpoints for efficacy and safety, the manufacturer may inaccurately estimate the incidence of specific events within the model. This is because the proportion of events applied to the incidence is applied directly from the trials, and is not meta-analysed. The ERG investigated the impact of applying incidence of MBE and CRNMB separately within the model (Section 5.5). The ERG did not consider the impact of applying rates of DVT and PE separately, because the combined clinical endpoint was considered to be appropriate and comparable with data for other treatments.
D2c: Costs	The manufacturer used the latest source of data where possible (NHS Reference Costs 2012/13 and Unit Costs for Health and Social Care 2012/13) and inflated costs to the year 2014. The ERG notes that the manufacturer imputed an inflation factor for 2013/14 because no such factor has yet been published. The ERG considers this unnecessary, and removed the imputed inflation factor in a scenario analysis (Section 5.5). The manufacturer used list prices for drugs included within the model. The ERG notes that NICE recommends use of eMIT to establish costs for drugs which receive a discount; data for the cost of warfarin treatment is available on eMIT. The ERG carried out an analysis in which this cost was applied within the model (Section 5.5).
D2d: Quality of life weights (utilities)	The manufacturer applied a general HRQoL value to patients within the model based upon their age and gender. The manufacturer then subtracted disutility from this value according

	to whether the patient experienced a recurrent VTE, PTS, CTEPH, MBE, CRNMBE, or whether the patient was treated with warfarin or LMWH monotherapy. In sensitivity analysis, the manufacturer also subtracted disutility for MI, UA and dyspepsia. The ERG has concerns around the following utility data used in the model: • the data analysis used to estimate VTE disutility may have slightly underestimated the impact of PE (Section 5.4.12.3); • the ERG notes that the manufacturer's analysis of recurrent VTE disutility implied that overall utility for a VTE event did not change with age; therefore, the ERG notes that applying disutility additively will overestimate the disutility associated with VTE for older populations. This is described in greater detail in Section 5.4.12.3; • the ERG is concerned that the data used to estimate a disutility associated with warfarin and LMWH treatment is unreliable (Section 5.4.12.5); • the ERG notes that the disutility applied to MBEs may have been estimated from EQ-5D data from patients who were not experiencing a MBE and may therefore underestimate disutility (Section 5.4.12.6).
D3: Data incorporation	Data incorporation was generally appropriate although the ERG does note a number of errors within the model, the impact of which was generally small.
Assessment of uncertainty	
D4a: Methodological	Appropriate.
D4b: Structural	Appropriate, the manufacturer included health states for MI, UA and dyspepsia within a sensitivity analysis.
D4c: Heterogeneity	Appropriate, the manufacturer presented results for patients requiring acute treatment and both treatment and secondary prevention. The manufacturer also included results for the population with cancer.
D4d: Parameter	Appropriate; uncertainty was assessed through deterministic and probabilistic sensitivity analysis.
Consistency	
C1: Internal consistency	The model is mathematically sound with the exception of a few minor errors. In addition model results for dabigatran and warfarin are comparable with clinical trial data. No data were provided for rivaroxaban and LMWH.
C2: External consistency	Not assessed.
Abbreviations used in table: DVT, deep vein thrombosis; ERG, evidence review group; HR, hazard ratio; HRQoL, health related quality of life; LMWH, low molecular weight heparin; MCRB, major or clinically relevant bleeding; MI, myocardial infarction; PE, pulmonary embolism; RR, relative risk; UA, unstable angina; VTE, venous thromboembolism.	

5.4.2 Model structure

5.4.2.1 Model structure developed by the manufacturer

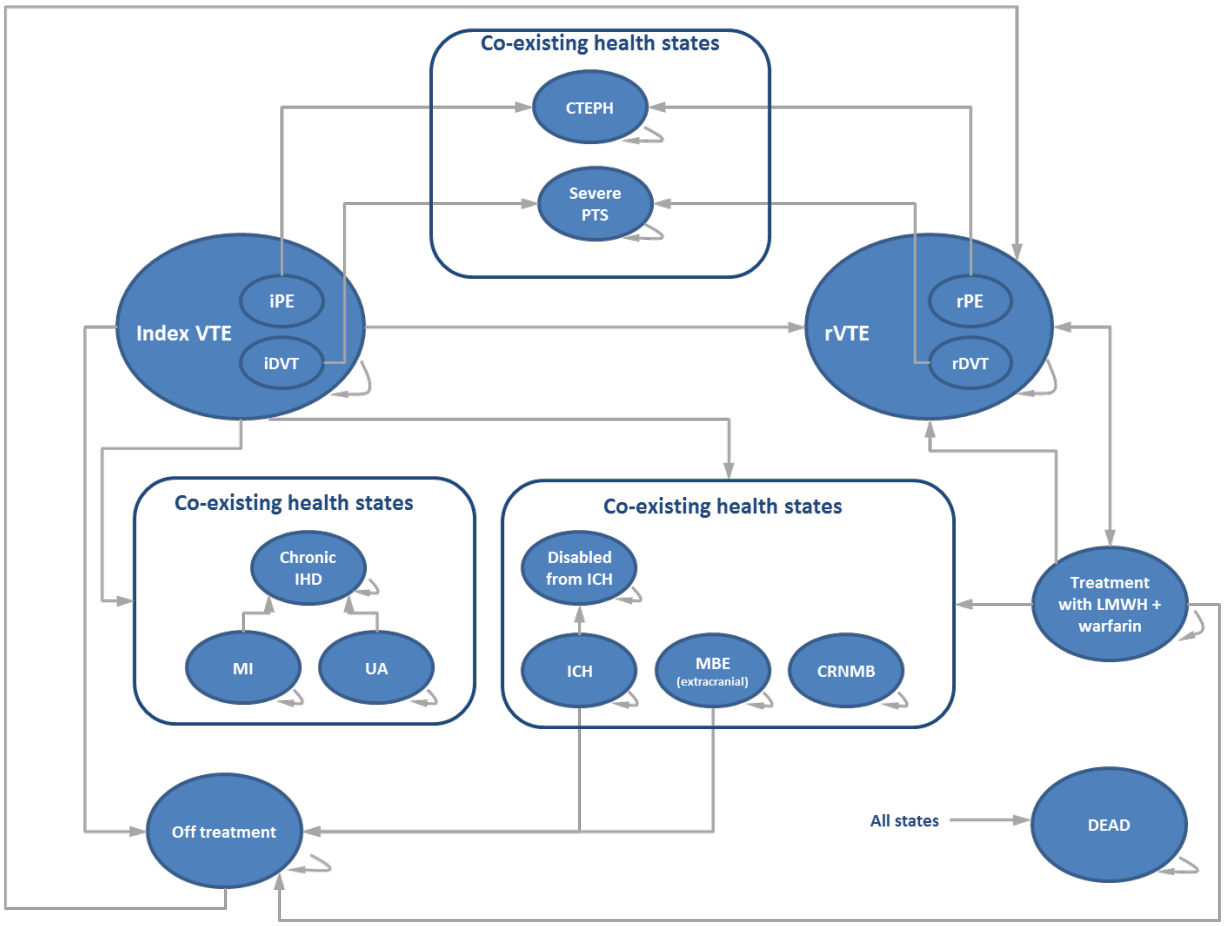
The manufacturer developed a *de novo* Markov cost-utility model in Microsoft Excel®. The model followed an average cohort through a lifetime time horizon in the base case, with a cycle length of one month (assumed to be 30 days). The manufacturer analysed two separate scenarios:

- acute treatment of DVT and PE only (hereafter referred to as "acute treatment"); and,
- acute treatment of DVT and PE followed by secondary prevention of future DVT and PE (hereafter referred to as "treatment and secondary prevention").

The acute treatment scenarios specifically related to a model in which people only receive acute treatment for their initial or recurrent DVT / PE. The treatment and secondary prevention scenarios specifically related to a model in which people receive acute treatment and secondary prevention for their initial DVT / PE, and acute treatment only for their recurrent DVT / PE. This is described in greater detail in the subsequent sections.

The model structure presented by the manufacturer is presented in Figure 11 below. The model structure applied to both the acute treatment, and the treatment and secondary prevention scenarios.

Figure 11. Manufacturer model structure (MS; Figure 29, pg 230)



Abbreviations used in figure: CTEPH, chronic thromboembolic pulmonary hypertension; CRNMB, clinically relevant non-major bleeding event; iDVT, index deep vein thrombosis; ICH, intracranial haemorrhage; IHD, ischemic heart disease; iPE, index pulmonary embolism; LMWH, low-molecular-weight heparin; MBE, major bleeding event; MI, myocardial infarction; pg, page; PTS, post thrombotic syndrome; rDVT, recurrent deep vein thrombosis; rPE, recurrent pulmonary embolism; rVTE, recurrent venous thromboembolism; UA, unstable angina; VTE, venous thromboembolism.

All patients begin in the "Index VTE" health state as having confirmed symptomatic (proximal) DVT, or confirmed symptomatic PE (with or without proximal DVT). These patients receive acute treatment with dabigatran (with 5 days parenteral LMWH treatment), warfarin (with 5 days parenteral

LMWH treatment), rivaroxaban, or LMWH (for people with active cancer). Patients who also receive secondary prevention at treatment for their initial VTE event (i.e., those in the treatment and secondary prevention scenario) additionally receive 6-18 months of treatment with dabigatran (duration depends upon the comparator selected), warfarin (18 months), rivaroxaban (6 months) or LMWH (6 months). Full details of the included interventions and comparators are described and critiqued in Section 5.4.4.

If a patient completes treatment (either acute treatment or secondary prevention) or withdraws from treatment (due to recurrent VTE, a major bleeding event [MBE], an adverse event, worsening of other pre-existing conditions, non-compliance with protocol, loss to follow-up, removal of consent; Section 5.4.10), they transition to the "off treatment" health state.

Patients on or off treatment are at risk of a recurrent VTE and are assumed to experience a maximum of two recurrent VTE events within the model. The risk of a recurrent VTE differs depending upon which treatment the patient is receiving, if any, and whether they are receiving acute treatment or secondary prevention for their initial VTE; details of the applied risks of a recurrent VTE are described in Section 5.4.6. All patients who experience a recurrent VTE event are treated acutely with LMWH for 5 days and warfarin for 6 months, regardless of the initial treatment received; no patients receive secondary prevention for a recurrent VTE.

During treatment for either the initial VTE or the recurrent VTE, patients are exposed to a risk of bleeding and can experience an MBE (intra- or extra-cranial haemorrhage) or a clinically-relevant non-major bleeding event (CRNMBE). The overall risk of bleeding and the type of bleed is assumed to vary by treatment. Intracranial haemorrhage (ICH) may result in death, permanent disability, or full recovery. An extra-cranial MBE may result in death or full recovery. CRNMBE results in full recovery. Patients experiencing an MBE who do not die, were assumed to withdraw permanently from treatment. The probability of bleeding, and the consequences of bleeds are described in Section 5.4.8.

Patients who experience a PE (initial or recurrent) are additionally at risk of chronic thromboembolic pulmonary hypertension (CTEPH); their risk is assumed to remain for 2 years after their PE. Patients who experience a DVT (whether initial or recurrent) are additionally at risk of severe post-thrombotic syndrome (PTS); their risk was assumed to remain for 5 years after their DVT. The probability of developing severe PTS and CTEPH, and the consequences of each complication are described in Section 5.4.7.

The cardiovascular health states presented in the manufacturer's model structure (Figure 11) are not assessed in the base case. In sensitivity analysis, patients can experience myocardial infarction (MI) or

unstable angina (UA) during treatment for their initial VTE event, of which chronic ischaemic heart disease (IHD) is a long-term consequence for a proportion of patients. In addition, dyspepsia is also included in sensitivity analysis. The ERG notes that the dyspepsia health state is not presented in Figure 11; however, the manufacturer confirmed during clarification that this health state was erroneously omitted from the diagrammatic representation of the model structure. These health states are described further in Section 5.4.8.

Each health state presented in Figure 11 is associated with a cost and utility. The following costs were included in the economic analysis: drug costs; monitoring costs; resource use cost; costs associated with adverse events; costs associated with severe PTS and CTEPH. A description of the costs included in the MS is provided in Section 5.4.13. The utilities applied in the manufacturer's analysis take into account the following: disutility associated with a VTE event; disutility associated with warfarin or LMWH treatment; disutility associated with an adverse event; disutility associated with PTS and CTEPH; and changes in general population utility, by age. A description of the utilities included within the manufacturer's analysis is provided in Section 5.4.12.

Patients in all health states have a probability of dying in each cycle; patients can die from a recurrent PE, an MBE (either intra- or extra-cranial), or for other causes (background mortality). In addition, in sensitivity analysis, patients can die from a MI. Mortality data applied within the manufacturer's model is described within Section 5.4.9.

5.4.2.2 ERG comments on the model structure developed by the manufacturer

Following discussion with clinical experts, and after review of the identified cost-effectiveness evidence (Section 5.3), the ERG considers that the key clinical aspects of the condition under review for this STA are:

- the risk of recurrent DVT or PE;
- the risk of bleeding associated with treatment and prevention for DVT or PE.

The ERG considers therefore that the model structure developed by the manufacturer is reasonable to capture these key aspects of the condition of interest, and notes that a Markov model with a lifetime time-horizon appears to provide an appropriate framework from which to capture the resultant key costs and consequences. The ERG also notes that clinical advisors considered the inclusion of complications associated with DVT and PE (i.e. PTS and CTEPH) to be of importance; consequently, the ERG considers it appropriate that the manufacturer captured these complications within the model structure.

The ERG considers that manufacturer made the following key assumptions around the model structure:

- the cycle length is assumed to be 30 days;
- the maximum number of VTE recurrences is set to two;
- cardiovascular health states and dyspepsia are considered in sensitivity analysis only;
- all patients who experience a recurrent VTE within the model receive warfarin treatment;
- patients who experience a recurrent VTE within the model do not receive secondary prevention for future VTE events;
- the incidence of severe PTS and CTEPH is captured through co-existing health states, rather than mutually exclusive health states;
- patients who experience an MBE stop acute treatment or secondary prevention for their VTE and do not restart treatment after the bleeding event.

The ERG comments upon these assumptions are provided below.

Cycle length is 30 days

The ERG notes that the manufacturer's assumption of a 30 day cycle results in a slight miscalculation of the length of one year, at 360 days. The ERG considers this to be a minor issue.

VTE recurrences set to a maximum of two

Clinical experts consulted by the ERG agreed that an assumption of VTE recurrences set to a maximum of two would capture the majority of patients of interest for this STA. Consequently, the ERG considers that this simplifying assumption is reasonable.

Cardiovascular health states and dyspepsia included in sensitivity analysis only

Following consultation with clinical experts, the ERG considers that restricting cardiovascular health states to sensitivity analysis was appropriate because these health states are not of direct relevance to the condition of interest for this STA. However, the ERG notes that these health states provide important information around adverse events associated with dabigatran use. The risks, costs and consequences reported by the manufacturer are described in Section 5.4.8, 5.4.13, 5.4.12 respectively. In addition, the manufacturer presents results of this sensitivity analysis within the MS, pgs 359-362 Table 148.

Following consultation with clinical experts, the ERG considers that dyspepsia is an important side effect associated with dabigatran treatment; consequently, the ERG considers that it may have been appropriate to include the impact of dyspepsia within the base case analysis. The ERG included a scenario in which dyspepsia was included in the model; results are presented in Section 6.2, **analysis B1**. The ERG notes that the impact of this analysis upon the manufacturer's base case results was small.

All patients who experience a recurrent VTE receive warfarin as treatment

The manufacturer assumed that, for both the full population and for the subgroup of patients with cancer, treatment at recurrence will be LMWH (5 days) plus warfarin (6 months).

For the full population, the manufacturer did not model treatment with rivaroxaban at recurrence. The ERG asked the manufacturer during the clarification stage was formed the basis of this assumption. The manufacturer's response is presented in Box 14.

Box 14. Manufacturer rationale for assuming that retreatment with rivaroxaban would not occur after recurrent VTE (manufacturer response to clarification; pg 45)

Current treatment guidelines do not stratify treatment choice based on history of VTE so that physicians have equal choice of treatment for each individual case of VTE, which is not dependent on the type of anticoagulant used for the treatment of index VTE. Based on the assumption of equal choice, for simplicity in the model it was assumed that all patients will be treated with WFR in case of recurrent VTE.
Abbreviations used in box: pg, page; VTE, venous thromboembolism; WFR, warfarin.

After reviewing the manufacturer's response, the ERG considers that, as well as providing a simplifying assumption, in many centres LMWH plus warfarin forms the majority share of prescribing for treatment of VTE. However, the ERG understands that clinical practice varies, and many centres are moving towards increased prescribing of novel oral anticoagulants such as rivaroxaban. As a scenario analysis, the ERG investigated the impact of prescribing rivaroxaban at recurrence, for the acute treatment of VTE. Results of the analysis are presented in Section 6.2, **analysis B2**; the impact of the analysis on model results was minimal.

For the population with cancer, the manufacturer did not model treatment with LMWH monotherapy at recurrence of VTE. The ERG sought clinical advice and considers that a more likely treatment option for these patients would be LMWH monotherapy. The ERG asked the manufacturer at the clarification stage the rationale for assuming recurrent treatment would be warfarin; the manufacturer's response is presented in Box 15.

Box 15. Manufacturer rationale for prescribing warfarin at recurrence of VTE for the population with cancer (manufacturer response to clarification; pg 45).

The model was built for the mixed patient population and patients with active cancer were only a subgroup. The model structure is universal to all type of patients, so that re-treatment with LMWH in unique patient subgroup with active cancer wasn't addressed.
Abbreviations used in box: LMWH, low-molecular-weight heparin; pg, page; VTE, venous thromboembolism.

Following review of the manufacturer's response, the ERG considers it appropriate to carry out an additional analysis in which LMWH monotherapy was used at recurrence of VTE in the population with cancer, rather than warfarin. Results are presented in Section 6.2 **analysis B4**; the ERG notes that the impact of the analysis on the manufacturer's base case ICERs was minimal.

Patients who experience a recurrent VTE do not receive secondary prevention for future VTE after acute treatment

The ERG consulted with clinical experts who advised that long-term anticoagulation is prescribed on the basis of the balance of risk of a further recurrence without treatment versus the risk of bleeding with treatment. Moreover, any patient experiencing multiple VTE recurrences is likely to go on to receive life-long anticoagulation. The ERG therefore considers that, for the scenarios assessing treatment and secondary prevention, the assumption that patients do not receive secondary prevention for future VTE events may not reflect clinical practice. The ERG asked the manufacturer the rationale for this assumption; the manufacturer's response is presented in Box 16.

Box 16. Manufacturer rationale for assuming that patients receive a maximum of 6 months treatment for a recurrent VTE (manufacturer response to clarification; pgs 45-46)

According to the NICE guidelines, patients should be offered at least 3 months of treatment with anticoagulants. After 3 months, the decision to continue or not has to be made, so that 6 months may cover both treatment and prevention of recurrent events as it currently defined in clinical practice. However, as agreed at the NICE Scoping Meeting, the 'treatment phase' was defined (arbitrarily) as 6 months. The secondary prevention 'phase' was defined as beyond 6 months.
Abbreviations used in box: NICE, The National Institute for Health and Care Excellence; pgs, pages; VTE, venous thromboembolism.

Based upon clinical advice, the ERG does not consider it is likely that patients experiencing multiple VTE events would receive 3 months acute treatment followed by 3 months secondary prevention; the ERG considers it more likely that a patient experiencing multiple VTE events would receive life-long secondary prevention unless precluded by the balance of risk of bleeding.

The ERG asked the manufacturer to provide an analysis in which secondary prevention for VTE was prescribed after recurrence. The manufacturer kindly provided an analysis comparing warfarin versus dabigatran for the treatment and secondary prevention scenario. In this scenario, the manufacturer extended treatment with warfarin to 24 months. The manufacturer concluded that "extending the retreatment period to 24 months has a small effect on the ICER" (manufacturer response to clarification; pg 56). In this scenario, the ICER increased by £466. The ERG notes that the manufacturer did not provide a model engine in order for the ERG to replicate the methodology used for this scenario. The ERG considers that, given the structure of the model engine, there is no simple

way of incorporating the costs and consequences of extended treatment with warfarin at recurrence of VTE. The ERG discusses qualitatively the potential direction of bias from omitting secondary prevention with warfarin at recurrence in Section 6.2, **analysis B5.** On balance, the ERG considers that the impact of this omission is unclear. The ERG notes that patients receiving warfarin at recurrence depends upon rates of recurrence on treatment (generally higher for dabigatran), and rates of recurrence off treatment (affected by the number of people discontinuing treatment due to bleeds, which is generally lower for dabigatran). However, as patients in all modelled comparisons are assumed to receive warfarin re-treatment at secondary prevention, the ERG considers it possible that any differences will be small, as indicated by the manufacturer's analysis.

The incidence of severe PTS and CTEPH was captured through co-existing health states, rather than mutually exclusive health states

The manufacturer calculated the number of patients developing severe PTS and CTEPH from the number of people experiencing a DVT or a PE (Section 5.4.7). These patients then entered a coexisting health state where the costs and consequences of severe PTS and CTEPH were applied. These patients also continued to cycle around the remaining model structure and could experience further events such as bleeds and recurrent VTE events.

The ERG considers that a potential disadvantage of this approach is that the manufacturer has been unable to account for the death of patients with severe PTS and CTEPH due to an MBE or a VTE occurring whilst the patient cycles around the rest of the model. In addition, it is possible that some patients with either severe PTS or CTEPH could experience a further VTE event, and again be exposed to the risk of developing severe PTS or CTEPH. As a consequence, the number of patients in the severe PTS or CTEPH health states may be overstated, which in turn may overestimate the cost and QALY impact of these complications.

The ERG was not able to amend the manufacturer's model structure in a straightforward way in order to investigate the impact of this. Qualitatively, the ERG notes that it is not possible to assess the direction of potential bias. That is because, although the probability of developing a recurrent VTE is greater for dabigatran compared with warfarin or rivaroxaban (Section 5.4.6.1), and thus the model results are likely to favour the comparator during treatment (because more patients will develop CTEPH or severe PTS with dabigatran and therefore will cost more and result in greater QALY decrements), more people discontinue treatment due to MBEs for warfarin and rivaroxaban versus dabigatran (Section 5.4.8.1), and are thus exposed to a higher risk of recurrent VTE (and thus complications) whilst off treatment. Consequently, the ERG notes that this is an area of uncertainty (Section 6.2, **analysis B15**).

Patients who experience an MBE (including ICH) stop acute treatment or secondary prevention for VTE and do not restart treatment after the bleeding event

Clinical experts advised that the choice to continue treatment following an MBE is made on the basis of the ongoing risk of recurrent VTE, as well as the risk of bleeding from treatment. In clinical practice, the ERG understands that a proportion of patients who have experienced a bleed will continue with their acute treatment for VTE, and their secondary prevention of future VTE; approximately one-half to two-thirds of patients may continue treatment in clinical practice.

The ERG is therefore concerned that the manufacturer's assumption that people with an MBE do not restart acute treatment or secondary prevention for VTE may not reflect clinical practice. Furthermore, the ERG notes that, within TA261, patients with an extra-cranial MBE could return to treatment a month after the bleeding event.[(49)] Similarly, in TA287, discontinuation of treatment was assumed to be for one month in the case of CRNMBEs and 3 months in the case of MBEs.[(65)] Permanent discontinuation could then occur, depending on the severity of the bleeding event.

The ERG asked the manufacturer to provide a rationale for assuming that all MBEs would result in discontinuation. The manufacturer's response is presented in Box 17.

Box 17. Manufacturer rationale for assuming that all MBEs would result in discontinuation (manufacturer response to clarification; pg 45)

The decision to reinitiate therapy is not well-addressed due to the paucity of data. Most of the guidelines recommend that following a major bleed, the decision about reinstitution of oral anticoagulants should be based on analysis of the individual patient risk of re-bleeding, balanced against risk of recurrent thromboembolic events. In order to eliminate the uncertainty linked with individual assessment two assumptions withdraw anticoagulant treatment or restart anticoagulant treatment were considered equal for the modelling. Given the fact that in the acute VTE trials (RE-COVER pooled) incidence of MBE (3.2% in WFR arm) HR (yes vs no) 1.61 (0.64, 4.00) and MBE + CRBE (13.7% in WFR arm) HR (yes vs no) 2.19 (1.50, 3.19) in patients with history of bleeding were relatively higher compare with incidence of rVTE in patients with history of VTE (2.1 in WFR arm) HR (yes vs no) 1.36 (0.92, 2.01), the preference has been given to the assumption to terminate treatment with anticoagulants after major bleed in the model.
Abbreviations used in box: CRBE, clinically relevant non-major bleeding event; HR, hazard ratio; MBE, major bleeding event; pg, page; rVTE, recurrent venous thromboembolism; VTE, venous thromboembolism.

The ERG asked the manufacturer to provide an analysis in which patients experiencing an MBE continued with treatment. The manufacturer kindly provided an analysis of dabigatran versus warfarin in the acute treatment phase. The manufacturer found that the ICER in this scenario increased by approximately £530. The ERG notes that no other scenarios were modelled by the manufacturer. For completeness, the ERG carried out an analysis for all relevant scenarios in which 50% of patients

experiencing an MBE continued with treatment; the results of this analysis are presented in Section 6.2, **analysis B6**. The impact of this analysis was minimal; the ERG notes that this is in contrast to the manufacturer's results. Unfortunately, the manufacturer did not provide an updated model in engine from which the ERG could review or replicate the results; therefore, it is unclear why the ERG results differ from the manufacturers.

5.4.3 Population

5.4.3.1 Population considered in the economic analysis versus the NICE final scope

The population considered by the manufacturer for this STA comprised adults with acute symptomatic proximal DVT and PE who either:

- require acute treatment for DVT or PE (acute treatment);
- require acute treatment for DVT or PE, and for whom long-term treatment and secondary prevention is appropriate (treatment and secondary prevention).

The manufacturer presented results for both scenarios (acute treatment, and treatment and secondary prevention) for the full population, and a sub-population with cancer.

Clinical advice indicated that, after acute treatment, future treatment options will be discussed and selected in consultation with the patient on the basis of their preferences, their risk of recurrence, the consequences of future DVT or PE, and the risk of bleeds. Results of these conversations are taken into account before secondary prevention is prescribed, resulting in two distinct patient populations. The ERG therefore considers it was appropriate for the manufacturer to separately analyse the acute treatment of patients with DVT or PE, and the acute treatment of patients with DVT or PE plus secondary prevention of future DVT or PE. Moreover, the ERG notes that the analysis of these two scenarios is in line with the NICE final scope which states that the analysis "should consider both those who require a limited period of anticoagulation (3-6 months) and those who require long-term anticoagulation (usually lifelong)" (NICE final scope; pg 3).[15]

The populations considered by the manufacturer are largely in adherence with requirements of the NICE final scope for this STA, in which a population of "people with deep vein thrombosis and/or pulmonary embolism" was defined.[15] The manufacturer limited the population to only those patients experiencing a proximal DVT; i.e. distal DVT was not included in the analysis. The ERG sought clinical advice, and considers that the exclusion of patients with distal DVT by the manufacturer was reasonable; proximal DVT and PE are considered to be the most important VTE events to capture within this STA.

The manufacturer presented results within the MS for the population with cancer. Within RE-COVER I and II (the key clinical trials of interest for this STA for acute treatment with dabigatran, Section

4.3), active cancer was defined as "a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within five years before enrolment; any treatment for cancer within five years before enrolment; or recurrent or metastatic cancer" (MS; pg 61). The ERG sought clinical advice around the definition of active cancer used by the manufacturer within RE-COVER I and II. Clinical experts advised that the treatment of patients with cancer would only differ to the full population during the episode of cancer itself, and any associated treatment for that cancer. For patients who enter remission and who are not being actively treated for cancer, their treatment options immediately revert to those of the full population. As patients were included in the cancer subgroup of RE-COVER I and II for up to 5 years after their cancer, the ERG is concerned that the subgroup presented by the manufacturer may not fully reflect the patients seen in UK clinical practice.

The ERG asked the manufacturer to clarify the number of patients within the population with active cancer, whose cancer was no longer present within one or more years of enrolment. Unfortunately, the manufacturer was unable to provide these data, because the data captured within RE-COVER I and II "did not include the date of the 'active cancer'" (manufacturer response to clarification; pg 8). The ERG is therefore concerned that the data presented for active cancer within the submission may not accurately reflect the population with cancer seen in clinical practice. The ERG notes that the results for this sub-group of patients are therefore subject to a degree of uncertainty. The ERG is unable to infer what impact this will have upon the results presented by the manufacturer; **analysis B39**, Section 6.2.

5.4.3.2 Generalisability of modelled population

The manufacturer utilised baseline characteristics from clinical trial data for a number of parameters including:

- baseline proportion of DVT events (69%, pooled data from RE-COVER I and II);
- baseline proportion of PE events (31% pooled data from RE-COVER I and II);
- average age of the population (to calculate the appropriate time horizon; 54.7 years from the dabigatran arm of RE-COVER I).

The ERG notes that the average age of all patients in RE-COVER I (i.e. including patients in the warfarin arm) was approximately 55 years. For RE-COVER II, the average age of patients at baseline was 54.9 years.

The ERG consulted with clinical experts around the generalisability of the baseline characteristics of patients contained within RE-COVER I and II. In general, it was considered that the clinical trials were largely representative of the patient population presenting in UK clinical practice, with the exception of the age of patients. In general, the clinical experts advised that the average age of patients within the clinical trials is younger than the average presenting age in clinical practice. The

ERG adjusted the time horizon in the model in a sensitivity analysis to reflect this difference (**analysis B9**); this analysis is described in greater detail in Section 5.4.5.

5.4.4 Interventions and comparators

5.4.4.1 Comparison with the NICE scope

The manufacturer considered the clinical and cost-effectiveness of the use of LMWH plus dabigatran (hereafter referred to as "dabigatran") compared with LMWH plus warfarin (hereafter "warfarin"), rivaroxaban and LMWH monotherapy (for the population with cancer) for the acute treatment of people with a confirmed DVT (proximal) or PE (with or without proximal DVT) and the secondary prevention of future DVTs or PEs.

The ERG notes that the comparators considered by the manufacturer correspond with three of the five comparators outlined within the NICE final scope; the two omitted comparisons were:

- initial treatment with fondaparinux followed by treatment with a vitamin-K antagonist;
- rivaroxaban (for the population with cancer).

The manufacturer justified the omission of the comparison with fondaparinux as follows: "[fondaparinux] is not approved for long-term prophylaxis of VTE and therefore is not considered a relevant comparator for dabigatran in the indication of treatment and long-term secondary prevention of VTE as detailed in this submission" (MS; pg 15).

The ERG notes that the NICE scope states "initial treatment with fondaparinux followed by treatment with a vitamin-K antagonist", and therefore the ERG considers that the manufacturer's rationale for exclusion does not address the use of fondaparinux in the required acute period. Nevertheless, following consultation with clinical experts, the ERG understands that fondaparinux is rarely used to treat acute DVT or PE in clinical practice. The ERG therefore considers that the exclusion of fondaparinux as a comparator by the manufacturer is reasonable.

The manufacturer did not provide a rationale for the lack of comparison with rivaroxaban in the population with cancer within the MS. The ERG asked the manufacturer to provide the rationale for omitting this comparison. The manufacturer's response is presented in Box 18.

Box 18. Manufacturer rationale for excluding comparison with rivaroxaban in the population with cancer (manufacturer response to clarification; pg 5)

In a previous NICE Technology Appraisal of rivaroxaban for the treatment and secondary prevention of recurrent VTE (TA 261), the Appraisal Committee made the following conclusion in relation to the use of rivaroxaban in the subgroup of patients with active cancer: 'Given the lack of clinical evidence for this group of patients, the Committee was unable to make specific recommendations on the use of

rivaroxaban in people with cancer but recognised the disadvantages of the currently available treatment, which involves regular injections, and which some patients might choose to decline.' Given this opinion from the Appraisal Committee, rivaroxaban was not considered to be a relevant treatment option in this subgroup and was therefore not included as a comparator to dabigatran for this subgroup in the submission.
Abbreviations used in box: NICE, the National Institute for Health and Care Excellence; pg, page; VTE, venous thromboembolism.

Based upon review of the clinical data, the ERG is aware that data for rivaroxaban in the population with cancer is limited to rates of recurrent VTE during acute treatment. No data are available for bleeding events, or recurrent VTE and bleeding during secondary prevention. Consequently, the ERG agrees with the manufacturer that, unfortunately, the lack of available clinical data prevents an informative comparison with rivaroxaban within this population.

5.4.4.2 Modelled treatment regimens

The treatment regimens modelled by the manufacturer for dabigatran and the included comparators are outlined in Table 81.

Table 81. Interventions and comparators modelled in the manufacturer's economic analysis

	Population		**Acute treatment modelled**	**Secondary prevention modelled**	**Comments**
	Full population?	Population with cancer?			
Intervention					
Dabigatran	Yes	Yes	5 days LMWH[a]/UFH[b] and 6 months treatment with dabigatran 220-300mg per day.	6-18 months dabigatran 220-300mg daily.	For secondary prevention, dabigatran is continued for 6 months for comparison with rivaroxaban and LMWH, and 18 months for comparison with warfarin.
Comparators					
Warfarin	Yes	No	5 days LMWH[a]/UFH[b] and 6 months treatment with warfarin.	18 months warfarin.	–
Rivaroxaban	Yes	No	6 months 20-30mg rivaroxaban.	6 months 20-30mg rivaroxaban.	–
LMWH	No	Yes	6 months dalteparin	6 months dalteparin.	For the population with cancer.

[a] for deep vein thrombosis: 24.75% enoxaparin; 49.5% dalteparin; 24.75% tinzaparin; for pulmonary embolism: 90% enoxaparin. [b] for deep vein thrombosis: 1% unfractionated heparin; for pulmonary embolism: 10% unfractionated heparin.

Abbreviations used in table: LMWH, low-molecular-weight heparin; mg, milligrams; UFH, unfractionated heparin; VKA, vitamin-K antagonist.

The ERG has two main concerns around the regimens modelled; specifically, the treatment duration applied, and the dose of dabigatran.

Treatment duration

For all analyses presented by the manufacturer, the treatment duration modelled for the acute treatment period was 6 months. After consultation with clinical experts, the ERG considers this treatment duration to reasonably reflect current clinical practice; however, the ERG acknowledges that more recently, and following publication of CG144, acute treatment duration of 3 months is increasingly common.[(66)] Therefore, for completeness, the ERG carried out a scenario analyses in which the duration of acute treatment was reduced from 6 months to 3 months; results of this analysis are presented in Section 6.2 **analysis B7.**

The impact on the ICER of **analysis B7** was such that, for the comparison of dabigatran with warfarin, the ICER for the acute treatment scenario moved from an ICER of £862, to dabigatran becoming the dominant treatment option (dabigatran less costly and more effective compared with warfarin). In the treatment and secondary prevention scenario, the ICER for dabigatran versus warfarin reduced from £8,319 to £6,032. The ERG notes that this difference is largely a consequence of a reduction in costs, driven by reduced cost of dabigatran treatment. Conclusions for the comparisons with rivaroxaban and LMWH in the population with cancer were unaffected.

Duration of secondary prevention was assumed to differ based upon the comparator of interest. The manufacturer assumed that treatment with a VKA (warfarin) would continue for 18 months after the acute treatment period. For rivaroxaban and LMWH, the manufacturer assumed there would be 6 months secondary prevention. The manufacturer assumed that the duration of dabigatran treatment would be the same as the comparator of interest. As a consequence of these assumptions, the duration of secondary prevention for dabigatran varied according to the comparator selected.

The ERG acknowledges that long-term efficacy and safety data for the novel oral anticoagulants (NOACs) is limited; however, the ERG notes that a key disadvantage of using different treatment durations by comparison is that the results arising from each analysis cannot be compared, and the analysis cannot be considered fully incremental. This is because the costs and QALYs associated with dabigatran will differ in each comparison. The ERG considers that this may limit the interpretation of the full range of comparisons presented; moreover, the NICE Guide to Methods of Technology Appraisal states that a fully incremental analysis, when appropriate, should be presented.[(67)]

The ERG sought clinical input around the duration of secondary prevention. The clinical experts asserted that in patients for whom the risk of recurrent VTE outweighed the risk of bleeding,

secondary prevention would be prescribed and would generally be life-long. In patients for whom the risk of recurrent VTE did not outweigh the risk of bleeding, secondary prevention would not be prescribed, with treatment ceasing after acute treatment of the initial VTE event. Moreover, the clinical experts did not consider that duration of treatment would differ by intervention.

The ERG is therefore concerned that the manufacturer has underestimated the likely treatment duration for dabigatran, warfarin, rivaroxaban and LMWH in clinical practice for secondary prevention. In addition, the ERG considers there is no clinical basis for the manufacturer's assumption that treatment duration for secondary prevention differs by comparator. To reflect clinical practice, the ERG carried out an analysis assuming life-long secondary prevention treatment for all interventions, for the treatment and secondary prevention scenarios. For the purposes of this analysis, the ERG assumed that treatment effectiveness and the adverse effects of treatment were maintained during the extended secondary prevention period. The ERG acknowledges that no data exist for this duration of treatment, and thus this analysis should be considered exploratory. The ERG further notes that is was not possible to easily increase the duration of secondary prevention with warfarin re-treatment due to the way the model engine was set up. Consequently, the ERG modelled lifelong treatment duration for the initial treatment only; i.e. dabigatran, rivaroxaban, warfarin and LMWH. Results of the analysis are presented in Section 6.2 **analysis B8**.

The impact of **analysis B8** was such that the ICER for dabigatran versus warfarin reduced from £8,319 to £6,868. The ERG notes that whilst the incremental costs associated with dabigatran for this scenario increased by £1,363 per patient versus warfarin (largely dabigatran drug cost), the incremental QALYs also increased by 0.210 per patient. The ERG considers that a large proportion of this increase in QALYs relates to the treatment disutility applied to warfarin; the ERG notes a number of concerns with the warfarin decrement in Section 5.4.12.5. The ERG is therefore cautious about drawing conclusions from this analysis.

The ICER for dabigatran versus rivaroxaban for **analysis B8** also changed, from dabigatran dominating rivaroxaban (less costly and more effective) to dabigatran being associated with an incremental cost per additional QALY of £157 versus rivaroxaban. The incremental cost changed from -£76 per patient (cost saving) to £7 per patient over the model lifetime (60 years) and related to dabigatran treatment cost; however, the ERG notes that total costs between dabigatran and rivaroxaban remained very similar. The incremental QALYs increased from 0.002 to 0.045 per patient over the life time of the model. The ERG considers that a large contributor of this change was increased bleeding events associated with rivaroxaban; the ERG notes a number of concerns with the warfarin decrement in Section 5.4.12.6.

The ICER for dabigatran versus LMWH in the population with cancer remained unchanged, with dabigatran dominating LMWH (less costly, more effective).

The dose of dabigatran

The draft summary of product characteristics (SmPC) for dabigatran for treatment and secondary prevention of DVT and PE states that the standard daily dose of dabigatran is 300mg per day, taken as one 150mg capsule twice daily. The draft SmPC also states that, for patients aged 80 years or above, or patients who receive concomitant verapamil, the daily dose shall be lowered to 220mg per day, taken as one 110mg capsule twice daily. By contrast, the clinical trials for dabigatran in DVT and PE (RE-COVER I, RE-COVER II, RE-MEDY, RE-SONATE) considered only the dose of 300mg per day, and therefore no clinical data is available at the dose of 220mg per day.

To reflect the SmPC, the manufacturer modelled dabigatran at a dose of 220mg to 300mg per day, with 5% of patients receiving a 220mg daily dose, and 95% patients receiving a 300mg daily dose. The basis of these proportions was the proportion of patients over 80 years of age within the dabigatran clinical trials.

Due to the lack of clinical data, the manufacturer assumed that efficacy and safety data for the 220mg dose would be equivalent to those associated with the 300mg dose within the economic analysis. Moreover, as the cost of a 220mg dose and a 300mg dose is identical (Section 5.4.13.2), the cost data associated with the lower dose was also assumed to be equivalent.

The ERG is concerned that, without any clinical data at 220mg per day for the population of patients with DVT or PE, it is impossible to say whether the manufacturer's assumption of equivalence in efficacy is reasonable. The ERG notes that the dose of 220mg dabigatran has been studied in patients with atrial fibrillation (AF) in RE-LY; in those patients, efficacy data were not found to be equivalent to the 300mg dose. Specifically, whilst dabigatran 150mg twice daily was associated with a statistically significant reduction in the incidence of stroke or systemic embolism compared with warfarin, no statistically significant difference was reported for the lower, 110mg twice daily dose of dabigatran.[68] Whilst it may therefore be possible to infer that a similar result would be seen in patients with DVT or PE, as there is no evidence specifically in acute treatment or secondary prevention of DVT or PE, the ERG considers that this conclusion would be speculative.

Furthermore, the ERG is concerned that the manufacturer may have underestimated the proportion of patients likely to receive the dose of 220mg in clinical practice. Following consultation with clinical experts, the ERG considers that the clinical trial population within RE-COVER, RE-MEDY and RE-SONATE are generally younger than the population seen in clinical practice (Section 5.4.3).

Consequently, in clinical practice a greater proportion of patients than 5% may be eligible for the 220mg dose on the basis of their age.

Due to a lack of clinical data, and uncertainty around what proportion of patients may receive the lower dose in clinical practice, the ERG considers it is not possible to infer what effect the dose of dabigatran will have on the model results. The ERG noted this uncertainty in Section 6.2, **analysis B41**.

5.4.5 Perspective, time horizon and discounting

Perspective and discounting

The manufacturer adopted an NHS and personal social services (PSS) perspective for the analysis, and applied a discount rate of 3.5% for costs and outcomes beyond the first year of the model. The ERG considers this to be appropriate and in line with the NICE reference case.

Time horizon

The time horizon for the analysis was set at lifetime. Following consultation with clinical experts and following review of the manufacturer's systematic review and the additional papers identified by the ERG (Section 5.3), the ERG considers this is an appropriate time-frame in which to capture the key costs and consequences of this condition.

To capture a lifetime time horizon, the manufacturer modelled 60-years in the base case. The manufacturer also presented results from scenario analyses in which the time horizon was set to 6-months (for the acute treatment scenario) and 1-year (for both the acute treatment and the treatment and secondary prevention scenarios). The justification provided for a 60-year time horizon was as follows: "the time horizon in the base case is 60 years (patients' lifetimes) in order to capture the lifetime of the youngest patients up to 100 years of age (17.6% of people in the UK were expected to reach 100 years of age in 2011). The applied age of the cohort at model start is 54.7 years which equals the average age of the trial population in RE-COVER I." (MS; pg 236).

The ERG notes that ISPOR modelling good practice guidelines present two common approaches to setting a sufficiently long time horizon: modelling to an average cohort age of 120 years, and tracking the modelled cohort until more than 99.9% of the individuals are dead.[(69)] The ERG is unclear why the manufacturer based the model duration upon the age of the youngest patient in the cohort, rather than the average cohort age.

The ERG consulted clinical experts who suggested that the average age of patients enrolled in RE-COVER I and II is likely to be younger than the age of patients seen in UK clinical practice (Section

5.4.3). Consequently, the ERG is concerned that a 60-year time frame in the base case may be larger than necessary to capture the full range of costs and consequences for the population of interest.

Within the model, 99.9% patients are dead by approximately 50 years in all scenarios modelled by the manufacturer. Moreover, as part of the submission, the manufacturer provided a subset of slides summarising a discussion with a UK panel of clinical experts in 2008 (five experts were present, although details around recruitment or elicitation of responses was not presented within the MS); the clinicians estimated the average age of patients for this condition to be 65 years of age.[70] Consequently, the ERG considers that setting a time-horizon of 50 years would sufficiently capture the patient group of interest according to the ISPOR modelling good practice guidelines, both by the percentage of patients dead (99.9%) and by the anticipated average age of the cohort (115 years of age). The ERG further notes that the time horizon adopted in TA261 and TA287 was 40 years, and therefore considers a time horizon of 50 years to be more than sufficient to capture the full range of future costs and consequences associated with the addition of dabigatran to the treatment pathway for VTE.

The ERG carried out an analysis in which the time horizon was reduced to 50 years and presents results in Section 6.2 **analysis B9**; the impact of this analysis on the manufacturer's ICERs was negligible.

5.4.6 Treatment effectiveness – recurrence of VTE

All people entering the model after an index VTE had a probability of experiencing up to two recurrent VTE events, comprising of either: a DVT (proximal); or a PE (fatal or non-fatal). The probability of recurrence differed according to whether the patient was on or off treatment. For patients on treatment, the probability of recurrence further differed according to which treatment the patient was receiving.

This section outlines the calculation of recurrent VTE used within the manufacturer's model, specifically the probability of recurrent VTE whilst:

- receiving initial treatment (Section 5.4.6.1);
- receiving treatment with warfarin following recurrence (Section 5.4.6.2);
- off treatment (Section 5.4.6.3).

5.4.6.1 Recurrent VTE whilst receiving initial treatment

To estimate the probability of a recurrent DVT (proximal) or PE (fatal or non-fatal), the manufacturer calculated the incidence of all recurrent VTE for each treatment, then attributed a proportion of the overall incidence to proximal DVT, fatal PE or non-fatal PE. Figure 12 provides a graphical summary of this approach and the remainder of this section describes this in greater detail.

Figure 12. Manufacturer's approach to estimating probability of recurrent DVT or PE applied within the model

Estimated incidence of all recurrent VTE (DVT, fatal PE, non-fatal PE)

Acute treatment	Incidence
D (full)	2.65%
W (full)	2.43%
R (full)	2.16%
D (cancer)	5.63%
L (cancer)	3.63%

Secondary prevention	Incidence
D (full)	1.82%
W (full)	1.26%
D (full)	0.45%
R (full)	1.01%
D (cancer)	0.45%
L (cancer)	3.54%

Methods:

1. Incidence estimated for a baseline treatment from clinical trial data
2. Baseline incidence multiplied by a HR or RR to estimate incidence for comparator treatment

Split by proportion of incidence attributable to DVT, fatal PE, non-fatal PE

Acute treatment	DVT	PE (nf)	PE (f)
D (full)	63%	34%	3%
W (full)	61%	34%	5%
R (full)	42%	55%	3%
D (cancer)	63%	34%	3%
L (cancer)	58%	39%	3%

Secondary prevention	DVT	PE (nf)	PE (f)
D (full)	62%	35%	4%
W (full)	72%	22%	6%
D (full)	67%	33%	0%
R (full)	71%	29%	0%
D (cancer)	67%	33%	0%
L (cancer)	58%	39%	3%

Methods:

1. Splits of VTE events estimated for each individual treatment from relevant clinical trials

Resulting incidence applied within the model

Acute treatment	DVT	PE (nf)	PE (f)
D (full)	1.7%	0.9%	0.1%
W (full)	1.5%	0.8%	0.1%
R (full)	0.9%	1.2%	0.1%
D (cancer)	3.5%	1.9%	0.2%
L (cancer)	2.1%	1.4%	0.1%

Secondary prevention	DVT	PE (nf)	PE (f)
D (full)	1.1%	0.6%	0.1%
W (full)	0.9%	0.3%	0.1%
D (full)	0.3%	0.1%	0.0%
R (full)	0.7%	0.3%	0.0%
D (cancer)	0.3%	0.1%	0.0%
L (cancer)	2.1%	1.4%	0.1%

Abbreviations used in figure: cancer, population with cancer; D, dabigatran; DVT, proximal deep vein thrombosis; f, fatal; full, full population; L, low-weight-molecular heparin; nf, non-fatal; PE, pulmonary embolism; R, rivaroxaban; W, warfarin.

Incidence of recurrent VTE

A summary of the manufacturer's modelled incidence of recurrent VTE for treatment and secondary prevention treatment is presented in Table 82 and described in greater detail below.

Table 82. Probability of recurrent VTE during treatment applied in the manufacturer's economic analysis

Comparison	Intervention	Population	Acute treatment period	Data source	Secondary prevention period	Data source
Dabigatran versus warfarin	Dabigatran	Full population	2.65%	RE-COVER I and II	1.82%	RE-MEDY
	Warfarin	Full population	2.43%		1.26%	
Dabigatran versus rivaroxaban	Dabigatran	Full population	2.65%	RE-COVER I and II; EINSTEIN-DVT and PE	0.45%	RE-SONATE; EINSTEIN-EXT
	Rivaroxaban	Full population	2.16%		1.01%	
Dabigatran versus LMWH	Dabigatran	Population with cancer	5.63%	RE-COVER I and II (cancer subgroup); meta-analysis	0.45%	RE-SONATE; DACUS
	LMWH	Population with cancer	3.63%		3.54%	
Abbreviation used in table: LMWH, low-molecular-weight heparin						

Acute treatment

For acute treatment, the manufacturer estimated a baseline probability of recurrent VTE for patients receiving warfarin. This figure differed for the full population and the population with cancer. The source of data used to estimate this probability was pooled trial data of the primary outcome from the warfarin arm in RE-COVER I and II. RE-COVER I and II were two similar trials which evaluated dabigatran 150mg twice daily versus warfarin in the acute treatment of DVT and PE (for a more detailed description of RE-COVER I and II, see Section 4.3). The estimates of baseline probability were based upon data analysed at 7 months (6 months treatment and 30 days follow-up), and related to the treated set of patients. The baseline probability of recurrent VTE during the acute treatment phase for patients receiving warfarin was estimated to be:

- 2.43% (full population, 62 patients out of 2,554).
- 7.41% (population with cancer, 12 patients out of 162).

The estimated baseline probability for warfarin was then multiplied by a hazard ratio (HR) or relative risk (RR) for each remaining treatment versus warfarin, to estimate a corresponding probability of recurrent VTE that treatment.

For the full population receiving dabigatran, the HR for dabigatran versus warfarin was estimated from the manufacturer's pair-wise meta-analysis of RE-COVER I and II, and was estimated to be 1.09 (MS; pg 117).

For the full population receiving rivaroxaban, the HR for rivaroxaban versus warfarin was estimated from a published pair-wise meta-analysis of EINSTEIN-DVT and EINSTEIN-PE using pooled 3, 6, and 12 month data, and was estimated to be 0.89 (for a description of these trials, see Section 4.8).[71]

For the population with cancer receiving dabigatran, the HR for dabigatran versus warfarin was estimated from the manufacturer's pair-wise meta-analysis of the cancer subgroup within RE-COVER I and II, and was estimated to be 0.76 (MS pg 118).

Finally, for the population with cancer receiving LMWH, the relative risk (RR) of LMWH versus warfarin was estimated from the manufacturer's pair-wise meta-analysis of five published studies, in patients with active cancer, and was estimated to be 0.49 (MS; pg 144).

The resulting probabilities for recurrent VTE during acute treatment are presented in Table 83.

Table 83. Probability of recurrent VTE during acute treatment

Comparison	Intervention	Population	Baseline probability	HR / RR versus baseline treatment	Resultant probability
Dabigatran versus warfarin	Dabigatran	Full population	2.43% (warfarin)	1.09	2.65%
	Warfarin	Full population		–	2.43%
Dabigatran versus rivaroxaban	Dabigatran	Full population		1.09	2.65%
	Rivaroxaban	Full population		0.89	2.16%
Dabigatran versus LMWH	Dabigatran	Subgroup of patients with active cancer	7.41% (warfarin)	0.76	5.63%
	LMWH	Subgroup of patients with active cancer		0.49	3.63%
Abbreviations used in table: HR, hazard ratio; LMWH, low-molecular-weight heparin; RR, relative risk.					

The manufacturer noted that the rates of recurrent VTE were observed to be higher in the first months after the index event, and gradually declined thereafter. The ERG consulted with clinical experts who agreed that a similar result is often seen in clinical practice. Therefore, the manufacturer log-transformed the Markov cycle probabilities for the acute treatment period.

Secondary prevention

For secondary prevention, a similar methodology to the acute period was used to estimate incidence of recurrent VTE.

For dabigatran versus warfarin, the manufacturer estimated a baseline probability of recurrent VTE for patients receiving warfarin treatment using primary outcome data for the warfarin arm in RE-MEDY. RE-MEDY compared extended use of dabigatran 150mg twice daily versus warfarin for secondary prevention of VTE (for a more detailed description of RE-MEDY, see Section 4.6). The data were analysed at 18 months, and were described by the manufacturer as being related to the intent-to-treat (ITT) set of patients. For the full population, the baseline probability of recurrent VTE during 18 months of treatment was estimated to be 1.26% (18 patients out of 1,426).

For dabigatran versus rivaroxaban for the full population, and dabigatran versus LMWH in the population with cancer, the manufacturer estimated a baseline probability of recurrent VTE for patients receiving placebo treatment using trial data from the placebo arm of RE-SONATE. RE-SONATE compared extended use of dabigatran 150mg twice daily versus placebo for secondary prevention of VTE (for a more detailed description of RE-SONATE, see Section 4.6.1). The data were analysed at 18 months, and were described by the manufacturer as being related to the randomised set of patients. The baseline probability of recurrent VTE was estimated to be 5.59% (37 patients out of 662, MS; pg 240).

The estimated baseline probability was then multiplied by a hazard ratio (HR) or relative risk (RR) for each remaining treatment versus warfarin or placebo, to estimate a probability of recurrent VTE for each remaining intervention.

For the full population receiving dabigatran in the comparison with warfarin, the HR of dabigatran versus warfarin was estimated from the manufacturer's analysis of RE-MEDY, and was estimated to be 1.44 (MS; pg 20).

For the full population receiving dabigatran in the comparison with rivaroxaban, the HR of dabigatran versus placebo was estimated from the manufacturer's analysis of RE-SONATE, and was estimated to be 0.08 (MS; pg 22).

For the full population receiving rivaroxaban, the HR of rivaroxaban versus placebo was estimated from EINSTEIN-EXT and was estimated to be 0.18 (MS; pg 128). EINSTEIN-EXT compared extended use of rivaroxaban versus warfarin for secondary prevention of VTE.

For the population with cancer, the HR of dabigatran versus placebo was estimated from the manufacturer's analysis of RE-SONATE, and was assumed to be the same as for the full population at 0.08 (MS; pg 22).

Finally, for the population with cancer, the HR of LMWH versus placebo was estimated from the DACUS study, and was estimated to be 0.63 (MS; pg 241).

The resulting probabilities for recurrent VTE in the secondary prevention phase are presented in Table 84.

Table 84. Probability of recurrent VTE during secondary prevention

Comparison	Intervention	Population	Baseline probability	HR / RR versus baseline treatment	Resultant probability
Dabigatran versus warfarin	Dabigatran	Full population	1.26% (warfarin)	1.44	1.82%
	Warfarin	Full population		–	1.26%
Dabigatran versus rivaroxaban	Dabigatran	Full population	5.59% (placebo)	0.08	0.45%
	Rivaroxaban	Full population		0.18	1.01%
Dabigatran versus LMWH	Dabigatran	Population with cancer	5.59% (placebo)	0.08	0.45%
	LMWH	Population with cancer		0.63	3.54%
Abbreviations used in table: HR, hazard ratio; LMWH, low-molecular-weight heparin; RR, relative risk.					

ERG comments

The ERG considers that the source of data selected by the manufacturer was generally applicable for the populations of interest for this STA. Specifically, the ERG considers that pooling data from RE-COVER I and II was not unreasonable due to the comparable populations within these analyses (Section 4). Moreover, the ERG considers that using pooled data for 3, 6, and 12 months from EINSTEIN-DVT and EINSTEIN-PE was appropriate. This is because in previous technology appraisals TA261 and TA287, it was considered that there was insufficient evidence to demonstrate that rivaroxaban had a substantially different effectiveness across treatment durations, and that no biological reason was considered to exist that would explain such a differential effect.

The ERG also notes that treatment duration within secondary prevention trials differed. RE-MEDY and RE-SONATE were initially designed to be 18 month trials, although this was extended, and planned treatment duration varied between 6 and 36 months. By contrast, EINSTEIN-EXT was designed to assess the extension of treatment by 6-12 months. On balance, the ERG considers that the data within these trials at the end of treatment are comparable. A more detailed description of this is provided in Section 4.

The ERG has three main concerns about the methods used to calculate recurrent VTE for those on treatment in the analysis.

Firstly, the ERG notes that, due to differing baseline probabilities used within the treatment and secondary prevention scenario, the results arising from these analyses for each comparator cannot be compared and therefore cannot be considered a fully incremental analysis, and each head-to-head comparison must be considered as a distinct analysis. This is because the costs and QALYs associated with dabigatran will differ for each comparison due to differing probabilities of recurrent VTE. The ERG considers that this may limit the interpretation of the full range of comparisons presented; moreover, the NICE Guide to Methods of Technology Appraisal states that a fully incremental analysis, when appropriate, should be presented.[(67)] For the full population analyses, the ERG considers there is no clinical basis on which to believe that the efficacy of dabigatran would differ by comparator.

Secondly, the ERG notes that the dataset used by the manufacturer for RE-COVER I and II relate to a time period of six months plus 30 days post treatment. The ERG asked the manufacturer the rationale for using these data in the analysis; the ERG reviewed the manufacturer's response (manufacturer response to clarification; pg 46) and remains unclear why these data were selected for use in the model.

Thirdly, the ERG was unable to verify the HR used by the manufacturer from DACUS, for the HR of LMWH versus placebo of 0.63 for the population with cancer analysis.[(72)]

To address the three above issues, the ERG carried out an analysis using data from the ERG NMA. Results are presented in Section 6.2, **analysis B10**. In order to calculate a monthly probability of recurrence from the end of trial NMA results, the ERG assumed that duration of acute treatment was 6 months, and duration of secondary prevention was 18 months.

The impact of **analysis B10** for the comparison of dabigatran versus warfarin was a slight increase in the ICER for the acute treatment scenario from £862 to £913; this increase relates to a very slight increase in the incremental probability of developing a recurrent VTE for dabigatran versus warfarin. For the treatment and secondary prevention scenario, the opposite was true, and the ICER for dabigatran versus warfarin fell from £8,319 to £7,800. The ERG considers that the reduction relates to a decrease in the incremental probability of developing a recurrent VTE for dabigatran versus warfarin in the secondary prevention phase; this outweighs the increase in the acute treatment phase because it relates to 18 months' worth of treatment, as opposed to 6 months' worth. The conclusions from the comparison of dabigatran versus rivaroxaban and LMWH in the population with cancer were largely unaffected.

In addition, the ERG notes a couple of minor issues with the calculations relating to incidence of recurrent VTE.

Firstly, the manufacturer multiplied baseline probabilities by HRs; thus, implicitly assuming that that the properties of a HR were equivalent to an RR. To multiply a baseline probability by a HR to estimate an alternative probability, it is first necessary to first convert the baseline probability into a rate prior to multiplication. The ERG notes that this is a minor issue. After multiplication it is then necessary to convert back into a probability.[73] The ERG amended the manufacturer's calculations for the relevant comparisons; a description of the analysis carried out is presented in Section 5.5.1, with results presented in Section 6.1; **analysis A1**. The impact upon the ICERs was negligible.

Secondly, the ERG considers that the manufacturer may have made a small mistake in calculating the baseline probability for warfarin for the acute treatment period, in patients with cancer who receive both treatment and secondary prevention. In this scenario, the baseline probability of recurrent VTE for warfarin used to estimate probabilities for the acute period is 2.43%, a result based upon the full population pooled analysis of RE-COVER I and II, rather than subgroup of patients with cancer (7.41%). The ERG considers that this is likely to have been a mistake, and corrected this in a sensitivity analysis. A description of the analysis carried out is presented in Section 5.5.1, with results presented in Section 6.1; **analysis A2**. The impact upon the ICERs was negligible.

Attributing the total incidence of recurrent VTE to rates of DVT and PE

Within the model, following calculation of the incidence of recurrent VTE, the manufacturer attributed a proportion of the incidence to: proximal DVT; non-fatal PE; and fatal PE. The proportions applied in the acute treatment period and secondary prevention period are presented in Table 85 and Table 86, respectively.

Table 85. Proportion of recurrent DVT and PE, by treatment, applied within the acute treatment period

Type of recurrent VTE	Dabigatran	Warfarin	Rivaroxaban	Dabigatran (population with cancer)	LMWH (population with cancer)
Recurrent DVT (proximal)	63%	61%	42%	63%	58%
Recurrent PE (non-fatal)	34%	34%	55%	34%	39%
Recurrent PE (fatal)	3%	5%	3%	3%	3%
Source	Pooled analysis of RE-COVER I and II		Pooled analysis of EINSTEIN-PE and EINSTEIN-DVT	Pooled analysis of RE-COVER I and II, cancer subgroup	Average of other presented data
Abbreviations used in table: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism.					

Table 86. Proportion of recurrent DVT and PE, by treatment, applied within the secondary prevention period

Type of recurrent VTE	Dabigatran	Warfarin	Dabigatran	Rivaroxaban	Dabigatran (population with cancer)	LMWH (population with cancer)
Recurrent DVT (proximal)	62%	72%	67%	71%	67%	58%
Recurrent PE (non-fatal)	35%	22%	33%	29%	33%	39%
Recurrent PE (fatal)	4%	6%	0%	0%	0%	3%
Source	RE-MEDY	RE-MEDY	RE-SONATE treated set (full population)	EINSTEIN-EXT	RE-SONATE treated set (full population)	As acute period
Abbreviations used in table: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism.						

The ERG notes that the proportion of each type of event differs by treatment, and is taken from clinical trial data without adjustment via meta-analysis between comparators. The ERG consulted with clinical experts around the basis for the difference in type of recurrent event and was advised that there was no clinical basis for expecting such a difference.

In addition, the ERG notes that, for secondary prevention analyses, the figures presented for dabigatran in Table 86 differ by comparison. Consequently, the results arising from each analysis cannot be compared with one another, and must be considered as head-to-head comparisons. The analysis cannot therefore be considered fully incremental. The ERG considers that there is no clinical

basis for analysing each comparator as a distinct population; therefore, the ERG considers this to be a weakness of the analysis.

To address both above issues, the ERG carried out a sensitivity analysis in which the proportion of each type of event was set to be the same as dabigatran in RE-COVER I and II, and RE-MEDY. Results are presented in Section 6.2 **analysis B11.** The impact of this analysis on the manufacturer model results was a modest increase in the ICERs associated with dabigatran versus warfarin in the acute treatment phase (£862 to £1,032) and the secondary prevention phase (£8,319 to £9,293). The ERG believes that the cause of this increase was related to a small reduction in incremental QALYs for dabigatran versus warfarin, as a consequence of a small reduction in the number of VTE-related deaths for warfarin.

For the comparison of dabigatran with rivaroxaban in the acute treatment phase for **analysis B11**, the ICER switched from dabigatran dominating rivaroxaban (less costly and more effective) to dabigatran being associated with an incremental cost per additional QALY gained of £21,066. The ERG believes that this is largely a consequence of an increase in relative cost of managing CTEPH as a result of fewer PE cases for rivaroxaban. The remaining comparisons were largely unaffected.

5.4.6.2 Recurrent VTE whilst receiving warfarin re-treatment

Within the manufacturer's model, patients who experience a recurrent VTE receive LMWH (5 days) and warfarin (6 months, Section 5.4.2). Whilst on treatment, the manufacturer assumed that the risk of recurrent VTE is as described in Table 87. Note; the values within this table are equivalent to the figures presented for warfarin for acute treatment in Section 5.4.6.1 above.

Table 87. Probability of recurrent VTE for warfarin treatment

Type of recurrent VTE	Warfarin
Probability of recurrence (over 7 months)	2.43%
Proportion DVT (proximal)	*61%*
Proportion PE	*34%*
Proportion fatal PE	*5%*
Source	Pooled analysis of RE-COVER I and II
Abbreviations used in table: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism.	

5.4.6.3 Recurrent VTE whilst off treatment

Whilst off treatment, either following completion of treatment or withdrawal from treatment, the probability of a recurrent VTE applied within the model is presented in Table 88.

Table 88. Probability of recurrent VTE whilst off-treatment

Recurrent VTE	Per cycle probability
Probability of recurrence (per 30 day cycle)	0.423%
Proportion DVT (proximal)	*65%*
Proportion PE	*23%*
Proportion fatal PE	*12%*
Source	Prandoni *et al.*[74]
Abbreviations used in table: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.	

The manufacturer estimated the figures in Table 88 using data from a study published in 2007 by Prandoni *et al*.[74] This paper describes a prospective cohort study in which 1,626 patients with a first episode of symptomatic proximal DVT and/or PE were followed-up for up to a maximum of 10 years after discontinuation from acute anticoagulation treatment. The aim of the analysis was to assess the rate of recurrent VTE after withdrawal of VKAs, and to identify clinical parameters associated with a higher likelihood of recurrent VTE. The study was carried out in Italy, and outpatients were recruited between May 1991 and April 2003. Patients with active cancer were excluded from this analysis, as were those who had experienced multiple VTE events. The average age of included patients was 66 years of age, with 66% patients presenting with DVT alone, and the remaining with PE (with or without DVT). The authors collected information on recurrent thromboembolism.

Prandoni *et al*. report the total number of recurrent VTE events (373), and the number of fatal PE events (43).[74] The paper also reports that PE occurred in 69 patients with initial PE and 61 patients with initial DVT; therefore, although not reported within the MS, the ERG considers it likely that the manufacturer has estimated the number of PE recurrences as 69 plus 61 (PE events) minus 43 (fatal PE events) = 87. The remaining patients are therefore assumed to have experienced a recurrent DVT (373 minus 69 minus 61 = 243). The estimated cumulative incidence of recurrent VTE was 39.9% (95% confidence interval [CI] 35.4%, 44.4%) after 10 years. The ERG notes that the manufacturer has correctly converted the cumulative probability of recurrent VTE to a cycle (30-day) probability of 0.423%.

Prandoni *et al*. appears to be largely representative of the UK population of interest, in particular the presenting age (average 66 years) and type of initial VTE event (67% initial DVT and 33% initial PE); however, the ERG notes that the data is not generalisable to those with active cancer as these patients were excluded from the study.[74]

The manufacturer did not describe the methods in which Prandoni *et al*. was identified and selected for use within the model. The ERG asked the manufacturer to clarify the rationale for the selection of this paper. The manufacturer stated that "the Prandoni cohort contained highest number of patients being followed up after treatment termination (1,626) along with longest median follow-up 50 months among all identified literature sources in the systematic literature review, so it was selected to derive inputs for the model" (manufacturer response to clarification; pg 47). The ERG notes that Prandoni *et al*. does not appear to have identified from the systematic review, and therefore the ERG remains unclear as to how this paper was identified and selected.

The ERG considers the data from Prandoni *et al*. to be generally applicable to this STA for the full population, and notes that both TA261 and TA287 used the estimate of recurrent VTE from Prandoni *et al*. within each respective model structure.[49;65;74] However, the ERG notes that patients with cancer were excluded from this analysis, and therefore the data may not be appropriate for the population with cancer. Nevertheless, the ERG did not run an updated systematic review to locate studies reporting recurrent VTE data or studies reporting data in the population with cancer, due to time constraints, and is therefore unaware of whether more recently applicable studies have been published.

5.4.7 Complications associated with VTE events

The manufacturer incorporated complications associated with VTE events within the model. Specifically, the manufacturer modelled the costs and consequences associated with severe PTS and CTEPH.

5.4.7.1 Post-thrombotic syndrome

Patients experiencing a DVT, either index or recurrent, were assigned a probability of developing severe PTS; the manufacturer did not include mild PTS within the model. The manufacturer justified the omission of mild PTS as "published evidence suggests that mild PTS had little detrimental effect on quality of life" (MS; pg 250). The probability of severe PTS was assumed to be the same for all treatments.

The manufacturer based the incidence of severe PTS applied within the model upon a study published in 1997 by Prandoni *et al*.[5] This study reports on severe PTS incidence for 528 patients with a first episode of confirmed DVT. The authors report the cumulative incidence of severe PTS to be 8.1% after five years; thereafter the cumulative incidence of severe PTS did not increase. In the model, the manufacturer applied a monthly probability of developing severe PTS for 5 years after the DVT event (0.14%). After 5 years, the probability of developing severe PTS was assumed to be zero.

Following consultation with clinical experts, and after review of the systematic review of cost-effectiveness evidence carried out by the manufacturer (Section 5.3), the ERG considers that it was appropriate to include severe PTS within the model. The ERG also notes that clinical experts consider it plausible that the probability of severe PTS does not vary by treatment.

The ERG notes that it is unclear how the study by Prandoni *et al*. was identified; the manufacturer did not supply a rationale for the selection of this paper within the submission. The ERG asked the manufacturer to explain the rationale for the selection of this paper within clarification. The manufacturer stated "among all studies identified in the systematic literature review, the longest and prospective cohort study was presented in the Prandoni et al publication" (manufacturer response to clarification; pg 48). The ERG notes that it does not appear that this paper was identified from the systematic review; therefore, the ERG remains unclear how this paper was identified.

The ERG considers the paper by Prandoni *et al*. to be generally appropriate to model the risk of severe PTS for this decision problem; however, the ERG was unable to carry out a systematic search to identify additional published evidence around the incidence of severe PTS and is therefore unable to comment upon whether Prandoni *et al*. contains the most relevant data. The ERG consulted clinical experts who asserted that the selection criteria for Prandoni *et al.* may have been stricter than current recommendations for PTS diagnosis; thus, it is possible that the incidence of severe PTS is underestimated within the model. A clinical expert suggested an alternative value to model for incidence of severe PTS could be taken from Kahn *et al.* This study investigated the efficacy of elastic compression stockings (ECS), compared with placebo stockings, for the prevention of PTS, over two years.[(75)] Patients presenting with a first symptomatic, proximal DVT were eligible to participate in the study. The authors found that between 12.7% (placebo) and 14.2% (ECS) patients (the difference was non-statistically significant $p = 0.58$). The ERG investigated the impact of increasing the estimate of severe PTS incidence within the model to 13.5%. In order to incorporate this analysis within the existing model structure, the ERG made a simplifying assumption that the incidence applied over 5 years. Results presented in Section 6.2, **analysis B23.**

The ICERs for dabigatran versus warfarin, and LMWH in the population with cancer for **analysis B23** were largely unaffected in both the acute treatment, and treatment and secondary prevention scenarios. For the analysis of dabigatran versus rivaroxaban in the acute treatment scenario, the ICER changed from dabigatran dominating rivaroxaban (less costly, more effective) to dabigatran being less costly but less effective when compared with rivaroxaban. The ERG notes that this is largely as a consequence of reduced QALYs from an increased relative amount of PTS cases for dabigatran versus rivaroxaban.

The ERG notes that the manufacturer applied the 5-year probability of developing severe PTS to all patients with an index DVT in the first cycle of the model. This was a simplifying assumption, and the ERG considers that the manufacturer could have modelled severe PTS with respect to time in order to correctly apply discounting. The ERG notes that, as modelled, the rates of CTEPH and severe PTS in the first cycle are identical for all comparators due to identical numbers of index events.

Additionally, the ERG considers that the manufacturer may have made a mistake in the calculation of number of people with severe PTS. In the engine, the number of people with severe PTS in each cycle is calculated as sum of the number of people with recurrent DVT in the current cycle plus the number of people with recurrent DVT in the previous 60 cycles (5 years). The manufacturer then multiplied the number of people with recurrent DVT in the last five years by the monthly risk of severe PTS. The ERG considers that the manufacturer overestimates the number of people with severe PTS in each cycle because some of the people with recurrent DVT in the previous cycles have already developed severe PTS, and the manufacturer double counts these patients. The ERG changed the formula in the engine so that the total number of people with severe PTS in the current cycle was equal to sum of the number of people with recurrent DVT in the current cycle plus the previous 60 cycles, minus the sum of previous severe PTS cases (calculated as the sum of people with recurrent DVT in the previous 60 cycles multiplied by the monthly risk of severe PTS), multiplied by risk of severe PTS. Results are presented in Section 6.1, **analysis A3**. The impact upon the ICERs was negligible.

Finally, the ERG notes that the estimated number or people with severe PTS is estimated alongside all other model calculations; i.e. does not form a separate mutually exclusive health state. Consequently, within the engine, the manufacturer accounts for general population mortality in each cycle, such that patients with severe PTS may have died. The ERG considers that the manufacturer should also have accounted for deaths due to MBEs and recurrent VTE. The impact of not removing these patients from the calculation of DVT is that disutility and cost is being applied to patients who have already died. Due to the way the model engine was developed, the ERG was unable to account for these deaths as the probability of dying differed depending upon whether the patients were on or off treatment, and which treatment the patient was receiving. In the engine, the ERG considers that there was no straightforward way of identifying these patients; thus the ERG is not able to comment upon the impact of this potential error on model results. However, for clarity, the ERG has added this uncertainty to the summary of additional analyses, **analysis B15**.

5.4.7.2 Chronic thromboembolic pulmonary hypertension

The manufacturer incorporated CTEPH within the economic model by applying a 2-year cumulative probability of CTEPH subsequent to a PE (3.8%), as reported within Pengo *et al.* to all patients who experienced a PE.[7] The probability of CTEPH did not vary by treatment.

For patients experiencing an index event, the manufacturer multiplied the number of PE events by the reported 3.8% probability to estimate the number of CTEPH cases over the following two years; this number was applied in cycle 1 of the model. For all subsequent recurrent PE events, the probability of CTEPH reported by Pengo *et al*. (3.8%) was converted appropriately to a monthly Markov cycle probability of 0.16%. This was applied to the sum of all people with a PE in the current cycle and, up to, the previous 23 months.

Following consultation with clinical experts, and after review of the systematic review of cost-effectiveness evidence carried out by the manufacturer (Section 5.3), the ERG considers that it was appropriate to include CTEPH within the model. The ERG also notes that clinical experts consider it plausible that the probability of CTEPH does not vary by treatment.

The ERG notes that it is unclear how the study by Pengo *et al*. was identified; the manufacturer did not supply a rationale for the selection of this paper within the submission. The ERG asked the manufacturer to explain the rationale for the selection of this paper within clarification. The manufacturer stated "this study provided the highest estimate of CTEPH incidence among all identified in the systematic literature review, thus from the perspective of conservative approach this was the source chosen for use in the model" (manufacturer response to clarification; pg 48). The ERG notes that it does not appear as though this study was identified from the systematic review; therefore the ERG remains unclear how this paper was identified.

The ERG considers the paper by Pengo *et al.* to be generally appropriate to model the probability of CTEPH for this decision problem; however, the ERG was unable to carry out a systematic search to identify additional published evidence around the incidence of CTEPH and is therefore unable to comment upon whether Pengo *et al*. contains the most relevant data.[7]

The ERG also notes that, within Pengo *et al*., results were presented for patients experiencing multiple PE events. For these patients, the authors estimated a 2-year cumulative probability of CTEPH of 33.3%. The ERG considers that patients within the model may be presenting with multiple PE events, and therefore the estimate from Pengo *et al*. of 1.38% cumulative probability at 2-years may underestimate the risk of CTEPH.[7] The ERG notes that the sample size used to estimate the 33.3% probability was small; 8 out of 24 people with multiple PEs developed CTEPH. The ERG carried out an exploratory analysis to investigate the impact of using the higher probability of CTEPH; results are presented in Section 6.2 **analysis B12.**

The conclusions of the **analysis B12** for dabigatran versus rivaroxaban and dabigatran versus LMWH in the population with cancer are largely unchanged; however, the ICERs for dabigatran versus warfarin increased from £862 to £4,144 (acute treatment scenario) and from £8,319 to £14,631

(treatment and secondary prevention). The main driver of the increase in the ICER was an increase in relative cost associated with CTEPH management for dabigatran versus warfarin. The ERG notes that the value of CTEPH incidence is likely to be overstated in this scenario; thus, these ICERs represent a more extreme change than is likely.

The ERG notes that the manufacturer applied the 2-year risk of CTEPH to all patients with an index PE in the first cycle of the model. The ERG notes that this is a simplifying assumption, and considers that the manufacturer could have modelled CTEPH with respect to time in order to correctly apply discounting. The ERG notes that the rate of CTEPH in cycle 1 is identical for all treatments, due to the same proportion of index VTE events at the start of the model.

Additionally, as with severe PTS, the ERG considers that the manufacturer may have made a mistake in the calculation of number of people with CTEPH. In the engine, the number of people with CTEPH in each cycle is calculated as sum of the number of people with recurrent PE in the current cycle plus the number of people with recurrent PE in the previous 23 cycles. The manufacturer then multiplied the number of people with recurrent PE in the last two years by the monthly risk of CTEPH. The ERG considers that the manufacturer overestimates the number of people with CTEPH in each cycle because some of the people with recurrent PE in the previous cycles have already developed CTEPH, and the manufacturer double counts these patients. The ERG changed the formula in the engine so that the total number of people with CTEPH in the current cycle was equal to sum of the number of people with recurrent PE in the current cycle plus the previous 23 cycles, minus the sum of previous CTEPH cases (calculated as the sum of people with recurrent PE in the previous 23 cycles multiplied by the monthly risk of CTEPH), multiplied by risk of CTEPH. A description of the analysis undertaken is provided in Section 5.5.1, with results presented in Section 6.1, **analysis A4**. The impact upon the ICERs was negligible.

Finally, as with severe PTS, the ERG notes that the estimated number or people with severe CTEPH is estimated alongside all other model calculations; i.e. does not form a separate mutually exclusive health state. Consequently, within the engine, the manufacturer accounts for general population mortality in each cycle, such that patients with CTEPH may have died. The ERG considers that the manufacturer should also have accounted for deaths due to MBEs and recurrent VTE. The impact of not removing these patients from the calculation of PE is that cost is being applied to patients who have already died. Due to the way the model engine was developed, the ERG was unable to account for these deaths as the probability of dying differed depending upon whether the patients was on or off treatment, and which treatment the patient was receiving. In the engine, the ERG considers that there was no straightforward way of identifying these patients; thus the ERG is not able to comment upon the impact of this potential error on model results; however, for clarity, the ERG has added this uncertainty to the summary of additional analyses, **analysis B15**.

5.4.8 Adverse effects of treatment

The manufacturer accounted for the following adverse events within the economic model:

- major and clinically relevant non-major bleeding events (Section 5.4.8.1);
- cardiovascular events (sensitivity analysis only, Section 5.4.8.2);
- dyspepsia (sensitivity analysis only, Section 5.4.8.3).

5.4.8.1 Major and clinically relevant non-major bleeding events

The manufacturer modelled the incidence of MBEs (including intra-cranial haemorrhage [ICH] and extra-cranial haemorrhage), and CRNMBEs. In the model, the manufacturer applied the combined incidence of an MBE and a CRNMBE for each treatment. This differed for the acute treatment phase and the secondary prevention phase. Then, the manufacturer attributed a proportion of the overall incidence to ICH, extra-cranial MBEs, and CRNMBEs. Figure 13 provides a graphical summary of this approach, and the remainder of this section describes this in greater detail.

Figure 13. Manufacturer's approach to estimating probability of MBE or CRNMB applied within the model

Estimated incidence of all major and clinically-relevant non-major bleeds

Acute treatment	Incidence
D (full)	5.27%
W (full)	8.50%
R (full)	7.90%
D (cancer)	17.46%
L (cancer)	14.91%

Secondary prevention	Incidence
D (full)	5.59%
W (full)	10.17%
D (full)	5.31%
R (full)	10.24%
D (cancer)	4.87%
L (cancer)	5.10%

Methods:
1. Incidence estimated for a baseline treatment from clinical trial data
2. Baseline incidence multiplied by a HR or RR to estimate incidence for comparator treatment

Split by proportion of incidence attributable to MBE EC (nf), MBE IC (nf), MBE (f), CRNMB

Acute treatment	MBE, EC (nf)	MBE, IC (nf)	MBE (f)	CRNMB
D (full)	25.0%	1.4%	0.7%	72.8%
W (full)	20.4%	2.2%	0.9%	76.5%
R (full)	8.3%	1.2%	0.8%	89.7%
D (cancer)	32.7%	1.9%	1.0%	64.5%
L (cancer)	10.3%	1.3%	0.8%	87.6%

Secondary prevention				
D (full)	13.8%	2.5%	0.0%	83.8%
W (full)	13.9%	2.6%	0.7%	82.8%
D (full)	5.6%	0.0%	0.0%	94.4%
R (full)	11.1%	0.0%	0.0%	88.9%
D (cancer)	5.6%	0.0%	0.0%	94.4%
L (cancer)	12.5%	1.5%	0.7%	85.3%

Methods:
1. Splits of bleeding events estimated for each individual treatment from relevant clinical trials

Resulting incidence applied within the model

Acute treatment	MBE, EC (nf)	MBE, IC (nf)	MBE (f)	CRNMB
D (full)	1.3%	0.1%	0.0%	3.8%
W (full)	1.7%	0.2%	0.1%	6.5%
R (full)	0.7%	0.1%	0.1%	7.1%
D (cancer)	5.7%	0.3%	0.2%	11.3%
L (cancer)	1.5%	0.2%	0.1%	13.1%

Secondary prevention	MBE, EC (nf)	MBE, IC (nf)	MBE (f)	CRNMB
D (full)	0.8%	0.1%	0.0%	4.7%
W (full)	1.4%	0.3%	0.1%	8.4%
D (full)	0.3%	0.0%	0.0%	5.0%
R (full)	1.1%	0.0%	0.0%	9.1%
D (cancer)	0.3%	0.0%	0.0%	4.6%
L (cancer)	0.6%	0.1%	0.0%	4.3%

Abbreviations used in figure: cancer, population with cancer; CRNMB, clinically relevant non-major bleed; D, dabigatran; full, full population; ICH, intracranial haemorrhage; L, low-weight-molecular heparin; MBE, major bleeding event; R, rivaroxaban; W, warfarin.

Incidence of major and clinically relevant non-major bleeding events

Table 89 presents the overall incidence of major and clinically relevant non-major bleeding events applied within the manufacturer's model for treatment and secondary prevention. The source of the data and a description of the relevant calculations are provided below.

Table 89. Probability of major and clinically relevant non-major bleeding during treatment applied in the manufacturer's economic analysis

Comparison	Intervention	Population	Acute treatment period	Data source	Secondary prevention period	Data source
Dabigatran versus warfarin	Dabigatran	Full population	5.27%	RE-COVER I and II	5.59%	RE-MEDY
	Warfarin	Full population	8.50%		10.17%	
Dabigatran versus rivaroxaban	Dabigatran	Full population	5.27%	RE-COVER I and II; EINSTEIN-DVT and PE	5.31%	RE-SONATE; EINSTEIN-EXT
	Rivaroxaban	Full population	7.90%		10.24%	
Dabigatran versus LMWH	Dabigatran	Population with cancer	17.46%	RE-COVER I and II (cancer subgroup); meta-analysis	4.87%	RE-SONATE; DACUS
	LMWH	Population with cancer	14.91%		5.10%	
Abbreviation used in table: LMWH, low-molecular-weight heparin						

Acute treatment

For acute treatment, the manufacturer estimated a baseline probability of major or clinically relevant non-major bleeding events for patients receiving warfarin in both the full population and the population with cancer. The source data used to estimate this probability was pooled trial data of the primary outcome from the warfarin arm in RE-COVER I and II (for a description of RE-COVER I and II, see Section 4.3). The estimates of baseline probability were based upon data analysed at 6 months. The baseline probability of major or clinically relevant non-major bleeding events during the acute treatment phase for patients receiving warfarin was estimated to be:

- 8.50% (full population, 217 patients out of 2,554)
- 14.20% (population with cancer, 23 patients out of 162; not reported within the MS)

The estimated warfarin baseline probability was multiplied by a HR or RR for each remaining treatment versus warfarin, to estimate a probability of major or clinically relevant non-major bleeding for each remaining intervention.

For the full population receiving dabigatran, the HR for dabigatran versus warfarin was estimated from the manufacturer's pair-wise meta-analysis of RE-COVER I and II to be 0.62 (MS pg 18).

For the full population receiving rivaroxaban, the HR for rivaroxaban versus warfarin was estimated from a published pair-wise meta-analysis of EINSTEIN-DVT and EINSTEIN-PE using pooled 3, 6, and 12 month data to be 0.93.[71]

For the population with cancer receiving dabigatran, the HR for dabigatran versus warfarin was estimated from the manufacturer's pair-wise meta-analysis of the cancer subgroup within RE-COVER I and II to be 1.23 (not reported within the MS).[76]

Finally, for the population with cancer receiving LMWH, the relative risk (RR) of LMWH versus warfarin was estimated from the manufacturer's pair-wise meta-analysis of four published studies, in patients with active cancer and was estimated to be 1.05.[76]

The resulting probabilities for major and clinically relevant non-major bleeding in the acute treatment phase are presented in Table 90.

Table 90. Major and clinically relevant non-major bleeding applied during the acute period

Comparison	Intervention	Population	Baseline probability	HR / RR versus baseline treatment	Resultant probability
Dabigatran versus warfarin	Dabigatran	Full population	8.50% (warfarin)	0.62	5.27%
	Warfarin	Full population		–	8.50%
Dabigatran versus rivaroxaban	Dabigatran	Full population		0.62	5.27%
	Rivaroxaban	Full population		0.93	7.90%
Dabigatran versus LMWH	Dabigatran	Population with cancer	14.20% (warfarin)	1.23	17.46%
	LMWH	Population with cancer		1.05	14.91%
Abbreviations used in table: HR, hazard ratio; LMWH, low-molecular-weight heparin; RR, relative risk					

As with recurrent VTE, the manufacturer noted within the submission that the rates of major and non-major clinically relevant bleeds were observed to be higher in the first months after the index event, and gradually declined thereafter. Therefore, the manufacturer log-transformed the Markov cycle probabilities for the acute treatment period.

Secondary prevention

For secondary prevention, a similar methodology was employed to estimate incidence of major and clinically relevant non-major bleeding.

For dabigatran versus warfarin, the manufacturer estimated a baseline probability of major and clinically relevant non-major bleeding for patients receiving warfarin treatment using trial data for the warfarin arm in RE-MEDY (for a description of RE-MEDY, see Section 4.6). The data were analysed

at 18 months, and related to the treated set of patients. For the full population, the baseline probability of major and clinically relevant non-major bleeding was estimated to be 10.17% (145 patients out of 1,426, MS; pg 240).

For dabigatran versus rivaroxaban for the full population, and dabigatran versus LMWH in the subgroup of patients with active cancer, the manufacturer estimated a baseline probability of major and clinically relevant non-major bleeding for patients receiving placebo treatment using trial data of the primary outcome from the placebo arm of RE-SONATE (for a description of RE-SONATE, see Section 4.6.1). The data were analysed at 18 months, and related to the treated set of patients. The baseline probability of major and clinically relevant non-major bleeding was estimated to be 1.97% (13 patients out of 659, MS; pg 240).

The estimated baseline probability was then multiplied by a HR or RR for each remaining treatment versus warfarin or placebo, to estimate a probability of major or clinically-relevant non-major bleeding for each remaining intervention.

For the full population receiving dabigatran in the comparison with warfarin, the HR of dabigatran versus warfarin estimated from the manufacturer's analysis of RE-MEDY was estimated to be 0.55 (MS pg 241).

For the full population receiving dabigatran in the comparison with rivaroxaban, the HR the HR of dabigatran versus placebo was estimated from RE-SONATE to be 2.69, (MS pg 241).

For the full population receiving dabigatran in the comparison with rivaroxaban, the HR the HR of rivaroxaban versus placebo was estimated from EINSTEIN-EXT to be 5.19, (MS pg 241).

For the population with cancer, the HR of dabigatran versus placebo was estimated from data presented for the active cancer subgroup in RE-SONATE to be 2.47 (not presented with the MS).

For the population with cancer, the RR of LMWH versus placebo was estimated from data presented in the DACUS study to be 2.58.[72]

The resulting probabilities for major and clinically-relevant non-major bleeding in the secondary prevention phase are presented in Table 91.

Table 91. Major and clinically relevant non-major bleeding applied during the secondary prevention period

Comparison	Intervention	Population	Baseline probability	HR / RR versus baseline treatment	Resultant probability
Dabigatran versus warfarin	Dabigatran	Full population	10.17% (warfarin)	0.55	5.59%
	Warfarin	Full population		–	10.17%
Dabigatran versus rivaroxaban	Dabigatran	Full population	1.97% (placebo)	2.69	5.31%
	Rivaroxaban	Full population		5.19	10.24%
Dabigatran versus LMWH	Dabigatran	Population with cancer		2.47	4.87%
	LMWH	Population with cancer		2.58	5.10%
Abbreviations used in table: HR, hazard ratio; LMWH, low-molecular-weight heparin; RR, relative risk					

ERG comments

The ERG considers that the source of data selected by the manufacturer was generally applicable for the populations of interest for this STA. Specifically, the ERG considers that pooling data from RE-COVER I and II was not unreasonable due to the comparable populations within these analyses (Section 4). Moreover, the ERG considers that using pooled data for 3, 6, and 12 months from EINSTEIN-DVT and EINSTEIN-PE was appropriate. This is because in previous technology appraisals TA261 and TA287, it was considered that there was no biological reason that would explain a differential effect.

The ERG also notes that treatment duration within secondary prevention trials differed. RE-MEDY and RE-SONATE were initially designed to be 18 month trials, although this was extended, and planned treatment duration varied between 6 and 36 months. By contrast, EINSTEIN-EXT was designed to assess the extension of treatment by 6-12 months. On balance, the ERG considers that the data within these trials at the end of treatment are comparable.

The ERG has three main comments about the methods used to calculate the incidence of major and clinically-relevant non-major bleeding for those on treatment in the analysis.

Firstly, the ERG was unclear why the manufacturer considered the incidence of MBE and CRNMBE together, and asked the manufacturer to provide a rationale for this methodology. The manufacturer stated that "to enable a credible indirect comparison vs rivaroxaban, the common safety endpoint was applied". The ERG notes that the manufacturer for rivaroxaban presented MBEs and CRNMBs separately within their submissions for TA261 and TA287; the ERG therefore considers that it would have been possible and more transparent to apply the rates of MBEs and CRNMBEs separately within the model.[49;65]

Secondly, the ERG notes that, due to differing baseline probabilities used within the treatment and secondary prevention scenario, the results arising from these analyses for each comparator cannot be compared and therefore cannot be considered a fully incremental analysis. This is because the costs and QALYs associated with dabigatran will differ in each comparison considered due to differing probabilities of bleeding. Consequently, each head-to-head comparison must be considered as a distinct analysis. The ERG considers that this may limit the interpretation of the full range of comparisons presented; moreover, the NICE Guide to Methods of Technology Appraisal states that a fully incremental analysis, when appropriate, should be presented.[67] For the full population analyses, the ERG considers there is no clinical basis on which to believe that the rate of major and clinically-relevant non-major bleeding for dabigatran would differ by comparator.

Thirdly, the ERG was unable to verify the HR used by the manufacturer from the DACUS study, for the HR of LMWH versus placebo of 2.58 for the population with cancer analysis.

Therefore, to address the three issues above, the ERG carried out an analysis using results from the ERG NMA for MBEs and CRNMBEs (Section 4.9). Results are presented in Section 6.2, **analysis B13**. In order to calculate a monthly probability of recurrence from the end of trial NMA results, the ERG assumed that duration of acute treatment was 6 months, and duration of secondary prevention was 18 months.

The ERG notes that the conclusions of the results of the analyses for dabigatran versus rivaroxaban and LMWH in the population with cancer were largely unchanged. For the comparison of dabigatran versus warfarin, the ICER reduced in the acute treatment scenario from £862 to £646, due to a slight increase in the relative rate of bleeding for warfarin versus dabigatran. In the treatment and secondary prevention scenario, the ICER increased from £8,319 to £9,281 as a result of a slight decrease in the relative rate of bleeding for warfarin versus dabigatran.

In addition, the ERG notes two minor issues with the calculations relating to incidence of major and clinically relevant non-major bleeding events.

Firstly, the manufacturer multiplied baseline probabilities by HRs; thus, implicitly assuming that that the properties of a HR are equivalent to an RR. To multiply a baseline probability by a HR to estimate an alternative probability, it is first necessary to first convert the baseline probability into a rate prior to multiplication. After multiplication it is then necessary to convert back into a probability.[73] The ERG amended the manufacturer's calculations for the relevant comparisons; a description of the analysis carried out is presented in Section 5.5.1, with results presented in Section 6.1; **analysis A5**.

Secondly, the ERG considers that the manufacturer may have made a small mistake in calculating the baseline probability for warfarin in patients with active cancer who receive both treatment and

secondary prevention. In this scenario, the baseline probability of recurrent VTE for warfarin used to estimate probabilities is 1.97%, the full population pooled analysis of RE-COVER I and II, rather than subgroup of patients with cancer (14.20%). The ERG considers that this is likely to have been a mistake, and corrected this in a sensitivity analysis. A description of the analysis carried out is presented in Section 5.5.1, with results presented in Section 6.1 **analysis A6**.

The combined impact of **analysis A5 and A6** on the ICERs was small.

Attributing the total incidence of major and clinically relevant non-major bleeding events to MBEs and CRNMBEs

Within the model, following calculation of the incidence of major and clinically relevant non-major bleeding events, the manufacturer attributed a proportion of the incidence to either an MBE (ICH or extra-cranial haemorrhage), or CRNMB. The proportions applied in the acute treatment period and secondary prevention period are presented in Table 92 and Table 93, respectively. In addition, a proportion of people experiencing an MBE had a probability of dying from their MBE, this is described in Section 5.4.9.2.

Table 92. Proportion of bleeds attributable as major bleeding events and clinically-relevant non-major bleeding events, applied within the acute treatment period

Type of bleeding event	Dabigatran	Warfarin	Rivaroxaban	Dabigatran (population with cancer)	LMWH (population with cancer)
MBE (ICH)	1%	2%	1%	2%	1%
MBE (extra-cranial)	26%	21%	9%	34%	11%
CRNMB	73%	76%	90%	65%	88%
Source	Pooled analysis of RE-COVER I and II	Pooled analysis of RE-COVER I and II	Pooled analysis of EINSTEIN-PE and EINSTEIN-DVT	Pooled analysis of RE-COVER I and II, cancer subgroup	Pooled trial data
Abbreviations used in table: CRNMB, clinically relevant non-major bleed; ICH, intracranial haemorrhage; LMWH, low-molecular-weight heparin; MBE, major bleeding event.					

Table 93. Proportion of bleeds attributable as major bleeding events and clinically relevant non-major bleeding events, applied within the secondary prevention period

Type of bleeding event	Dabigatran	Warfarin	Dabigatran	Rivaroxaban	Dabigatran (population with cancer)	LMWH (population with cancer)
MBE (ICH)	2.5%	2.8%	0.0%	0.0%	0.0%	1.6%
MBE (extra-cranial)	13.8%	14.5%	5.6%	11.1%	5.6%	13.1%
CRNMB	83.8%	82.8%	94.4%	88.9%	94.4%	85.3%
Source	RE-MEDY	RE-MEDY	RE-SONATE treated set (full population)	EINSTEIN-EXT	RE-SONATE treated set (full population)	Pooled trial data
Abbreviations used in table: CRNMB, clinically relevant non-major bleed; ICH, intracranial haemorrhage; LMWH, low-molecular-weight heparin; MBE, major bleeding event.						

The ERG notes that the proportion of each type of event differs by treatment, and is taken from clinical trial data without adjustment via meta-analysis between comparators. The ERG consulted with clinical experts around the basis for the difference in type of bleeding event and was advised that there was no clinical basis for expecting a difference in type of bleeding by treatment.

In addition, the ERG notes that, for secondary prevention analyses, the figures presented for dabigatran in Table 93 differ by comparison. Consequently, the results arising from each analysis cannot be compared with one another, and must be considered as head-to-head comparisons. The analysis cannot therefore be considered fully incremental. The ERG considers that there is no clinical basis for analysing each comparator as a distinct population; therefore, the ERG considers this to be a weakness of the analysis.

To address both above issues, the ERG carried out a sensitivity analysis in which the proportion of each type of event was set to be the same for all interventions, at the value for dabigatran in RE-COVER I and II, and RE-MEDY. Results are presented in Section 6.2, **analysis B14.** The ERG notes that the conclusions of the results of the analyses for dabigatran versus rivaroxaban and LMWH in the population with cancer were largely unchanged. For the comparison of dabigatran versus warfarin, the ICERs increased from £862 to £2,244 (acute treatment scenario) and from £8,319 to £11,394 (treatment and secondary prevention scenario). The ERG believes that this change is a result both of an increase in the incremental cost associated with dabigatran as a result of reduced ICH event costs, and a decrease in the incremental QALYs associated with dabigatran as a result of a reduction in the number of people disabled from an ICH for warfarin.

Finally, the ERG considers that the manufacturer may have made a small mistake in calculating the proportion of people in the acute period with intra-cranial MBE, extra-cranial MBE and CRNMB for dabigatran in the population with cancer who receive both treatment and secondary prevention. In this

scenario, the proportions used in the acute treatment period are based upon the full population pooled analysis of RE-COVER I and II, rather than subgroup of patients with cancer. The ERG considers that this is likely to have been a mistake, and corrected this in a sensitivity analysis; results of the analysis are presented in Section 6.1 **analysis A7**. The impact upon the ICERs for dabigatran versus LMWH (in the population with cancer) for the secondary prevention scenarios was negligible.

Major and clinically relevant non-major bleeding events for warfarin re-treatment

Within the manufacturer's model, patients who experience a recurrence receive LMWH for 5 days followed by warfarin re-treatment for 6 months (Section 5.4.2). Whilst on-treatment, the manufacturer assumes that the risk of bleeding is as described in Table 94. Note; the values within this table are equivalent to the figures presented for warfarin for acute treatment, in Table 92 above.

Table 94. Probability of major and clinically relevant non-major bleeding event for warfarin retreatment

Type of bleeding event	Warfarin
Probability of major and clinically relevant non-major bleeding event	8.5%
MBE (ICH)	*2%*
MBE (extra-cranial)	*21%*
CRNMB	*76%*
Source	Pooled analysis of RE-COVER I and II
Abbreviations used in table: CRNMB, clinically relevant non-major bleeding; ICH, intracranial haemorrhage; LMWH, low-molecular-weight heparin; MBE, major bleeding event.	

Consequences of bleeding events

Patients who experienced an MBE (both intra- and extra-cranial) had a probability of dying from the bleeding event. The probability applied by the manufacturer within the model is described in Section 5.4.9.2.

In addition to the probability of dying from a MBE, patients experiencing an ICH were assumed to have a probability of being permanently disabled from their ICH. The manufacturer assumed that 65% patients experiencing a non-fatal ICH would be permanently disabled. The value of 65% was estimated from Rosand *et al.*, a study of 435 patients attending a tertiary hospital as a consequence of an ICH.[77] The manufacturer did not describe how this paper was identified and selected.

The authors investigated the impact of warfarin use on ICH outcome. They estimated that, among survivors of ICH who were taking warfarin (n=102), 34.7% achieved a good clinical outcome, i.e., a Glasgow Outcome Score of 4 or 5, compared with 42.3% of survivors of ICH unrelated to warfarin use (n=333). The manufacturer used the proportion of patients receiving warfarin in the calculation of the proportion of patients becoming permanently disabled (100% - 34.7% = 65.3%). After consultation with clinical experts, the ERG considers that this figure is not unreasonable.

5.4.8.2 Cardiovascular events (manufacturer sensitivity analysis only)

The manufacturer included the costs and consequences of cardiovascular events, specifically MI and UA, within a sensitivity analysis. MI was assumed to be fatal or non-fatal. The probabilities for cardiovascular events applied within the sensitivity analysis are presented by treatment in Table 95. The manufacturer assumed that events would occur in cycle four; this was a simplifying assumption designed to represent the mid-point of trial follow-up.

Table 95. Cardiovascular events applied within the manufacturer's model in sensitivity analysis

Treatment	Proportion of patients			Reference / comments
	Non-fatal MI	Fatal MI	UA	
Acute treatment period				
Dabigatran	0.31%	0%	0.04%	RE-COVER I and II
Warfarin	0.16%	0%	0.04%	RE-COVER I and II
Rivaroxaban	0.27%	0.07%	0.27%	EINSTEIN-DVT + PE
LMWH (in patients with cancer)	0.31%	0%	0%	Assumed to be the same as dabigatran
Secondary prevention period				
Dabigatran	0.63%	0.21%	0%	RE-MEDY
Warfarin	0.07%	0.21%	0%	RE-MEDY
Dabigatran	0.15%	0%	0%	RE-SONATE
Rivaroxaban	0%	0.5%	0%	EINSTEIN-EXT
LMWH (in patients with cancer)	0.15%	0%	0%	Assumed to be the same as dabigatran
Treatment for recurrence				
Warfarin	0.16%	0.04%	0.00%	RE-COVER I and II
No treatment				
Off-treatment	0.00%	0.00%	0.00%	Assumption
Abbreviations used in table: LMWH, low-molecular-weight heparin; MI, myocardial infarction; UA, unstable angina.				

The manufacturer further assumed that 60% of patients experiencing an MI or UA who survived would develop chronic IHD; this figure was based upon clinical expert opinion.

The ERG notes that in the secondary prevention period the manufacturer applied different rates of MI and UA for dabigatran depending upon whether the comparison was with warfarin, or rivaroxaban and LMWH. The ERG considers that there is no clinical basis for assuming that the rate of MI or UA would differ by comparator, and notes that this approach prevents comparison of final costs and QALYs between comparators. The ERG considers this to be a weakness of the sensitivity analysis.

5.4.8.3 Dyspepsia (sensitivity analysis only)

The manufacturer included the costs and consequences of dyspepsia within a sensitivity analysis. The manufacturer excluded dyspepsia from the base case analysis because "the prevalence was low in clinical studies (1-3%) and dyspepsia was felt not to be relevant to the disease pathway considered in the submission" (MS; pg 251). The ERG consulted with clinical experts around the relevance of dyspepsia as a health state for this STA. The advice received suggested that dyspepsia was an important outcome associated with dabigatran use that should be included within the base case analysis.

The probability of dyspepsia applied within the sensitivity analysis was described by the manufacturer to be "3.0% incidence in dabigatran, 1.0% incidence in WFN [warfarin]" (MS; pg 332). These figures were selected "based on AE rate reporting in dabigatran clinical trials programme" (MS; pg 332). The ERG was unable to identify the figures described by the manufacturer. Instead, the ERG reviewed the CSRs for RE-COVER I and II, and estimated that the proportion of people experiencing dyspepsia was 2.00% for dabigatran (based upon 3.1% in RE-COVER I, CSR pg 237*(26)* and 1.0% in RE-COVER II, CSR pg 184*(25)*) and 0.4% for warfarin (based upon 0.7% in RE-COVER I, CSR pg 237*(26)* and 0.2% in RE-COVER II, CSR pg 184*(25)*).

In addition, although the manufacturer described the probability of dyspepsia as "converted to monthly Markov cycle probabilities for use in the economic model" (MS; pg 251) and applied "for the duration of treatment" (MS; pg 232), the ERG notes that the manufacturer applied a one off probability of dyspepsia at cycle 4. The ERG notes that this was a modelling simplification to apply the probability of dyspepsia for the acute period. The ERG considers that the manufacturer could also have applied a probability of dyspepsia during secondary prevention.

The ERG carried out a scenario analysis in which the rates estimated by the ERG and described above (2.00% [dabigatran] and 0.4% [warfarin]) were applied within the model; for rivaroxaban, the ERG adopted the manufacturer's strategy and assumed the probability of dyspepsia was 0%. In addition, the ERG assumed that the probability of dyspepsia for LMWH in the population with cancer was 0%, based upon a lack of data. The ERG also amended the model engine to apply these rates for the full duration of treatment with dabigatran; results are presented in Section 6.2 **analysis B1**. The impact of this analysis upon the manufacturer's base case results was small.

5.4.9 Mortality

The manufacturer assumed that people could die within the model for the following reasons:

- due to VTE recurrence (a fatal PE event, Section 5.4.9.1);
- due to an MBE (intra- and extra-cranial, Section 5.4.9.2);

- due to an MI (in sensitivity analysis only, Section 5.4.9.5);
- for any other cause, based upon age and gender (background mortality, Section 5.4.9.3).

The ERG notes that the manufacturer did not model death due to CTEPH; the ERG considers this to be an important omission. The ERG discusses this issue in Section 5.4.9.4.

5.4.9.1 Death due to VTE recurrence

In the model, patients experiencing a VTE recurrence were assumed to have a chance of dying from their recurrence; specifically, people could die from a PE. The manufacturer assumed that the probability of death as a consequence of VTE event varied by treatment. The data used by the manufacturer within the model for death due to VTE recurrence was presented and discussed within Section 5.4.6. Table 96 provides a summary of these data.

Table 96. Probability of dying due to a recurrent VTE

Event	Off treatment	Dabigatran	Warfarin	Dabigatran	Rivaroxaban	Dabigatran (population with cancer)	LMWH (population with cancer)
Acute treatment							
Fatal PE	12%	3%	5%	3%	3%	3%	3%
Source	Prandoni *et al.* [74]	Pooled analysis of RE-COVER I and II			Pooled analysis of EINSTEIN-PE and EINSTEIN-DVT	Pooled analysis of RE-COVER I and II (cancer subgroup)	Unclear
Secondary prevention							
Fatal PE	12%	4%	6%	0%	0%	0%	3%
Source	Prandoni *et al.* [74]	RE-MEDY		RE-SONATE treated set (full population)	EINSTEIN-EXT	RE-SONATE treated set (full population)	Unclear
Abbreviations used in table: LMWH, low-molecular-weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism.							

The ERG notes that the manufacturer assumed that the proportion of fatal PE events on treatment varied by treatment. Moreover, the proportion of fatal PE varied for dabigatran in the secondary prevention period depending upon which comparator was modelled. The ERG consulted clinical experts who advised there was no clinical basis for the proportion of events by type to differ by treatment; consequently, the ERG carried out an analysis in which the rate of events on treatment was assumed to be equal for all treatments to those observed for dabigatran in RE-COVER I and II, and RE-MEDY; results are presented in Section 6.2 **analysis B11**.

As described previously in Section 5.4.6.1, the impact of **analysis B11** on the manufacturer model results was a modest increase in the ICERs associated with dabigatran versus warfarin in the acute treatment phase (£862 to £1,032) and the secondary prevention phase (£8,319 to £9,293). The ERG believes that the cause of this increase was related to a small reduction in incremental QALYs for dabigatran versus warfarin, as a consequence of a small reduction in the number of VTE-related deaths for warfarin. For the comparison of dabigatran with rivaroxaban in the acute treatment phase, the ICER switched from dabigatran dominating rivaroxaban (less costly and more effective) to dabigatran being associated with an incremental cost per additional QALY gained of £21,055. The ERG believes that this is largely a consequence of an increase in relative cost of managing CTEPH as a result of fewer PE cases for rivaroxaban. The remaining comparisons were largely unaffected.

5.4.9.2 Death due to a major bleeding event

The manufacturer assumed that all patients experiencing a MBE had a probability of dying from their bleed. The incidence of MBEs applied within the model was described in Section 5.4.8.1; MBEs included both intra and extra-cranial MBEs. The probability of dying from a MBE was assumed to be the same for an ICH and for an extra-cranial haemorrhage. The data applied within the model are described in Table 97.

Table 97. Probability of dying due to a MBE

Event	Dabigatran	Warfarin	Dabigatran	Rivaroxaban	Dabigatran (population with cancer)	LMWH (population with cancer)
Acute treatment						
Proportion of people with MBE who die from their bleed	3%	4%	3%	8%	3%	6%
Source	Pooled analysis of RE-COVER I and II			Pooled analysis of EINSTEIN-PE and EINSTEIN-DVT	Pooled analysis of RE-COVER I and II (cancer subgroup)	Unclear
Secondary prevention						
Proportion of people with MBE who die from their bleed	0%	4%	0%	0%	0%	5%
Source	RE-MEDY		RE-SONATE treated set (full population)	EINSTEIN-EXT	RE-SONATE treated set (full population)	Unclear
Abbreviations used in table: LMWH, low-molecular-weight heparin; MBE, major bleeding event.						

The ERG notes that the split of proportion of people who die from a MBE is assumed to differ by treatment. The ERG consulted with clinical experts around the clinical basis for the difference in type of recurrent event. The clinical experts advised that the number of deaths from MBE may be expected to differ in clinical practice if the rates of gastrointestinal MBEs differed. The ERG reviewed the CSRs for RE-COVER I and II and notes that the rates of MBEs in which the location of the bleed was gastrointestinal were 3.19% for dabigatran (RE-COVER I, CSR pg 229[26], 9 patients out of 22; RE-COVER II, CSR pg 174[25], 6 patients out of 15) and 3.40% for warfarin (RE-COVER I, CSR pg 229[26], 5 patients out of 25; RE-COVER II, CSR pg 174[25], 10 patients out of 22). For rivaroxaban, review of Prins *et al*. a pooled analysis of EINSTEIN-DVT and EINSTEIN-DVT presented the rates of MBEs in which the location of the bleed was gastrointestinal for rivaroxaban and a VKA as 2.5% (1 patient out of 40) and 1.4% (3 patients out of 72) respectively.[71] The ERG therefore considers the rates of GI bleeds to be similar, and thus the ERG considers it useful to present an analysis in which the rate of death for MBEs does not differ by treatment.

Furthermore, the ERG notes that the figures presented for dabigatran in Table 97 differ by comparison for the secondary prevention analyses. Consequently, the results arising from each analysis cannot be

compared with one another, and must be considered as head-to-head comparisons. The ERG considers that there is no clinical basis for analysing each comparator as a distinct population.

To address the two issues above, the ERG assumed the probability of death from MBE was the same for all treatments, and was equal to the value for dabigatran in RE-COVER I and II, and RE-MEDY; results are presented in Section 6.2 **analysis B14**. The ERG notes that the conclusions of the results of the analyses for dabigatran versus rivaroxaban and LMWH in the population with cancer were largely unchanged. For the comparison of dabigatran versus warfarin, the ICERs increased from £862 to £2,244 (acute treatment scenario) and from £8,319 to £11,394 (treatment and secondary prevention scenario). The ERG believes that this change is a result both of an increase in the incremental cost associated with dabigatran as a result of reduced ICH event costs, and a decrease in the incremental QALYs associated with dabigatran as a result of a reduction in the number of people disabled from an ICH for warfarin.

The ERG also notes that the estimate of death from MBE was combined for intra- and extra-cranial MBE. The ERG considers that this is likely to incorrectly reflect the number of deaths in the model. This is because the probability of dying from an ICH has been reported elsewhere to be much larger than 0-5%. In Rosand *et al*., the probability of dying from an ICH was found to be 39.5% at 3 months after an ICH.[77] The ERG therefore carried out an analysis in which patients experiencing an ICH were subject to a probability of dying of 39.5%, assumed for simplicity to occur in the month of the event. Results are presented in Section 6.2 **analysis B16**. The ICERs for dabigatran versus warfarin decreased from £862 to £404 (acute treatment) and from £8,319 to £6,381 (treatment and secondary prevention). The ICERs for the other comparisons were not affected.

5.4.9.3 Background mortality

The manufacturer accounted for death from other causes within the model using age and gender-specific mortality rates for the UK, obtained from the Office of National Statistics. The manufacturer applied the mortality associated with the average age of patients starting the model (54.7 years) in cycle 1. For subsequent cycles, an adjustment was made to account for the increased risk of death as patients' aged. Specifically, the manufacturer fitted an exponential function to the mortality rate in successive age bands.

The applied probability of death from other causes is presented in Table 98. These data were calculated from the economic model and are presented in 5-yearly intervals as the average of the monthly probabilities applied in that 5-year period. Note, within the model the manufacturer calculated the monthly probability of dying and did not group estimates of mortality by 5-yearly periods; the data in Table 98 is for presentation purposes.

Table 98. Average monthly probability of dying applied within the manufacturer's model for all causes

Year	Average age of cohort in the model	Average monthly probability of dying for other causes applied in that period
1-5	55-59	0.04%
6-10	60-64	0.07%
11-15	65-69	0.11%
16-20	70-74	0.18%
21-25	75-79	0.34%
26-30	80-84	0.56%
31-35	85-89	0.94%
36-40	90-94	1.41%
41-45	95-99	2.35%
46-50	100-104	3.91%
51-55	105-109	6.51%
56-60	110-114	10.83%

Thus, for patients in year 56 of the model, where the average age of survivors was 110, the manufacturer estimated the average monthly probability of dying to be 10.83%, equating to an annual probability of dying of approximately 75%.

The ERG was unfortunately unable to identify the source data for the manufacturer's calculations using the manufacturer's reference, and therefore the ERG was unable to replicate the manufacturer's calculations. Consequently, the ERG independently estimated the monthly probability of death using ONS data (Table 99) as follows:

- the total number of deaths and the total population size were extracted, by age group, from 2013 population estimates from the Office for National Statistics[78];
- the probability of death, by age-group, was calculated by dividing total deaths by total population;
- the annual probability of death for that age-group was converted to a monthly probability;
- for ages beyond 90 (for which no ONS data were available), the ERG extrapolated the data for younger age-groups using an exponential distribution to estimate the probability of death from other causes for older age-groups.

Table 99. ERG estimated average monthly probability of dying from all causes

Year	Average age of cohort in the model	Average monthly probability of dying for other causes applied in that period	Source
1-5	55-59	0.04%	ONS data[79]
6-10	60-64	0.06%	
11-15	65-69	0.10%	
16-20	70-74	0.17%	
21-25	75-79	0.29%	

26-30	80-84	0.53%	
31-35	85-89	1.00%	
36-40	90-94	2.33%	
41-45	95-99	2.90%	Exponential extrapolation of ONS data
46-50	100-104	4.97%	
51-55	105-109	8.52%	
56-60	110-114	14.59%	
Abbreviations used in table: ERG, evidence review group; ONS, Office for National Statistics.			

Thus, for patients in year 56 of the model, where the average age of survivors was 110, the ERG estimated the average monthly probability of dying to be 14.59%, equating to an annual probability of dying of approximately 85%.

The ERG notes that the ERG estimate of probability of death from other causes are larger than the manufacturer's estimates; however, the ERG also considers that an annual probability of dying of 85% at the age of 110 is likely to be an underestimate. The ERG is unclear of the source of the discrepancy between the manufacturer and ERG estimates as the ERG was unable to replicate the manufacturer's calculations. As a scenario analysis, the ERG applied the ERG-calculated probability of death from other causes within the model; the ERG assumed that patients in the model were aged 65 at the start of the model to ensure the modelling of age was in line with the ERGs conclusions from Section 5.4.3. Results from this analysis presented in Section 6.2 **analysis B17**.

The ERG notes that the conclusions of the results of **analysis B17** for dabigatran versus rivaroxaban and LMWH in the population with cancer were largely unchanged. For dabigatran versus warfarin the ICERs increased from £862 to £1,256 (acute treatment scenario) and from £8,319 to £9,405 (treatment and secondary prevention). The ERG notes that the increase in the ICERs was largely a result of a decrease in incremental QALYs for dabigatran versus warfarin.

The ERG notes a potential error in the application of general population mortality in the model engine. The manufacturer applies general population mortality to:

- a trace of patients as to whether they are on initial treatment, off treatment, on warfarin re-treatment or dead
- to patients experiencing all types of events; non-fatal VTE, fatal VTE, non-fatal MBEs, fatal MBEs, CRNMBEs, MI, UA, dyspepsia

However, the ERG notes that the number of patients experiencing each type of event feeds from the patient trace. Consequently, the manufacturer double counts general population mortality in each cycle. The ERG corrected this potential error by removing the adjustment for general population

mortality from the number of patients experiencing each type of event; results are presented in Section 6.1 **analysis A8**. The impact of the analysis was negligible.

5.4.9.4 Mortality associated with CTEPH

The manufacturer did not apply a risk of death associated with CTEPH. The ERG notes in TA261, death associated with CTEPH was incorporated within the model structure.[80] Specifically, a three-monthly mortality risk of 2.48% (estimated from Condliffe *et al*.[81]).

The ERG consulted with clinical experts around the appropriateness or otherwise of including mortality for CTEPH. The clinical experts advised that CTEPH was associated with a mortality risk, and it was therefore appropriate to incorporate deaths from CTEPH within the model structure. The ERG notes that, due to the manufacturer's model structure, patients with CTEPH continue to cycle around the model; consequently, the ERG considers that there is no simple way to identify these patients and apply a mortality risk within the structure of the current model. The ERG therefore discusses the potential impact of including a risk of death associated with CTEPH qualitatively in Section 6.2 **analysis B18**.

5.4.9.5 Death due to a MI (manufacturer sensitivity analysis only)

In sensitivity analysis, the manufacturer modelled a probability of death associated with MI. The data used by the manufacturer within the model for death due to MI was presented and discussed within Section 5.4.8.2. Table 100 provides a summary of these data.

Table 100. Probability of dying from an MI (sensitivity analysis only)

Treatment	Proportion of patients with fatal MI
Acute treatment period	
Dabigatran	0%
Warfarin	0%
Rivaroxaban	0.07%
LMWH (population with cancer)	0%
Secondary prevention period	
Dabigatran	0.21%
Warfarin	0.21%
Dabigatran	0%
Rivaroxaban	0.5%
LMWH (population with cancer)	0%
Treatment for recurrence	
Warfarin	0.04%
No treatment	
Off-treatment	0.00%
Abbreviations used in table: LMWH, low-molecular-weight heparin; MI, myocardial infarction.	

The ERG notes that the manufacturer assumed that the proportion of fatal MI events varied by treatment. Moreover, the proportion of fatal MI varied for dabigatran in the secondary prevention period depending upon which comparator was modelled. The ERG considers that there is no clinical basis for assuming that the rate of MI or UA would differ by comparator, and notes that this approach prevents comparison of final costs and QALYs between comparators. The ERG considers this to be a weakness of the sensitivity analysis.

5.4.10 Treatment discontinuation

Within the model, patients could discontinue treatment for the following reasons:

- after a recurrent VTE during treatment or secondary prevention;
- after an MBE (ICH or extra-cranial haemorrhage);
- due to any other reason captured within the clinical trials (worsening of other pre-existing diseases, other adverse events, non-compliance with trial protocol, loss to follow-up, consent withdrawal).

The manufacturer assumed that discontinuation rates differed by treatment. Discontinuation from treatment was assumed to be permanent; however, patients were assumed to return to treatment if they experienced a recurrent VTE. The ERG has previously commented on the appropriateness of assuming permanent discontinuation from treatment after an MBE, and tested this assumption in sensitivity analysis (Section 5.4.2).

For discontinuation due to recurrent VTE and MBEs, rates were dependent upon the incidence data presented in Section 5.4.6 and Section 5.4.8.1. For discontinuation due to any other reason captured within the clinical trials, the applied rates of discontinuation are presented in Table 101.

Table 101. Treatment discontinuation rates applied within the model, adapted from MS (pgs 258-259)

Comparison	Intervention	Rate observed	Duration of observation period	1-month cycle probability	Source
Acute treatment					
All full population analyses	Dabigatran	12.2%	6 months	2.1%	RE-COVER I and II
	Warfarin	10.9%	6 months	1.9%	
	Rivaroxaban	10%	7.5 months	1.4%	EINSTEIN-DVT and EINSTEIN-PE
Population with cancer	Dabigatran	12.2%	6 months	2.1%	
	LMWH	Assumed to be the same as dabigatran			
Secondary prevention					
Dabigatran versus warfarin (full	Dabigatran	16.6%	18 months	1.0%	RE-MEDY
	Warfarin	16.1%	18 months	1.0%	

population)					
Dabigatran versus rivaroxaban (full population)	Dabigatran	8.3%	6 months	1.4%	RE-SONATE
	Rivaroxaban	12.3%	8.4 months	1.5%	EINSTEIN-EXT
Dabigatran versus LMWH (population with cancer)	Dabigatran	16.6%	18 months	1.0%	RE-MEDY
	LMWH	Assumed to be the same as dabigatran			
Abbreviations used in table: LMWH, low-molecular-weight heparin; MS, manufacturer's submission.					

The ERG notes that the manufacturer applied discontinuation rates directly from clinical trial data and did not adjust between comparisons using meta-analysis. The ERG also notes that the manufacturer used full population data to estimate treatment discontinuation for the population with cancer. The ERG is unclear what impact this would have on the final results.

Furthermore, the ERG notes that the rate of discontinuation in the secondary prevention period differed depending upon which comparison was considered. The ERG considers that there is no clinical basis for assuming that the rate of discontinuation would differ according to the comparator selected. The ERG carried out a scenario analysis in which the rates of discontinuation for dabigatran versus rivaroxaban were set equal to the monthly rate used for the comparison of dabigatran versus warfarin (1%). The results of this analysis are presented in Section 6.2 **analysis B42**. Dabigatran remained dominant versus rivaroxaban in the treatment and secondary prevention scenario.

5.4.11 Warfarin INR control

The INR control of patients receiving warfarin in the dabigatran clinical trials (RE-COVER I and II, RE-MEDY) has been described previously in Section 4. As a summary, the average percentage time in therapeutic INR range for the full population was estimated to be as follows:

- RE-COVER I: 59.9%
- RE-COVER II: 56.9%
- RE-MEDY: 61.5%

Within the model, the manufacturer assumed that INR control for warfarin was, on average, 58.4%. This figure was estimated as the average of the RE-COVER I and RE-COVER II figures, weighted by the number of patients within each respective warfarin arm. This figure was not used to adjust the base case efficacy or safety data.

The ERG consulted with clinical experts around rates of INR control seen in clinical practice. The clinical experts consulted reported INR control of between approximately 65% to 80% in their clinical experience. Furthermore, the ERG notes that, in all three clinical study reports (CSRs) estimating INR control for warfarin, the manufacturer reports that percentage INR control increased throughout the duration of each clinical trial (Box 19). In RE-COVER I, INR control increased to an average of 65.7% after 6 months of treatment (MS CSR; pg 158*(26)*); In RE-COVER II, INR control increased to an average of 58.9% after 6 months of treatment, with a peak in month 5 of 62.2% (MS CSR; pg 133) (25); In RE-MEDY, INR control increased to an average of 69.8% at months 31-33 after first warfarin dose (MS CSR; pg 14*(47)*).

Box 19. INR control over time, as reported in the manufacturer's CSRs*(25;26;47)*

RE-COVER I "The mean percentage of patient time in the INR target range increased over time. In Month 6, patients in the warfarin group were in the INR target range for a mean of 65.7% of the time." MS CSR(26) page 158 **RE-COVER II** "Throughout the trial, the percentages of patients who were less than 49% or 49% to <67% of their time in the INR target range decreased, and the percentage of patients with at least 67% of time in the INR target range increased." MS CSR(25) page 134 **RE-MEDY** "In all 4 groups, INR control increased over time as in the overall population." MS CSR(47) page 141.
Abbreviations used in box: CSR, clinical study report; INR, international normalized ratio; MS, manufacturer's submission.

Within TA261 the Appraisal Committee noted that the mean time in therapeutic range for rivaroxaban with EINSTEIN-DVT was 58%, which the committee considered to be lower than might be expected in routine UK clinical practice.[(82)] However, the Appraisal Committee heard from clinical experts that control of INR is more difficult when warfarin is first started and before stabilisation on longer-term treatment, and therefore concluded that the data from the warfarin arm in the trial was applicable to routine UK practice.

The ERG considers that, based upon advice from clinical experts, the data contained within the manufacturer CSRs, and after reviewing previous relevant technology appraisals, an INR control of 58%, as assumed by the manufacturer, is not unreasonable in the acute treatment period. However, the ERG considers that INR control for UK warfarin patients is likely to increase once patients are stable on treatment, during secondary prevention, to a level of 60% or higher.

In a sensitivity analysis, the manufacturer adjusted the probability of a recurrent VTE event and the probability of bleeding based upon an analysis carried out using the General Practice Research Database (GPRD) data. The purpose of the sensitivity analysis was to quantify the possible differences in efficacy and safety outcomes that might be seen in clinical practice compared with those seen in clinical trials; with differences arising as a consequence of differences in INR control.

GPRD data (and linked Hospital Episode Statistics [HES] data, where available) were used to identify patients with an index VTE event, and an analysis was carried out to investigate the relationship between INR control, recurrent VTE events, and bleeding events. Specifically, the manufacturer estimated a HR using a Cox proportion model between patients in routine clinical practice (all selected GPRD patients) and a subgroup of GPRD patients chosen to represent patients in the RE-COVER trial for endpoints of interest. Table 102 presents the reported relationship between INR control and VTE events or bleeding, as estimated by the manufacturer. The ERG notes that the analysis for bleeding considered all types of bleeding, specifically: major bleeding; clinically-relevant non-major bleeding; minor bleeding; unspecified bleeding.

Table 102. Effect of a 1% decrease in time in international normalised ratio range (reproduced from MS; pg 242, Table 100)

Endpoint	HR (95% CI)
Recurrent VTE	1.011 (1.003, 1.019)
Any bleeding	1.016 (0.999, 1.033)
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; MS, manufacturer's submission; VTE, venous thromboembolism.	

The manufacturer notes that the INR control estimated for the full population of patients identified using GPRD data was 54.2%; this figure is lower than the INR control seen in the dabigatran clinical trials. Therefore, in a sensitivity analysis, the manufacturer increased the probability of a recurrent VTE and the probability of bleeds for people treated with warfarin by the factors described in Table 102 for the percentage difference in INR control.

The ERG has a number of concerns around the analysis carried out by the manufacturer using GPRD data and is unclear what impact these concerns would have on the results.

Firstly, the manufacturer stated that 60% included patients in the GPRD data set did not receive a prescription for warfarin reported on their data record. The manufacturer chose to include these patients, *"given that most patients with a VTE event would be treated with warfarin in the United Kingdom".(83)* Furthermore, the manufacturer states that *"the impact of this patient inclusion assumption is likely to be minimal and when faced with a choice of excluding many patients or assuming that all patients were treated, the latter is likely to be less influential on the overall results"*.(83) The ERG considers that it would have been preferable to include only patients who are

confirmed to be receiving warfarin within the analysis of warfarin INR control. The ERG is particularly concerned due to the high proportion of missing data (~60%). The ERG considers that it is feasible that some of the patients included in the analysis were those who either: refused to receive any medication; whose risk to benefit ratio suggested that it was preferable to receive no medication; or who were treated with an alternative intervention. The ERG also considers it feasible that the results of the analysis would differ if only warfarin patients were included.

Secondly, only 20% of included patient records contained sufficient INR data from which to calculate % time in therapeutic range.

Thirdly, the outcome for safety recorded all types of bleeding, specifically: major bleeding; clinically-relevant non-major bleeding; minor bleeding; unspecified bleeding. This is in contrast to the model which considers only major bleeding and clinically-relevant non-major bleeding.

Finally, the manufacturer found it challenging to distinguish clearly between an index VTE and a recurrent VTE from the data. As a consequence, the relationship between INR control and probability of recurrence is likely to have been impacted.

As a consequence of the above limitations of the analysis, the ERG is not confident that the results reported in Table 102 reflect the true relationship between INR control and recurrent VTE or recurrent bleeding, and expresses caution around interpretation of the related sensitivity analysis. Moreover, the ERG has concerns around the robustness of the average estimate of INR control in clinical practice reported by the manufacturer at 54.2%.

The ERG is unable to quantitatively describe the impact of INR control in UK clinical practice on the economic results presented by the manufacturer. This is because the ERG is not confident in the accuracy of the relationship estimated by the manufacturer between INR control and recurrence or bleeding. Instead, the ERG qualitatively describes the likely impact upon results in Section 6.2 **analysis B19**. The ERG notes that the ICER for dabigatran versus warfarin in the treatment and secondary prevention scenario is likely to increase if INR control for warfarin improved.

5.4.12 Health-related quality of life (HRQoL)

The manufacturer accounted for differences in HRQoL for the following health states:

- VTE events (Section 5.4.12.3);
- complications associated with VTE events (Section 5.4.12.4);
- treatment disutility for warfarin and LMWH (Section 5.4.12.5);
- adverse effects of treatment (Section 5.4.12.6).

This section outlines and critiques the values used within the manufacturers' model for each of these health states, as well as describing the manufacturer's systematic review of the HRQoL literature (Section 5.4.12.1).

5.4.12.1 Manufacturer systematic literature review for health-related quality of life data

The manufacturer carried out a systematic review in February 2013 (updated in April 2014) to identify HRQoL studies relevant to the health states considered in the model. The following electronic databases were searched: Medline, Medline In-Process, EconLIT, Embase, BIOSIS and The Cochrane Library. The manufacturer used terms to capture the health condition of interest (VTE, adverse events) and study type (HRQoL study). Details of the search strategy, inclusion and exclusion criteria are provided in the MS (p266-267 and Appendix 12 [p478-489]). In addition to the database search, the manufacturer also reviewed clinical and economic conference websites (MS; Appendix 12), and screened the reference lists of included studies.

The database searches were limited to records published from January 2000; the manufacturer justified this restriction "because economic data published before that time were unlikely to be relevant to current treatment practices" (MS; pg 478). Conference abstracts were searched from January 2011 to present because "high-quality studies reported in abstract form before 2011 were expected to have been published in a peer-reviewed journal" (MS; pg 478). There were no date restrictions on the searches for HTA documentation.

A total of 31 studies were identified from the February 2013 search (27 studies) and April 2014 search (4 studies) that reported utility estimates. The manufacturer extracted data from these studies and presented these within the submission (MS; pgs 269–295). Of the 31 studies identified after the updated search, three related to index or recurrent DVT or PE.[84-86] Table 103 summarises the HRQoL data contained within these studies.

Table 103. HRQoL studies identified from the manufacturer's search related to index or recurrent DVT or PE

Study (country)	Study population	Health-state description	Methods of elicitation and valuation	Utility estimate
Hogg *et al.*, 2013[84] (Canada)	214 patients diagnosed with either lower extremity DVT or PE, with a history of VTE. Mean age 56, 52% male.	• acute DVT; • acute PE; • gastrointestinal bleeding; • minor intracranial haemorrhage; • major intracranial haemorrhage.	30 minute interventions with patient eliciting health state valuations using the SG technique	Median SG utility value • acute DVT: 0.81 • acute PE: 0.75 • minor intracranial haemorrhage: 0.75 • gastrointestinal bleeding: 0.65 • major intracranial haemorrhage: 0.15 Median SG utility value for patients within 4 weeks of diagnosis

				• acute DVT: 0.75 • acute PE: 0.65 Median utility value for cancer patients • acute DVT: 0.75 • acute PE: 0.71
Tavoly *et al.*, 2013[86] (Norway)	208 patients surviving acute PE, 114 age- and sex-matched controls with no history of VTE recruited between 2002 and 2011. Mean age 61 years.	• full health • surviving acute PE	Patients and controls completed the EQ-5D	Mean EQ-5D index value (standard deviation) • surviving acute PE: 0.81 (0.22) • controls: 0.92 (0.16) • mean difference, 0.11 ($p < 0.001$)
Sullivan *et al.*, 2011[85] (USA)	EQ-5D data collected from patients with initial VTE event receiving dabigatran etexilate (1,149) or warfarin (1,150) for 6 in the RE-COVER trial.	Model health-states: • 6-months post VTE • 3 months post VTE • recurrent DVT • underweight • female • morbidly obese • recurrent PE • heart failure • age >65 • clinically relevant bleeding	Patients completed the EQ-5D at baseline, 3 and 6 months. Scores were regressed on treatment, time since index VTE, age, gender, race, ethnicity, smoking status, body weight, and various clinical characteristics and conditions.	• 6-months post VTE (+ 0.21) • 3 months post VTE (+0.192) • recurrent DVT (-0.17) • underweight (-0.09) • female (-0.08) • morbidly obese (-0.07) • recurrent PE (-0.06) • heart failure (-0.05) • age >65 (-0.04) • clinically relevant bleeding (-0.03) No differences were statistically significantly different.
Abbreviations used in table: CRNM, clinically relevant non-major; DVT, deep vein thrombosis; HRQoL, health-related quality of life; PE, pulmonary embolism; SG, standard gamble; VTE, venous thromboembolism.				

In addition to data identified for recurrent VTE events, the manufacturer considered that 29 of the 31 identified studies included utility data for adverse events or complications of treatment, specifically:

- dyspepsia[87-89];
- major bleeds[84;90;91];
- myocardial infarction[92-100];
- post-thrombotic syndrome[101];

- pulmonary hypertension[102-111] (plus two additional abstracts from 2010 which the ERG was unable to identify the references for; Harris et al., 2010; Mychaskiw et al., 2010);
- stroke[92;108];
- unstable angina[112].

The ERG considers that the search terms and inclusion/exclusion criteria used by the manufacturer were comprehensive and appropriate; however, the ERG is concerned that the manufacturer limited searches by date as relevant publications may have been omitted. To assess the extent to which the manufacturer may have omitted evidence, the ERG reviewed the included HRQoL studies within TA261and TA287.[49;65] The ERG notes that a key paper identified within both systematic reviews for these STAs and published before the year 2000 was a paper published in 1997 by Lenert *et al*.[113] The ERG notes that, whilst the manufacturer did not identify this paper within the systematic review, the disutility for severe PTS included within the manufacturer's model was extracted from this paper. By way of explanation, the manufacturer stated that, as no suitable studies were identified from the systematic review for severe PTS, the manufacturer "resorted to a study outside the time span covered by the literature searches" (MS; pg 301). It is not clear how this particular paper was identified and selected by the manufacturer.

Moreover, the ERG notes that the manufacturer did not identify Locadia *et al*. within the searches for HRQoL.[114] The ERG notes that Locadia *et al*. formed the basis of DVT and PE utility values used within TA261 and TA287.[49;65] The ERG would have expected this study to be identified from the outlined search strategy, and, for completeness, provides a summary of the data contained with Locadia *et al*. in Table 104.

Table 104. HRQoL data contained within Locadia *et al.*[114]

Study (country)	Study population	Health-state description	Health state valuation	Utility estimate
Locadia *et al.*, 2004[114] (Netherlands)	Patients in the Netherlands recruited from October 2000 to June 2002. Valuations of outcomes after VTE were elicited from: • 53 patients who had experienced a VTE • 23 patients who had experienced a MBE during treatment • 48 patients with PTS	Four chronic health states: • non-fatal; • haemorrhagic stroke; • PTS; • no VKA treatment; • own current health. Five temporary health states: • DVT; • PE; • gastro-intestinal bleeding; • muscular bleeding; • VKA treatment.	TTO	Median valuation (IQR) for each health state: • non-fatal haemorrhagic stroke: 0.33 (0.14 to 0.53) • PTS: 0.82 (0.66 to 0.97) • no VKA treatment: 0.96 (0.82 to 1.00) • own current health: 0.95 (0.814 to 1.00) • DVT: 0.84 (0.64 to 0.98) • PE: 0.63 (0.36 to 0.86) • gastro-intestinal bleeding: 0.65 (0.49 to 0.86) • muscular bleeding: 0.76 (0.59 to 0.985) • VKA treatment : 0.92 (0.77 to 0.98)
Abbreviations used in table: DVT, deep vein thrombosis; HRQoL, health-related quality of life; IQR, interquartile range; PE, pulmonary embolism; PTS, post thrombotic syndrome; TTO, time trade-off; VKA, vitamin K agonist; VTE, venous thromboembolism.				

5.4.12.2 Overview of utilities applied within the manufacturer's economic analysis

Table 105 summarises the HRQoL values used within the manufacturer's economic analysis, the source of these data, and the manufacturer's stated rationale for selection. Sections 5.4.12.3 to 5.4.12.6 below describe the data used in greater detail.

Table 105. HRQoL data applied within the manufacturer's model

Modelled event	Disutility	Source	Identified from the manufacturer systematic review?	Rationale for source used
VTE events				
Initial and recurrent DVT	-0.25	Analysis of EQ-5D data collected in RE-COVER I and II	N/A	"Disutility values calculated are pursuant to the NICE reference case" MS pg 301
Initial and recurrent PE				
Complications associated with VTE events				
Severe PTS	-0.07	Lenert *et al.* (1997)(113)	No	NR
CTEPH	-0.12	See text below, value of -0.1 applied in the model in error, value of -0.12 taken from Keogh et al., (2007)*(115)* (MS; pg 300)	No	NR
Treatment with warfarin and LMWH				
During active warfarin treatment	-0.012	Marchetti *et al.(56)*	No	NR
During active LMWH treatment	-0.008			
Adverse effects of treatment				
Disabled from ICH	-0.5	Wolowacz *et al.*[116] (taken from Ingelgard *et al.*[117])	No	NR
MBE	-0.13	Analysis of EQ-5D data collected in the pivotal RE-COVER trials	N/A	"Disutility values calculated are pursuant to the NICE reference case" MS pg 301
CRNMB	-0.04			
Myocardial infarction	-0.063	Sullivan *et al.*[118]	No	NR
Unstable angina	-0.085			
Dyspepsia	-0.04	Gerson *et al.*[89]	Yes	NR
Abbreviations used in table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT deep vein thrombosis; ICH, intracranial haemorrhage; LMWH, low-molecular-weight heparin; MBE, major bleeding event; MS, manufacturer's submission; N/A, not applicable; NR, not reported; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.				

5.4.12.3 Disutility associated with VTE events

The manufacturer estimated the disutility associated with (proximal) DVT and PE using EQ-5D scores collected within RE-COVER I and II. In the model, disutility was subtracted from published utility values for the general public, by age-group.

EQ-5D data in RE-COVER I and II were collected at baseline, 3-months and 6-months from any patient who took at least one dose of study drug. The EQ-5D data collected within RE-COVER I and II were converted to utilities using published valuations provided by a sample of the UK general public, using time-trade-off (TTO) methodology. The manufacturer used data from the baseline assessment to estimate utility decrements for VTE events. In total, 5,045 patients (RE-COVER I, 2,511; RE-COVER II, 2,534) completed baseline EQ-5D assessments. The manufacturer's justification for the use of baseline data is presented in Box 20.

Box 20. Manufacturer justification for use of baseline EQ-5D data collected within RE-COVER I and RE-COVER II (MS; pg 264)

In the RE-COVER trials, baseline EQ-5D assessments were made for patients entering the trial with a VTE event. This represents a large sample of patients experiencing a VTE (e.g., in the RE-COVER I trial; 1,749 patients entered the trial with a DVT and 786 with PE with or without DVT). The number of patients with recurrent VTE events was small by comparison (e.g., in RE-COVER I there were 20 recurrent PE events and 34 recurrent DVT events). In addition, EQ-5D assessments may not have coincided with recurrent VTE events, while the baseline assessments (at randomisation) represent the health state immediately after an event. Therefore, the utility decrements for both the initial and recurrent VTE events in the model were estimated using baseline utility data.
Abbreviations used in box: DVT, deep vein thrombosis; PE, pulmonary hypertension; VTE, venous thromboembolism.

The manufacturer estimated the utility decrement associated with (proximal) DVT and PE to be 0.25. The estimate of decrement was calculated by comparing EQ-5D data collected at baseline to EQ-5D data collected at 3 months (Table 106). The implicit assumption made by the manufacturer was therefore that EQ-5D data collected at 3-months reflected the utility values for those without VTE events. Note; the estimate of utility decrement for PE related to patients within RE-COVER I and II who only experienced a PE, i.e. who did not also have a DVT.

Table 106. EQ-5D data collected in RE-COVER I and II at baseline, and change from baseline to 3 months, adapted from MS (pgs 264 to 265)

Time point	DVT (95% CI)	PE (95% CI)
Baseline (day 1)	0.58 (0.56, 0.60)	0.58 (0.55, 0.61)
Change from baseline to 3 months	0.25 (0.24, 0.26)	0.25 (0.23, 0.27)
Abbreviations used in table: CI, confidence interval; DVT, deep vein thrombosis; MS, manufacturer's submission; PE, pulmonary embolism.		

In the model, the calculated utility decrement was subtracted from the utility of general population, according to age-group, and applied to patients experiencing an index or a recurrent VTE event. The estimate of general population utility, presented by age and gender, was taken from the Health Survey

for England 1996, edited by Prescott-Clarke *et al*.[119] The manufacturer did not describe how this report was identified and selected.

The disutility was applied within the model for 6-weeks. The ERG notes an inconsistency within the MS; the manufacturer describes that the disutility associated with DVT or PE was assumed to last for alternatively, one month (MS; pg 265) and 6 weeks (MS; pgs 261, 300 to 301). The ERG notes that within the model, the disutility associated with a DVT or PE is applied for 6-weeks; therefore the ERG considers that the text on page 265 of the submission was an error. The rationale provided by the manufacturer for applying the disutility for 6-weeks is presented in Box 21.

Box 21. Manufacturer justification for duration of VTE disutility applied within the model (MS; pg 261)

The duration for which utility decrements after initial and recurrent VTE should be applied is uncertain. The change from baseline was very similar at 3 months and 6 months […]. Therefore, VTE events appear to impact HRQL for 3 months or less. In the base case analysis, the duration of the disutility is set to conservative 6 weeks which is half of the possible 3 months
Abbreviations used in box: HRQL, health-related quality of life; MS, manufacturer's submission; VTE, venous thromboembolism.

The ERG has a number of comments upon the manufacturer's calculation of index and recurrent VTE utility, specifically:

- use of EQ-5D data at baseline from RE-COVER I and II as the base case disutility value;
- use of PE without DVT data;
- duration of application of disutility;
- use of a utility decrement calculated from baseline to 3-months;
- effect of subtracting a disutility from age-adjusted general population utility values.

Use of EQ-5D data at baseline from RE-COVER I and II as the base case utility value

The ERG notes that the manufacturer's estimate of disutility associated with PE and DVT are the same (-0.25). The ERG notes that this result may be considered surprising as a PE is a more serious condition which might be expected to be associated with a larger decrement in HRQoL compared with DVT. In addition, the HRQoL values previously used within similar STAs (TA261, TA287) for PE and DVT differed, with PE and DVT associated with a HRQoL of 0.63 and 0.84 respectively.[49;65] Nevertheless, the ERG agrees with the manufacturer that it was appropriate to use the EQ-5D data collected within the RE-COVER I and II trials within the model, rather than other published estimates of utility. This is because the sample size for which the values are based is large (n=5,045), considerably larger than those used in previous similar STAs (53 patients with VTE[114]). Moreover,

the ERG considers the trial population to be largely representative of the patients observed in UK clinical practice, with the exception of average age which is likely to be slightly younger than the average age of patients presenting in clinical practice (Section 5.4.3).

The ERG notes that the estimate of disutility has been calculated without adjustment for covariates such as age or other baseline characteristics. The ERG is unclear what impact such adjustments would have had on the results.

The ERG also agrees that use of data from the baseline assessment was appropriate. This is because, as explained by the manufacturer, the EQ-5D questionnaire was applied at the point of the VTE event, by contrast with data collected at 3 or 6-months which may include both people experiencing and those not experiencing a VTE event.

Use of PE without DVT data

The manufacturer estimated the decrement associated with PE using data from people in RE-COVER I and II who experienced an index PE without a DVT. The ERG notes that 460 people within RE-COVER I and II experienced both a PE and DVT. The HRQoL for patients with both a PE and DVT was found by the manufacturer to be statistically significantly lower (at the 95% confidence level) than the HRQoL for patients with a PE and no DVT (Table 107).

Table 107. Baseline EQ-5D index reported by the manufacturer from RE-COVER I and II, by index event (EQ-5D report[21], Table 3.1.2, pg 153)

	Symptomatic DVT only	Symptomatic PE only	Symptomatic PE and symptomatic DVT	p-value
Number of baseline measurements	3,457	1,118	460	–
Mean EQ-5D index score at baseline (sd)	0.58 (0.32)	0.58 (0.36)	0.53 (0.36)	0.0057
Abbreviations used in table: DVT, deep vein thrombosis; MS, manufacturer's submission; PE, pulmonary embolism; sd, standard deviation.				

The ERG considers that it would have been appropriate to use data for PE with and without DVT within the calculations of disutility to reflect the population within the clinical data and clinical practice. The ERG notes that, after weighting for the number of patients experiencing each VTE event, the average utility value for PE (with or without DVT) was 0.565; this represents a small decrease in the utility associated with PE or, alternatively, an 0.015 increase in the utility decrement associated with PE. The ERG carried out a sensitivity analysis in which the utility decrement associated with PE was increased to 0.265. Results are presented in Section 6.2 **analysis B20;** the impact upon model results of this change was negligible.

Duration of application of disutility

For a patient experiencing a VTE within one cycle (one 30-day month), the manufacturer applied 6-weeks of disutility. The ERG notes that a consequence of this is that, for patients who go on to experience a further VTE event in the following cycle, or for patients who die in the following cycle, disutility associated with VTE may be overestimated. For example, for a two month period, a patient who experiences two VTE events will receive 12 weeks' worth of disutility.

In addition, the ERG notes that the utility associated with DVT and PE events were applied for one month in TA261, TA287 and CG144.[49;65;66] The ERG therefore carried out a sensitivity analysis in which the duration of disutility was set to one month (30 days, the manufacturer's assumed monthly duration). Results are presented in Section 6.2 **analysis B21**. The impact of this analysis on model results was negligible.

Use of a utility decrement calculated from data at baseline to data at 3-months in RE-COVER I and II

The ERG is concerned that the manufacturer estimated a utility decrement by subtracting the baseline utility value estimated from RE-COVER I and II from the 3-month utility estimate in RE-COVER I and II. The ERG notes that patients within the RE-COVER clinical trials at 3-months may have experienced a recurrent VTE event. The ERG is therefore concerned that the decrement associated with VTE events may be underestimated, as HRQoL for patients at 3-months may not be equivalent to HRQoL for the general population without VTE. The ERG is also unclear why the manufacturer calculated the decrement using data from 3-months, rather than 6-months or end of treatment.

As a sensitivity analysis, the ERG applied the utility values estimated for DVT and PE by the manufacturer (0.58, Table 107) directly within the model engine, negating the need for calculation of a disutility. Results are presented in Section 6.2 **analysis B22**.

The ICERs for dabigatran versus warfarin for **analysis B22** increased from £862 to £1,156 (acute treatment scenario) and from £8,319 to £11,878 (treatment and secondary prevention) as a result of this change. The ICER for dabigatran versus rivaroxaban in the acute treatment scenario flipped from dabigatran being dominant (less costly and more effective) to less costly and less effective compared with rivaroxaban. The ICERs for dabigatran versus LMWH in the population with cancer were largely unchanged.

The effect of subtracting a disutility from age-adjusted general population utility values

The ERG notes that the manufacturer subtracted the estimated disutility associated with a VTE event from the general population utility values estimated from the Health Survey for England 1996.[119] The ERG is unclear how this source of general population utility values was identified and selected, and notes that another reference commonly used to provide general population utility values is a 1999 discussion paper by Kind *et al.*[120] The ERG carried out an analysis in which general population

utility values from Kind *et al.* were used within the manufacturer's model. In addition to using the utility values from Kind *et al*. the ERG also adjusted the starting age of patients in the model from 54.7 years to 65 years to reflect the concerns raised in Section 5.4.5. Results are presented in Section 6.2 **analysis B3**.

The ICERs for dabigatran versus warfarin in **analysis B3** increased from £862 to £1,301 (acute treatment scenario) and from £8,319 to £9,528 (treatment and secondary prevention). The ERG considers it is likely that the change is largely as a result of the change in cohort age. The ICERs for dabigatran versus rivaroxaban and LMWH in the population with cancer were largely unchanged.

By subtracting the estimate of disutility from age-adjusted general population utility values, the overall utility for a patient experiencing a VTE event falls as they age. Whilst this may not appear an unreasonable assumption, the ERG notes that, within RE-COVER I and II, the manufacturer collected, analysed and presented EQ-5D data by age group. Table 108 summarises these data collected at baseline. The ERG notes that these data indicate that the utility associated with an index VTE event does not appear to reduce with age.

Table 108. EQ-5D data at baseline in RE-COVER I and II, by age and treatment received (reproduced from MS, EQ-5D report[21;121], Table 7.1.4.7 and Table 7.2.4.7)

Age group	Dabigatran		Warfarin	
	n	EQ-5D index (sd)	n	EQ-5D index (sd)
18 ≤ age < 40	492	0.52 (0.34)	495	0.54 (0.33)
40 ≤ age < 50	444	0.57 (0.33)	447	0.57 (0.33)
50 ≤ age < 65	813	0.57 (0.33)	776	0.58 (0.33)
65 ≤ age < 75	489	0.61 (0.32)	484	0.62 (0.32)
≥ 75	284	0.59 (0.34)	311	0.57 (0.34)

Abbreviations used in table: LMWH, low-molecular-weight heparin; MS, manufacturer's submission; sd, standard deviation.

The ERG compared the baseline utility values for DVT and PE by age, as analysed by the manufacturer in Table 108, with the estimate of utility applied within the model for DVT and PE. The applied model estimate of EQ-5D was estimated by the ERG as the general population utility value by age, less the estimated disutility associated with DVT and PE (-0.25). The results are presented in Table 109.

Table 109. Utility estimate for PE and DVT by age group, RE-COVER I and II compared with data applied within the model

Age group	EQ-5D data applied within the model, by age					Collected EQ-5D data, by age
	General population utility (HSE 1996)		Decrement for PE and DVT	Resultant PE and DVT EQ-5D applied in the model		Baseline EQ-5D score from RE-COVER I and II*
	Females	Males		Females	Males	
16 – 24	0.90	0.91	-0.25	0.65	0.66	0.53[a]
25 – 34	0.90	0.92		0.65	0.67	
35 – 44	0.87	0.89		0.62	0.64	
45 – 54	0.84	0.85		0.59	0.61	0.57[b]
55 – 64	0.78	0.80		0.53	0.55	0.575[c]
65 – 74	0.76	0.80		0.51	0.55	0.615
75 +	0.71	0.76		0.46	0.51	0.58

* estimated as the average of the treatment specific EQ-5D scores presented in Table 108

[a] data for people aged 18 – 40; [b] data for people aged 40 – 50; [c] data for people aged 50 – 65

Abbreviations used in table: DVT, deep vein thrombosis; HSE, Health Survey for England; PE, pulmonary embolism.

The ERG notes that at younger age groups (aged 16 – 44), it appears as though the utility value used within the model may overestimate the absolute utility associated with PE or DVT, whilst at older age groups (45 years and older), the utility value used within the model may underestimate the absolute utility associated with PE or DVT. The ERG notes that the starting age of patients within the model is 54.7 years of age, therefore, the utility values applied within the model may underestimate the absolute utility associated with a PE or DVT or, equivalently, may overestimate the disutility. The ERG considers that it would have been more appropriate for the manufacturer to estimate the disutility associated with DVT / PE by age, and apply these figures to the age-adjusted general population utility values.

To investigate the impact of the manufacturer's methodology, the ERG carried out an analysis in which the utility values estimated for DVT and PE by the manufacturer (0.58) were applied directly within the model engine, negating the need for calculation of a disutility. Results are presented in Section 6.2 **analysis B22**. The ICERs for dabigatran versus warfarin for **analysis B22** increased from £862 to £1,156 (acute treatment scenario) and from £8,319 to £11,878 (treatment and secondary prevention) as a result of this change. The ICER for dabigatran versus rivaroxaban in the acute treatment scenario changed from dabigatran being dominant (less costly and more effective) to less costly and less effective compared with rivaroxaban. The ICERs for dabigatran versus LMWH in the population with cancer were largely unchanged.

5.4.12.4 Disutility of complications associated with VTE events

The manufacturer applied a disutility for patients experiencing either severe PTS or CTEPH. The disutility, the source, and the duration of disutility applied within the model for each complication are presented in Table 110.

Table 110. Disutility, source and duration of applied disutility for complications of VTE events

Complication	Disutility; mean (95% CI)	Source	Duration of disutility
Severe PTS	-0.07 (-0.048, -0.092)	Lenert *et al.(113)*	Lifetime
CTEPH	Unclear: • -0.12 (-0.080, -0.120) (MS; pgs 300-301) • -0.1 (model)	Unclear; • Keogh et al.*(115)* and HSE 1996 (MS; pg 300) • Assumption (model)	Unclear: • lifetime (MS; pgs 300-301) • one month (MS; pg 232, model)
Abbreviations used in table: CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; HSE, Health Survey for England; MS, manufacturer's submission; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.			

Severe PTS

The disutility applied by the manufacturer for severe PTS was obtained from Lenert *et al.*[(113)] Lenert *et al*. was not identified from the manufacturer's systematic review of the HRQoL literature (Section 5.4.12.1). The manufacturer stated that, as no suitable studies were identified from the systematic review for severe PTS, the manufacturer "resorted to a study outside the time span covered by the literature searches" (MS; pg 301). It is not clear how this paper was identified; however, the ERG notes that this paper was identified and used within TA261 and TA287 as the source of PTS utility.[(49;65)]

The study by Lenert *et al*. used standard gamble techniques to elicit the preference valuations from 30 female volunteers for the health state "severe PTS"; the resulting utility value estimated was 0.93 (0.76 – 1.00).[(113)] From this figure, the manufacturer estimated an associated utility decrement of 0.07 (1 minus 0.93) and applied this to all patients developing severe PTS for their lifetime. The ERG notes that the sample used to estimate the decrement associated with severe PTS was small (n=30) and generally not representative of the UK population experiencing proximal DVT (Section 5.4.3; 100% female, median age 25 years old).

Due to time constraints, the ERG was unable to re-run the systematic review for estimates of disutility associated with severe PTS; however, the ERG carried out a simplistic search of PUBMED using the search terms "post thrombotic syndrome and EQ-5D" on the 7th July 2014. Two studies were identified, one of which, Enden *et al.*, provided an estimate of disutility associated with PTS using the EQ-5D.[(122)]

The study by Enden *et al*. was published in 2013 and considered 189 Norwegian patients with proximal DVT who were treated with either catheter-directed thrombolysis or anticoagulation and compression stockings. The aim of the study was to assess quality of life of the enrolled patients, by treatment, using EQ-5D. The authors also combined EQ-5D data for both treatment arms to investigate the impact of PTS on HRQoL. The authors reported that, independent of treatment arms, patients with PTS had poorer outcomes than patients without PTS, with a mean EQ-5D index score difference of 0.02 (95% CI−0.08 to 0.28) after 6 months, and 0.09 (95% CI 0.03 to 0.15) after 24 months.

The ERG notes that the definition of PTS within Enden *et al*. included both mild and severe PTS.[122] The ERG also notes that the questionnaire was completed by Norwegian patients, rather than UK patients. Nevertheless, the ERG considers that this study may provide a useful alternative estimate of disutility associated with PTS. This is because the sample on which the EQ-5D questionnaire were based were a relevant patient population (population with proximal DVT); the sample size was larger than Lenert *et al*. (189 versus 30), and the paper more recent (2013 versus 1997).[113;122] Moreover, as Lenert *et al*. found no decrement in utility associated with mild PTS, the ERG considers that the decrement within Enden *et al*. is likely to largely represent that of severe PTS.

The ERG considers that the decrement in Enden *et al.* (0.02 – 0.09) is similar to the decrement applied by the manufacturer (0.07), therefore the ERG considers the figure used by the manufacturer to be reasonable. However, the ERG notes that this paper was not identified from the manufacturer's systematic review of the HRQoL literature. Given the search terms used, the ERG would have expected this study to be identified and is unclear why it was omitted from the included studies.

The ERG also notes a potential error in the application of severe PTS disutility within the model. As described within Section 5.4.7, the ERG believes the number of people with severe PTS has been overestimated due to a calculation error in the model engine; this was corrected in sensitivity **analysis A3,** described in Section 5.5.1 with results presented in Section 6.1. The impact upon the ICERs was negligible.

Chronic thromboembolic pulmonary hypertension

Within the MS, the manufacturer states that the disutility associated with CTEPH was estimated using Keogh *et al*. and the Health Survey for England 1996.[115;119] Within the model, the manufacturer states that the disutility associated with CTEPH is based upon an assumption that -0.1 is an appropriate decrement. The ERG asked the manufacturer which value was intended to be used within the base case analysis. The manufacturer stated that "the 0.12 value is the correct one (0.10 was a prior assumption). 'Input data'!H1237 may be amended accordingly" (manufacturer response to clarification; pg 64). The ERG therefore corrected this mistake; a description of the analysis

undertaken is provided in Section 5.5.1 with results presented in Section 6.1 **analysis A9.** The impact on the ICERs was negligible.

Keogh *et al*. report the effect of bosentan (an oral dual endothelin receptor antagonist) on quality of life in patients with WHO Functional Class III or IV pulmonary arterial hypertension (PAH).[115] Quality of life was assessed using the SF-36, converted to SF-6D utilities. The average age of included patients was 55.4 years, 74% female, with median duration of PAH of 1.22 years.

According to the MS, the mean utility of functional class I patients reported within Keogh *et al*. was subtracted from the weighted baseline utility for 54.7 year-olds (the average age of dabigatran patients reported in RE-COVER I) from the Health Survey for England 1996 to estimate the monthly decrement associated with CTEPH (0.85 minus 0.73 = 0.12).[115;119] The manufacturer stated that the decrement was applied in the model for, alternatively, one month (MS; pg 232), or for the remaining lifetime of patients with CTEPH (MS; pg 300-301). The ERG notes that within the model the disutility is applied for one month.

The ERG has a number of comments around the selection and application of CTEPH disutility in the model. Firstly, the ERG notes that Keogh *et al*. was not identified from the systematic review of the HRQoL literature, and the manufacturer did not describe how this paper was identified or selected. In addition, the ERG notes that 12 studies[102-111] (plus two abstracts published in 2010 which the ERG was unable to identify from the manufacturers' reference) were identified relating to pulmonary hypertension within the manufacturer's systematic review; the manufacturer did not state the rationale for excluding these studies from the analysis.

The ERG considers that the study by Keogh *et al*. is not entirely representative of the patient population of interest for this STA. The condition of interest reported within Keogh *et al*. relates to PAH, classified as pulmonary hypertension WHO group 1, whereas CTEPH is classified as pulmonary hypertension WHO group 4. Furthermore, the ERG notes that the manufacturer estimated the disutility associated with CTEPH using the mean utility reported for PAH functional class I patients within Keogh *et al*.; class 1 patients represent those with the mildest form of PAH; specifically those patients without resulting limitation of physical activity, and physical activity that does not cause dyspnoea or fatigue, chest pain or near syncope. The ERG consulted with clinical experts and considers that, on average, the use of class 1 data might underestimate the symptoms and therefore disutility experienced for people with CTEPH.

The ERG notes that, in TA261 and TA287, a utility value for CTEPH was taken from Meads *et al*.; this study was identified from the manufacturer's systematic review of the HRQoL literature but was not incorporated into the analysis.[49;65;106] The study reported by Meads *et al*. aimed to validate the

responsiveness of a condition specific utility index, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). The ERG reviewed Meads *et al*. and notes that a utility value associated with CTEPH is reported. A total of 314 patients with CTEPH completed the CAMPHOR QoL questionnaire, and were estimated to have a mean HRQoL of 0.56 (standard deviation, 0.29). It is not clear from Meads *et al*. how preferences were elicited to value each health state; however, the ERG notes that a paper by McKenna *et al*. provides further details.[(105)] The CAMPHOR QoL scale was used to create 36 health states that were valued by 249 people representative of the UK adult population, using TTO.

The ERG considers that the data presented in Meads *et al*. provides an estimate of utility for CTEPH using methods that are considered acceptable according to the NICE Guide to Methods of Technology Appraisal 2013.[(67)] Moreover, the ERG considers that the description of the CTEPH health state specifically offers an advantage over Keogh *et al*. in which the health state relating to PAH is valued.[(115)] The ERG was unable to easily incorporate the Meads *et al*. data within the manufacturer's model structure because the value represented a utility, rather than a disutility. Instead, the ERG estimated a disutility associated with CTEPH by subtracting 0.56 from the general population utility value for 65 year olds, to reflect the anticipated average age of patients (Section 5.4.3.2). Thus, the disutility was estimated to be (0.78 [average of female and male values, Table 109] – 0.56 = -0.22). The ERG acknowledges that this figure is a crude estimate and represents an exploratory analysis only. The results from this analysis are presented in Section 6.2 **analysis B24**. The impact upon the ICERs was negligible.

The ERG notes that the manufacturer alternatively described the disutility for CTEPH as applying for lifetime for those patients developing the condition (MS; pg 300 – 301) and for one month (MS; pg 232). The ERG considers that the manufacturer text on page 300 – 301 is a mistake, because the manufacturer applies the disutility for one month within the model; however, the ERG notes that within TA261 CTEPH was considered a chronic condition.[(49)] The ERG consulted with clinical experts and considers that the disutility associated with CTEPH would typically apply for the remaining lifetime of that patient. The ERG carried out a scenario analysis in which CTEPH disutility was applied for the lifetime of patients developing CTEPH. Results are presented in Section 6.2 **analysis B25**. The impact upon model results was negligible.

In addition, the ERG notes a possible calculation error. As with PTS, and as discussed in Section 5.4.7, the ERG considers that the manufacturer may have made a mistake in the calculation of number of people with CTEPH. An analysis correcting for this potential error is discussed in Section 5.5.1 and presented in Section 6.1, **analysis A4**. The impact upon the ICERs for dabigatran versus warfarin, rivaroxaban (for the full population) and LMWH (for the population with cancer) for both the acute treatment, and the treatment and secondary prevention scenarios was negligible.

5.4.12.5 Disutility associated with warfarin and LMWH treatment

Within the model, the manufacturer applied a disutility associated with warfarin use and LMWH use. The disutility associated with LMWH use was limited to the use within the subgroup of patients with active cancer who were receiving LMWH monotherapy. The applied disutilities are presented in Table 111. The estimate of disutility was calculated using data from a study by Marchetti *et al*.[56]

Table 111. Disutility applied within the model for treatment with warfarin and LMWH

	Disutility applied within the model Mean (95% CI)	**Source of estimate**
Treatment with warfarin	-0.012 (-0.008, -0.016)	Marchetti *et al.*
Treatment with LMWH	-0.008 (-0.005, -0.011)	
Abbreviations used in table: CI, confidence interval; LMWH, low-molecular weight heparin.		

The study by Marchetti *et al*. aimed to compare the cost-utility of LMWH with that of oral anticoagulants in preventing recurrences after an episode of VTE. To calculate QALYs, the published literature was searched to establish the HRQoL associated with stroke and post-thrombophlebitis syndrome. In addition, to establish the HRQoL associated with use of warfarin and LMWH, a total of 48 patients who were receiving warfarin or LMWH completed a TTO questionnaire. Of the 48 patients within this study, 10 patients would have accepted trading some days of life to avoid warfarin (and therefore 38 would not) or 8 patients would have accepted trading some days of life to avoid LMWH (and therefore 40 would not). On average, these patients would have traded 4 days to avoid warfarin and 2.7 days to avoid LMWH. This led to a mean utility of 0.988 for warfarin and 0.992 for LMWH.

The manufacturer subtracted the mean utility values presented within Marchetti *et al*. from perfect health (1.00) to estimate the disutility applied within the model. The disutility was converted to a monthly probability, and applied for the duration of warfarin or LMWH treatment.

The ERG reviewed the manufacturer's incorporation of warfarin disutility within the model. The ERG considers that the manufacturer may have made a mistake in the application of disutility which biases against warfarin in the comparison of dabigatran versus warfarin.

Specifically, within both the engine for dabigatran and warfarin, the manufacturer applied 6 months' worth of disutility associated with warfarin to patients having a recurrent VTE event in each cycle, to represent the future 6 months' worth of warfarin treatment the individual would experience as a result of their recurrence. In addition, in the warfarin engine, the manufacturer also applied disutility associated with warfarin each month up until the end of acute treatment (6 months) and secondary prevention (18 months). The disutility was applied to all patients off-treatment and all patients on-

treatment. The ERG believes that patients off treatment have therefore incorrectly received an additional months' worth of disutility associated with warfarin.

The ERG corrected this error by removing the disutility applied to patients off treatment. Results from this analysis are presented in Section 6.1, **analysis A16**. The ICER for dabigatran versus warfarin increased from £862 to £884 (acute treatment) and from £8,319 to £9,082 (treatment and secondary prevention).

The ERG notes that treatment with warfarin is associated with a number of factors which may negatively impact HRQoL including the need for regular monitoring of INR, which can be disruptive, and a requirement of adjusting and monitoring diet and lifestyle. The ERG therefore acknowledges that there may be cause to believe that warfarin treatment would be associated with a disutility.

Nevertheless, the ERG has a number of comments upon the disutilities applied within the manufacturer's model. Firstly, the ERG notes that the manufacturer did not identify Marchetti *et al*. from the systematic review of the HRQoL literature (Section 5.4.12.1), nor did the manufacturer describe how this paper was identified and selected for use within the model.

Furthermore, the ERG is concerned that the estimates calculated by the manufacturer using data from Marchetti *et al*. may not provide a robust estimate of disutility. The ERG's main concerns with this paper relate to the small sample size and therefore generalisability of the results (n=48), the use of patient preferences to value the health states, and the inability to determine the equivalent decrement for treatment with dabigatran. Specifically, it is not clear whether the willingness to trade life to avoid treatment relates specifically to the treatments warfarin and LMWH, or whether it relates to having to take any treatment. Without dabigatran treatment being included in the study, it is difficult to determine whether dabigatran would also have been associated with a decrement.

The ERG notes that this study was used within TA261 and TA287 to estimate a disutility associated with warfarin treatment.[49;65] The utility value from Marchetti *et al*. was discussed within the final appraisal document (FAD) for TA261.[82]

Box 22 presents text from TA261 describing the deliberations around the warfarin disutility value. The Appraisal Committee concluded that warfarin treatment was likely to result in further disutility compared with rivaroxaban.

Box 22. Appraisal Committee deliberations for warfarin disutility from TA261[82]

The Committee heard from the patient experts that warfarin has an impact on quality of life [...]. The Committee considered that although treatment with rivaroxaban could be associated with a small disutility, it was satisfied that treatment with warfarin was associated with a higher disutility than treatment with rivaroxaban, and the relative difference in disutility could be even higher than 0.012 for people who may have to take it for many years or lifelong. The Committee concluded that although it was not convinced that the utility decrement used by the manufacturer was supported by strong evidence, it was of the opinion that the relative difference in disutility was at least as great as the value used by the manufacturer in its long-term model.

Although due to time constraints the ERG was unable to carry out a systematic review of the HRQoL literature to identify other values for warfarin decrement, the ERG carried out a simplistic PUBMED search to supplement the manufacturer's systematic review. The search was carried out on the 10th July using the search terms "(disutility or quality of life) and (warfarin or VKA or vitamin K antagonist or vitamin-K antagonist or low molecular weight heparin)". Search terms were limited to title and abstract. A total of 231 studies were identified. One health economist reviewed the titles of the included studies and a total of 3 studies were considered relevant for the discussion of warfarin decrement.

- Alegret *et al.*[123] reported the HRQoL impact (using a condition specific measure) of the use of novel oral anticoagulants versus a VKA in 416 patients with atrial fibrillation receiving prophylaxis for cardioembolic events. The authors found that, at initiation of anticoagulant treatment, a worse HRQoL was observed in some dimensions of the condition specific measure for patients treated with a VKA compared with patients treated with a novel oral anticoagulant (NOAC). The authors noted, however, that this difference disappeared after 6 months of treatment.
- Monz *et al.*[124] reported the HRQoL impact (assessed using EQ-5D) of the use of warfarin or dabigatran etexilate for stroke prevention in patients with atrial fibrillation (AF) as part of the RE-LY clinical trial. A total of 1,435 people provided data. The authors concluded that, over the course of one year, EQ-5D scores between the dabigatran and warfarin treatment groups were comparable, which was "unexpected given the known complexities of warfarin treatment".
- Lancaster *et al.*[125] reported the results from a study of 333 people participating in a randomised controlled trial of warfarin for the prevention of stroke in non-rheumatic atrial fibrillation. The authors reported that no significant differences between warfarin-treated and control patients were found on measures of functional status, well-being, and health perceptions. The authors concluded that "warfarin therapy is not usually associated with a significant decrease in perceived health, unless a bleeding episode has occurred. Negative effects of warfarin treatment on health perceptions may be balanced by confidence in its protective effects."

Although the studies described by Alegret *et al*., Monz *et al*. and Lancaster *et al*. were not carried out in patients with VTE; the ERG considers that the information provided around warfarin treatment may be of interest.[123;124 (125)] In particular, the head-to-head comparison of warfarin and dabigatran in RE-LY, a trial for stroke prevention in AF, reported in Monz *et al*. which indicated no long term difference in the EQ-5D scores for patients receiving each treatment, may be of relevance for this STA.

The ERG considers that on balance, following review of the simplistic search, after discussion with clinical experts, and following review of the Appraisal Committee deliberations in previous related STAs, that whilst there may be a difference in utility associated with treatment with warfarin or dabigatran, this disutility is likely to be small, and may reduce over time as people become used to their warfarin regimen. However, the ERG notes that there is a great degree of uncertainty around this figure.

As a scenario analysis, to reflect the findings of the ERG review of the evidence, the ERG removed the decrement associated with warfarin treatment during secondary prevention. Results of this analysis are presented in Section 6.2 **analysis B26.** The ICER for dabigatran versus warfarin increased in the treatment and secondary prevention scenario (£8,319 to £12,367).

Comment on disutility associated with LMWH treatment

The ERG considers that the concerns raised above for warfarin around both the methods for identifying and selecting Marchetti *et al.(56)* and the applicability of this study, also hold for treatment disutility with LMWH. Furthermore, the ERG notes that a decrement associated with LMWH was not applied within either TA261 or TA287 for the population with cancer.[49;65] The ERG further notes that no study was identified in the simplistic search reported above that related to HRQoL in patients treated with LMWH.

The ERG therefore considers that there is no robust evidence to suggest that LMWH is associated with a decrement in utility. The ERG carried out a scenario analysis in which this decrement was removed for the population with cancer. Results are presented in Section 6.2 **analysis B27.** The impact of the analysis on model results was small.

5.4.12.6 Disutility associated with adverse events of treatment

The manufacturer applied a disutility to the following adverse events of treatment:

- MBE (ICH and extra-cranial haemorrhage);
- CRNMBE;
- MI (sensitivity analysis only);

- UA (sensitivity analysis only);
- dyspepsia (sensitivity analysis only).

A summary of the applied disutilities is presented in Table 112, with each disutility described in detail in the remainder of this section.

Table 112. Summary of disutilities associated with adverse effects of treatment applied within the manufacturer's model

Adverse effect	Applied disutility	Manufacturer described duration of disutility	Source
MBE	-0.13	1 month	Analysis of EQ-5D data collected in the pivotal RE-COVER trials
CRNMB	-0.04	1 month	
Disabled from ICH	-0.5	Lifetime	Wolowacz *et al*., (2009)*(116)*, taken from Ingelgard *et al*., [2002]*(117)*
Myocardial infarction	-0.063	1 month	Sullivan *et al*., (2011)*(118)*
Unstable angina	-0.085	1 month	
Dyspepsia	-0.04	During acute treatment	Gerson *et al*., (2005)*(89)*
Abbreviations used in table: CRNMBE, clinically relevant non-major bleeding event; ICH, intracranial haemorrhage; MBE, major bleeding event.			

Major bleeding event

The manufacturer applied a disutility of 0.13 to all MBEs within the model, including ICH. The disutility was assumed to last for one cycle (one 30-day month). The estimate of disutility was calculated from analysis of EQ-5D data collected in the RE-COVER trials. The disutility of a MBE was assumed to be equal to the change in mean EQ-5D index score from baseline visit to visit 9 between patients with "Index VTE event only" and patients with "Index VTE event and MBE only" (0.16 minus 0.29 = -0.13) and was applied in the month the event occurred.

The ERG has two main comments upon the disutility applied within the manufacturer's model for MBEs. Firstly, the ERG is concerned that EQ-5D data collected with the RE-COVER trials at month 9 may include people who have recovered from their bleeding event or may be experiencing other events, and may therefore not reflect the utility decrement associated with a MBE.

Secondly, the ERG is concerned that by estimating the combined impact of an extra-cranial major bleed and an intra-cranial haemorrhage on HRQoL, the manufacturer may be losing an important granularity. This is both as a consequence of the impact of the event upon HRQoL, but also the duration of the impact.

In previous STAs TA261 and TA287, and in CG144, utility for extra-cranial and intra-cranial major bleeds were applied within the respective model structures separately.[49;65;66] For TA261 and TA287, a utility value of 0.33 was applied for an ICH for three months after the event, and a utility value of

0.65 was applied for an extra-cranial MBE for one month after the event. These values were taken from Locadia *et al*. a study which aimed to investigate health state valuations associated with VKA treatment and treatment preferences, in 53 patients with a VTE, 23 patients with a MBE and 48 patients with PTS.[114] Preferences were elicited using time-trade of techniques. The estimate of 0.33 for ICH was taken from the health state of "non-fatal haemorrhagic stroke", and the estimate of 0.65 for MBE was taken from the health state of "gastro-intestinal bleeding".

By contrast however, in CG144 an estimate of disutility of 0.325 was applied to all patients with an MBE in the month of the event. This estimate was taken from Sarasin *et al*. and was calculated as the disutility associated with a major gastrointestinal bleeding event.[126]

Furthermore, the ERG considers that the manufacturer has made a mistake in the application of MBE disutility in the engine. The manufacturer does not convert the disutility of -0.13 each month into a QALY; the manufacturer does not account for the duration of time for which the disutility is experienced, i.e. the month. The ERG believes that the manufacturer should have accounted for time within the engine before summation to a QALY, and applied a monthly disutility of -0.13/12 = -0.0108. The ERG corrected this in a sensitivity analysis. The results are presented in Section 6.1, **analysis A15.** The impact of the analysis was a small increase in the ICERs associated with dabigatran versus warfarin, and a change for dabigatran versus rivaroxaban from dominance (less costly and more effective) to dabigatran less costly and less effective than rivaroxaban in the acute treatment scenario.

On balance, the ERG considers that the estimate of disutility applied by the manufacturer for a MBE may underestimate the actual disutility because HRQoL data from recovered patients may be included in the calculation. Consequently, the ERG carried out an analysis in which the estimate of disutility used within CG144 (-0.325) was applied within the model, for the month of the MBE (i.e., a monthly QALY decrement of -0.027). Results are presented in Section 6.2 **analysis B28.** The impact of the analysis was a small decrease in the ICERs associated with dabigatran versus warfarin, and a change for dabigatran versus rivaroxaban from dominance (less costly and more effective) to dabigatran less costly and less effective than rivaroxaban in the acute treatment scenario.

Clinically relevant non-major bleeding event

The manufacturer applied a disutility of -0.04 for CRNMBEs within the analysis. The disutility value estimated for CRNMBEs was assumed to be equal to the change in mean EQ-5D index score from baseline visit to visit 9 for patients enrolled in RE-COVER I and II between patients with an "Index VTE event only" and patients with an "Index VTE event and CRNMBE only" (0.25 minus 0.29 = -0.04) and was applied for the month the event occurred.

As with MBE, the ERG is concerned that the utility value elicited from the manufacturer's analysis may not reflect the utility decrement associated with a CRNMBE; this is because it is unclear whether patients were currently experiencing a CRNMBE or other events at the point that EQ-5D data were collected.

Furthermore, the ERG notes that in previous STAs TA261 and TA287, a disutility associated with clinically-relevant non-major bleeding events was not applied within the model.[49;65] Consequently, the ERG consulted clinical experts as to whether a months' worth of disutility would likely be experienced from the CRNMBEs outlined within RE-COVER I and II. The clinical experts advised that not all CRNMBEs would be associated with a month's disutility, for example "spontaneous nose bleed", "gingival bleeding" or "spontaneous skin haematoma".

As a sensitivity analysis, the ERG removed the disutility associated with CRNMBEs within the model. Results are presented in Section 6.2 **analysis B29.** The impact of the analysis was largely small; the comparison of dabigatran versus rivaroxaban changed in both the acute treatment scenario and the treatment and secondary prevention scenario from dabigatran being less costly and more effective compared with rivaroxaban, to dabigatran being less costly and less effective compared with rivaroxaban.

In addition, as with MBEs, the ERG considers that the manufacturer has made a mistake in the application of CRNMBE disutility in the engine. The manufacturer does not convert the disutility of -0.04 each month into a QALY; the manufacturer does not account for the duration of time for which the disutility is experienced, i.e. the month. The ERG believes that the manufacturer should have accounted for time within the engine before summation to a QALY, and applied a monthly disutility of -0.13/12 = -0.0108. The ERG corrected this in a sensitivity analysis. The results are presented in Section 6.2, **analysis A15.** The impact of the analysis was a small increase in the ICERs associated with dabigatran versus warfarin, and a change for dabigatran versus rivaroxaban from dominance (less costly and more effective) to dabigatran less costly and less effective than rivaroxaban in the acute treatment scenario.

Disabled from ICH

The disutility associated with disability arising from an ICH was modelled by the manufacturer as -0.5. This disutility was stated as taken from Wolowacz *et al.(116)* Wolowacz *et al*. was not identified from the systematic review of HRQoL data (Section 5.4.12.1); therefore, the ERG is unclear how this paper was identified and selected. Within Wolowacz *et al*., the utility decrement of 0.5 is described as the "average of 109 decrements for stoke"; however, no reference is provided within the text for the included studies, nor is a description of the calculation provided. The ERG is therefore unable to validate this figure.

The ERG had insufficient time to carry out a systematic review of the literature for more recent or more relevant utility values for disabled following ICH. Consequently, the ERG carried out an extreme value analysis to assess what effect this variable had on final results. ICH disutility was alternatively set to 0 and to 1. Results are presented in Section 6.2 **analysis B30.** The ERG notes that the model results were not sensitive to changes in this parameter.

Cardiovascular events

The manufacturer applied a disutility associated with MI (-0.063) and UA (-0.085) within a sensitivity analysis. The disutilities were applied in cycle 4. The ERG notes that this was a modelling simplification to apply the probability of MI and UA during the acute period, i.e. 6 months.

The utility decrements for survivors of MI and UA were taken from Sullivan *et al*.[118] In this study, community-based UK preference values were applied to EQ-5D questionnaire responses from 79,522 individuals in the US-based Medical Expenditure Panel Survey (MEPS). EQ-5D index scores and disutilities were derived using US based tariffs for a variety of conditions according to the International Classification of Diseases, Ninth Revision (ICD-9) and Clinical Classification Categories (CCC) codes.

The ERG notes that the manufacturer only applied MI and UA in the acute treatment period. The ERG further notes that a proportion of patients who experience MI or UA go on to develop chronic IHD (Section 5.4.8.2). These patients are not assigned a disutility within the sensitivity analysis; despite an ICD code published within Sullivan *et al*. for "ICD9 414 - Oth Chr Ischemic Hrt Dis" at -0.0627. The ERG considers that these omissions are a weakness of the sensitivity analysis, and will lead to an overestimate of the QALYs associated with dabigatran compared with warfarin, rivaroxaban and LMWH.

In addition, as with MBEs and CRNMBEs, the ERG considers that the manufacturer has made a mistake in the application of disutility in the engine. The manufacturer does not convert the disutility of for MI and UA into a QALY; thus the manufacturer essentially applies a yearly disutility associated with MI and UA to all patients in cycle 4. The ERG believes that the manufacturer meant to apply the disutility during the acute period, i.e. 6 months, and therefore should have accounted for time within the engine before summation to a QALY, and applied a monthly disutility of -0.063/12x6 = -0.0315 (MI) and -0.085/12x6 = -0.0425 (UA).

The ERG notes that these figures apply only in a sensitivity analysis, and therefore did not correct these values.

Dyspepsia

The HRQoL impact of dyspepsia was included within a sensitivity analysis. The ERG consulted with clinical experts around the relevance of dyspepsia as a health state for this STA. The advice received suggested that dyspepsia was an important outcome associated with dabigatran use that should be included within the base case analysis. The ERG incorporation of dyspepsia within the base case analysis is described in Section 5.4.8.3.

The disutility associated with dyspepsia was modelled by the manufacturer as -0.04 and was describing as applied for the duration of treatment. The estimate of disutility was calculated using TTO data from Gerson *et al.(89)* The purpose of the study was to derive health state utilities for patients with chronic heartburn symptoms. A total of 222 patients were invited to participate in the study, of which 118 patients had reflux alone. The average age of included patients with reflux alone was 53 years, 77% male, with mean duration of reflux of 11.5 years. Utility estimates were derived using both TTO and standard gamble techniques. The mean utility decrement using TTO for dyspepsia (-0.04) was calculated by subtracting the mean utility for patients off medication (0.90) from the mean utility for patients on medication (0.94). The mean difference when considering the results for standard gamble was zero.

The ERG notes that, to incorporate the disutility associated with dyspepsia within the model engine, the manufacturer applied the decrement (-0.04) for one year. This accounted for 12 months' worth of treatment. The ERG notes that treatment duration for the comparison with warfarin is 24 months, and therefore within the scenario analysis including dyspepsia within the model, the ERG applied a monthly decrement associated with dyspepsia throughout the model (-0.04/12 = -0.0033). Results are presented in Section 6.2 **analysis B1.** The impact of this analysis upon the manufacturer's base case results was small.

5.4.13 Resources and costs

Section 5.4.13.1 outlines the systematic review carried out by the manufacturer to identify resource use and cost evidence for use within the economic model. In addition, Sections 5.4.13.2 to 5.4.13.5 describe the costs applied within the economic model:

- costs of index VTE event (Section 5.4.13.2);
- costs of recurrent VTE events (Section 5.4.13.3);
- complications associated with VTE events (Section 5.4.13.4);
- adverse effects of treatment (Section 5.4.13.5)

5.4.13.1 Systematic review for resource use and costs

The manufacturer carried out a systematic review to identify resource use and cost studies relevant to the health states considered in the model. The following electronic databases were searched: Medline, Medline In-Process, Embase, EconLit, BIOSIS and The Cochrane Library. The search was carried out in February 2013 and updated in April 2014. The manufacturer used terms to capture the health condition of interest (DVT / PE) and intervention and study type (cost study). In addition to database searches, the manufacturer also carried out a number of internet searches to identify conference abstracts and published HTAs, and reviewed reference lists of included studies. Details of the search strategy are provided in the MS (p219-221 and Appendix 10 [p453-471]). The ERG considers that the search terms, the inclusion and exclusion criteria used by the manufacturer to identify resource use and cost data were comprehensive and appropriate.

The database searches were limited to records published from January 2000; the manufacturer justified this restriction "because economic data published before that time were unlikely to be relevant to current treatment practices" (MS; pg 478). The ERG is concerned that a limit by date may have resulted in relevant studies being omitted; however the ERG notes that no studies were identified within TA261 and TA287 for the treatment and prevention of VTE that were published before the year 2000 that were used to inform cost-effectiveness models.[49;65]

A total of 35 studies were identified from the February 2013 search (26 studies) and April 2014 search (9 studies) that reported resource use and cost estimates. The manufacturer stated that the 35 studies identified from the search were presented within the submission; however, the ERG notes that 33 studies are described. The two remaining studies were Fanikos *et al*.[127] and an un-named study carried out in Columbia. The study by Fanikos *et al*. was identified in both the original search and the updated search; therefore, it was only extracted once. The manufacturer did not provide any further details of the Columbian study; thus the ERG is unable to comment upon this analysis. Seven studies identified from the literature search for resource use and cost adopted a UK NHS perspective.[128-133] One study published in 2002 was referenced by the manufacturer as Anderson *et al.*; unfortunately, the ERG was unable to identify this study. Each of these studies reported estimates that the manufacturer considered appropriate for use in a cost-effectiveness model and are summarised in the MS, pg 306-307 and MS Table 114.

5.4.13.2 Costs of index VTE event and initial treatment

The costs associated with an index VTE event considered within the manufacturer's model comprised costs of hospitalisation; drug acquisition; drug administration; monitoring. These costs are described in the remainder of this section.

Hospitalisation

The manufacturer assumed that patients would be treated for their index DVT or PE in either an inpatient or an outpatient setting. In the base case, the manufacturer assumed that 52% of acute proximal DVT patients, and 90% of PE patients received inpatient care. The admission rates used by the manufacturer were based on hospitalisation records from the EINSTEIN trials.[134]

The costs and mean length of stay applied within the model were taken from NHS Reference Costs 2012/13, adjusted to 2014 prices.[11] The manufacturer used data for elective stay, non-elective short stay and non-elective long stay, weighted by the number of finished consultant episodes. The manufacturer assumed that cost and mean length of stay estimates applied for all treatments. The costs and length of stay applied within the model are presented in Table 113.

Table 113. Costs of inpatient stay for the index VTE event, adapted from MS (pg 325, Table 118)

VTE event	Average LOS	Weighted average cost of inpatient stay	Reference
DVT	5.68	£955.69	NHS Reference Costs 2012/13; elective, non-elective short stay and non-elective long stay, weighted (by finished consultant episodes) average of QZ20A-QZ20E, inflated to 2014 prices.
PE	6.09	£1,520.67	NHS Reference Costs 2012/13; elective, non-elective short stay and non-elective long stay, weighted (by finished consultant episodes) average of DZ09D-DZ09H, inflated to 2014 prices.
Abbreviations used in table: DVT, deep vein thrombosis; HRG, Healthcare Resource Group; LOS, length of stay; MS, manufacturer's submission; PE, pulmonary embolism; VTE, venous thromboembolism.			

The ERG has three main comments upon the manufacturer's calculation of cost associated with inpatient stay.

Firstly, the ERG notes that the manufacturer restricted the data to elective, non-elective short stay and non-elective long stay. In addition, the manufacturer weighted the cost by the number of finished consultant episodes. As a sensitivity analysis, the ERG considered all data presented within NHS Reference Costs 2012/13 for the same HRG codes, weighted by total activity; the cost associated with a DVT and PE was estimated by the ERG to be £731.78 and £1,519.31 respectively (the calculation of this figure is presented in Table 114). The ERG notes that the estimates are reasonably similar to those calculated by the manufacturer for TA287 (£785.67 [DVT], £1,511.29 [PE]).[65] The ERG carried out a scenario analysis using the cost of hospitalisation estimated using all activity data. Results are presented in Section 6.2 **analysis B31.** The impact of the analysis on the manufacturer's results was negligible.

Table 114. NHS Reference Costs 2012/13, HRG codes relating to deep vein thrombosis and pulmonary embolism

HRG code	Activity	Unit cost	Total cost
QZ20A Deep Vein Thrombosis with CC Score 12+	3,108	£726	£2,257,078
QZ20B Deep Vein Thrombosis with CC Score 9-11	3,093	£884	£2,734,927
QZ20C Deep Vein Thrombosis with CC Score 6-8	4,773	£1,102	£5,260,318
QZ20D Deep Vein Thrombosis with CC Score 3-5	9,441	£869	£8,207,923
QZ20E Deep Vein Thrombosis with CC Score 0-2	16,764	£522	£8,746,762
Weighted (by activity) average cost of deep vein thrombosis			£731.74
DZ09D Pulmonary Embolus with CC Score 12+	1,174	£4,011	£4,709,423
DZ09E Pulmonary Embolus with CC Score 9-11	2,973	£2,862	£8,507,425
DZ09F Pulmonary Embolus with CC Score 6-8	7,160	£2,025	£14,500,122
DZ09G Pulmonary Embolus with CC Score 3-5	15,283	£1,429	£21,834,772
DZ09H Pulmonary Embolus with CC Score 0-2	17,007	£981	£16,685,753
Weighted (by activity) average cost of pulmonary embolism			£1,519.31
Abbreviations used in table: CC, complications and comorbidities; HRG, Healthcare Resource Group.			

Secondly, the ERG consulted clinical experts around the proportion of people with proximal DVT and PE who would typically receive inpatient care for their VTE event. The clinical experts advised that approximately one third of patients with proximal DVT and 80% of patients with PE are likely to be treated as inpatients in UK clinical practice. The ERG carried out a sensitivity analysis in which the proportion of patients receiving inpatient care was changed to the above proportions. Results are presented in Section 6.2 **analysis B32.** The impact of the analysis on model results was negligible.

Finally, the ERG considers that using data from NHS Reference Costs 2012/13 was appropriate; however, the ERG is unclear why the manufacturer inflated costs to 2014 prices when no inflation factor is published that would enable this calculation. The ERG notes that the manufacturer estimated the relevant inflation factor by assuming the increase in hospital pay and prices from 2012/13 to 2013/14 would be identical to the increase in hospital pay and prices from 2011/12 to 2012/13, as recorded in the Unit Costs for Health and Social Care 2013.[(10)] The ERG considers this extrapolation to be unnecessary, as the data provided in NHS Reference Costs 2012/13 forms the most up-to-date information currently available.[(11)] The ERG further notes that all NHS Reference Costs from 2012/13 and other publications for which the most recent publication date was 2013 (i.e. the Unit Costs for Health and Social Care) described throughout the remainder of this section were subject to this inflation factor. For brevity the ERG does not critique this methodology again; however, the ERG carried out an analysis in which no inflation factor was applied for 2013 to 2014. A description of this analysis is provided in Section 5.5.1, and results are presented in Section 6.1 **analysis A10**.

The impact upon the ICER for dabigatran versus warfarin (for the full population) for both the acute treatment, and the treatment and secondary prevention scenarios was a small increase in the ICER,

from £862 to £1,164 (acute treatment) and £8,319 to £8,616 (treatment and secondary prevention). The impact on the remaining ICERs was small.

Drug acquisition

A summary of the drug cost per patient applied within the manufacturer's model is presented in Table 115. Note, figures may not sum exactly, due to rounding.

Table 115. Summary of the applied drug cost per patient, by intervention and comparator

Intervention	Drug	% patients	Average total cost per patient (acute period)		Average total cost per patient (secondary prevention period)	
			Days (acute period)	Drug acquisition costs	Days (secondary prevention period)	Drug acquisition costs
Dabigatran	LMWH/UFH parenteral treatment	100%	5	£48 DVT £39 PE	0	–
	Dabigatran (Pradaxa®) 220mg per day	5%	180	£395	180 to 540[a]	£395 to £1,186
	Dabigatran (Pradaxa®) 300mg per day	95%	180	£395	180 to 540[a]	£395 to £1,186
Warfarin[b]	LMWH/UFH parenteral treatment	100%	5	£48 DVT £39 PE	0	–
	Warfarin	100%	180	£12	540	£35
Rivaroxaban	Rivaroxaban (Xarelto®) 30mg per day	100%	21	£88	0	–
	Rivaroxaban (Xarelto®) 20mg per day	100%	159	£334	180	£378
LMWH	Dalteparin	100%	180	£1,313	180	£1,292

[a] secondary prevention period differs for dabigatran depending upon the comparator selected (Section 5.4.4.2)
[b] note, costs for warfarin in the acute period also apply to re-treatment costs
Abbreviations used in table: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; mg, milligrams; PE, pulmonary embolism; UFH, unfractionated heparin.

The manufacturer estimated drug acquisition costs for each intervention by multiplying the average daily dose for each drug, by unit cost data taken from MIMS March to May 2014.[(135)] The unit costs and dosages modelled for dabigatran, warfarin and rivaroxaban are presented in Table 116; unit costs and dosages modelled for LMWH and UFH are presented in Table 117 and Table 118. Each cost is described below. Note, figures may not sum exactly, due to rounding.

Table 116. Drug acquisition costs for dabigatran, warfarin and rivaroxaban used within the manufacturer's model, adapted from MS (pg 322, Table 115)

Treatment	Strength	Cost per pack	Capsules per pack	Cost per capsule	Average daily dose	Average daily cost
Dabigatran (Pradaxa®)	110mg	£65.90	60	£1.10	220mg	£2.20
	150mg	£65.90	60	£1.10	300mg	£2.20
Warfarin	1mg 3mg	£0.89 £0.93	28 28	£0.031 £0.033	4mg	£0.07
Rivaroxaban (Xarelto®)	15mg	£210.00	100	£2.10	30mg	£4.20
	20mg	£210.00	100	£2.10	20mg	£2.10
Abbreviations used in table: mg, milligram; MS, manufacturer's submission.						

Dabigatran

To estimate the cost of dabigatran, the manufacturer modelled the cost of two different dosing regimens; 110mg twice daily, and 150mg twice daily. The standard dose of dabigatran is 150mg twice daily; in addition to the standard dose, the manufacturer stated that patients aged 80 years or above or patients who receive concomitant verapamil would receive the lower dose of dabigatran (110mg twice daily) in clinical practice, based upon text contained within the draft SmPC (MS; pg 237). Within the model, the manufacturer assumed that approximately 5% patients would receive a dose of 110mg twice daily, with the remaining 95% patients receiving 150mg twice daily. The manufacturer estimated these proportions based upon the percentage of people aged over 80 years enrolled within the dabigatran clinical trials.

Drug costs for the 150mg and 110mg capsule are identical in the UK at £1.10 per tablet (Table 116); consequently, alternative dosing has no impact upon estimated total cost; however, ERG concerns around the lack of evidence base for efficacy and safety of the 110mg dose are discussed in Section 5.4.4.

Warfarin

Warfarin is dose adjusted such that each patient achieves an INR between 2.0 and 3.0. To estimate the cost of warfarin, the manufacturer modelled an average dose of warfarin of 4mg per day. Cost was estimated as the sum of 1mg warfarin (89p per 28 tablet pack) and 3mg warfarin (93p per 28 tablet pack).

The ERG notes that the NICE Guides to Methods of Technology Appraisal 2013 recommend that *"the public list prices for technologies (for example, pharmaceuticals or medical devices) should be used in the reference-case analysis. When there are nationally available price reductions, for example for medicines procured for use in secondary care through contracts negotiated by the NHS Commercial Medicines Unit, then the reduced price should be used in the reference-case analysis to*

best reflect the price relevant to the NHS. The Commercial Medicines Unit publishes information on the prices paid for some generic drugs by NHS trusts through its Electronic Marketing Information Tool (eMIT)".[67] The ERG reviewed data contained within eMIT and notes that the cost of warfarin for the 28 tablet pack at 1mg is £0.17 (based upon 376,214 data points), and the cost of warfarin for the 28 tablet pack at 3mg is £0.20 (based upon 261,606 data points). Costs for 0.5mg warfarin and 5mg warfarin (28 tablet packs) were £0.57 and £0.24 respectively. Costs for other therapies included within this STA were not found to be present within eMIT.

The ERG estimated the cost of warfarin per mg using all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg). The ERG weighted the estimated cost per mg using the quantity of warfarin items prescribed as reported by Prescription Cost Analysis Data (PCA) 2013[136] for primary care in England. A description of this analysis is provided in Section 5.5.1, with results presented in Section 6.1, **analysis A11**. The impact upon the ICER for dabigatran versus warfarin for both the acute treatment, and the treatment and secondary prevention scenarios was a small increase in the ICER from £862 to £1,128 (acute treatment) and from £8,319 to £8,722 (treatment and secondary prevention). The impact upon the remaining ICERs was small.

Rivaroxaban

The rivaroxaban dosing schedule modelled by the manufacturer was 30mg per day (15mg twice daily) for 21 days, followed by 20mg per day for the remainder of treatment. The ERG notes that this modelled regimen is in line with the SmPC for rivaroxaban.

LMWH and UFH

The manufacturer modelled the use of LMWH as an option, along with UFH, for parenteral treatment for the treatment strategies including dabigatran and warfarin. Additionally, the manufacturer modelled the use of LMWH as a monotherapy for the population with cancer.

For parenteral treatment, LMWH and UFH prescribing was assumed to differ depending upon whether the VTE event was a DVT or a PE. The proportion of LMWH / UFH prescribing by type of VTE event applied in the model was based upon results from a 2008 clinical expert panel (5 clinicians) carried out by the manufacturer.[70] Table 117 summarises the split and associated cost of LMWH (enoxaparin, dalteparin, tinzaparin) and UFH applied within the manufacturer's model. Note, figures may not sum exactly, due to rounding.

Table 117. Drug costs of acute parenteral anticoagulation treatment, adapted from the MS (pg 323, Table 116)

Acute parenteral treatment	Regimen	Regimen cost	% people with DVT receiving treatment	% people with PE receiving treatment
Heparin sodium, regimen 1	5,000 units (IV) followed by 1000-2000 units per hour IV for 5 days	£21.58	0.5%	5%
Heparin sodium, regimen 2	5,000U (IV) followed by 15,000 U twice daily (SC) for 5 days	£7.05	0.5%	5%
Enoxaparin	1.5 mg/kg (150 IU/kg) per day (SC) for 5 days	£41.63	24.75%	90%
Dalteparin regimen 1	200 IU/kg body weight (SC), once daily (not exceeding 18,000 IU), for 5 days	£58.82	24.75%	0%
Dalteparin regimen 2	100 IU/kg body weight (SC), twice daily for patients with increased risk for bleeding, for 5 days	£58.82	24.75%	0%
Tinzaparin	175 IU/kg body weight once daily, for 5 days	£34.67	24.75%	0%
Abbreviations used in table: DVT, deep vein thrombosis; IU, international unit; IV, intra-venous; PE, pulmonary embolism; SC, subcutaneous; U, unit; UFH, unfractionated heparin;				

The ERG consulted clinical experts around the appropriateness of assuming that prescribing proportions of LMWH and UFH would differ according to type of VTE event. Clinical advice was mixed; however, the ERG notes that UFH may be used more frequently in massive PE which may explain the difference in prescribing. Overall, the ERG considers that the scenario modelled by the manufacturer is not unreasonable.

The manufacturer estimated the cost of parenteral treatment using the lowest price per unit for each drug from those reported in MIMS.[135] The ERG considers that this may underestimate the cost of LMWH and UFH applied within the model, but notes that the impact of this will be small.

In addition, the calculation of dose and subsequently cost for enoxaparin, dalteparin and tinzaparin, is dependent upon patient weight (kgs). To estimate an average dose and cost for each treatment within the model, the manufacturer assumed an average body weight of 75kgs; this figure was based upon clinical expert opinion. The ERG reviewed the average body weight used in TA261 (80kg) and TA287 (80kg) to estimate cost. Consequently, as a sensitivity analysis, the ERG increased average body weight to 80kg. Results are presented in Section 6.2 **analysis B33.** The impact of the analysis on model results was negligible.

For LMWH as a monotherapy for the population with cancer, the costs applied within the model are presented in Table 118. The manufacturer assumed that dalteparin was the selected LMWH; the ERG notes that dalteparin is specifically licensed for use in cancer.

The cost of dalteparin differed in the acute treatment period and the secondary prevention period. In the acute period, the average cost was based upon a regimen of 200 IU/kg for 1 month, followed by

150 IU/kg for remainder of treatment, resulting in an estimated cost of £7.29 per day. In the secondary prevention period, the average cost was based upon a regimen of 150 IU/kg resulting in an estimated cost of £7.18 per day, from start of treatment (i.e. during the acute period as well).

The ERG notes that, to estimate cost, the manufacturer assumed that one syringe of LMWH would last for one day; however, the ERG considers that the strength of pack selected by the manufacturer is insufficient for the average daily dose required. The ERG further notes that, following review of the BNF 67, the ERG was unable to identify the manufacturer presented costs for dalteparin.*(137)* The ERG re-estimated the costs associated with LMWH treatment for monotherapy only (Table 118), and applied these costs in a sensitivity analysis; results are presented in Section 6.1, **analysis A12**. In the acute treatment period, the ICER for dabigatran versus LMWH decreased; note, the decrease in the ICER for dabigatran versus LMWH indicates a slight worsening in position for dabigatran, as the ICER is in the south-west quadrant, i.e. dabigatran is less costly and less effective. In the treatment and secondary prevention scenario for dabigatran versus LMWH (in the population with cancer), dabigatran remained the dominant treatment option (less costly and more effective).

Table 118. Updated cost of LMWH monotherapy applied by the ERG for the population with cancer

Treatment	Treatment period	Patient dose	Duration of treatment	Pack strength	Cost per pack	Pack size	Average daily dose*	ERG estimate average daily cost
Dalteparin (Fragmin®)	Acute treatment	200 IU/kg	30 days	25,000 UI/mL	£48.66	4mL (100,000 IU)	15,000	£7.30
		150 IU/kg	330 days	25,000 UI/mL	£48.66	4mL (100,000 IU)	11,250	£5.47
		Average daily cost						**£5.63**
	Acute and secondary prevention	150 IU/kg	330 days	25,000 UI/mL	£48.66	4mL (100,000 UI)	11,250	£5.47
		Average daily cost						**£5.47**

* assuming an average weight of 75kg

Abbreviations used in table: ERG, evidence review group; IU, international units; mL, millilitres; LMWH, low-molecular-weight heparin.

Drug administration

The cost of drug administration included within the manufacturer's model related specifically to the administration of LMWH. The cost of LMWH administration differed for people who were not admitted to hospital for their index VTE, compared with the cost for people who were initially hospitalised. The difference in cost was assumed to arise because patients admitted to hospital would have their administration cost accounted for within the hospitalisation cost. The manufacturer

therefore captured the costs for patients not admitted to hospital, but also patients admitted to hospital where treatment was longer than the average length of stay.

The average cost per patient for administering LMWH for each relevant intervention is presented in Table 119.

Table 119. Average cost of LMWH administration included within the manufacturer's model, per patient

Intervention / comparator	% patients receiving LMWH (duration)	Average cost of LMWH administration per patient
Dabigatran	100% (5 days)	£7.69
Warfarin	100% (5 days)	£7.69
LMWH	100% (acute treatment period, 180 days)	£129.30
	100% (secondary prevention treatment period, 180 days)	£129.30
Abbreviations used in table: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism.		

The calculation of average cost was based upon the proportion of patients who were eligible for the cost of LMWH administration (i.e. were not hospitalised, or experienced parenteral treatment longer than the average length of hospital stay) who received either:

- self-administration of LMWH at home (86% patients);
- nurse-administration of LMWH at home (6% patients);
- administration of LMWH at clinic (7% patients).

The remaining 1% patients were assumed to receive UFH.

The manufacturer assumed that 86% of patients self-injected LMWH at home. The cost associated with self-injected LMWH was assumed to be zero. The percentage of patients self-injecting was obtained from Watts *et al*., a study in which the compliance of 40 consecutive patients undergoing lower limb arthroplasty with self-administration of a recommended subcutaneous chemotherapeutic agent was assessed.[138] The authors concluded that self-administration was considered feasible in 87% of patients. The manufacturer multiplied this figure by 99% to represent the proportion of patients receiving LMWH (i.e. 1% of patients received UFH), resulting in a figure of 86%. The remaining 13% of discharged patients were assumed to receive home nurse visits for LMWH injections (6%), or attend clinic visits each day for LMWH injections (7%). The cost associated with nurse-administration of LMWH at home was taken from NHS Reference Costs 2012/13 (adjusted to 2014 prices), and was estimated to be £39.18 per day.[11] The cost associated with administration of LMWH at clinic was also obtained using NHS Reference Costs 2012/13 (adjusted to 2014 prices), and was estimated to be £27.99.[11]

The ERG considers that, following consultation with clinical experts, the assumption that 86% people prescribed LMWH would self-inject is reasonable, and the costs estimated by the manufacturer to be generally appropriate.

The ERG notes that, for patients experiencing an index VTE who are treated with dabigatran, rivaroxaban, or LMWH monotherapy, the manufacturer has not included an initial appointment where people are prescribed treatment and receive any training around how to take their medication. The ERG notes that a proportion of patients would have their medication initiated in hospital; however, not all patients are admitted to hospital (48% patients with a DVT, and 10% of patients with a PE are not admitted). By contrast, all patients receiving warfarin are assumed to attend an initial anticoagulation appointment at which treatment would be initiated, even those who have been admitted to hospital for their index VTE. Therefore, the ERG is concerned that the manufacturer has both overestimated the number of appointments for admitted warfarin patients (as they will not require an initial anticoagulation visit), but has also underestimated the number of appointments required for dabigatran, rivaroxaban or LMWH monotherapy, as non-hospitalised patients will require an initial appointment.

Consequently, the ERG considers that the cost of administering dabigatran versus warfarin may be underestimated. The ERG carried out a sensitivity analysis in which the initial anticoagulation appointment for warfarin was removed; this was a simplification designed to reflect the approach taken by the manufacturer for dabigatran, rivaroxaban and LMWH monotherapy. Results are presented in Section 6.2 **analysis B34.** The ICERs for dabigatran versus warfarin increased from £862 to £3,345 (acute treatment scenario) and from £8,319 to £9,395 (treatment and secondary prevention).

Monitoring costs

The manufacturer assumed that patients treated with warfarin would receive an initial anticoagulation clinic visit, and four additional anticoagulation clinic visits within the titration period (costs applied within the first cycle), followed by a visit once a month for the remainder of the treatment period. By contrast, patients receiving dabigatran, or rivaroxaban, were assumed to have a single follow-up visit at 5 months (MS; pg 323). Patients with cancer receiving LMWH monotherapy did not receive an additional cost associated with monitoring; instead, costs associated with administration were applied (see above).

The costs of monitoring were taken from NHS Reference Costs 2012/13[(11)] and adjusted to 2014 prices. The cost of an initial consultant-led anticoagulation clinic attendance cost was estimated to be £62.56; this cost applied only to warfarin treatment (as described above). The cost of follow-up visits was estimated to be £27.99, based upon a weighted (by activity) average of consultant led and non-consultant led visits. The costs of monitoring applied within the model are summarised in Table 120.

Table 120. Average cost of monitoring applied within the model for the index VTE event

Intervention	Average total cost per patient (acute period)		Average total cost per patient (secondary prevention period)	
	Number of visits	Cost of monitoring	Number of visits	Cost of monitoring
Dabigatran	1 (1 at £27.99)	£27.99	0 (over 6 – 18 months)	£0
Warfarin	10 (1 at £62.56, 9 at £27.99)	£314.51	18 (over 18 months, all at £27.99)	£503.86
Rivaroxaban	1 (1 at £27.99)	£27.99	0 (over 6 months)	£0
Abbreviation used in table: LMWH, low-molecular-weight heparin.				

The ERG consulted clinical experts around the monitoring schedule modelled by the manufacturer. The clinical experts approached by the ERG considered the modelled monitoring schedule in the acute period for warfarin to be generally appropriate. The clinical experts considered that, in the secondary prevention phase, the schedule modelled by the manufacturer may overestimate the number of monitoring appointments typically required in clinical practice. The clinical experts advised that in the secondary prevention phase, warfarin monitoring would typically occur once every three months. The ERG carried out an analysis whereby the number of appointments in the secondary prevention period for warfarin monitoring was reduced to one every three months. Results are presented in Section 6.2 **analysis B35.** The ICER for dabigatran versus warfarin increased from £8,319 to £12,859.

The clinical experts considered the monitoring schedule for dabigatran and rivaroxaban was not unreasonable; however, it was noted that patients receiving both therapies may return to their GP annually. The ERG carried out an analysis in which patients receiving dabigatran and rivaroxaban experienced an annual GP visit during secondary prevention. Results are presented in Section 6.2 **analysis B36.** Appointments were assumed to occur at 12 months, 24 months, 36 months and so on, up until the end of the model. The ICER for dabigatran versus warfarin increased from £8,319 to £9,496.

In addition, clinical experts advised that for follow-up visits in clinical practice it is typical for nurses to provide the majority of contact. As a sensitivity analysis, the ERG based the cost of follow-up visits on non-consultant-led (£10.61) anticoagulation clinic attendance. Results are presented in Section 6.2 **analysis B37.** The impact of the analysis was an increase in the ICER associated with dabigatran versus warfarin from £862 to £6,212 (acute treatment scenario) and from £8,319 to £14,867 (treatment and secondary prevention).

As described above, the ERG notes that, for patients experiencing an index event who are treated with dabigatran, rivaroxaban, or LMWH monotherapy, the manufacturer has not included an initial appointment where people are prescribed their treatment. As described above, the ERG carried out a

sensitivity analysis in which the initial anticoagulation appointment for warfarin was removed; the ERG considers that this reflects the approach taken by the manufacturer for dabigatran, rivaroxaban and LMWH monotherapy. Results are presented in Section 6.2 **analysis B34.** The ICERs for dabigatran versus warfarin increased from £862 to £3,345 (acute treatment scenario) and from £8,319 to £9,395 (treatment and secondary prevention).

5.4.13.3 Costs of recurrent VTE events

The costs associated with recurrent VTE events estimated by the manufacturer comprised costs of: diagnosis; hospitalisation; drug acquisition; administration; monitoring.

Diagnosis

The manufacturer estimated the total cost of diagnosing a proximal DVT and a PE to be £156.14 and £291.78 respectively (Table 121). The manufacturer assumed that patients presenting with proximal DVT symptoms would require an outpatient visit and one Doppler ultrasound scan for diagnosis. Patients presenting with PE symptoms were assumed to require one outpatient visit, a computed tomography scan, a chest x-ray, and an electrocardiogram. The costs associated with diagnosis were estimated using NHS Reference Costs 2012/13, adjusted to 2014 prices.

Table 121. Cost of diagnosis for recurrent VTE events applied within the manufacturer's model

Resource	Source of data (NHS Reference costs 2012/13 HRG code)	Cost per patient (DVT)	Cost per patient (PE)
Outpatient visit	Non-Admitted Face to Face Attendance, Follow-up, Clinical Haematology	£92.79	£92.79
Doppler ultrasound	Ultrasound Scan, 20 minutes and over (RA24Z, Diagnostic Imaging)	£63.35	NA
Computed tomography pulmonary angiogram	Computerised Tomography Scan, three areas without contrast (RA50Z, Diagnostic Imaging)	NA	£115.59
Chest x-ray	Direct Access Plain Film (DAPF)	NA	£28.93
Electrocardiogram	Electrocardiogram Monitoring and stress testing (EA47Z, DADS)	NA	£54.47
Total cost of diagnosis per suspected case		£156.14	£291.78
Abbreviations used in table: DVT, deep vein thrombosis; HRG, Healthcare Resource Group; PE, pulmonary embolism; VTE, venous thromboembolism.			

The ERG notes within TA261 and TA287, the cost of a D-dimer was included within the cost of diagnosis. Moreover, costs associated with an emergency presentation were included within the cost of diagnosis, and an outpatient visit was not included. The ERG consulted clinical experts around what resource would be required during diagnosis; the clinical experts advised that, for many patients,

the cost of a D-dimer is used. The experts also considered that, although most patients with DVT would be diagnosed as outpatient or day cases, many patients with PE would be diagnosed as inpatients. Overall, the ERG therefore considers that the costs presented in Table 121 may underestimate the cost associated with diagnosis.

Hospitalisation

The cost of hospitalisation at recurrence was assumed to be equivalent to the cost of hospitalisation during the index event. This cost has been described in Section 5.4.13.2.

Drug acquisition

After a recurrent VTE event, it was assumed by the manufacturer that all patients would initiate a treatment course of LMWH (5 days) and warfarin (6 months, MS; pg 233). The cost of treatment with warfarin at recurrence is assumed to be the same as the cost of treatment with warfarin at the index event (Table 122). This cost has been described in detail in Section 5.4.13.2.

Table 122. Summary of the drug cost per patient applied within the model, by intervention and comparator

Intervention	Drug	% patients	Average total cost per patient (acute period)		Average total cost per patient (secondary prevention period)	
			Days (acute period)	Drug acquisition costs	Days (secondary prevention period)	Drug acquisition costs
Warfarin	LMWH/UFH parenteral treatment	100%	5	£48 DVT £39 PE	0	–
	Warfarin	100%	180	£12	540	£35
Abbreviations used in table: DVT, deep vein thrombosis; PE, pulmonary embolism; LMWH, low-weight-molecular heparin; UFH, unfractionated heparin.						

Administration

The cost of drug administration included within the manufacturer's model related specifically to the administration of LMWH; specifically during parenteral pre-treatment. The cost applied within the model was equivalent to those described in Section 5.4.13.2, and was assumed to be £7.69 per patient.

Monitoring

The cost of monitoring applied after a recurrent VTE event related specifically to warfarin monitoring. The manufacturer modelled the cost of an initial anticoagulation clinic visit and four further visits during the first month, followed by one anticoagulation clinic visit each month for the next five months (Table 123). The costs applied within the model are equivalent to those applied during the acute period for the index VTE event (Section 5.4.13.2).

Table 123. Average cost of monitoring applied within the model for a recurrent VTE event

Intervention	Number of visits	Average total cost of monitoring per patient
Warfarin	10 (1 at £62.56, 9 at £27.99)	£314
Abbreviation used in table: VTE, venous thromboembolism.		

5.4.13.4 Complications associated with VTE events

The manufacturer incorporated the costs of severe PTS and CTEPH within the model. Table 124 presents the acute and long-term costs associated with severe PTS and CTEPH modelled by the manufacturer.

Table 124. Summary of the costs associated with severe PTS and CTEPH included within the manufacturer's model

Complication	Intervention	Cost per patient	Proportion of patients incurring cost	When cost is applied	Reference
Severe PTS	3 vascular surgery outpatient appointments in the first year	£442	100%	Year 1	• Proportion of patients, assumption • Cost based upon a first vascular surgery visit, from NHS Reference Costs 2012/13, weighted average of the following HRG codes: WF01B to WF02B. Plus, two follow-up visits based upon weighted average of the following HRG codes: WF01A to WF02A. Costs inflated to current prices.
	2 GP visits per year	£92	100%	Year 2+	• Proportion of patients, assumption • Cost of two surgery consultation lasting 11.7 minutes, including qualification and direct care staff costs taken from the Unit Costs for Health and Social Care 2013, and inflated to current prices.
CTEPH	Pulmonary endarterectomy	£7,447	50.3%*	Month 1	• Proportion of patients requiring pulmonary endarterectomy: Condliffe *et al*.[139] • Cost of pulmonary endarterectomy from NHS Reference Costs 2012/13, weighted average of DZ02D to DZ02G: Complex Thoracic Procedures. Data for elective inpatients, non-elective inpatients (long stay), non-elective inpatients (short stay); inflated to current prices.
	Ongoing monthly cost	£1,365	100%	Month 1+	• Proportion of patients requiring ongoing monthly cost, assumption.

					• Monthly cost stated as taken from Bayer submission for TA261; cost within Bayer submission was £3,719.17 per 3 months. Referenced within Bayer submission as NICE CG92; figure within NICE CG92 was £1,219 per month. Inflated to current prices.
* Note, manufacturer states that 50.5% patients receive a pulmonary endarterectomy within the MS pg 329; however, within the model the figure is 50.32% and, moreover, 50.32% corresponds to the data contained within Condliffe *et al.*[139] Abbreviations used in table: CTEPH, chronic thromboembolic pulmonary hypertension; CG, clinical guideline; HRG, Healthcare Resource Group; PEA, pulmonary endarterectomy; PTS, post-thrombotic syndrome					

The ERG considers that the costs outlined in Table 124 appear reasonable; however, the ERG notes that the estimated 1st year cost (£442) described in Table 124 for severe PTS is applied to all new CTEPH patients in their first cycle with CTEPH. The ERG considers it would have been more appropriate to apply 1/12 of the 1st year cost, i.e. a monthly cost, within the engine for the first 12 cycles of a newly presenting CTEPH patient. The ERG notes that this is unlikely to significantly affect the ICER.

5.4.13.5 Adverse effects of treatment

The manufacturer included the costs of the following adverse events within the model:

- ICH;
- extra-cranial MBE;
- CRNMBE;
- MI (sensitivity analysis only);
- UA (sensitivity analysis only);
- dyspepsia (sensitivity analysis only).

A summary of the cost per patient applied by the manufacturer within the economic model is presented in Table 125, with a detailed description provided in the remainder of this section.

Table 125. Summary of adverse event costs included within the manufacturer's model

Adverse event		Cost per patient	% patients	Reference
ICH	Initial management	£10,182	100%	Youman *et al.*[133]
	Long-term care	£1,867	65% of surviving patients	
Extra-cranial MBE		£2,357	100%	Weighted average of the following NHS Reference Costs 2012/13: FZ38G – FZ38L

				Gastrointestinal Bleed, with Multiple Interventions
CRNMB	Inpatient	£1,102	30%	Weighted average of the following NHS Reference Costs 2012/13: MA22Z, MA23Z, MA24Z, MA25Z: Lower and Upper Genital Tract Minor Procedures
	Outpatient	£92	70%	NHS Reference Costs 2012/13 WF01A: Non-Admitted Face to Face Attendance, Follow-up, Clinical Haematology
MI	Acute	£4,724	100%	Ara *et al*.[128]
	Long-term	£34	60%	
UA	Acute	£4,588	100%	
	Long-term	£34	60%	
Dyspepsia		£46	100%	Latimer *et al*.[132]
Abbreviations used in table: CRNMB, clinically-relevant non-major bleeding; HRG, Healthcare Resource Group; ICH, intracranial haemorrhage; IHD, ischemic heart disease; MBE, major bleeding event; MI, myocardial infarction; NA, not applicable; NR, not reported; UA, unstable angina.				

Intracranial haemorrhage

Initial management

The manufacturer calculated the cost of an ICH as the cost of initial management (incurred within the cycle the ICH is experienced) and the cost of long-term management for patients surviving the ICH who were permanently disabled as a consequence of the ICH.

For initial management, the manufacturer used data from a study carried out by Youman *et al*.[133] Youman *et al*. was a cost-of-illness study which aimed to estimate stroke-related costs over a 5-year period. The cost estimates were based on data collected from 457 people treated for stroke in the UK. Data were collected over a period of 1 year following stroke, and were extrapolated using a Markov framework to estimate costs over 5 years. The authors reported a 5-year cost to the NHS of £15,306, increasing to £29,405 if informal care costs were included (cost year, 2001/2).

The cost of initial management applied within the model by the manufacturer was £10,182. This figure was based upon the acute cost of a mild (£5,099), moderate (£4,816), severe (£10,555) and fatal (£6,781) stroke presented within Youman *et al*., weighted by the proportion of patients experiencing each type of stroke (mild 15.2%, moderate 22.1%, severe 43.7%, fatal 19%). The weights were taken from Youman *et al*. which in turn referenced Kalra *et al*.[133;141]

The manufacturer did not describe the rationale for selecting Youman *et al*. for use within the model; however, the ERG notes that the manufacturer identified Youman *et al*. within their systematic review of resource use and costs (Section 5.4.13.1). The ERG also notes that the manufacturer identified a study by Connock *et al.*, which the manufacturer described as containing annual cost estimates for

fatal stroke and disabled patients.[130] The manufacturer did not describe the rationale for selecting Youman *et al*. rather than Connock *et al*. as the source of data.

The ERG notes that, within the model, the cost of initial management for ICH is applied only to the proportion of patients experiencing a severe ICH (Section 5.4.8.1). Consequently, the ERG is unclear why costs of mild and moderate stroke were included in the cost calculation. In a scenario analysis, the ERG used only the cost associated with a severe stroke (£10,555) in the calculation of initial management cost. The average cost applied for the initial management period for a non-fatal ICH for the ERG sensitivity analysis was £14,777; this cost reflected the cost of severe stroke (£10,555) inflated to 2013 prices. Results are presented in Section 6.2 **analysis B38.** For the comparison of dabigatran versus warfarin, the ICERs reduced slightly from £862 to £642 (acute treatment scenario) and from £8,319 to £8,126 (treatment and secondary prevention scenario).

Finally, the ERG notes a minor error; the manufacturer has estimated the inflated cost of initial management of ICH on the basis that the cost year was 2004; the ERG notes that the cost year was 2002. The ERG carried out an analysis correcting the minor error stated above. A description of the analysis is provided in Section 5.5.1, with results presented in Section 6.1, **analysis A13**. The impact of the analysis on the ICERs was small.

Long-term care

The manufacturer assumed that the cost associated with long term care would differ by ICH severity (mild, moderate, severe) and by whether the patient was institutionalised as a result of the ICH, or was cared for at home.

The proportion of people with a mild (17%), moderate (19%) or severe (64%) ICH was estimated from Rosand *et al*.[77] The proportion of people institutionalised or cared for at home (by ICH severity), and the annual cost of long term care applied within the model by the manufacturer was taken from Youman *et al*.[133]

The annual costs of long-term care applied within the model were estimated from Youman *et al*. to be £22,178 per year for institutionalised patients (estimated from a figure of £3,872 per three months, inflated to current prices), and £1,867 per year for patients treated at home (estimated from a figure of £326 per three months, inflated to current prices).

The ERG believes that the manufacturer has made a mistake in the application of cost within the model. The manufacturer excluded 50% of the estimated cost of long-term management of patients who were institutionalised for their ICH within the model. This is because the manufacturer associated 50% of the cost to informal care; as the data within Youmans *et al*. relates specifically to costs associated with the health service, the ERG considers this is likely to be a mistake. The ERG

altered the calculation to include all costs associated with institutionalisation. The analysis is described in Section 5.5.1 and results presented in Section 6.1, **analysis A14**. The impact of the analysis on the ICER for dabigatran versus warfarin in both the acute treatment scenarios, and the treatment and secondary prevention scenarios was a reduction in the ICER from £862 to £161 (acute treatment) and from £8,319 to £7,726 (treatment and secondary prevention). For dabigatran versus rivaroxaban (full population) and LMWH (for the population with cancer), the impact upon the ICER for the acute treatment scenario was small.

Extra-cranial MBE

The manufacturer included the costs of extra-cranial MBEs within the model; these costs were applied in the engine to all patients experiencing a MBE, regardless of whether the MBE was fatal or non-fatal. The cost was estimated to be £2,357, based upon the weighted average of NHS Reference Costs 2012/13(11) data, inflated to 2014 values. The data used from NHS Reference Costs were elective, non-elective short stay, and non-elective long stay for Gastrointestinal Bleed with single or multiple interventions, with cost weighted by finished consultant episodes. The ERG considers that the cost used by the manufacturer is reasonable.

CRNMBE

The manufacturer included the costs of CRNMBEs within the model; these costs were applied in the engine in the month of the event, to all patients experiencing a CRNMBE. The cost was estimated to be £396, based upon 70% patients with a CRNMBE receiving an outpatient visit (£93) and 30% patients receiving an inpatient visit (£1,102).

The outpatient cost was estimated using NHS Reference Costs 2012/13 HRG "Non-Admitted Face to Face Attendance, Follow-up, Clinical Haematology" inflated to 2014 prices. The inpatient cost was based upon a weighted average of HRG codes for genital tract minor procedures (MA22Z to MA25Z).

The ERG consulted with clinical experts around the typical resource use required for CRNMBEs in clinical practice. The clinical experts advised that spontaneous skin haematoma, spontaneous nose bleed, or gingival bleeding would likely require a GP appointment rather than attendance at hospital.

The ERG was unable to identify the costs stated by the manufacturer for inpatient stay within NHS Reference Costs 2012/13. The ERG notes that, using NHS reference costs for "all activity" results in a weighted average cost of £257; note this includes outpatient appointments.

As a sensitivity analysis, the ERG modelled a scenario whereby the cost associated with a CRNMBE was the cost of a GP appointment for 50% patients (£40, Unit Costs for Health and Social Care), and the cost of an inpatient or outpatient appointment (NHS Reference Costs MA22Z to MA25Z,

weighted by activity) for 50% patients (£257). The average cost per patient applied within the model was therefore £148. The ERG notes that within TA261 and TA287 the cost associated with CRNMBEs was £126, which is similar to the ERG estimate.[49;65] Results are presented in Section 6.2 **analysis B40.** The ICERs for the comparison of dabigatran versus warfarin increased slightly from £862 to £1,130 (acute treatment scenario) and from £8,319 to £8,575 (treatment and secondary prevention scenario).

Other adverse events

The manufacturer included the costs associated with MI, UA and dyspepsia within a sensitivity analysis. The applied costs are presented in Table 126.

Table 126. Cost of MI and UA applied in sensitivity analysis

Adverse event		Cost	Source	Proportion of patients	Source
MI	Acute	£4,724 (year 1)	Ara *et al.(128)*	100%	Assumption
	Long-term cost of chronic IHD	£34 (per month)		60%	
UA	Acute	£4,588 (year 1)		100%	
	Long-term cost of chronic IHD	£34 (per month)		60%	
Dyspepsia		£46	Latimer *et al.(132)*	100%	
Abbreviations used in table: MI, myocardial infarction; UA, unstable angina.					

The costs associated with MI and UA events were taken from Ara *et al*., a study which evaluated the cost-effectiveness of treatment with high-dose versus moderate-dose statins for individuals with acute coronary syndrome (ACS), and inflated to 2014 prices.[128] MI and UA were estimated to be associated with a cost of £3,991 and £3,876, respectively, in year 1. In addition, the manufacturer assumed that 60% patients with MI or UA went on to develop chronic IHD; the cost associated with these patients was assumed to be £34 per month, based upon data contained in Ara *et al*. (£340 per year converted to a monthly cost and inflated to 2014 prices).[128] The estimated proportion of patients developing chronic IHD was based upon clinical expert opinion.

The ERG notes that Ara *et al*. was identified from the manufacturer's systematic review of resource use and costs (Section 5.4.13.1). In addition, the ERG notes that the acute cost of MI and UA was applied as a one-off cost in the model at month 4. The ERG notes that this was a modelling simplification to apply cost during the acute period.

The cost of managing dyspepsia was taken from Latimer *et al*., inflated to 2014 prices.[132] The study authored by Latimer was an investigation of the cost-effectiveness of cyclo-oxygenase-2 selective

inhibitors and traditional non-steroidal anti-inflammatory drugs (NSAIDs), and the addition of proton pump inhibitors to these treatments, for people with osteoarthritis. A cost associated with dyspepsia was included within this paper. This study was identified from the manufacturer's systematic review of resource use and costs (Section 5.4.13.1)

The estimate of cost presented within Latimer *et al*. was £40; this cost was a three-month cost, and included secondary care costs taken from NHS Reference Costs as well as primary care costs. The manufacturer inflated this cost to 2014 prices, and also applied this cost as a one-off cost at month 4 within the model.

The ERG considers the costs applied by the manufacturer to be reasonable.

5.4.14 Cost effectiveness results

The manufacturer presented deterministic and probabilistic results for acute treatment and treatment and secondary prevention separately. The base case results were calculated deterministically (using mean parameter values only) as well as probabilistically (assessing the simultaneous effect of parameter uncertainty). Section 5.4.14.1 outlines the results for the acute treatment scenarios, and Section 5.4.14.2 outlines the results for the treatment and secondary prevention scenarios.

5.4.14.1 Cost effectiveness results – acute treatment

Results presented by the manufacturer for the acute treatment scenarios are presented in Table 127.

Table 127. Results for the acute treatment scenario, adapted from MS (pg 356, Table 145)

Intervention	Total cost	Total QALYs	Incremental cost associated with dabigatran	Incremental QALYs associated with dabigatran	ICER***
Deterministic results – full population					
Warfarin	£7,482	12.428	–	–	–
Dabigatran	£7,503	12.452	£21	0.024	£862
Rivaroxaban	£7,523	12.451	-£20	-0.0003	Rivaroxaban dominated by dabigatran
Deterministic results – population with cancer					
Dabigatran	£4,152*	5.805*	–	–	–
LMWH	£5,522	5.817	£1,370	0.012	£110,742, dabigatran is less costly and less effective
Probabilistic results – full population					
Dabigatran	£7,570	12.449**	–	–	–
Warfarin	£7,545	12.431	£25	0.0241	£1,016
Rivaroxaban	£7,480	12.449	-£17 (vs dabigatran)	0.0003 (vs dabigatran)	Rivaroxaban dominated by dabigatran
Probabilistic results – population with cancer					
LMWH	£5,496	5.815	–	–	–
Dabigatran	NR	NR	-£1,349	-0.0144	£93,431, dabigatran is less costly and less effective

* Note, data contained within the economic model and not presented within the MS

** Note, estimated as figure in MS erroneously set to the number of life-years-gained

*** Note, the probabilistic ICERs are calculated as the average ICER from 1,000 simulations, not the ICER of the average incremental cost and QALY presented within the table

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin; MS, manufacturer's submission; NR, not reported; QALYs, quality-adjusted life years.

The base case results for the comparison of dabigatran versus warfarin for the acute treatment phase for deterministic and probabilistic analyses were comparable at £862 and £1,016 respectively. Similarly, the base case results for the acute treatment phase for dabigatran versus rivaroxaban were comparable, with dabigatran estimated to be the dominant strategy in both the deterministic and probabilistic analyses. In addition, for the population with cancer, the deterministic and probabilistic results were comparable, with both scenarios finding dabigatran to be less effective and less costly than LMWH.

The ERG notes that the costs and QALYs estimated by the manufacturer for the full population analyses in the acute treatment period were very similar. Costs varied between all three treatment strategies by £40 in the deterministic analyses; QALYs varied by approximately 0.02 per patient over a lifetime. In particular, the ERG notes that, for the dabigatran comparison with rivaroxaban, the

estimated total QALYs differed by 0.0003 over a lifetime for one patient. Therefore, the ERG considers that whilst dabigatran dominates rivaroxaban in the manufacturer base case, the average total costs and QALYs estimated by the manufacturer imply that these treatments are similar.

5.4.14.2 Cost effectiveness results –treatment and secondary prevention

The manufacturer presented cost-effectiveness results for the treatment and secondary prevention scenarios within the submission in a table designed to present fully incremental analyses. The analyses for treatment and secondary prevention cannot be considered fully incremental due to differing baseline values for dabigatran in each comparison for: treatment duration; probability of recurrent VTE, probability of bleeding; probability of discontinuation. Consequently, the ERG has represented the manufacturer results as a series of head-to-head analyses (Table 128).

Table 128. Results for the treatment and secondary prevention scenarios, adapted from MS (pg 356, Table 146)

Comparison	Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER*
Deterministic results – full population						
Dabigatran versus warfarin	Warfarin	£7,861	12.464	–	–	–
	Dabigatran	£8,319	12.519	£458	0.0551	£8,319
Dabigatran versus rivaroxaban	Dabigatran	£7,785 (from manufacturer's model)	12.480 (from manufacturer's model)	–	–	–
	Rivaroxaban	£7,852	12.478	£67	-0.0020	Rivaroxaban is dominated by dabigatran
Deterministic results – population with cancer						
Dabigatran versus LMWH	Dabigatran	£7,821 (from manufacturer's model)	12.471 (from manufacturer's model)	–	–	–
	LMWH	£11,161	12.451	-£3,340	0.0197	LMWH is dominated by dabigatran
Probabilistic results – full population						
Dabigatran versus warfarin	Warfarin	£7,839	12.460	–	–	–
	Dabigatran	£8,305	12.510	£466	0.0527	£8,848
Dabigatran versus rivaroxaban	Dabigatran	NR	NR	–	–	–
	Rivaroxaban	£7,878	12.470	-£63	0.0096	Rivaroxaban is dominated by dabigatran
Probabilistic results – population with cancer						
Dabigatran versus LMWH	Dabigatran	NR	NR	–	–	–
	LMWH	£11,118	12.450	-£3,342	0.0226	LMWH is dominated by dabigatran
* Note, the probabilistic ICERs are calculated as the average ICER from 1,000 simulations, not the ICER of the average incremental cost and QALY presented within the table						
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin; MS, manufacturer's submission; NR, not reported; QALYs, quality-adjusted life years.						

The base case results for the comparison of dabigatran versus warfarin for the acute treatment phase for deterministic and probabilistic analyses were comparable at £8,319 and £8,848 respectively. Similarly, the base case results for the acute treatment phase for dabigatran versus rivaroxaban were comparable, with dabigatran estimated to be the dominant strategy in both the deterministic and

probabilistic analyses. In addition, for the population with cancer, the deterministic and probabilistic results were also comparable, with both scenarios finding LMWH to be dominated by the dabigatran.

The ERG notes that, as with acute treatment, the scenario for dabigatran versus rivaroxaban reflects very similar costs and QALYs between the two treatment strategies. The cost difference between dabigatran and rivaroxaban differed by £67 to £76 in the deterministic and probabilistic analyses, respectively. Moreover, the QALY differential between the two treatment strategies differed by less than 0.01 per patient over their lifetime. Therefore, the ERG considers that whilst dabigatran dominates rivaroxaban in the base case, as for acute treatment, the average total costs and QALYs estimated by the manufacturer imply that these treatments are similar.

5.4.15 Sensitivity analyses

The manufacturer carried out a series of sensitivity analyses to test the robustness of model results to changes in model parameters. Specifically, the manufacturer presented result of deterministic (Section 5.4.15.1) and probabilistic (Section 5.4.15.2) sensitivity analyses.

5.4.15.1 Deterministic sensitivity analysis

The deterministic sensitivity analyses presented by the manufacturer in the MS were limited to 11 scenario analyses. Table 129 summarises the scenarios explored, and the manufacturer's justification for each scenario.

Table 129. List of scenario analyses carried out by the manufacturer, adapted from MS (pg 332, Table 123)

	Parameter to be changed	Default parameter value	New parameter value	Justification
1	Adjustment to TTR	Based upon analysis presented in Table 102.		Treatment effects may differ depending on differences in TTR.
2	LMWH duration for rivaroxaban regimen	0 days	1.1 for DVT; 1.4 for PE	Rather than assuming no parenteral treatment use, the parenteral use observed in the rivaroxaban pivotal trials will be explored.
3	Utility decrement for WFN	-0.012	0.000	Test the impact of no utility decrement for WFN use.
4	Dyspepsia	0.000	3.0% incidence in dabigatran, 1.0% incidence in WFN	Based on AE rate reporting in dabigatran clinical trials programme.
5	Time horizon for treatment	Lifetime (60 years)	6 months	To see the results after 6 months have passed.
6	Time horizon for treatment	Lifetime (60 years)	1 year	To see the results after 1 year has passed.
7	Time horizon for treatment then secondary	Lifetime (60 years)	1 year	To see the results after 1 year has passed.

	prevention			
8	Bleeding event counting	Bleeds counted from start of single dummy period (i.e., counted whilst on LMWH for dabigatran or warfarin regimen)	Bleeds counted from double dummy period (i.e., for dabigatran, after 5 days of LMWH)	To estimate the impact across the dabigatran treatment pathway, rather than just the entire treatment pathway.
9	Myocardial infarction and unstable angina (i.e. cardiovascular events)	Events excluded in the base case	Included in the scenario analysis	To estimate the effect of including myocardial infarction and unstable angina (i.e. cardiovascular events) in the analysis.
10	Unexplained death	Treatment and secondary prevention indication only: excluded unexplained deaths	Treatment and secondary prevention indication only: to include unexplained deaths	To explore the effects of unexplained deaths on the result.
11	Rivaroxaban pre-specified treatment duration	Pooled 3, 6 and 12 month treatment durations	6 month treatment duration only	To compare results from the 6 month treatment period of the rivaroxaban trials with the RE-COVER II trials as the results match more closely.
Abbreviations used in table: AE, adverse event; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; TTR, time in therapeutic range; WFN, warfarin.				

The results of the scenario analyses are presented in the MS, pgs 359 to 362, and replicated in Appendix 1 for ease of reference. Overall, the manufacturer found that base case estimates were robust to the analysed scenarios.

The manufacturer concluded that, for the analyses comparing dabigatran versus warfarin for acute treatment, “the base case results remain well below £10,000 per QALY” (MS; pg 363) for all scenarios considered. Similarly, for treatment and secondary prevention, the ICER for dabigatran versus warfarin remains below £20,000 in all scenarios considered.

For dabigatran versus rivaroxaban, the manufacturer found that dabigatran was the dominant treatment strategy for all scenarios modelled for treatment and secondary prevention, and all scenarios modelled for acute treatment with the exception of “bleeding event counting” (Table 129). For this scenario, dabigatran was found to be less costly and less effective than rivaroxaban.

For dabigatran compared with LMWH monotherapy in the population with cancer, dabigatran remained less costly and less effective than LMWH during acute treatment, for all scenarios modelled. Similarly, dabigatran remained the dominant treatment strategy during the treatment and secondary prevention phase for all scenarios modelled.

In addition to the scenario analyses presented, the ERG asked the manufacturer during clarification to present results of one-way sensitivity analysis, specifically the top-ten most sensitive variables for each scenario. The manufacturer provided these data in tabular format (manufacturer response to clarification; pgs 49 to 55); however, it is not clear from the manufacturer's reporting which quadrant the reported ICERs relate to. That is, whether a positive value indicates a result in the north-east quadrant (dabigatran is more costly and more effective) or the south-west quadrant (dabigatran is less costly and less effective); and similarly whether a negative value indicates a result in the south-east quadrant (dabigatran is less costly and more effective) or north-west quadrant (dabigatran is more costly and less effective). In addition, the manufacturer did not present the upper and lower values of the parameters used to estimate the ICERs. Consequently, the ERG has not presented these data within the report.

5.4.15.2 Probabilistic sensitivity analysis (PSA)

Parameter uncertainty was explored using PSA. Individual parameters within the model were assigned a probability distribution from which estimates were simultaneously sampled for 1,000 iterations. The inputs stated as varied in PSA and the assigned distributions are outlined in the MS. The results of the PSA are presented in the MS, pgs 364 to 371.

Table 130 summarises the manufacturer estimates of probability of cost-effectiveness at a willingness-to-pay (WTP) threshold of £20,000 and £30,000. In addition, the results of the PSA as presented upon the cost-effectiveness plane are replicated in Figure 15 to Figure 19 below.

Table 130. Manufacturer estimated probability of cost-effectiveness for each head-to-head comparison

Dabigatran versus:	**Probability of dabigatran being considered cost-effective at a WTP threshold of:**	
	£20,000 per additional QALY	**£30,000 per additional QALY**
Acute treatment		
Warfarin	93%	94%
Rivaroxaban	57%	57%
LMWH (population with cancer)	92%	86%
Secondary prevention		
Warfarin	92%	96%
Rivaroxaban	81%	79%
LMWH (population with cancer)	100%	100%
Abbreviations used in table: LMWH, low-molecular-weight heparin; QALY, quality-adjusted life year; WTP, willingness-to-pay.		

Figure 14. Cost-effectiveness plane for dabigatran versus warfarin, acute treatment (reproduced from MS; Figure 40)

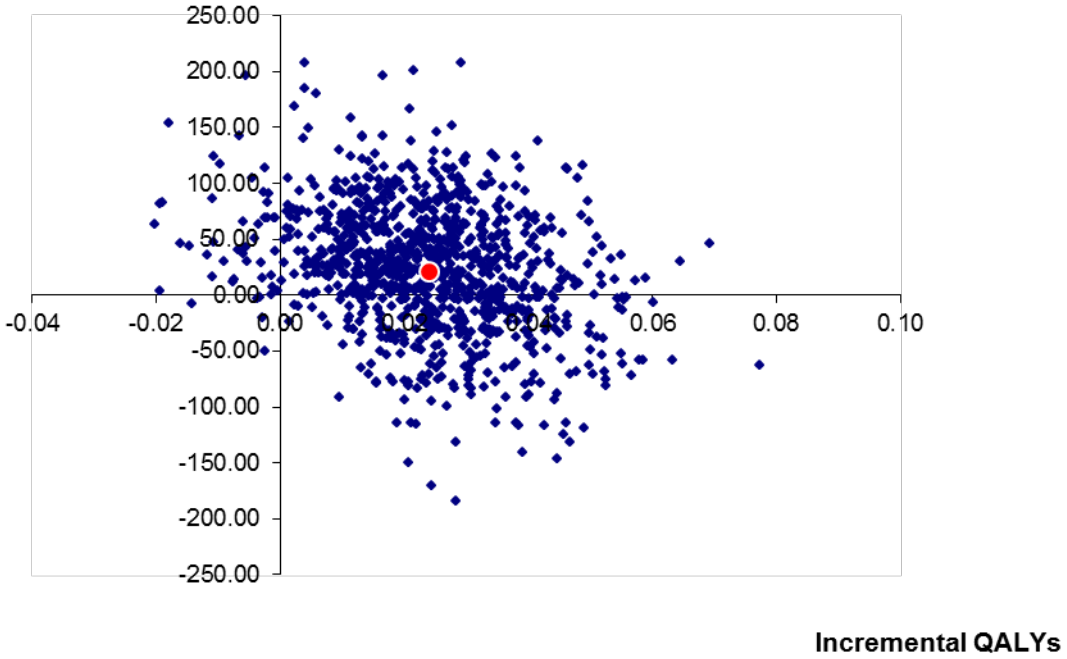


Figure 15. Cost-effectiveness plane for dabigatran versus rivaroxaban, acute treatment (reproduced from MS; Figure 42)

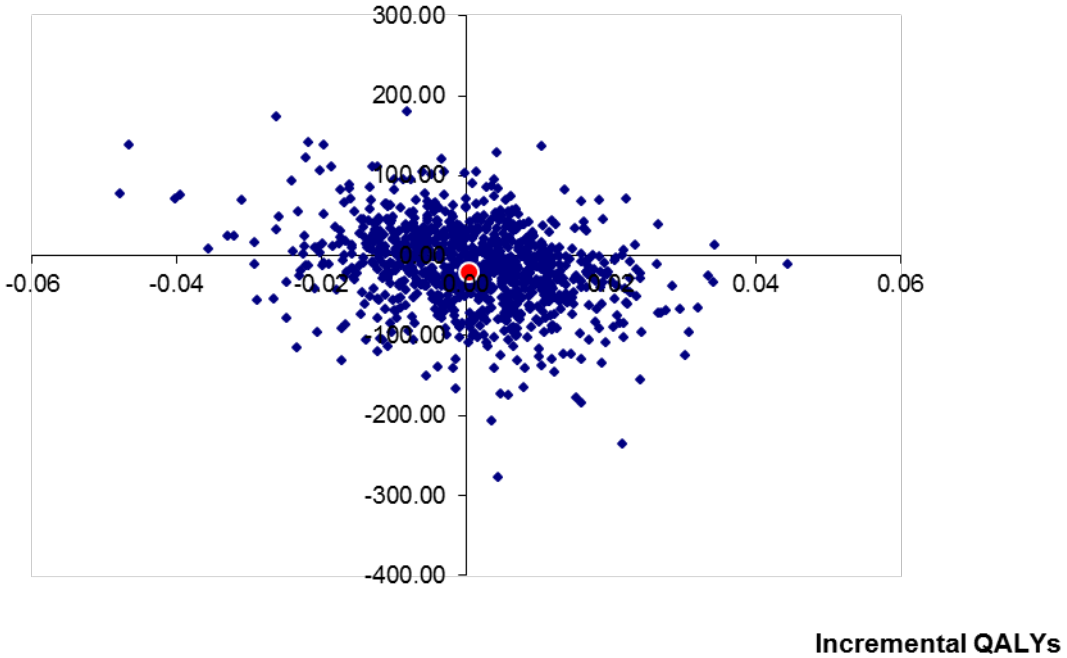


Figure 16. Cost-effectiveness plane for dabigatran versus LMWH (population with cancer), acute treatment (reproduced from MS; Figure 44)

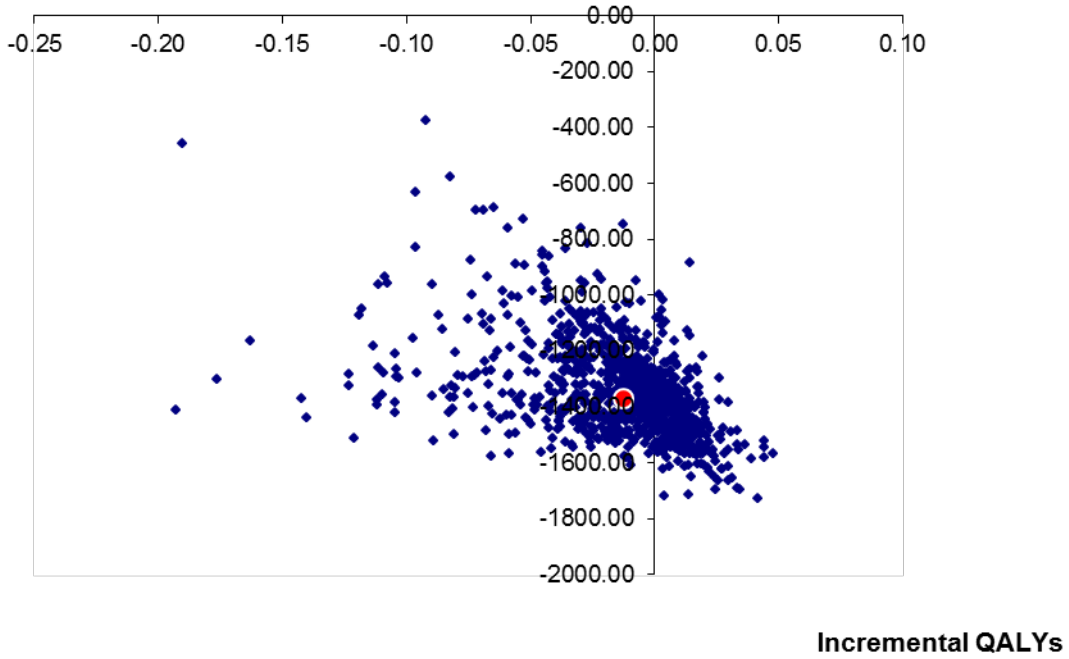


Figure 17. Cost-effectiveness plane for dabigatran versus warfarin, treatment and secondary prevention (reproduced from MS; Figure 46)

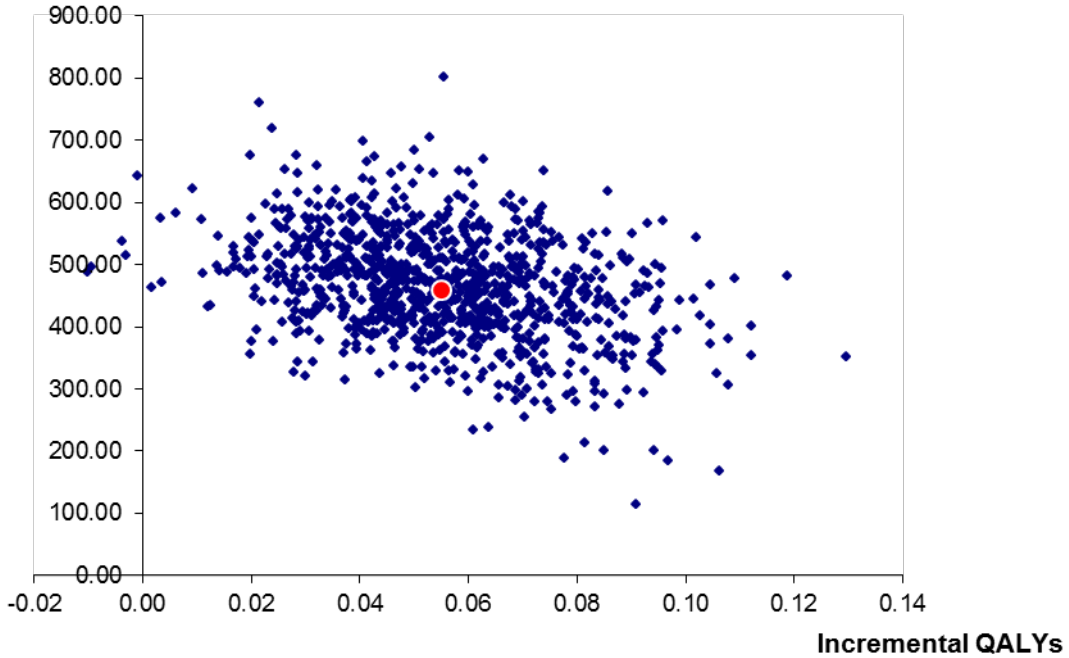


Figure 18. Cost-effectiveness plane for dabigatran versus rivaroxaban, treatment and secondary prevention (reproduced from MS; Figure 48)

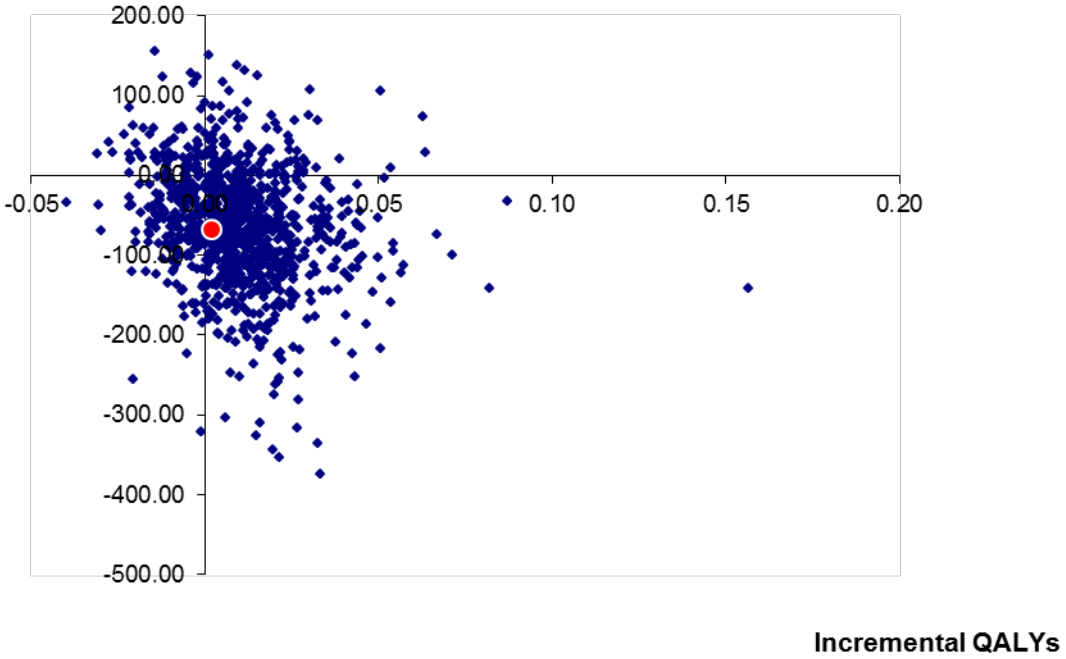
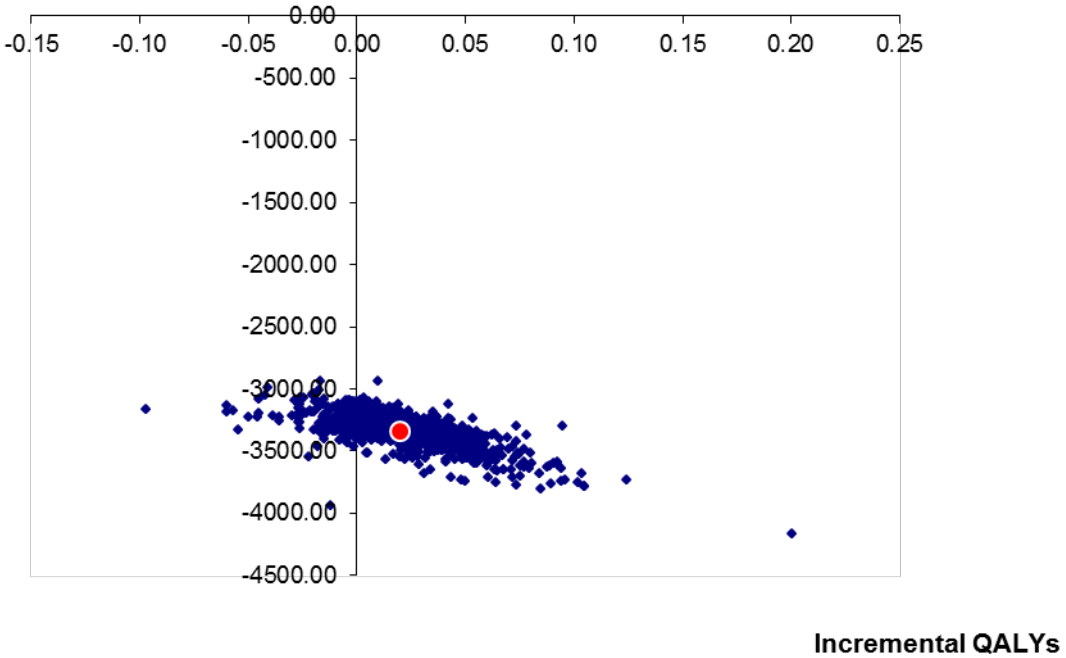


Figure 19. Cost-effectiveness plane for dabigatran versus LMWH (population with cancer), treatment and secondary prevention (reproduced from MS; Figure 50)



The ERG notes that disutility parameters were assigned to a Gamma sampling distribution for the PSA calculations, with the exception of VTE disutility which was assigned a normal distribution. The manufacturer did not provide a rationale for these distribution choices, and the ERG considers that a

beta distribution may have been more appropriate. Similarly, the ERG considers that it may have been appropriate to assign a beta distribution, rather than a normal distribution, to the probability of recurrent VTE after off-treatment. Finally, the ERG notes that discontinuation rates were not varied in PSA.

Furthermore, the ERG notes that, to estimate the probability of cost-effectiveness at various WTP thresholds, the manufacturer did not take into account the impact simulations falling into the south-west quadrant; i.e. those simulations in which dabigatran was less costly and less effective than the comparator. The consequence of this is a miscalculation of the probability of cost-effectiveness, and a number of counter-intuitive results. For example, for the comparison with warfarin in the acute treatment phase and the comparison with rivaroxaban in the secondary prevention phase, the proportion of simulations that can be considered cost-effective at various WTP thresholds falls as the WTP threshold increases.

The ERG re-ran the PSA for the manufacturer's base case using the beta distribution for disutilities, and assuming that all simulations falling in the south-west quadrant were not considered cost-effective at either a £20,000 or £30,000 WTP threshold. The results are detailed below in a replica of Table 131.

Table 131. ERG estimated probability of cost-effectiveness (manufacturer base case)

dabigatran versus:	**Probability of dabigatran being considered cost-effective at a WTP threshold of:**	
	£20,000 per additional QALY	**£30,000 per additional QALY**
Acute treatment		
warfarin	92%	92%
Rivaroxaban	52%	52%
LMWH (population with cancer)	38%	38%
Secondary prevention		
warfarin	82%	89%
Rivaroxaban	73%	73%
LMWH (population with cancer)	82%	82%
Abbreviations used in table: LMWH, low-molecular-weight heparin; QALY, quality-adjusted life year; WTP, willingness-to-pay.		

The ERG notes that the probability of dabigatran being considered cost-effective at a WTP threshold of £20,000 and £30,000 versus LMWH (in the population with cancer) falls considerably from the estimate presented by the manufacturer. The probability of cost-effectiveness in the acute treatment phase falls from approximately 92%, to 38% for both a WTP threshold of £20,000 and £30,000. This is due to 62% of simulations for that comparison falling within the south-west quadrant; i.e. dabigatran is less costly and less effective in 62% of simulations. Similarly, in the treatment and

secondary prevention phase the probability of cost-effectiveness falls from 100% to 82%. Again, this is due to 18% simulations for that comparison falling within the south-west quadrant.

The ERG considers it important to further note that the manufacturers' analysis indicates that, for the comparison of dabigatran versus rivaroxaban, in the acute treatment phase, it is equally likely for dabigatran to be considered cost-effective versus rivaroxaban as it is to not be considered cost-effective. This is due to the similar costs and QALYs estimated by the manufacturer for both treatment strategies, as discussed in Section 5.4.13.5.

5.4.16 Model validation and face validity check

The manufacturer stated that the following measures were taken to validate and verify the calculations within the economic model:

- the model structure, assumptions and techniques were discussed with a panel of clinical experts (MS; pg 330);
- internal verification of the analysis was performed by staff not involved in the model development (MS; pg 331);
- an external agency was commissioned to perform a final quality assurance of the model which involved a detailed review of inputs and calculations (MS; pg 331).

The ERG considers that the quality of the model submitted by the manufacturer was reasonable; however, the ERG identified a number of errors and inconsistencies of reporting between the MS and the economic model. The cumulative impact of these errors on model results was generally small for the comparisons of dabigatran versus warfarin and LMWH (Section 6.1). For the comparison of dabigatran versus rivaroxaban, due to the very similar costs and QALYs estimated for these treatments, the ICERs changed from dabigatran being the dominant treatment strategy (less costly and more effective) to dabigatran being less costly and less effective (Section 6.1).

In addition to validation of model calculations, the manufacturer compared model predictions for dabigatran versus warfarin with empirical data (MS; pg 334). Table 132 summarises the data presented by the manufacturer.

Table 132. Comparison of Model predictors with empirical data, adapted from MS (pg 334, Table 124)

Source of empirical data	Empirical estimate	Model prediction
RE-COVER I		
Incidence of recurrent VTE at 7 months, dabigatran (%)	2.67%	2.70%
Incidence of recurrent VTE at 7 months, warfarin (%)	2.53%	2.57%
Incidence of major and clinically relevant non-major bleeds at 6 months, dabigatran (%)	4.73%	4.65%
Incidence of major and clinically relevant non-major bleeds at 6 months, warfarin (%)	8.15%	8.06%
RE-COVER II		
Incidence of recurrent VTE at 7 months, dabigatran (%)	2.66%	2.66%
Incidence of recurrent VTE at 7 months, warfarin (%)	2.33%	2.38%
Incidence of major and clinically relevant non-major bleeds at 6 months, dabigatran (%)	4.15%	4.00%
Incidence of major and clinically relevant non-major bleeds at 6 months, warfarin (%)	7.21%	7.15%
Recurrent VTE after trial follow-up		
Incidence of recurrent VTE at 10 years, warfarin/VKA (%)	39.90% (35.4% to 44.4%)	47.53%
Mean life expectancy for the general population aged 55, years	26 years	26 years
Survival at 5 years for cancer population (%)	Relative survival 67%	Relative survival 61%
Abbreviations used in table: VKA, vitamin-k antagonist; VTE, venous thromboembolism.		

The ERG notes that data presented in Table 132 imply that the model generated values are generally consistent with the observed values; however, the ERG notes that the manufacturer did not provide data for rivaroxaban or LMWH and is therefore unable to comment upon consistency for these comparisons.

5.5 Exploratory and sensitivity analyses undertaken by the ERG

Following review of the MS and submitted economic model, the ERG carried out a number of additional analyses. The purpose of these analyses was to both correct a number of potential model errors, and to test the robustness of model results to changes in parameters. The following sections outline the analyses carried out (model corrections, Section 5.5.1; scenario analyses, Section 5.5.2) and Section 6 presents the results of each of these analyses.

All analyses were carried out using the manufacturer's deterministic analysis rather than the probabilistic analysis. This was due to ERG time constraints, and because model results were found by the manufacturer to be consistent between deterministic and probabilistic estimates (Section 5.4.14)

5.5.1 ERG model corrections

The ERG identified the following potential errors in the manufacturer's model:

- **analysis A1:** the manufacturer multiplied the baseline probability of recurrent VTE by a HR without first converting the baseline probability into a rate (Section 5.4.6.1);
- **analysis A2:** for the population with cancer analyses, the manufacturer used the baseline probability for recurrent VTE for the full population (2.43%) during the acute phase of treatment and secondary prevention rather than 7.41%, the value for the population with cancer (Section 5.4.6.1);
- **analysis A3:** the manufacturer double counted a small proportion of severe PTS cases (Section 5.4.7.1)
- **analysis A4:** the manufacturer double counted a small proportion CTEPH cases (Section 5.4.7.2);
- **analysis A5:** the manufacturer multiplied the baseline probability of major and clinically relevant non-major bleeds by a HR without first converting the baseline probability into a rate (Section 5.4.8.1);
- **analysis A6:** for the population with cancer analyses, the manufacturer used the baseline probability for a major and clinically relevant non-major bleed for the full population (1.97%), rather than data from the population with cancer (14.20%) (Section 5.4.8.1);
- **analysis A7:** the manufacturer assumed that the proportion of people experiencing a MBE or CRNMBE in the population with cancer receiving dabigatran were assigned the same proportions of bleeds as for the full population, in the acute period for the treatment and secondary prevention scenario, rather than to data for the subgroup of patients with cancer (Section 5.4.8.1);
- **analysis A8:** the manufacturer double counted population mortality by applying the rate of general mortality to both the patient trace and the number of patients experiencing each event (Section 5.4.9.3);
- **analysis A9:** the manufacturer erroneously applied a utility decrement of -0.1 for CTEPH within the model, rather than -0.12 as stated within the submission (Section 5.4.12.4);
- **analysis A10:** the manufacturer imputed an inflation factor for 2013-14 which the ERG considers to be unnecessary (Section 5.4.13.2);
- **analysis A11:** the manufacturer used list prices for warfarin cost, and did not consider the use of eMIT drug cost data (Section 5.4.13.2);
- **analysis A12:** the manufacturer used drug cost data for dalteparin that the ERG could not identify, and assumed that a single syringe per day would be sufficient for treatment (Section 5.4.13.2);
- **analysis A13:** the manufacturer erroneously presented the cost year for initial management of ICH at 2004, rather than 2002 (Section 5.4.13.5);

- **analysis A14:** the manufacturer attributed 50% cost of long term management of ICH to personal cost rather than NHS and PSS cost (Section 5.4.13.5);
- **analysis A15:** the manufacturer did not adjust the disutility of MBE and CRMBE to account for time, before summing as QALYs (Section 5.4.8.1);
- **analysis A16:** the manufacturer incorrectly applied warfarin disutility to patients off treatment.

5.5.2 ERG scenario analyses

In addition to the model corrections detailed in Section 5.5.1, the ERG carried out the following scenario analyses:

- **analysis B1:** including dyspepsia within the base case analysis and extending the experience of dyspepsia during the full duration of treatment and secondary prevention, using ERG estimated incidence of dyspepsia;
- **analysis B2:** 100% rivaroxaban prescribing at recurrence of VTE for both dabigatran and the selected comparator, note assuming no monitoring appointments for simplicity;
- **analysis B3:** Use of general population utility from Kind *et al.*, and assuming the starting age of patients in the model is 65;
- **analysis B4:** 100% LMWH prescribing at recurrence of VTE for the population with cancer;
- **analysis B5:** inclusion of secondary prevention at recurrence of VTE for the secondary prevention scenarios (qualitative assessment);
- **analysis B6:** 50% of patients experiencing a MBE and surviving return to treatment or secondary prevention, for simplicity, the 50% patients with an MBE who remained on treatment did so during the month of the event, and patients who were receiving re-treatment returned to month 1 of warfarin re-treatment;
- **analysis B7:** acute treatment duration set to 3 months;
- **analysis B8:** secondary prevention duration set to lifelong for the initial treatment.
- **analysis B9:** time horizon reduced to 50 years;
- **analysis B10**: use of ERG NMA results for recurrent VTE;
- **analysis B11:** use of a consistent figure for proportion of DVT and PE, set to equal dabigatran values in RE-COVER I and II, and RE-MEDY;
- **analysis B12:** use of 33.3% probability of developing CTEPH from Pengo *et al.(7)*;
- **analysis B13:** use of ERG NMA results for MBEs and CRNMBEs (note, where data are unavailable for LMWH in the population with cancer, these are set to equal the figures for dabigatran);

- **analysis B14:** use of a consistent figure for proportion of MBEs and CRNMBEs, set to equal dabigatran values in RE-COVER I and II, and RE-MEDY, and probability of death from MBE set to equal dabigatran values in RE-COVER I and II, and RE-MEDY;
- **analysis B15:** qualitative discussion of the impact of not accounting for death due to VTE or bleeding events for people with severe PTS or CTEPH;
- **analysis B16:** probability of dying from an ICH based upon figures in Rosand *et al*.*(77)*, at 39.5%;
- **analysis B17:** background mortality estimated from ERG figures and adjustment in model cohort age;
- **analysis B18:** inclusion of a risk of death from CTEPH (qualitative);
- **analysis B19:** qualitative appraisal of the impact of increasing INR control in the secondary prevention period;
- **analysis B20:** increase in utility decrement for PE to 0.265;
- **analysis B21:** duration of utility decrement for VTE set to one month (30 days);
- **analysis B22:** utility associated with VTE applied directly in the model (0.58);
- **analysis B23:** incidence of severe PTS set to 13.5%, assumed to apply over 5-years in order to be easily incorporated into the model engine;
- **analysis B24:** disutility associated with CTEPH set at -0.22;
- **analysis B25:** CTEPH disutility applied for the lifetime of patients;
- **analysis B26:** disutility associated with warfarin treatment removed from the secondary prevention period;
- **analysis B27:** disutility associated with LMWH treatment removed from the model;
- **analysis B28:** disutility associated with MBE set to -0.325;
- **analysis B29:** disutility associated with CRNMBE set to 0;
- **analysis B30:** disutility associated with ICH set alternatively to 1 and 0;
- **analysis B31:** cost of inpatient stay for DVT and PE set to £731.78 and £1,519.31 respectively;
- **analysis B32:** proportion of people with DVT and PE requiring an inpatient stay set to 33% and 80%;
- **analysis B33:** average body weight increased to 80kg;
- **analysis B34:** initial anticoagulation appointment for warfarin removed;
- **analysis B35:** warfarin monitoring in the secondary prevention period set to one appointment every three months;
- **analysis B36:** annual GP appointment for dabigatran and rivaroxaban included within the model, appointments were assumed to occur at 12 months, 24 months, 36 months and so

on until the end of the model, at a cost of £45 (per patient contact lasting 11.7 minutes, including costs of qualifications);

- **analysis B37:** cost of follow-up anticoagulation clinic attendance based upon non-consultant-led visits (£10.61);
- **analysis B38:** cost of non-fatal ICH set to £14,777;
- **analysis B39:** population with active cancer may include people with cancer up to five years prior to enrolment into the RE-COVER clinical trials, and may therefore not reflect the population with cancer in clinical practice;
- **analysis B40:** cost associated with CRNMBE set to £148;
- **analysis B41**: patients over 80 years of age or receiving concomitant verapamil, receiving a reduced dose of dabigatran (110mg twice daily) in clinical practice;
- **analysis B42**: discontinuation rates for dabigatran in secondary prevention set equal to those in RE-MEDY for all comparisons.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The Evidence Review Group (ERG) carried out a series of model corrections (Section 6.1), and scenario analyses (Section 6.2) on the manufacturer's model. In addition, the ERG presents a most plausible base case incremental cost-effectiveness ratio (ICER) estimate, for each of the relevant comparisons in this Single Technology Appraisal (STA) (Section 6.3).

6.1 Model corrections

Table 133 and Table 134 present the results of the model corrections undertaken by the ERG, as summarised in Section 5.5.1. After accounting for all model corrections, the ERG estimates that the ICERs are as follows.

For the **acute treatment** scenarios, for dabigatran versus:

- warfarin: £831
- rivaroxaban: £86,610 (south-west quadrant, dabigatran less costly and less effective)
- LMWH (population with cancer): £132,147 (south-west quadrant, dabigatran less costly and less effective)

For the **treatment and secondary prevention** scenarios, for dabigatran versus:

- warfarin: £9,973
- rivaroxaban: £17,248 (south-west quadrant, dabigatran less costly and less effective)
- LMWH (population with cancer): dabigatran is dominant (dabigatran less costly and more effective)

These results imply, for the acute treatment period, a slight reduction in the ICER for dabigatran versus warfarin, a modest increase in the ICER for dabigatran versus LMWH in the population with cancer (note, this implies an improvement of the ICER for dabigatran as the ICERs exist within the south-west quadrant), and a change from dabigatran dominance versus rivaroxaban (dabigatran less costly, more effective) to the south-west quadrant (dabigatran less costly, less effective).

For the treatment and secondary prevention period, these results imply a small overall increase in the ICER for dabigatran versus warfarin, no change in the comparison of dabigatran versus LMWH in the population with cancer (i.e. dabigatran remains less costly and more effective when compared with LMWH), and a change from dabigatran dominance versus rivaroxaban (dabigatran less costly, more effective) to the south-west quadrant (dabigatran less costly, less effective).

Table 133. Impact of ERG model corrections for acute treatment scenarios

Dabigatran versus >>>	Full population		Population with cancer
	Warfarin	Rivaroxaban	LMWH
Base case ICER (deterministic)	£862	Dabigatran dominant	£110,742 (SW quadrant)
Analysis A1 and A2	£857	Dabigatran dominant	£109,565 (SW quadrant)
Analysis A3	£862	Dabigatran dominant	£110,750 (SW quadrant)
Analysis A4	£862	Dabigatran dominant	£110,744 (SW quadrant)
Analysis A5 and A6	£921	Dabigatran dominant	£115,592 (SW quadrant)
Analysis A7	NA	NA	NA
Analysis A8	£862	Dabigatran dominant	£110,102 (SW quadrant)
Analysis A9	£862	Dabigatran dominant	£110,740 (SW quadrant)
Analysis A10	£1,164	Dabigatran dominant	£109,809 (SW quadrant)
Analysis A11	£1,128	Dabigatran dominant	£110,749 (SW quadrant)
Analysis A12	NA	NA	£88,159 (SW quadrant)
Analysis A13	£819	Dabigatran dominant	£110,653 (SW quadrant)
Analysis A14	£161	Dabigatran dominant	£110,037 (SW quadrant)
Analysis A15	£922	£115,100 (SW quadrant)	£165,787 (SW quadrant)
Analysis A16	£884	NA	NA
All model corrections	**£831**	**£86,610 (SW quadrant)**	**£132,147 (SW quadrant)**
Abbreviations used in table: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin; NA, not applicable; SW, south-west.			

Table 134. Impact of ERG model corrections for treatment and secondary prevention scenarios

Dabigatran versus >>>	Full population		Population with cancer
	Warfarin	Rivaroxaban	LMWH
Base case ICER (deterministic)	£8,319	Dabigatran dominant	Dabigatran dominant
Analysis A1 and A2	£8,308	Dabigatran dominant	Dabigatran dominant
Analysis A3	£8,319	Dabigatran dominant	Dabigatran dominant
Analysis A4	£8,318	Dabigatran dominant	Dabigatran dominant
Analysis A5 and A6	£8,436	£8,640 (SW quadrant)	Dabigatran dominant
Analysis A7	NA	NA	Dabigatran dominant
Analysis A8	£8,317	Dabigatran dominant	Dabigatran dominant
Analysis A9	£8,319	Dabigatran dominant	Dabigatran dominant
Analysis A10	£8,616	Dabigatran dominant	Dabigatran dominant
Analysis A11	£8,722	Dabigatran dominant	Dabigatran dominant
Analysis A12	NA	NA	Dabigatran dominant
Analysis A13	£8,281	Dabigatran dominant	Dabigatran dominant
Analysis A14	£7,726	Dabigatran dominant	Dabigatran dominant
Analysis A15	£8,876	£83,566 (SW quadrant)	Dabigatran dominant
Analysis A16	£9,082	NA	NA
All model corrections	**£9,973**	**£17,248 (SW quadrant)**	**Dabigatran dominant**
Abbreviations used in table: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin; NA, not applicable; SW, south-west.			

6.2 ERG scenario analyses

Table 135 and Table 136 present the results of the model scenario analyses undertaken by the ERG, as summarised in Section 5.5.2.

The ERG notes that, in the comparison of dabigatran versus warfarin in the full population, no individual scenario was identified in which the ICER increased above approximately £6,000 (acute treatment scenario) and £15,000 (treatment and secondary prevention scenario). The ERG considers that, for the comparison of dabigatran versus warfarin, the model was most sensitive to changes in:

- a reduction in cost of warfarin monitoring, either through a decreased cost of monitoring, or through removal of the initial monitoring appointment;
- a reduction in the duration of acute treatment to 3 months;
- an increase in the incidence of CTEPH.

The ERG notes that the increase in the incidence of CTEPH via analysis B12 is likely to be overstated, consequently, the ERG considers the results associated with this analysis are likely to overestimate the ICER.

For the comparison of dabigatran versus rivaroxaban in the full population, dabigatran was found to be dominant (less costly and more effective) in the majority of the individual scenarios modelled. However, the ERG notes that a number of scenarios resulted in a switch from dominance, to dabigatran being less costly and less effective than rivaroxaban. These included:

- increase in severe PTS incidence (acute treatment scenario only);
- increase in disutility associated with MBEs (acute treatment scenario only);
- removal of warfarin disutility (secondary prevention scenario only);
- decrease in disutility associated with CRNMBEs.

Finally, for the comparison of dabigatran versus LMWH in the population with cancer, the ERG notes that model results for the acute treatment scenario and the treatment and secondary prevention scenario remained essentially unchanged with all individual analyses carried out. That is, in the acute treatment scenario, all explored sensitivity analyses resulted in an ICER where dabigatran was less costly and less effective than LMWH, as in the manufacturer's base case. Similarly, in the treatment and secondary prevention scenario dabigatran remained the dominant treatment option when compared to LMWH in the population with cancer for all modelled scenarios.

Table 135. Impact of ERG scenario analyses for acute treatment scenarios

Dabigatran versus >>>	Full population		Population with cancer
	Warfarin	Rivaroxaban	LMWH
Base case ICER (deterministic)	£862	Dabigatran dominant	£110,742 (SW quadrant)
Analysis B1 (dyspepsia)	£896	Dabigatran dominant	£110,376 (SW quadrant)
Analysis B2 (rivaroxaban at recurrence)	£860	Dabigatran dominant	£116,533 (SW quadrant)
Analysis B3 (use of Kind et al and change in model cohort age)	£1,301	Dabigatran dominant	£128,013 (SW quadrant)
Analysis B4 (LMWH at recurrence)	NA	NA	£113,776 (SW quadrant)
Analysis B5 (warfarin secondary prevention)	NA	NA	NA
Analysis B6 (50% MBEs return to treatment)	£861	Dabigatran dominant	£110,703 (SW quadrant)
Analysis B7 (acute treatment duration 3 months)	Dabigatran dominant	Dabigatran dominant	£53,148 (SW quadrant)
Analysis B8 (extending secondary prevention to lifelong)	NA	NA	NA
Analysis B9 (50 year time horizon)	£862	Dabigatran dominant	£110,747 (SW quadrant)
Analysis B10 (ERG NMA results for VTE)	£913	Dabigatran dominant	£142,357 (SW quadrant)
Analysis B11 (consistent proportion of VTE events)	£1,032	£21,055	£115,744 (SW quadrant)
Analysis B12 (CTEPH incidence set to 33.3%)	£4,144	Dabigatran dominant	£99,652 (SW quadrant)
Analysis B13 (ERG NMA results for bleeding)	£646	Dabigatran dominant	>£1 million (SW quadrant)
Analysis B14 (consistent proportion of bleeding events)	£2,244	Dabigatran dominant	£305,637 (SW quadrant)
Analysis B15 (possible overestimate of CTEPH and severe PTS patients)	Unclear	Unclear	Unclear
Analysis B16 (rate of death from ICH set at 39.5%)	£404	Dabigatran dominant	£114,400 (SW quadrant)
Analysis B17 (ERG probability of death and change in model cohort age to 65 years)	£1,256	Dabigatran dominant	£66,626 (SW quadrant)
Analysis B18 (risk of death associated with CTEPH)	Likely direction of bias: unclear, but likely to be small. Dabigatran has similar rates of CTEPH compared with warfarin.	Likely direction of bias: unclear. Dabigatran has lower rates of CTEPH compared with rivaroxaban; therefore	Likely direction of bias: unclear. Dabigatran has higher rates of CTEPH compared with LMWH; therefore relative QALYs

		relative QALYs will improve, but relative costs will worsen.	will worsen, but relative costs will improve.
Analysis B19 (INR control)	NA	NA	NA
Analysis B20 (disutility associated with PE set to 0.265)	£862	Dabigatran dominant	£110,696 (SW quadrant)
Analysis B21 (disutility applied for 30 days)	£862	Dabigatran dominant	£112,127 (SW quadrant)
Analysis B22 (utility associated with VTE applied directly in the engine)	£1,156	£2,109 (SW quadrant)	£40,143 (SW quadrant)
Analysis B23 (incidence of severe PTS set to 13.5% over 5 years)	£876	£88,751 (SW quadrant)	£106,733 (SW quadrant)
Analysis B24 (CTEPH disutility from Meads et al)	£862	Dabigatran dominant	£110,732 (SW quadrant)
Analysis B25 (lifetime disutility associated with CTEPH)	£864	Dabigatran dominant	£109,984 (SW quadrant)
Analysis B26 (no warfarin disutility in the secondary prevention period)	NA	NA	NA
Analysis B27 (no LMWH disutility)	NA	NA	£80,896 (SW quadrant)
Analysis B28 (disutility associated with MBEs - 0.325)	£828	£21,015 (SW quadrant)	£67,543 (SW quadrant)
Analysis B29 (no disutility associated with CRNMBEs)	£901	£19,629 (SW quadrant)	£104,063 (SW quadrant)
Analysis B30 (disutility set to 0)	£1,158	£25,931 (SW quadrant)	£148,928 (SW quadrant)
Analysis B30 (disutility set to 1)	£687	Dabigatran dominant	£88,142 (SW quadrant)
Analysis B31 (alternative cost of hospitalisation)	£852	Dabigatran dominant	£110,889 (SW quadrant)
Analysis B32 (alternative proportions of inpatient stay)	£841	Dabigatran dominant	£110,925 (SW quadrant)
Analysis B33 (body weight 80kgs)	£862	Dabigatran dominant	£110,491 (SW quadrant)
Analysis B34 (initial anticoagulation appointment for warfarin removed)	£3,345	Dabigatran dominant	£110,813 (SW quadrant)
Analysis B35 (appointments in the secondary prevention period reduced to once every three months)	NA	NA	NA
Analysis B36 (annual monitoring for	NA	NA	NA

dabigatran and rivaroxaban)			
Analysis B37 (non-consultant led follow-up visits)	£6,212	Dabigatran dominant	£111,994 (SW quadrant)
Analysis B38 (cost of severe stroke £14,777)	£642	Dabigatran dominant	£110,287 (SW quadrant)
Analysis B39 (definition of cancer patients in the RE-COVER clinical trials)	NA	NA	Unclear
Analysis B40 (cost of CRNMBE set at £148)	£1,130	Dabigatran dominant	£110,345 (SW quadrant)
Analysis B41 (reduced dose of dabigatran)	Unclear	Unclear	Unclear
Analysis B42 (secondary prevention discontinuation rates)	NA	NA	NA
Abbreviations used in table: ERG, Evidence Review Group; CRNMBE, clinically relevant non-major bleeding event; CTEPH, chronic thromboembolic pulmonary hypertension; ICER, incremental cost-effectiveness ratio; ICH, intra-cranial haemorrhage; INR, international normalised ratio; LMWH, low-molecular-weight heparin; MBE, major bleeding event; NA, not applicable; NMA, network meta-analysis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QALY, quality-adjusted life year; SW, south-west; VTE, venous thromboembolism.			

Table 136. Impact of ERG scenario analyses for treatment and secondary prevention scenarios

Dabigatran versus >>>	Full population		Population with cancer
	Warfarin	Rivaroxaban	LMWH
Base case ICER (deterministic)	£8,319	Dabigatran dominant	Dabigatran dominant
Analysis B1 (dyspepsia)	£8,416	Dabigatran dominant	Dabigatran dominant
Analysis B2 (rivaroxaban at recurrence)	£8,300	Dabigatran dominant	Dabigatran dominant
Analysis B3 (use of Kind et al and change in model cohort age)	£9,528	Dabigatran dominant	Dabigatran dominant
Analysis B4 (LMWH at recurrence)	NA	NA	Dabigatran dominant
Analysis B5 (warfarin secondary prevention)	Unclear; number of patients receiving warfarin at recurrence depends upon rates of recurrence on treatment (generally higher for dabigatran), and rates of recurrence off treatment (affected by number of people discontinuing treatment due to bleeds, generally lower for dabigatran). As all modelled comparators result in warfarin re-treatment at secondary prevention, the ERG considers it possible that any differences will be small.		
Analysis B6 (50% MBEs return to treatment)	£8,381	Dabigatran dominant	Dabigatran dominant
Analysis B7 (acute treatment duration 3 months)	£6,032	Dabigatran dominant	Dabigatran dominant
Analysis B8 (extending secondary prevention to lifelong)	£6,868	£157	Dabigatran dominant
Analysis B9 (50 year time horizon)	£8,319	Dabigatran dominant	Dabigatran dominant
Analysis B10 (ERG NMA results for VTE)	£7,800	Dabigatran dominant	Dabigatran dominant
Analysis B11 (consistent proportion of VTE events)	£9,293	Dabigatran dominant	Dabigatran dominant
Analysis B12 (CTEPH incidence set to 33.3%)	£14,631	Dabigatran dominant	Dabigatran dominant
Analysis B13 (ERG NMA results for bleeding)	£9,281	Dabigatran dominant	Dabigatran dominant
Analysis B14 (consistent proportion of bleeding events)	£11,394	Dabigatran dominant	Dabigatran dominant
Analysis B15 (possible overestimate of CTEPH and severe PTS patients)	Unclear	Unclear	Unclear
Analysis B16 (rate of death from ICH set at 39.5%)	£6,381	Dabigatran dominant	Dabigatran dominant
Analysis B17 (ERG probability of death and change in model cohort age to 65 years)	£9,405	Dabigatran dominant	Dabigatran dominant

Analysis B18 (risk of death associated with CTEPH)	Likely direction of bias: unclear. Dabigatran has higher rates of CTEPH compared with warfarin; therefore relative QALYs will worsen, but relative costs will improve.	Likely direction of bias: unclear. Dabigatran has lower rates of CTEPH compared with rivaroxaban; therefore relative QALYs will improve, but relative costs will worsen.	Likely direction of bias: unclear. Dabigatran has lower rates of CTEPH compared with rivaroxaban; therefore relative QALYs will improve, but relative costs will worsen.
Analysis B19 (improvement in INR control)	ICER likely to be underestimated, as an improvement in INR control would likely lead to fewer VTE events and fewer bleeds. The degree of the bias is unclear.	NA	NA
Analysis B20 (disutility associated with PE set to 0.265)	£8,320	Dabigatran dominant	Dabigatran dominant
Analysis B21 (disutility applied for 30 days)	£8,309	Dabigatran dominant	Dabigatran dominant
Analysis B22 (utility associated with VTE applied directly in the engine)	£11,878	Dabigatran dominant	Dabigatran dominant
Analysis B23 (incidence of severe PTS set to 13.5% over 5-years)	£8,365	Dabigatran dominant	Dabigatran dominant
Analysis B24 (CTEPH disutility from Meads et al)	£8,319	Dabigatran dominant	Dabigatran dominant
Analysis B25 (lifetime disutility associated with CTEPH)	£8,352	Dabigatran dominant	Dabigatran dominant
Analysis B26 (no warfarin disutility in the secondary prevention period)	£12,367	NA	NA
Analysis B27 (no LMWH disutility)	NA	NA	Dabigatran dominant
Analysis B28 (disutility associated with MBEs - 0.325)	£7,993	Dabigatran dominant	Dabigatran dominant
Analysis B29 (no disutility associated with CRNMBEs)	£8,678	£77,202 (SW quadrant)	Dabigatran dominant
Analysis B30 (disutility set to 0)	£10,605	Dabigatran dominant	Dabigatran dominant
Analysis B30 (disutility set to 1)	£6,843	Dabigatran dominant	Dabigatran dominant
Analysis B31 (alternative cost of hospitalisation)	£8,310	Dabigatran dominant	Dabigatran dominant
Analysis B32 (alternative proportions of inpatient stay)	£8,295	Dabigatran dominant	Dabigatran dominant
Analysis B33 (body weight 80kgs)	£8,319	Dabigatran dominant	Dabigatran dominant

Analysis B34 (initial anticoagulation appointment for warfarin removed)	£9,395	Dabigatran dominant	Dabigatran dominant
Analysis B35 (appointments in the secondary prevention period reduced to once every three months)	£12,859	Dabigatran dominant	Dabigatran dominant
Analysis B36 (annual monitoring for dabigatran and rivaroxaban)	£9,496	Dabigatran dominant	Dabigatran dominant
Analysis B37 (non-consultant led follow-up visits)	£14,867	Dabigatran dominant	Dabigatran dominant
Analysis B38 (cost of severe stroke £14,777)	£8,126	Dabigatran dominant	Dabigatran dominant
Analysis B39 (definition of cancer patients in the RE-COVER clinical trials)	NA	NA	Unclear
Analysis B40 (cost of CRNMBE set at £148)	£8,575	Dabigatran dominant	Dabigatran dominant
Analysis B41 (reduced dose of dabigatran)	Unclear	Unclear	Unclear
Analysis B42 (secondary prevention discontinuation rates)	NA	Dabigatran dominant	NA
Abbreviations used in table: ERG, Evidence Review Group; CRNMBE, clinically relevant non-major bleeding event; CTEPH, chronic thromboembolic pulmonary hypertension; ICER, incremental cost-effectiveness ratio; ICH, intra-cranial haemorrhage; INR, international normalised ratio; LMWH, low-molecular-weight heparin; MBE, major bleeding event; NA, not applicable; NMA, network meta-analysis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; QALY, quality-adjusted life year; SW, south-west; VTE, venous thromboembolism.			

6.3 ERG base case ICER

Based upon the model corrections and a selection of the scenario analyses outlined above in Section 6.1 and Section 6.2, the ERG presents below an ERG base case ICER for the comparisons of dabigatran versus warfarin, and dabigatran versus rivaroxaban in the full population for the acute treatment scenario and the treatment and secondary prevention scenario.

The ERG has omitted an estimate of an ICER for the comparison of dabigatran with LMWH in the population with cancer. This is because the ERG has concerns over the reliability of the data, and therefore the applicability of the findings for this comparison. Specifically, it is unclear whether the population contained within RE-COVER I and II represent the population with cancer seen in clinical practice (Section 4), and the ERG further notes that the ERG NMA found insufficient evidence to populate bleeding event data for LMWH and dabigatran in the population with cancer (Section 4.9). The ERG considered deterministic results only. This was for simplicity because the manufacturer's model results were consistent between deterministic and probabilistic results. The ERG notes that the

manufacturer's base case results for dabigatran versus LMWH were robust to the majority of analyses undertaken by the ERG.

The ERG results are presented in more detail in Table 139 to Table 142. These outline the ERG base case ICER for the comparisons of dabigatran versus warfarin, and dabigatran versus rivaroxaban in the acute treatment scenario and the treatment and secondary prevention scenario. The tables include the incremental effect of including the following scenarios:

- all model corrections (Section 6.1);
- analysis B6, 50% of patients surviving an MBE return to treatment;
- analysis B8, lifelong secondary prevention for the initial event (secondary prevention only);
- analysis B9, time horizon reduced to 50 years;
- analysis B10, ERG NMA results for VTE recurrence;
- analysis B11, consistent proportion of VTE events;
- analysis B13, ERG NMA results for bleeding events;
- analysis B14, consistent proportion of bleeding events;
- analysis B16, probability of death due to ICH based upon figures in Rosand *et al.* at 39.5%;
- analysis B17, background mortality estimated from ERG figures and adjustment in model cohort age to 65 years old at model start;
- analysis B20, increase in utility decrement for PE to 0.265
- analysis B21, VTE disutility applied for 30 days rather than 6 weeks;
- analysis B34, initial anticoagulation appointment removed for warfarin;
- analysis B35, warfarin monitoring in the secondary prevention period set to one appointment every three months
- analysis B37, non-consultant led follow-up visits for warfarin;
- analysis B38, cost of non-fatal ICH set to £14,777
- analysis B42, discontinuation rate for dabigatran set equal to the value in RE-MEDY (secondary prevention only).

Acute treatment scenario

The deterministic ICERs for dabigatran versus warfarin and dabigatran versus rivaroxaban in the acute treatment scenario were estimated to be:

- £18,240 per additional QALY (dabigatran versus warfarin);
- dabigatran dominates rivaroxaban.

The incremental results are presented in Table 137.

The results correspond to the manufacturer's results for the comparison of dabigatran versus rivaroxaban; the manufacturer also estimated that dabigatran was dominant (less costly and more effective) when compared with rivaroxaban. The ERG considers it important to note that the cost difference estimated through this analysis was £3 per patient over the lifetime of the model, with a QALY difference of 0.0018. Thus, the ERG notes that dabigatran and rivaroxaban are associated with very similar costs and consequences.

The estimate for dabigatran versus warfarin differs to the manufacturer's estimate of £862 per additional QALY. The ERG considers that the single largest driver of this difference was the reduction in cost associated with warfarin monitoring as a result of assuming that follow-up visits would be non-consultant led.

Table 137. ERG base case results for the acute treatment scenario

Intervention	Total cost	Total QALYs	Incremental cost per patient	Incremental QALYs per patient	ICER versus previous non-dominated intervention
Warfarin	£5,440	9.820	–	–	–
Dabigatran	£5,663	9.833	£223	0.012	£18,240
Rivaroxaban	£5,666	9.833	£3	-0.0018	Dabigatran dominates
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

Treatment and secondary prevention scenario

The deterministic ICERs for dabigatran versus warfarin and dabigatran versus rivaroxaban in the acute treatment scenario were fully incremental, and estimated to be:

- rivaroxaban extendedly dominated by dabigatran;
- £35,768 per additional QALY (dabigatran versus warfarin).

The incremental results are presented in Table 138.

The estimate for dabigatran versus warfarin differs to the manufacturer's estimate of £8,319 per additional QALY. The ERG considers that the largest drivers of this difference were: an increase in cost associated with dabigatran from lifelong secondary prevention for the initial event; a reduction in the cost associated with warfarin monitoring by assuming one appointment every three months rather than every month in the secondary prevention period; a reduction in cost associated with warfarin monitoring as a result of assuming that follow-up visits would be non-consultant led.

Table 138. ERG base case results for the treatment and secondary prevention scenario

Intervention	Total cost	Total QALYs	Incremental cost per patient	Incremental QALYs per patient	ICER versus previous non-dominated intervention
Warfarin	£5,676	9.935	–	–	
Rivaroxaban	£8,386	9.955	£2,710	0.020	Extendedly dominated by dabigatran
Dabigatran	£9,006	10.028	£3,331	0.093	£35,768
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

The ERGs revised base case ICER did not incorporate the removal of warfarin disutility in the secondary prevention period. This is because the ERG is not clear what value is most appropriate to capture the HRQoL impact of warfarin treatment. The ERG notes that this parameter is a key driver in the ERG base case result, and removal of the disutility associated with warfarin treatment in the secondary prevention period results in a large increase in the ICER associated with the comparison of dabigatran and warfarin, to approximately £90,000 per additional QALY. This is because the model with the ERG scenarios incorporated is increasingly sensitive to changes in QALYs.

Table 139. Dabigatran versus warfarin, acute treatment scenario, deterministic results

Scenario	Total cost (dabigatran)	Total cost (warfarin)	Incremental cost per patient	Total QALYs (dabigatran)	Total QALYs (warfarin)	Incremental QALYs per patient	ICER	Cumulative ICER
Base case ICER	£7,503	£7,482	£21	12.452	12.428	0.024	£862	**NA**
All model corrections	£7,363	£7,345	£18	12.456	12.435	0.022	£831	**NA**
All subsequent analyses include model corrections								
B6, 50% of patients surviving an MBE return to treatment	£7,367	£7,349	£18	12.457	12.435	0.022	£833	**£833**
B8, lifelong secondary prevention for the initial event (secondary prevention only)	NA							
B9, time horizon reduced to 50 years	£7,362	£7,344	£18	12.456	12.435	0.022	£831	**£833**
B10, ERG NMA results for VTE recurrence	£7,371	£7,352	£19	12.457	12.436	0.022	£892	**£893**
B11, consistent proportion of VTE events	£7,361	£7,345	£17	12.456	12.440	0.016	£1,016	**£1,102**
B13, ERG NMA results for bleeding events	£7,388	£7,379	£9	12.454	12.433	0.022	£420	**£533**
B14, consistent proportion of bleeding events	£7,351	£7,302	£49	12.458	12.442	0.016	£3,044	**£5,471**
B16, probability of death due to ICH based upon figures in Rosand *et al.* at 39.5%	£7,337	£7,331	£5	12.456	12.428	0.028	£194	**£2,617**
B17, background mortality estimated from ERG figures and adjustment in model cohort age to 65 years old at model start	£5,860	£5,834	£27	9.820	9.802	0.018	£1,439	**£3,448**
B20, increase in utility	£7,363	£7,345	£18	12.456	12.434	0.022	£831	**£3,448**

decrement for PE to 0.265								
B21, VTE disutility applied for 30 days	£7,363	£7,345	£18	12.471	12.449	0.022	£830	**£3,442**
B34, initial anticoagulation appointment removed for warfarin	£7,297	£7,221	£76	12.456	12.435	0.022	£3,514	**£8,226**
B35, warfarin monitoring in the secondary prevention period set to one appointment every three months	NA							
B37, non-consultant led follow-up visits for warfarin	£7,191	£7,049	£142	12.456	12.435	0.022	£6,533	**£18,401**
B38, cost of non-fatal ICH set to £14,777	£7,369	£7,356	£14	12.456	12.435	0.022	£625	**£18,240**
B42, discontinuation rate for dabigatran set equal to the value in RE-MEDY (secondary prevention only)	NA							
Summary of cumulative ICER								
All analyses	£5,663	£5,440	£223	9.833	9.820	0.012	£18,240	**NA**
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ICH, intra-cranial haemorrhage; MBE, major bleeding event; NA, not applicable; NMA, network meta-analysis; QALY, quality-adjusted life year; PE, pulmonary embolism; VTE, venous thromboembolism.								

Table 140. Dabigatran versus rivaroxaban, acute treatment scenario, deterministic results

Scenario	Total cost (dabigatran)	Total cost (rivaroxaban)	Incremental cost per patient	Total QALYs (dabigatran)	Total QALYs (rivaroxaban)	Incremental QALYs per patient	ICER	Cumulative ICER
Base case ICER	£7,503	£7,523	-£20	12.452	12.451	0.0003	Dabigatran is dominant	**NA**
All model corrections	£7,363	£7,384	-£22	12.456	12.457	-0.0003	£81,610 (SW quadrant)	**NA**

All subsequent analyses include model corrections								
B6, 50% of patients surviving an MBE return to treatment	£7,367	£7,388	-£21	12.457	12.457	-0.0002	£102,774 (SW quadrant)	**£102,774 (SW quadrant)**
B8, lifelong secondary prevention for the initial event (secondary prevention only)	NA							
B9, time horizon reduced to 50 years	£7,362	£7,384	-£22	12.456	12.456	-0.0003	£81,608 (SW quadrant)	**£102,772 (SW quadrant)**
B10, ERG NMA results for VTE recurrence	£7,371	£7,395	-£24	12.457	12.457	-0.0002	£103,085 (SW quadrant)	**£136,324 (SW quadrant)**
B11, consistent proportion of VTE events	£7,361	£7,334	£27	12.456	12.456	0.0009	£30,197	**£26,610**
B13, ERG NMA results for bleeding events	£7,388	£7,413	-£26	12.454	12.453	0.0018	Dabigatran dominates	**£7,747**
B14, consistent proportion of bleeding events	£7,351	£7,403	-£52	12.458	12.458	0.0008	Dabigatran dominates	**Rivaroxaban dominates**
B16, probability of death due to ICH based upon figures in Rosand *et al.* at 39.5%	£7,337	£7,372	-£35	12.456	12.454	0.0018	Dabigatran dominates	**Dabigatran dominates**
B17, background mortality estimated from ERG figures and adjustment in model cohort age to 65 years old at model start	£5,860	£5,874	-£14	9.820	9.820	-0.0002	£61,935 (SW quadrant)	**Dabigatran dominates**
B20, increase in utility decrement for PE to 0.265	£7,363	£7,384	-£22	12.456	12.456	-0.0003	£83,130 (SW quadrant)	**Dabigatran dominates**
B21, VTE disutility applied for 30 days	£7,363	£7,384	-£22	12.471	12.471	-0.0002	£95,344 (SW quadrant)	**Dabigatran dominates**
B34, initial anticoagulation appointment removed for warfarin	£7,297	£7,319	-£22	12.456	12.457	-0.0003	£82,140 (SW quadrant)	**Dabigatran dominates**
B35, warfarin monitoring in	NA							

the secondary prevention period set to one appointment every three months								
B37, non-consultant led follow-up visits for warfarin	£7,191	£7,212	-£21	12.456	12.457	-0.0003	£80,379 (SW quadrant)	**Dabigatran dominates**
B38, cost of non-fatal ICH set to £14,777	£7,369	£7,392	-£23	12.456	12.457	-0.0003	£85,033 (SW quadrant)	**Dabigatran dominates**
B42, discontinuation rate for dabigatran set equal to the value in RE-MEDY (secondary prevention only)	NA							
Summary of cumulative ICER								
All analyses	£5,663	£5,666	-£3	9.833	9.831	0.0018	Dabigatran dominates	**NA**
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ICH, intra-cranial haemorrhage; MBE, major bleeding event; NA, not applicable; NMA, network meta-analysis; QALY, quality-adjusted life year; PE, pulmonary embolism; VTE, venous thromboembolism.								

Table 141. Dabigatran versus warfarin, treatment and secondary prevention, deterministic results

Scenario	Total cost (dabigatran)	Total cost (warfarin)	Incremental cost per patient	Total QALYs (dabigatran)	Total QALYs (warfarin)	Incremental QALYs per patient	ICER	Cumulative ICER
Base case ICER	£8,319	£7,861	£458	12.519	12.464	0.0551	£8,319	**NA**
All model corrections	£8,198	£7,733	£466	12.526	12.479	0.0467	£9,973	**NA**
All subsequent analyses include model corrections								
B6, 50% of patients surviving an MBE return to treatment	£8,211	£7,743	£468	12.527	12.480	0.0468	£10,013	**£10,013**
B8, lifelong secondary prevention for the initial event (secondary prevention only)	£10,822	£8,958	£1,864	12.715	12.595	0.1193	£15,634	**£15,789**
B9, time horizon reduced to	£8,198	£7,732	£466	12.526	12.479	0.0467	£9,973	**£15,789**

50 years								
B10, ERG NMA results for VTE recurrence	£8,178	£7,730	£449	12.530	12.482	0.0481	£9,336	**£14,622**
B11, consistent proportion of VTE events	£8,197	£7,746	£451	12.526	12.487	0.0393	£11,481	**£15,654**
B13, ERG NMA results for bleeding events	£8,212	£7,742	£470	12.525	12.482	0.0428	£10,996	**£18,709**
B14, consistent proportion of bleeding events	£8,188	£7,682	£505	12.528	12.494	0.0340	£14,875	**£24,878**
B16, probability of death due to ICH based upon figures in Rosand *et al.* at 39.5%	£8,152	£7,718	£433	12.522	12.462	0.0599	£7,237	**£17,409**
B17, background mortality estimated from ERG figures and adjustment in model cohort age to 65 years old at model start	£6,690	£6,216	£474	9.874	9.833	0.0407	£11,647	**£19,580**
B20, increase in utility decrement for PE to 0.265	£8,198	£7,733	£466	12.525	12.478	0.0467	£9,974	**£19,581**
B21, VTE disutility applied for 30 days	£8,198	£7,733	£466	12.540	12.493	0.0467	£9,959	**£19,563**
B34, initial anticoagulation appointment removed for warfarin	£8,136	£7,613	£524	12.526	12.479	0.0467	£11,215	**£20,184**
B35, warfarin monitoring in the secondary prevention period set to one appointment every three months	£8,198	£7,488	£710	12.526	12.479	0.0467	£15,208	**£31,238**
B37, non-consultant led follow-up visits for warfarin	£8,035	£7,221	£813	12.526	12.479	0.0467	£17,419	**£35,942**
B38, cost of non-fatal ICH set to £14,777	£8,209	£7,752	£457	12.526	12.479	0.0467	£9,781	**£35,768**

B42, discontinuation rate for dabigatran set equal to the value in RE-MEDY (secondary prevention only)	£8,198	£7,733	£466	12.526	12.479	0.0467	£9,973	**£35,768**
Summary of cumulative ICER								
All analyses	£9,006	£5,676	£3,331	10.028	9.935	0.0931	£35,768	**NA**
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ICH, intra-cranial haemorrhage; MBE, major bleeding event; NA, not applicable; NMA, network meta-analysis; QALY, quality-adjusted life year; PE, pulmonary embolism; VTE, venous thromboembolism.								

Table 142. Dabigatran versus rivaroxaban, treatment and secondary prevention, deterministic results

Scenario	Total cost (dabigatran)	Total cost (rivaroxaban)	Incremental cost per patient	Total QALYs (dabigatran)	Total QALYs (rivaroxaban)	Incremental QALYs per patient	ICER	Cumulative ICER
Base case ICER	£7,785	£7,852	-£67	12.480	12.478	0.0020	Dabigatran dominates	**NA**
All model corrections	£7,665	£7,688	-£23	12.486	12.487	-0.0013	£17,248 (SW quadrant)	**NA**
All subsequent analyses include model corrections								
B6, 50% of patients surviving an MBE return to treatment	£7,672	£7,693	-£21	12.486	12.488	-0.0012	£17,887 (SW quadrant)	**£17,887 (SW quadrant)**
B8, lifelong secondary prevention for the initial event (secondary prevention only)	£10,073	£9,847	£226	12.699	12.687	0.0120	£18,915	**£18,423**
B9, time horizon reduced to 50 years	£7,665	£7,688	-£23	12.486	12.487	-0.0013	£17,247 (SW quadrant)	**£18,424**
B10, ERG NMA results for VTE recurrence	£7,668	£7,681	-£13	12.487	12.489	-0.0017	£7,902 (SW quadrant)	**£58,110**
B11, consistent proportion of VTE events	£7,663	£7,642	£22	12.484	12.482	0.0021	£10,291	**£26,553**
B13, ERG NMA results for	£7,658	£7,709	-£51	12.484	12.483	0.0010	Dabigatran	**£5,249**

bleeding events							dominates	
B14, consistent proportion of bleeding events	£7,782	£7,768	£14	12.477	12.482	-0.0051	Rivaroxaban dominates	**Dabigatran dominates**
B16, probability of death due to ICH based upon figures in Rosand *et al.* at 39.5%	£7,639	£7,676	-£36	12.485	12.485	0.0007	Dabigatran dominates	**Dabigatran dominates**
B17, background mortality estimated from ERG figures and adjustment in model cohort age to 65 years old at model start	£6,166	£6,179	-£13	9.843	9.844	-0.0011	£12,056 (SW quadrant)	**Dabigatran dominates**
B20, increase in utility decrement for PE to 0.265	£7,665	£7,688	-£23	12.485	12.486	-0.0013	£17,335 (SW quadrant)	**Dabigatran dominates**
B21, VTE disutility applied for 30 days	£7,665	£7,688	-£23	12.500	12.501	-0.0013	£17,289 (SW quadrant)	**Dabigatran dominates**
B34, initial anticoagulation appointment removed for warfarin	£7,601	£7,624	-£23	12.486	12.487	-0.0013	£17,313 (SW quadrant)	**Dabigatran dominates**
B35, warfarin monitoring in the secondary prevention period set to one appointment every three months	NA							
B37, non-consultant led follow-up visits for warfarin	£7,496	£7,518	-£22	12.486	12.487	-0.0013	£16,916 (SW quadrant)	**Dabigatran dominates**
B38, cost of non-fatal ICH set to £14,777	£7,671	£7,695	-£24	12.486	12.487	-0.0013	£17,944 (SW quadrant)	**Dabigatran dominates**
B42, discontinuation rate for dabigatran set equal to the value in RE-MEDY (secondary prevention only)	£7,670	£7,688	-£18	12.486	12.487	-0.0010	£18,077 (SW quadrant)	**£8,473**
Summary of cumulative ICER								
All analyses	£9,006	£8,386	£621	10.028	9.955	0.0733	£8,473	**NA**

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; ICH, intra-cranial haemorrhage; MBE, major bleeding event; NA, not applicable; NMA, network meta-analysis; QALY, quality-adjusted life year; PE, pulmonary embolism; VTE, venous thromboembolism.

7 OVERALL CONCLUSIONS

7.1 Summary of clinical-effectiveness issues

The manufacturer presents data for the safety and efficacy of dabigatran in the acute treatment (0 to 6 months post VTE) and long-term secondary prevention of VTE (over 3 months after acute VTE) based on four clinical trials. The ERG considers the four dabigatran trials, RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE, presented in the MS for this STA, to be well conducted, international, double-blind, RCTs.

The primary efficacy endpoint of the four key trials presented in the MS was the composite of recurrent symptomatic VTE and deaths related to VTE (RE-SONATE also included unexplained deaths as they were deemed to be a result of fatal PE). Dabigatran was proven to be non-inferior to warfarin (RE-COVER, RE-COVER II and RE-MEDY), and superior to placebo (RE-SONATE) for acute treatment and secondary prevention of VTE (DVT and PE).

The manufacturer also conducted extensive subgroup analyses to demonstrate consistency of the treatment effect of dabigatran. Subgroup data according to index VTE event (i.e. PE or DVT) demonstrated no significant difference in the efficacy of dabigatran in relation to prevention of VTE and VTE-related mortality. The results of the subgroup analyses by cTTR suggested that the safety and efficacy of dabigatran compared with warfarin were independent of the level of warfarin control, i.e. %TTR. In addition, the manufacturer submitted additional data for a comparator, placebo, which was not specified in the final scope issued by NICE.

The ERG notes that PTS, heart failure and CTEPH were listed as outcomes of interest in the final scope issued by NICE and were not presented as outcomes in the clinical effectiveness data of the MS. However, the ERG acknowledges that data for these outcomes were not specifically collected in RE-COVER, RE-COVER II, RE-MEDY or RE-SONATE. The effectiveness of dabigatran in reducing the VTE related adverse effects of PTS, heart failure and CTEPH is thus an area of uncertainty. In addition, there is an absence of long-term HRQoL data for dabigatran in acute treatment and secondary prevention of VTE.

The ERG also considers it important to highlight that the manufacturer did not present any clinical trial data for the safety or efficacy of the 110 mg BD dose of dabigatran although this is likely to be the recommended dose of dabigatran for people aged over 80 years or those on concomitant verapamil. The ERG therefore considers the effectiveness of 110 mg BD dabigatran in VTE prevention is unknown.

The ERG note that there are currently no direct head-to-head data for dabigatran versus rivaroxaban and so the ability to draw conclusions for this comparison is limited by the uncertainty around the indirect effect estimates generated from the AICs and NMAs.

With respect to the subgroup of people with cancer, the ERG notes that the population of the dabigatran trials comprised only of a small number of people with active cancer. In addition, the definition of active cancer used in the dabigatran trials was broader than that used in UK clinical practice according to the ERGs clinical advisers. The ERG also notes that there are currently no head-to-head clinical trials for the comparison of dabigatran versus rivaroxaban or dabigatran versus LMWH in people with active cancer. The limited data provided within the MS is thus from indirect comparisons and associated with large amounts of uncertainty. The ERG thus considers that head-to-head trials are required to address the question of the effectiveness of dabigatran in VTE prevention in people with cancer.

The manufacturer used data from head-to-head trials for the comparison with warfarin and from AICs for comparison with rivaroxaban and LMWH. As no single analysis encapsulated all treatments of interest, this meant the manufacturer performed separate economic evaluations for each individual comparison rather than one analysis of all comparisons. This led to the results from the manufacturer's economic model not being comparable with one another and not being able to be presented as fully incremental results. The ERG conducted an exploratory NMA, which was used as the basis for a health economic scenario analysis.

7.2 Summary of cost-effectiveness issues

The manufacturer developed a *de novo* Markov cost-utility model to investigate the cost-effectiveness of dabigatran compared with warfarin and rivaroxaban in the full population, and LMWH monotherapy in a population with cancer, for:

- the acute treatment of people with a confirmed proximal DVT or PE (with or without proximal DVT); and
- the acute treatment and the secondary prevention of future DVTs or PEs.

The model developed by the manufacturer followed an average cohort through a lifetime time-horizon (60 years), with a model cycle length of one month (assumed to be 30 days). The manufacturer assumed that acute treatment would continue for 6 months, and secondary prevention would continue for 6 to 18 months, depending upon the comparator selected.

For the acute treatment of people with a confirmed proximal DVT or PE, the manufacturer estimated, the deterministic incremental cost-effectiveness ratios (ICERs) were estimated in the base case to be:

- dabigatran versus warfarin, £862 per additional QALY gained;
- dabigatran versus rivaroxaban, dabigatran dominant (less costly and more effective).

The probabilistic results were comparable, with the ICER for dabigatran versus warfarin estimated to be £1,016, and dabigatran estimated to be dominant versus rivaroxaban (less costly and more effective). The manufacturer estimated the probability that dabigatran would be considered cost-effective at a willingness-to-pay threshold of £20,000 per additional quality-adjusted life year (QALY) to be 93% (dabigatran versus warfarin), and 57% (dabigatran versus rivaroxaban).

For the analysis of dabigatran versus LMWH in the population with cancer, the deterministic ICER was estimated in the base case to be £110,742, where dabigatran was less costly and less effective than LMWH. The probabilistic results were comparable, with the ICER for dabigatran versus LMWH estimated to be £93,431, where dabigatran was estimated to be less costly and less effective than LMWH. The manufacturer estimated the probability that dabigatran would be considered cost-effective at a willingness-to-pay threshold of £20,000 per additional QALY versus LMWH to be 92%.

The costs and QALYs estimated by the manufacturer for the full population analyses across the lifetime time-horizon were very similar. Costs varied between all three treatment strategies by £40 in the deterministic analyses and QALYs varied by approximately 0.02 per patient. In particular, for dabigatran versus rivaroxaban, the estimated total QALYs differed by 0.0003 over a lifetime for one patient. Therefore, whilst dabigatran was found to dominate rivaroxaban in the manufacturer's base case, the average total costs and QALYs estimated by the manufacturer imply that these treatments result in very similar costs and consequences.

For the acute treatment and secondary prevention of people with a confirmed proximal DVT or PE, the manufacturer did not provide a fully incremental analysis. That is, the costs and QALYs associated with dabigatran differed for each head-to-head comparison as a consequence of differing model inputs for each analysis. Specifically, the manufacturer used alternative estimates for dabigatran for: treatment duration; the probability of recurrent VTE; the probability of bleeding; and the probability of discontinuing treatment. The deterministic ICERs were estimated in the base case to be:

- dabigatran versus warfarin, £8,319 per additional QALY gained;
- dabigatran versus rivaroxaban, dabigatran dominant (less costly and more effective).

The probabilistic results were comparable, with dabigatran versus warfarin estimated to result in an ICER of £8,848, and dabigatran was found to be dominant versus rivaroxaban (less costly and more effective). The manufacturer estimated the probability that dabigatran would be considered cost-

effective at a willingness-to-pay threshold of £20,000 per additional QALY to be 92% (dabigatran versus warfarin), and 81% (dabigatran versus rivaroxaban).

For the analysis of dabigatran versus LMWH in the population with cancer, the manufacturer estimated dabigatran to dominate LMWH in the base case (less costly and more effective). The probabilistic results were comparable, with the ICER for dabigatran versus LMWH estimated to also result in dabigatran dominance over LMWH. The manufacturer estimated the probability that dabigatran would be considered cost-effective at a willingness-to-pay threshold of £20,000 per additional QALY versus LMWH to be 100%.

As with acute treatment, the costs and QALYs estimated by the manufacturer for the full population analyses across the lifetime time-horizon were particularly similar for the comparison of dabigatran versus rivaroxaban. The total lifetime cost difference per patient between dabigatran and rivaroxaban differed by £67 in the deterministic analysis. Moreover, the QALY differential between the two treatment strategies differed by less than 0.002 per patient over their lifetime. Therefore, the ERG considers that, whilst dabigatran dominates rivaroxaban in the base case, as with acute treatment, the average total costs and QALYs estimated by the manufacturer imply that these treatments are similar.

The ERG notes that the modelling approach adopted by the manufacturer was reasonable and consistent with previous economic evaluations in the acute treatment and secondary prevention of DVT and PE. The ERG notes that the model was generally well constructed and transparent, although the ERG identified a number of errors within the model, and several inconsistencies between the numbers reported in the manufacturer's submission and the model.

The ERGs main criticisms of the cost-effectiveness analyses were:

- a lack of a fully incremental analysis for the treatment and secondary prevention scenario;
- duration of secondary prevention set to 6-18 months rather than life-long for the treatment and secondary prevention analyses;
- a potential overestimate of cost associated with warfarin monitoring;
- uncertainty in model results arising as a consequence of:
    - lack of robust evidence supporting a utility decrement for warfarin treatment;
    - lack of clinical effectiveness and safety data for the reduced dose of dabigatran (110mg twice daily);

These concerns are described in more detail below. Other, more minor concerns were also identified and tested in scenario analyses.

Lack of a fully incremental analysis for the treatment and secondary prevention scenario

For the treatment and secondary prevention scenarios, the manufacturer used different data for dabigatran in the comparison with warfarin, rivaroxaban (for the full population) and LMWH (in the population with cancer). Specifically, the manufacturer assumed that the following model inputs would differ by comparison:

- the probability of recurrent VTE whilst receiving dabigatran;
- the split of type of recurrent VTE whilst receiving dabigatran (i.e. DVT, fatal PE, non-fatal PE);
- the probability of a major or clinically relevant non-major bleeding event whilst receiving dabigatran;
- the split of type of major or clinically relevant non-major bleeding event whilst receiving dabigatran (i.e. intra-cranial haemorrhage, other major bleed, fatal bleeding event, clinically relevant non-major bleeding event);
- the duration of treatment with dabigatran (6 months for the comparison with rivaroxaban and LMWH, and 18 months for the comparison with warfarin);
- the probability of discontinuing from dabigatran treatment.

The ERG acknowledges that, for the population with cancer, it is plausible that parameters may differ; however, the ERG consulted with clinical experts and considers that there is no clinical basis from which to assume that the above parameters would differ for dabigatran when in comparison with warfarin or rivaroxaban in the full population.

The ERG notes that a key disadvantage of using alternative model parameters for dabigatran is that the results arising from each analysis cannot be compared, because the costs and QALYs associated with dabigatran will differ in each case.

Duration of secondary prevention set to 6-18 months rather than lifelong

The manufacturer modelled the duration of secondary prevention for the initial therapy as alternatively 6 months (dabigatran in comparison with rivaroxaban, and LMWH) and 18 months (dabigatran in comparison with warfarin).

The ERG sought clinical input around the duration of secondary prevention. The clinical experts asserted that in patients for whom the risk of recurrent VTE outweighed the risk of bleeding, secondary prevention would generally be life-long. The ERG is therefore concerned that the manufacturer has underestimated the likely treatment duration for dabigatran, warfarin, rivaroxaban and LMWH in clinical practice for secondary prevention.

A potential overestimate of cost associated with warfarin monitoring

The ERG notes that the manufacturer assumed that warfarin monitoring in the secondary prevention period would occur monthly, and that the appointment would be a mix of consultant-led and non-consultant led appointments.

Following clinical advice, the ERG considers that it is likely that appointments during secondary prevention would reduce to one every three months as patients become better controlled on warfarin. Moreover, the ERG understands that these appointments would generally be non-consultant led.

Uncertainty in model results arising from a lack of robust data for warfarin utility decrement

The ERG notes that the manufacturer has modelled a decrement in utility associated with warfarin treatment. This decrement was applied to reflect the burden upon health-related quality of life (HRQoL) of warfarin treatment, because warfarin is associated with a number of factors which may negatively impact HRQoL, including the need for regular monitoring of INR, and a requirement of adjusting and monitoring diet and lifestyle.

To establish the HRQoL associated with use of warfarin and LMWH, the manufacturer used data from an analysis of 48 patients who were receiving warfarin. The ERG is concerned that the data supporting the utility decrement for warfarin may not provide a robust estimate of disutility. This is due to a small sample size for the analysis which may limit generalisability of the results, the use of patient preferences to value the health states, and the lack of a similar analysis for dabigatran.

The ERG carried out a rapid and non-systematic search of the literature, and was unable to identify any further appropriate estimates of warfarin disutility in the treatment and secondary prevention of VTE. Instead, the ERG identified a number of studies reviewing the impact of warfarin treatment on HRQoL in atrial fibrillation. The ERG notes that a head-to-head comparison of warfarin and dabigatran from RE-LY, a trial for stroke prevention in AF, indicated that there was no long term difference in the EQ-5D scores for patients receiving warfarin and dabigatran.

The ERG considers that there is therefore uncertainty in what value is appropriate to model to reflect the HRQoL burden associated with warfarin treatment.

Uncertainty in model results arising from a lack of robust data for dabigatran 100mg twice daily

The draft summary of product characteristics (SmPC) for dabigatran for treatment and secondary prevention of DVT and PE states that the standard daily dose of dabigatran is 300mg per day, taken as one 150mg capsule twice daily. The draft SmPC also states that, for patients aged 80 years or above, or patients who receive concomitant verapamil, the daily dose shall be lowered to 220mg per day, taken as one 110mg capsule twice daily. By contrast, the clinical trials for dabigatran in DVT and PE

(RE-COVER I, RE-COVER II, RE-MEDY, RE-SONATE) considered only the dose of 300mg per day, and therefore no clinical data is available at the dose of 220mg per day.

Due to the lack of clinical data, the manufacturer assumed that efficacy and safety data for the 220mg dose would be equivalent to those associated with the 300mg dose within the economic analysis. Moreover, as the cost of a 220mg dose and a 300mg dose is identical, the cost data associated with the lower dose was also assumed to be equivalent.

The ERG is concerned that, without any clinical data at 220mg per day for the population of patients with DVT or PE, it is impossible to say whether the manufacturer's assumption of equivalence in efficacy is reasonable. The ERG notes that the dose of 220mg dabigatran has been studied in patients with atrial fibrillation (AF) in RE-LY; in those patients, efficacy data were not found to be equivalent to the 300mg dose. However, due to a lack of clinical data in the treatment and secondary prevention of VTE, the ERG considers it is not possible to infer what effect the dose of dabigatran will have on the model results.

To address these concerns, the ERG carried out a number of model corrections and scenario analyses to investigate alternative parameters and assumptions within the model structure. The ERG considered deterministic results only; this was for simplicity because the manufacturer's model results were consistent between deterministic and probabilistic results.

The ERG estimated a revised deterministic base case incremental cost-effectiveness ratio (ICER) for the comparisons of dabigatran and warfarin, and dabigatran and rivaroxaban in the acute treatment scenario, and the treatment and secondary prevention scenario. The ERG did not attempt to estimate a base case ICER for dabigatran versus LMWH in the population with cancer. This is because the ERG has concerns over the reliability of the data in the population with cancer, and therefore the applicability of the findings for this comparison. Specifically, it is unclear whether the population contained within RE-COVER I and II represent the population with cancer seen in clinical practice, and clinical data for this population were found to be less reliable. The ERG notes that the manufacturer's base case results for dabigatran versus LMWH were robust to the majority of analyses undertaken by the ERG.

The deterministic ICERs for dabigatran versus warfarin and dabigatran versus rivaroxaban in the acute treatment scenario were estimated to be:

- £18,240 per additional QALY (dabigatran versus warfarin);
- dabigatran dominates rivaroxaban.

The results correspond to the manufacturer's results for the comparison of dabigatran versus rivaroxaban; the manufacturer also estimated that dabigatran was dominant (less costly and more effective) when compared with rivaroxaban. The ERG considers it important to note that the cost difference estimated through this analysis was £3 per patient over the lifetime of the model, with a QALY difference of 0.0018. Thus, the ERG notes that dabigatran and rivaroxaban are associated with very similar costs and consequences.

The estimate for dabigatran versus warfarin differs to the manufacturer's estimate of £862 per additional QALY. The ERG considers that the single largest driver of this difference was the reduction in cost associated with warfarin monitoring as a result of assuming that follow-up visits would be non-consultant led.

The deterministic ICERs for dabigatran versus warfarin and dabigatran versus rivaroxaban in the treatment and secondary prevention scenario were fully incremental, and estimated to be:

- rivaroxaban extendedly dominated by dabigatran;
- £35,768 (dabigatran versus warfarin).

The estimate for dabigatran versus warfarin differs to the manufacturer's estimate of £8,319 per additional QALY. The ERG considers that the largest drivers of this difference were: an increase in cost associated with dabigatran from lifelong secondary prevention for the initial event; a reduction in the cost associated with warfarin monitoring by assuming one appointment every three months rather than every month in the secondary prevention period; a reduction in cost associated with warfarin monitoring as a result of assuming that follow-up visits would be non-consultant led.

The ERGs revised base case ICER did not incorporate the removal of warfarin disutility in the secondary prevention period. This is because the ERG is not clear what value is most appropriate to capture the HRQoL impact of warfarin treatment. The ERG notes that this parameter is a key driver in the ERG base case result, and removal of the disutility associated with warfarin treatment in the secondary prevention period results in a large increase in the ICER associated with the comparison of dabigatran and warfarin, to approximately £90,000 per additional QALY. This is because the model with the ERG scenarios incorporated is increasingly sensitive to changes in QALYs.

7.3 Implications for research

The ERG considers that there is a need for further research into:

- the safety and efficacy of the 110mg BD dose of dabigatran in acute treatment and secondary prevention of VTE;
- the safety and clinical benefit of dabigatran compared with rivaroxaban;
- a head-to-head trials comparing dabigatran, LMWH and rivaroxaban in patients with cancer may be informative for service provision within the NHS;
- health-related quality of life data related to warfarin use.

8 REFERENCES

(1) Piazza G, Goldhaber SZ. Venous thromboembolism and atherothrombosis: an integrated approach. Circulation 2010 May 18;121(19):2146-50.

(2) Boehringer-Ingelheim. Technology Appraisal no. 157; Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults:manufacturer submission. 2008.

(3) Flinterman LE, van H, V, Cannegieter SC, Rosendaal FR. Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. PLoS Med 2012 Jan;9(1):e1001155.

(4) Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000 May;83(5):657-60.

(5) Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A, et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica 1997 Jul;82(4):423-8.

(6) Murin S, Romano PS, White RH. Comparison of outcomes after hospitalization for deep venous thrombosis or pulmonary embolism. Thromb Haemost 2002 Sep;88(3):407-14.

(7) Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004 May 27;350(22):2257-64.

(8) NICE. Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. 2012.

(9) NICE. Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. 2013.

(10) Curtis L. Unit Costs of Health & Social Care 2013. Personal Social Services Research Unit. 2013. Personal Social Services Research Unit.

(11) Department of Health. NHS Reference Costs 2012 to 2013. 2013. 1-8-2014.

(12) Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: A population-based cohort study in patients without active cancer. Thromb Haemost 2014 Aug 1;112(2):255-63.

(13) Office for National Statistics. Summary Results, 2012-based National Population Projections. 2013.

(14) National Joint Registry. NJR StatsOnline: Summary of annual statistics (England and Wales. 2014.

(15) National Institute for Health and Care Excellence. Deep vein thrombosis, pulmonary embolism - dabigatran etexilate (treatment, prevention): final scope (ID483). http://admin nice org uk/guidance/TAG/361/Scope/pdf/English 2013 [cited 2014 Aug 4];Available from: URL: http://admin.nice.org.uk/guidance/TAG/361/Scope/pdf/English

(16) Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009 Dec 10;361(24):2342-52.

(17) Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014 Feb 18;129(7):764-72.

(18) Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013 Feb 21;368(8):709-18.

(19) European Medicines Agency. Pradaxa (dabigatran etexilate) - Summary of opinion (post authorisation) . 2014.

(20) European Agency for the Evaluation of Medicinal Products. Clinical investigation of medicinal products for the treatment of venous thromboembolic disease. 2009.

(21) MAPI. Description of the EQ-5D data collected in the RE-COVER and RE-COVER II studies comparing dabigatran to warfarin in patients with confirmed acute symptomatic VTE: Summary report BI5850A. 2013.

(22) Bayer PLC. Single technology appraisal (STA) 256: Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation. 2011.

(23) Snapinn SM. Noninferiority trials. Curr Control Trials Cardiovasc Med 2000;1(1):19-21.

(24) Spackman E., Burch J., Faria R., Corbacho B., Fox D., Woolacott N. Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: Evidence Review Group Report. 2011.

(25) Boehringer Ingelheim. Clinical Trial Report 1160.46 (RE-COVER II). 2011.

(26) Boehringer Ingelheim. Clinical Trial Report 1160.53 (RE-COVER). 2009.

(27) Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997 Jun;50(6):683-91.

(28) Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010 Dec 23;363(26):2499-510.

(29) Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012 Apr 5;366(14):1287-97.

(30) Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost 2006 Oct;12(4):389-96.

(31) Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med 2006 Dec;119(12):1062-72.

(32) Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003 Jul 10;349(2):146-53.

(33) Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 2002 Aug 12;162(15):1729-35.

(34) Romera A, Cairols MA, Vila-Coll R, Marti X, Colome E, Bonell A, et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. Eur J Vasc Endovasc Surg 2009 Mar;37(3):349-56.

(35) Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-extension study). Expert Rev Cardiovasc Ther 2011 Jul;9(7):841-4.

(36) Malato, Siragusa. The optimal duration of anticoagulant therapy in patients with cancer-related deep vein thrombosis: the advantage of using residual vein thrombosis (the Cancer-Dacus study). Journal of Thrombosis and Haemostasis 9 (Suppl 2). 2011.

Ref Type: Abstract

(37) Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999 Mar 25;340(12):901-7.

(38) Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med 2001 Jul 19;345(3):165-9.

(39) Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003 Jul 1;139(1):19-25.

(40) Schulman S, Granqvist S, Holmstrom M, Carlsson A, Lindmarker P, Nicol P, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. N Engl J Med 1997 Feb 6;336(6):393-8.

(41) Farraj RS. Anticoagulation period in idiopathic venous thromboembolism. How long is enough? Saudi Med J 2004 Jul;25(7):848-51.

(42) Edwards SJ, Borrill J. Network meta-analysis: importance of appropriate trial selection. Value Health 2010 Aug;13(5):681-2.

(43) Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005 Oct 15;331(7521):897-900.

(44) Dempster AP. The direct use of likelihood for significance testing. Statistics and Computing 1997;7(4):247-52.

(45) Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. Stat Med 2002 Jun 15;21(11):1575-600.

(46) Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology) 2002 Oct 1;64(4):583-639.

(47) Boehringer Ingelheim. Clinical Trial Report 1160.47 (RE-MEDY). 2011.

(48) Boehringer Ingelheim. Clinical Trial Report (revision no. 1) 1160.63 (RE-SONATE). 2011.

(49) Bayer PLC. Single technology appraisal (STA) 261: Rivaroxaban in the treatment of deep vein thrombosis and prevention of recurrent venous thromboembolic events. 2011.

(50) Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for secondary prophylaxis of cancer-related venous thromboembolism. Thromb Haemost 2005 Mar;93(3):592-9.

(51) Aujesky D, Smith KJ, Roberts MS. Oral anticoagulation strategies after a first idiopathic venous thromboembolic event. Am J Med 2005 Jun;118(6):625-35.

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

(53) Gomez-Outes A, Rocha E, Martinez-Gonzalez J, Kakkar VV. Cost effectiveness of bemiparin sodium versus unfractionated heparin and oral anticoagulants in the acute and long-term treatment of deep vein thrombosis. Pharmacoeconomics 2006;24(1):81-92.

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

(55) Perez-de-Llano LA, Leiro-Fernandez V, Golpe R, Nunez-Delgado JM, Palacios-Bartolome A, Mendez-Marote L, et al. Comparison of tinzaparin and acenocoumarol for the secondary prevention of venous thromboembolism: a multicentre, randomized study. Blood Coagul Fibrinolysis 2010 Dec;21(8):744-9.

(56) Marchetti M, Pistorio A, Barone M, Serafini S, Barosi G. Low-molecular-weight heparin versus warfarin for secondary prophylaxis of venous thromboembolism: a cost-effectiveness analysis. Am J Med 2001 Aug;111(2):130-9.

(57) National Institute for Health and Care Excellence. Single technology appraisal (STA) 287 Final Appraisal Determination (FAD): Rivaroxaban for treating pulmonary embolism and preventing recurrent venous thromboembolism. http://www nice org uk/guidance/ta287/resources/pulmonary-embolism-acute-treatment-vte-prevention-rivaroxaban-final-appraisal-determination-document2 2013 [cited 2014 Aug 1]; Available from: URL: http://www.nice.org.uk/guidance/ta287/resources/pulmonary-embolism-acute-treatment-vte-prevention-rivaroxaban-final-appraisal-determination-document2

(58) National Institute for Health and Care Excellence. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. http://www nice org uk/guidance/cg144 2012 [cited 2014 Aug 11]; Available from: URL: http://www.nice.org.uk/guidance/cg144

(59) Department of Health. NHS Reference Costs 2010 to 2011. 2011. 4-8-2014.

(60) Curtis L. Unit Costs of Health & Social Care 2011. Personal Social Services Research Unit. 2011. Personal Social Services Research Unit.

(61) British National Formulary. BNF 64. 2012.

(62) Department of Health. NHS Reference Costs 2009 to 2010. 2010. 4-8-2014.

(63) Curtis L. Unit Costs of Health & Social Care 2010. Personal Social Services Research Unit. 2010. Personal Social Services Research Unit.

(64) Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004 Sep;8(36):iii-xi, 1.

(65) Bayer PLC. Single technology appraisal (STA) 287: Rivaroxaban for the treatment of pulmonary embolism and the prevention of recurrent venous thromboembolism . 2012.

(66) National Institute for Health and Care Excellence. Clinical Guideline 144: Venous thrombolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. http://www nice org uk/guidance/cg144/resources/guidance-venous-thromboembolic-diseases-the-management-of-venous-thromboembolic-diseases-and-the-role-of-thrombophilia-testing-pdf 2012 [cited 2014 Aug 4]; Available from: URL: http://www.nice.org.uk/guidance/cg144/resources/guidance-venous-thromboembolic-diseases-the-management-of-venous-thromboembolic-diseases-and-the-role-of-thrombophilia-testing-pdf

(67) National Institute for Health and Care Excellence. NICE Guide to the Methods of Technology Appraisal 2013. 2013. 1-8-2014.

(68) National Institute for Health and Care Excellence. Single technology appraisal (STA) 249 Final Appraisal Determination (FAD):Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation. http://www nice org uk/guidance/ta249/resources/atrial-fibrillation-dabigatran-etexilate-final-appraisal-determination3 2011 [cited 2014 Aug 4];Available from: URL: http://www.nice.org.uk/guidance/ta249/resources/atrial-fibrillation-dabigatran-etexilate-final-appraisal-determination3

(69) Siebert U, Alagoz O, Bayoumi A, Jahn B, Owens D, Cohen D, et al. State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices. Med Decis Making 2012;32:690-700.

(70) RTI Health Solutions. UK Clinical Expert Panel. 2008.

(71) Prins MH, Lensing AW, Bauersachs R, van BB, Bounameaux H, Brighton TA, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thromb J 2013;11(1):21.

(72) Siragusa S, Malato A, Saccullo G, Iorio A, DiIanni M, Caracciolo C, et al. Residual vein thrombosis for assessing duration of anticoagulation after unprovoked deep vein thrombosis of the lower limbs: The extended DACUS study. American Journal of Hematology 2011;86(11):914-7.

(73) Briggs A, Claxton K, Sculpher M. Chapter 3: Further developments in decision analytic models for economic evaluation. Decision Modelling for Health Economic Evaluation. Oxford University Press; 2006. p. 51.

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

(75) Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. Lancet 2014 Mar 8;383(9920):880-8.

(76) RTI Health Solutions. Report for Boehringer Ingelheim: Meta-analysis of efficacy and safety data in the treatment and secondary prevention of venous thromboembolism. 2013.

(77) Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med 2004 Apr 26;164(8):880-4.

(78) Office for National Statistics. UK Population Estimates. http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/sty-population-estimates.html . 2013. 1-8-2014.

(79) Office of National Statistics. UK Population Estimates. http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/2013/sty-population-estimates.html . 2013. 1-8-2014.

(80) School of Health and Related Research (ScHARR). Single technology appraisal (STA) 261 ERG Report: Rivaroxaban for the treatment of deep vein thrombosis and secondary prevention of venous thromboembolism. 2011.

(81) Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2008 May 15;177(10):1122-7.

(82) National Institute for Health and Care Excellence. Single technology appraisal (STA) 261 Final Appraisal Determination (FAD): Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. http://www nice org uk/guidance/ta261/resources/venous-thromboembolism-treatment-and-long-term-secondary-prevention-rivaroxaban-final-appraisal-determination-guidance2 2012 [cited 2014 Aug 1];Available from: URL: http://www.nice.org.uk/guidance/ta261/resources/venous-thromboembolism-treatment-and-long-term-secondary-prevention-rivaroxaban-final-appraisal-determination-guidance2

(83) RTI Health Solutions. Economic Analyses of Anti-Coagulants for Treatment and Secondary Prevention of Venous Thromboembolism. GPRD Statistical Analyses Report—Final, Version 2. 2013.

(84) Hogg K, Kimpton M, Carrier M, Coyle D, Wells P. Quality of life in acute deep vein thrombosis and pulmonary embolism- a case-control study. Journal of Thrombosis and Haemostatis 2013;11:82-3.

(85) Sullivan P, Fraessdorf M, Feuring M, Schulman S, Hass B. Health-Related Quality of Life After Venous Tromboembolism. Value in Health: the journal of the International Society for Pharmacoeconomics and Outcomes Research 14[7], 1-11. 2011.

(86) Tavoly M, Wik HS, Nori F. Health-related quality of life after pulmonary embolism- a case-control study. Journal of Thrombosis and Haemostasis [11], 603. 2013.

(87) Delaney BC, Qume M, Moayyedi P, Logan RF, Ford AC, Elliott C, et al. Helicobacter pylori test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). BMJ 2008 Mar 22;336(7645):651-4.

(88) van Kerkhoven LA, van Rossum LG, van Oijen MG, Tan AC, Laheij RJ, Jansen JB. Upper gastrointestinal endoscopy does not reassure patients with functional dyspepsia. Endoscopy 2006 Sep;38(9):879-85.

(89) Gerson LB, Ullah N, Hastie T, Triadafilopoulos G, Goldstein M. Patient-derived health state utilities for gastroesophageal reflux disease. Am J Gastroenterol 2005 Mar;100(3):524-33.

(90) Sanz MA, Aledort L, Mathias SD, Wang X, Isitt JJ. Analysis of EQ-5D scores from two phase 3 clinical trials of romiplostim in the treatment of immune thrombocytopenia (ITP). Value Health 2011 Jan;14(1):90-6.

(91) Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. J Health Serv Res Policy 2001 Apr;6(2):92-8.

(92) Bach JP, Riedel O, Pieper L, Klotsche J, Dodel R, Wittchen HU. Health-related quality of life in patients with a history of myocardial infarction and stroke. Cerebrovasc Dis 2011;31(1):68-76.

(93) Fitzgerald P, Goodacre SW, Cross E, Dixon S. Cost-effectiveness of point-of-care biomarker assessment for suspected myocardial infarction: the randomized assessment of treatment using panel Assay of cardiac markers (RATPAC) trial. Acad Emerg Med 2011 May;18(5):488-95.

(94) Kuch B, Wende R, Barac M, von SW, Kling B, Greschik C, et al. Prognosis and outcomes of elderly (75-84 years) patients with acute myocardial infarction 1-2 years after the event: AMI-elderly study of the MONICA/KORA Myocardial Infarction Registry. Int J Cardiol 2011 Jun 2;149(2):205-10.

(95) Schweikert B, Hunger M, Meisinger C, Konig HH, Gapp O, Holle R. Quality of life several years after myocardial infarction: comparing the MONICA/KORA registry to the general population. Eur Heart J 2009 Feb;30(4):436-43.

(96) Shah P, Najafi AH, Panza JA, Cooper HA. Outcomes and quality of life in patients>or=85 years of age with ST-elevation myocardial infarction. Am J Cardiol 2009 Jan 15;103(2):170-4.

(97) Pettersen K, Kvan E, Rollag A, Stavern K, Reikvam A. Health-related quality of life after myocardial infarction is associated with level of left ventricular ejection fraction. BMC Cardiovascular Disorders 2008;8(28).

(98) Lenzen M, Scholte Op RW, Norekval TM, De GS, Fridlund B, Heikkila J, et al. Pharmacological treatment and perceived health status during 1-year follow up in patients diagnosed with coronary artery disease, but ineligible for revascularization. Results from the Euro Heart Survey on Coronary Revascularization. Eur J Cardiovasc Nurs 2006 Jun;5(2):115-21.

(99) Schweikert B, Hahmann H, Leidl R. Validation of the EuroQol questionnaire in cardiac rehabilitation. Heart 2006 Jan;92(1):62-7.

(100) Nowels D, McGloin J, Westfall JM, Holcomb S. Validation of the EQ-5D quality of life instrument in patients after myocardial infarction. Qual Life Res 2005 Feb;14(1):95-105.

(101) Kumar R, Rodriguez V, Matsumoto JM, Khan SP, Weaver AL, McBane RD, et al. Health-related quality of life in children and young adults with post-thrombotic syndrome: results from a cross-sectional study. Pediatr Blood Cancer 2014 Mar;61(3):546-51.

(102) Roman A, Barbera JA, Castillo MJ, Munoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. Arch Bronconeumol 2013 May;49(5):181-8.

(103) Roman A, Escribano P, Barbera JA, Roman SJ, Munoz R. Quality Of Life In Patients Diagnosed With Pulmonary Arterial Hypertension- SQUALY Study. American Thoracic Society International Conference Abstracts . 2010.

(104) Pepke-Zaba J, Beardsworth A, Chan M, Angalakuditi M. Tadalafil therapy and health-related quality of life in pulmonary arterial hypertension. Curr Med Res Opin 2009 Oct;25(10):2479-85.

(105) McKenna SP, Ratcliffe J, Meads DM, Brazier JE. Development and validation of a preference based measure derived from the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) for use in cost utility analyses. Health Qual Life Outcomes 2008;6:65.

(106) Meads DM, McKenna SP, Doughty N, Das C, Gin-Sing W, Langley J, et al. The responsiveness and validity of the CAMPHOR Utility Index. Eur Respir J 2008 Dec;32(6):1513-9.

(107) Pepke-Zaba J, Gilbert C, Collings L, Brown MC. Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. Chest 2008 Jan;133(1):183-9.

(108) Lindgren P, Kahan T, Poulter N, Buxton M, Svarvar P, Dahlof B, et al. Utility loss and indirect costs following cardiovascular events in hypertensive patients: the ASCOT health economic substudy. Eur J Health Econ 2007 Mar;8(1):25-30.

(109) Shafazand S, Goldstein MK, Doyle RL, Hlatky MA, Gould MK. Health-related quality of life in patients with pulmonary arterial hypertension. Chest 2004 Nov;126(5):1452-9.

(110) Sitbon O, Gressin V, Speich R, Macdonald PS, Opravil M, Cooper DA, et al. Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2004;170(11):1212-7.

(111) Highland KB, Strange C, Mazur J, Simpson KN. Treatment of pulmonary arterial hypertension: a preliminary decision analysis. Chest 2003 Dec;124(6):2087-92.

(112) Arnold SV, Morrow DA, Wang K, Lei Y, Mahoney EM, Scirica BM, et al. Effects of ranolazine on disease-specific health status and quality of life among patients with acute coronary syndromes: results from the MERLIN-TIMI 36 randomized trial. Circ Cardiovasc Qual Outcomes 2008 Nov;1(2):107-15.

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

(114) Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thromb Haemost 2004 Dec;92(6):1336-41.

(115) Keogh AM, McNeil KD, Wlodarczyk J, Gabbay E, Williams TJ. Quality of life in pulmonary arterial hypertension: improvement and maintenance with bosentan. J Heart Lung Transplant 2007 Feb;26(2):181-7.

(116) Wolowacz SE, Roskell NS, Maciver F, Beard SM, Robinson PA, Plumb JM, et al. Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism after total knee and hip replacement surgery. Clin Ther 2009 Jan;31(1):194-212.

(117) Ingelgard A, Hedner E, Stigendal J, Carlsson J. Patient-reported outcomes in patients with deep vein thrombosis treated with warfarin. Presented at: 17th International Congress on Thrombosis. 2002.

(118) Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making 2011 Nov;31(6):800-4.

(119) Prescott-Clarke P, Primatesta P. The Health Survey for England 1996. London: The Stationery Office; 1996.

(120) Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. The University of York Centre for Health Economics Discussion Papers 1999;Discussion Paper 172.

(121) MAPI. Analysis of EQ-5D data collected in RE-COVER and RE-COVER II studies, and in RE-SONATE study. Statistical Outputs BI15850AB . 2013.

(122) Enden T, Wik HS, Kvam AK, Haig Y, Klow NE, Sandset PM. Health-related quality of life after catheter-directed thrombolysis for deep vein thrombosis: secondary outcomes of the randomised, non-blinded, parallel-group CaVenT study. BMJ Open 2013;3(8):e002984.

(123) Alegret JM, Vinolas X, Arias MA, Martinez-Rubio A, Rebollo P, Rafols C, et al. New oral anticoagulants vs vitamin K antagonists: benefits for health-related quality of life in patients with atrial fibrillation. Int J Med Sci 2014;11(7):680-4.

(124) Monz BU, Connolly SJ, Korhonen M, Noack H, Pooley J. Assessing the impact of dabigatran and warfarin on health-related quality of life: results from an RE-LY sub-study. Int J Cardiol 2013 Oct 3;168(3):2540-7.

(125) Lancaster TR, Singer DE, Sheehan MA, Oertel LB, Maraventano SW, Hughes RA, et al. The impact of long-term warfarin therapy on quality of life. Evidence from a randomized trial. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. Arch Intern Med 1991 Oct;151(10):1944-9.

(126) Sarasin FP, Gaspoz JM, Bounameaux H. Cost-effectiveness of new antiplatelet regimens used as secondary prevention of stroke or transient ischemic attack. Arch Intern Med 2000;160(18):2773-8.

(127) Fanikos J, Rao A, Seger AC, Carter D, Piazza G, Goldhaber SZ. Hospital costs of acute pulmonary embolism. Am J Med 2013 Feb;126(2):127-32.

(128) Ara R, Pandor A, Stevens J, Rafia R, Ward SE, Rees A, et al. Prescribing high-dose lipid-lowering therapy early to avoid subsequent cardiovascular events: is this a cost-effective strategy? Eur J Prev Cardiol 2012 Jun;19(3):474-83.

(129) Bakhai A, Ferrieres J, Iniguez A, Sartral M, Belger M, Schmitt C, et al. Clinical outcomes, resource use, and costs at 1 year in patients with acute coronary syndrome undergoing PCI: results from the multinational APTOR registry. J Interv Cardiol 2012 Feb;25(1):19-27.

(130) Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, et al. Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. Health Technol Assess 2007 Oct;11(38):iii-66.

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

(132) Latimer N, Lord J, Grant RL, O'Mahony R, Dickson J, Conaghan PG. Cost effectiveness of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitor for people with osteoarthritis. BMJ 2009;339:b2538.

(133) Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. Pharmacoeconomics 2003;21 Suppl 1:43-50.

(134) van BB, Bamber L, Correa de CF, Prins M, Wang M, Lensing AW. Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and pulmonary embolism. Curr Med Res Opin 2014 May;30(5):829-37.

(135) Monthly Index of Medical Specialities. MIMS May-March 2014. 2014.

(136) Office of National Statistics. Prescription Cost Analysis, England: 2013. Health and Social Care Information Centre . 2014.

(137) British National Formulary. BNF 67. 2014.

(138) Watts AC, Howie CR, Simpson AH. Assessment of a self-administration protocol for extended subcutaneous thromboprophylaxis in lower limb arthroplasty. J Bone Joint Surg Br 2006 Jan;88(1):107-10.

(139) Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, et al. Prognostic and aetiological factors in chronic thromboembolic pulmonary hypertension. Eur Respir J 2009 Feb;33(2):332-8.

(140) National Collaborating Centre for Acute Care. Clinical Guideline 92: Venous Thromboembolism. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients undergoing surgery. 2010. 4-8-2014.

(141) Kalra L, Evans A, Perez I, Knapp M, Donaldson N, Swift CG. Alternative strategies for stroke care: a prospective randomised controlled trial. Lancet 2000 Sep 9;356(9233):894-9.

9 APPENDICES

Appendix 1

Results of the manufacturer's scenario analyses, acute treatment

Scenario	Comparator	Dabigatran		
		Incremental costs	Incremental QALYs	ICER
Base case				
WFN		£21	0.0239	£862
Rivaroxaban		-£20	0.0003	Dabigatran is dominant
LMWH mono-therapy (active cancer patients)		-£1,370	-0.0124	Dabigatran is less costly and less effective
Sensitivity analysis				
Adjustment to TTR	Warfarin	£19	0.0242	£778
	Rivaroxaban	-£19	0.0001	Dabigatran is dominant
	LMWH (population with cancer)	-£1,370	-0.0123	Dabigatran is less costly and less effective
LMWH duration for rivaroxaban regimen	Warfarin	–	–	–
	Rivaroxaban	-£30	0.0003	Dabigatran is dominant
	LMWH (population with cancer)	–	–	–
Utility decrement for WFN	Warfarin	£21	0.0170	£1,217
	Rivaroxaban	–	–	–
	LMWH (population with cancer)	–	–	–
Dyspepsia	Warfarin	£21	0.0236	£911
	Rivaroxaban	–	–	–
	LMWH (population with cancer)	–	–	–
Time horizon for treatment (6 months)	Warfarin	£48	0.0090	£5,317
	Rivaroxaban	£15	0.0003	£46,274
	LMWH (population with cancer)	-£1,401	-0.0012	Dabigatran is less costly and less effective
Time horizon for treatment (1 year)	Warfarin	£47	0.0095	£4,963
	Rivaroxaban	£15	0.0003	£44,142
	LMWH (population with cancer)	-£1,398	-0.0019	Dabigatran is less costly and less effective
Time horizon for treatment then secondary prevention (1 year)	Warfarin	–	–	–
	Rivaroxaban	–	–	–
	LMWH (population with cancer)	–	–	–

Bleeding event counting	Warfarin	£32	0.0226	£1,435
	Rivaroxaban	-£24	-0.0005	Dabigatran is less costly and less effective
	LMWH (population with cancer)	-£1,425	-0.0078	Dabigatran is less costly and less effective
Myocardial infarction and unstable angina (i.e. cardiovascular events	Warfarin	£33	0.0239	£1,390
	Rivaroxaban	-£23	0.0067	Dabigatran is dominant
	LMWH (population with cancer)	-£1,364	-0.0124	Dabigatran is less costly and less effective
Unexplained death	Warfarin	–	–	–
	Rivaroxaban	–	–	–
	LMWH (population with cancer)	–	–	–
Rivaroxaban pre-specified treatment duration	Warfarin	–	–	–
	Rivaroxaban	-£40	0.0023	Dabigatran is dominant
	LMWH (population with cancer)	–	–	–
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin; QALY, quality-adjusted life year; TTR, time in therapeutic range.				

Results of the manufacturer's scenario analyses, treatment and secondary prevention

Scenario	Comparator	Dabigatran		
		Incremental costs	Incremental QALYs	ICER
Base case				
WFN		£458	0.0551	£8,319
Rivaroxaban		-£67	0.0020	Dabigatran is dominant
LMWH mono-therapy (active cancer patients)		-£3,340	0.0197	Dabigatran is dominant
Sensitivity analysis				
Adjustment to TTR	Warfarin	£454	0.0556	£8,160
	Rivaroxaban	-£66	0.0018	Dabigatran is dominant
	LMWH (population with cancer)	-£3,341	0.0198	Dabigatran is dominant
LMWH duration for rivaroxaban regimen	Warfarin	–	–	–
	Rivaroxaban	-£76	0.0020	Dabigatran is dominant
	LMWH (population with cancer)	–	–	–
Utility decrement for WFN	Warfarin	£458	0.0306	£14,947
	Rivaroxaban	–	–	–
	LMWH (population with	–	–	–

	cancer)			
Dyspepsia	Warfarin	£459	0.0536	£8,556
	Rivaroxaban	–	–	–
	LMWH (population with cancer)	–	–	–
Time horizon for treatment (6 months)	Warfarin	–	–	–
	Rivaroxaban	–	–	–
	LMWH (population with cancer)	–	–	–
Time horizon for treatment (1 year)	Warfarin	–	–	–
	Rivaroxaban	–	–	–
	LMWH (population with cancer)	–	–	–
Time horizon for treatment then secondary prevention (1 year)	Warfarin	£209	0.0162	£12,905
	Rivaroxaban	-£22	0.0030	Dabigatran is dominant
	LMWH (population with cancer)	-£3,225	0.0083	Dabigatran is dominant
Bleeding event counting	Warfarin	£459	0.0550	£8,350
	Rivaroxaban	-£69	0.0013	Dabigatran is dominant
	LMWH (population with cancer)	-£3,362	0.0214	Dabigatran is dominant
Myocardial infarction and unstable angina (i.e. cardiovascular events	Warfarin	£515	0.0547	£9,425
	Rivaroxaban	-£115	0.0108	Dabigatran is dominant
	LMWH (population with cancer)	-£3,340	0.0197	Dabigatran is dominant
Unexplained death	Warfarin	£459	0.0618	£7,427
	Rivaroxaban	–	–	–
	LMWH (population with cancer)	–	–	–
Rivaroxaban pre-specified treatment duration	Warfarin	–	–	–
	Rivaroxaban	-£86	0.0041	Dabigatran is dominant
	LMWH (population with cancer)	–	–	–
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin; QALY, quality-adjusted life year; TTR, time in therapeutic range.				