Edoxaban tosylate 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 company's submission

The company of edoxaban tosylate (Lixiana®, Daiichi Sankyo) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of edoxaban tosylate for the treatment and secondary prevention of deep vein thrombosis (DVT) and/or pulmonary embolism (PE). At the time of writing edoxaban tosylate (hereafter referred to as edoxaban) 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 the company has filed for and a favourable approval was obtained from the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) on the 23rd April 2015.

The final scope developed by NICE for this STA focused on a population of patients with DVT and/or PE. The intervention of interest was edoxaban compared to low molecular weight heparin (LMWH) or fondaparinux, vitamin K antagonist (VKA) or other New Oral Anticoagulants (NOACs) (rivaroxaban or dabigatran). The outcomes in the final scope were; mortality, venous thromboembolism (VTE) recurrence, complications of DVT or PE including post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH), adverse events of treatment (particularly bleeding) and health-related quality of life (HRQoL).

The final scope also included a request for evidence for "other considerations", for example those who require a limited period of anticoagulation (3–6 months), those people who require long-term treatment (usually lifelong), and people in whom the need for anticoagulation is uncertain and aspirin or no preventative treatment might be considered. The final scope also requested evidence from patients who had active cancer and the effect edoxaban had on their treatment.

The ERG considered the company's submission lacked data for some elements from the final scope; there were no data for initial treatment with fondaparinux submitted as this was unavailable from the single pivotal trial (Hokusai-VTE). Additionally, only one type of low molecular weight heparin (LMWH) (enoxaparin) and one type of VKA (warfarin). Clinical experts have advised the ERG that warfarin is the most commonly used VKA in the UK and the type of LMWH prescribed varies by NHS Trust (with dalteparin and enoxaparin having the largest market share), based on this feedback the ERG has concluded that the company's approach typifies clinical practice in the UK.

The company did not provide an analysis of data from patients with active cancer, patients who had cancer for which long term treatment with LMWH was anticipated were excluded from Hokusai-VTE. While Hokusai-VTE did not define active cancer patients the ERG clinical experts have

informed the ERG that active cancer would be defined in the UK as patients those within one year of undergoing treatment for cancer.

The ERG is aware of a recent systematic review and meta-analysis published in 2015 by Vedovati and colleagues to compare the effectiveness of NOACs with warfarin for patients with active cancer. The meta-analyses presented in the publication contains data from 6 trials including patients from the Hokusai-VTE trial. The results show no statistically significant differences in the numbers of recurrent VTEs, major bleeds (MBs) or Clinically Relevant Major Bleeds (CRNMB) between NOACs and comparator anticoagulants. However, the ERGs clinical experts have confirmed that standard practice in the UK is for patients with active cancer to receive LMWH and therefore the relevance of these analyses to routine clinical practice is unclear.

Of those outcomes specified in the scope, the primary outcome chosen by the company was recurrent VTE. The ERG notes that no data for PTS or CTEPH specified in the scope are reported in the submission and neither were they reported in the Hokusai-VTE trial report.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness trial data for edoxaban presented in the company's submission (CS) for long term secondary prevention of VTE is from one trial; Hokusai-VTE. This double blind, double dummy, multi-centre, non-inferiority trial compared edoxaban 60 mg daily with warfarin for patients with VTE.

The Hokusai-VTE trial incuded patients over the age of 18 years with a diagnosis of VTE. Eligible patients were stratified according to the index diagnosis (DVT or PE with or without DVT) and other baseline risk factors including provoked VTE (immobilisation, recent surgery, trauma), and the need for a dose reduction before randomisation according to a 1:1 design.

The primary objective of Hokusai-VTE was to compare outcomes of patients receiving initial LMWH followed by edoxaban alone with LMWH overlapping with warfarin followed by warfarin alone for the treatment and prevention of recurrence of acute symptomatic VTE. The duration of Hokusai-VTE was 12 months and patients were intended to receive treatment for a minimum of 3 months and a maximum of 12, at the discretion of the treating physician. The ERG's clinical experts have advised that in routine clinical practice treatment for PE acute treatment is more likely to be 6 months and for DVT 3 months unless requiring ongoing treatment or secondary prevention in which case treatment will also be lifelong

The trial design permitted alterations to the duration of the drug and also to its dose: edoxaban could be taken for a time period between 3 and 12 months based on the discretion of the physician and at a dose of 60mg or 30mg depending on poor hepatic or renal function, frailty and low body weight. This specific aspect of the trial design distinguishes edoxaban from the other trials of NOACs.

Regarding comparators, there were no *head-to-head* comparisons for edoxaban with the other NOAC drugs specified within the NICE scope and the company therefore presented network meta-analyses (NMAs) for:

- initial treatment with a LMWH and continued warfarin (VKA);
- rivaroxaban; and
- dabigatran.

Health-related quality of life (HRQoL) data were collected and reported in the Hokusai-VTE trial. However, this was based on small numbers of respondents (n=[redacted]) and did not permit an analysis of the differential effects of edoxaban and warfarin on HRQoL and the CS recommends the HRQoL data are interpreted with caution.

The number of patients randomised (1:1) to either edoxaban or warfarin were 8,292 in Hokusai-VTE; 4,143 patients were randomised to edoxaban and 4,149 patients received warfarin. The company reported data in the CS from two different analysis sets; the main efficacy analysis presented in the CS was a modified intention to treat analysis set (mITT) and the safety analysis set, used for the analyses pertaining to the secondary outcomes (major and CRNMB).

The mITT 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. The safety analysis comprised 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 mITT and safety set populations were the same size.

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 Hokusai-VTE was an INR in the range of 2.0 to 3.0. The mean TTR for patients across the Hokusai-VTE was 63.5%. This is similar to the observed INR for patients taking warfarin on trials of dabigitran.

Regarding discontinuations, 16.9% of those in the edoxaban arm and 17.4% of those in the warfarin group were lost to follow up in Hokusai-VTE, but the patient numbers were well balanced between

treatment groups. The majority of patients lost to follow up were as a result of adverse events (particularly gastrointestinal bleeding or intracranial bleeding or recurrent VTE).

The CS reported the primary objective of Hokusai-VTE was to prove the non-inferiority of edoxaban versus warfarin in the prevention of recurrent symptomatic VTE at 12 months following an acute VTE event. Non-inferiority was proven based on the non-inferiority margin for the hazard ratio (HR) <1.5 (upper bound of the HR). The ERG notes that the company reported that edoxaban 60mg OD demonstrated non-inferiority to adjusted-dose warfarin for the primary efficacy outcome (HR, 0.89; 95% CI: 0.703 to 1.128) However, following the attainment of non-inferiority, superiority was tested for, but was not reached.

For patients receiving warfarin the company reported data for the INR according to the TTR. TTR was 63.5 % at INR 2.0 to 3.0 and 77.1% for INR of 1.8 to 3.2. The subgroup analysis based on centres with different levels of TTR was reported and demonstrated no statistically significant differences between study drugs.

The primary safety endpoint was major bleeding events in Hokusai-VTE. Statistically significantly fewer patients in the edoxaban group (298/4118) had MBs and CRNMBs compared to the warfarin group (368/4122). However, the statistical significance of this composite outcome is driven by the significant reduction for CRNMB (HR 0.80, 95% CI: 0.68 to 0.93). The CS reported edoxaban also had numerically fewer MBs than warfarin (56 (1.4%) vs 66 (1.6%)), but this was not statistically significant. The ERG notes the number of fatal bleeds in the two groups was 2 (<0.1%) in the edoxaban group and 10 (0.2%) in the warfarin group.

Bleeding was reported in a number of anatomical sites in patients in both arms of the Hokusai-VTE trial. The CS reported the bleeding events in the edoxaban group were lower or equal to that of the warfarin group at all sites except for the gastrointestinal tract and vagina. Despite this claim the ERG notes results from the tests of statistical significance were not provided for these anatomical sites of bleeding.

Edoxaban demonstrated a broadly consistent bleeding profile across pre-specified subgroups. In subgroups typically associated with a high risk of bleeding edoxaban was associated with numerically lower rates of bleeding than warfarin. However, the ERG notes that the estimates for only 18/47 categories of subgroups analyses are presented in the CS. The company's assertion that there was no difference between edoxaban and warfarin with regards to additional safety endpoints, including major adverse events and with regards to all-cause mortality was not explicitly tested for statistically.

The CS reported that all cause mortality was comparable between the two groups; n=35 (0.8%) in the edoxaban group and n=33 (0.8%) in the warfarin group (Table 16). Although the CS referred to data

for the overall study period the ERG notes the data in Table B 19 (CS, pg76) relates to the study on-treatment period only. The ERG notes the lack of tests of statistical significance mean the potential relevance of these events is not explicitly made in the CS.

Edoxaban is reported as being superior to warfarin for the principal safety end point (composite of MB and CRNMB). The ERG notes edoxaban was not superior to warfarin for MBs.

As a result of the absence of head-to-head trials, the company conducted NMAs aimed to provide relative treatment effect estimates between different NOACs using warfarin as a common comparator. The trial network created by the company for the trials identified in their systematic review forms a "radiating star" in which warfarin is the treatment that links the other treatments together. The impact of which is that as there are no "cross-links" and only the separate NOAC studies vs warfarin inform the treatment effect of each comparator in the network.

The results demonstrate that edoxaban has a similar risk profile compared to the other NOACs (and warfarin) for VTE recurrence, MB, VTE-related death and net clinical benefit (composite of VTE recurrence events and MBs). The ERG notes that the result for net clinical benefit (composite of VTE recurrence events and MBs) is not available for dabigatran. The ERG also considers that the non-inferiority design of the original studies has limited the opportunity for any NOAC in the network to have demonstrated a significant difference from any other treatment in the network, should one exist for prevention of VTE recurrence.

The ERG requested details on the frequency and nature of monitoring in Hokusai-VTE during the clarification stage and remains uncertain as to whether the monthly monitoring arrangements used in the trial would be required for edoxaban in clinical practice. The ERG is aware that a potential key advantage of NOACs as stated in the CS is the lack of need for routine monitoring. The ERG notes that the dose of edoxaban is related to variable patient factors and the ERG thus considers that clinicians will be required to at least periodically weigh patients, measure their creatinine clearance (CrCl) and monitor their use of permeability-glycoprotein (P-gp) medication.

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

The primary objective of Hokusai-VTE was to compare outcomes of patients receiving initial LMWH followed by edoxaban alone with LMWH overlapping with warfarin followed by warfarin alone for the treatment and prevention of recurrence of acute symptomatic VTE. The ERG notes that patients with low body weight (≤ 60kg), moderate renal impairment or concomitant potent P-gp inhibitor use were recommended to take the lower 30mg dose of edoxaban. The ERG notes that trial patients were monitored on a monthly basis but is uncertain as to whether the monitoring arrangements used in the trial would also be required for edoxaban in clinical practice.

The duration of Hokusai-VTE was 12 months and patients were intended to receive treatment for a minimum of 3 months and a maximum of 12, at the discretion of the treating physician. The ERG's clinical experts have advised that in routine clinical practice treatment for PE acute treatment is more likely to be 6 months and for DVT 3 months unless requiring ongoing treatment or secondary prevention in which case treatment will also be lifelong. The ERG received clarification from the company about the number of patients who were still on treatment at 6 months, this represented 5674/8230 (69%) of study patients. The ERG notes both the company and clinical experts are aware that this high proportion of trial patients who received longer-than-usual durations of treatment may indicate the Hokusai-VTE study population is high-risk and consequently may not reflect the population of patients routinely seen in UK clinical practice.

Clinical experts have advised that the Hokusai-VTE had a younger population and a higher percentage of Asians than they would expect, which does not represent the VTE population who are generally seen in the UK. However, clinical experts advising the ERG have commented that similar differences exist in trial populations for other NOAC drugs.

The primary efficacy outcome in the Hokusai-VTE trial was incidence of symptomatic recurrent VTE (composite of recurrent DVT, new non-fatal symptomatic PE, and fatal PE) during the 12-month study period. The ERG clinical experts advise this is a reasonable length of follow-up.

The primary safety outcome, major bleeding events was a composite of MB and CRNMB occurring either during treatment or within 3 days after interrupting or stopping the study drug. The secondary efficacy outcome in Hokusai-VTE was a composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period.

A total of 8292, patients were recruited to the trial but 52 did not receive a single dose of the study drugs and were not included in the analysis. The modified intention to treat (mITT) analysis was based on 8240 patients and 130 (3.2%) in the edoxaban group and 146 (3.5%) in the warfarin group experienced the primary outcome.

In the subgroup analysis of the Centres with TTR, the ≥25th to <50th percentile (55.82%–64.03%) produces a HR 1.09 (95% CI: 0.641 to 1.848) and Center-Level INR-TTR for Warfarin subjects ≥ 50 < 75% Percentile (70.41%) produces a HR 1.05 (95% CI: 0.681 to 1.610) (CS, pg 70). The ERG agrees that there are no significant differences in the primary efficacy endpoint by centre level INR-TTR. However, given the magnitude of unce rtainty in the individual estimates (as illustrated by the wide 95% CIs), there is insufficient evidence to establish that TTR has no impact on the relative efficacy of edoxaban compared to warfarin.

The ERG notes a non-statistically significant difference in recurrent endpoint events for patients with index DVT taking edoxaban in the first 30 days of the trial (21 edoxaban vs 15 warfarin). This effect was much less marked in the index PE group (9 edoxaban vs 7 warfarin) no test of statistical significance is presented by the company.

1.4 Summary of cost effectiveness evidence submitted by the company

The company developed a *de novo* cohort Markov model in Microsoft Excel®. The base case model assumes that patients receive treatment for 12 months, either with warfarin, edoxaban or other NOAC. The company reports that the model captures both the treatment and management of VTE.

All VTE patients enter the model in the on treatment health state. This health state also portrays the VTE index health state as all patients entering the model have been diagnosed with VTE (acute DVT, with or without PE, or PE). Whilst on treatment, patients can experience a recurrent VTE event or suffer a treatment-related adverse event like heparin-induced thrombocytopenia (HIT), CRNMB or a MB. Patients on treatment can also develop CTEPH, which can develop into long-term CTEPH (LT-CTEPH), or experience a stroke. Patients, who do not die from a stroke, move on to the post-stroke health state. Patients experiencing a HIT event, a CRNMB, a MB, CTEPH or a stroke are assumed to stop anticoagulation treatment whilst experiencing the event.

After 12 months of anticoagulation therapy (with edoxaban or any of the comparator drugs), all patients (if alive) move to the off treatment health state where they stay for the remaining 49 years of the analysis. During the initial 12-month treatment period, patients can also move into the off treatment health state if they experience events such as HIT, CRNM, MB and CTEPH. After moving to the off treatment health state at 12 months, patients can still experience recurrent VTE however they do not receive any drug therapy after they move from the recurrent event health state.

Whilst in the on treatment and off treatment health states, patients are at risk of developing post-thrombotic syndrome (PTS). Patients can die at any point in the model. In their submission, the company reports that the probability of VTE recurrence varies with time, with the highest risk of recurrent VTE occurring within the first year after the index event. It is stated that the model takes this into account by using five different time periods since the index event.

Treatment effectiveness within the model is implemented through transition probabilities between the different health states. Clinical inputs used in the economic model were taken from Hokusai-VTE, the NMA and published literature.

In the model, treatment effectiveness impacts a patient's transition from the on treatment (i.e. VTE index event) to the recurrent VTE health state. It also impacts the probability of patients experiencing CRNMB and MB and discontinuing treatment thereafter. This means that in the economic analysis,

the type of anticoagulation therapy the patient receives (warfarin or a NOAC) determines the likelihood of a patient experiencing a recurrent VTE event (acute DVT, with or without PE, or PE), a bleeding event (CRNMB or MB) and discontinuing treatment after bleeding. All other transition probabilities are assumed independent of the type of anticoagulation therapy given to patients. All transition probabilities after one year were assumed to be equal to the respective probability between the 99th day and the 364th day.

The probability of recurrence and bleeding in the intervention arm of the model (and in the dabigatran and rivaroxaban arms) was estimated by taking the probability of recurrence for warfarin estimated in Hokusai-VTE and then applying the six-month odds rations (ORs) obtained through the NMA, comparing warfarin to the other NOACs.

The mortality associated with specific events in the model was estimated mainly using Hokusai-VTE data but also with data found in the published literature. Age-dependant mortality was included in the model, along with disease specific mortality. Events such as index VTE, VTE recurrence, MB, CTEPH (long-term or not) and stroke are assumed to be associated with an increased mortality risk.

Within the model, all patients are assigned a baseline utility value adjusted by age according to the UK population norm taken from Kind *et al*. 1998. Health state-related disutilities were then applied to a patient's baseline utility value in each health state. For the majority of the health states, disutilities were applied multiplicatively whilst for VTE recurrence and HIT, the disutilities were applied additively. The utility associated with the index VTE event was derived from the Hokusai-VTE EQ-5D data, whilst all other utility values were taken from available literature.

Warfarin, edoxaban and dabigatran treatments are costed together with an initial (or simultaneous in the case of warfarin) dose of parenteral heparin (LMWH or unfractionated heparin). The company also estimated INR monitoring costs for patients receiving warfarin treatment. The remaining anticoagulant regimens were assumed not to require any monitoring visits throughout the duration of treatment. During their recurring VTE treatment period patients incur the costs of diagnosis and hospitalisation.

Edoxaban plus initial heparin parental treatment presents a cost per QALY gained of £2,451 compared with warfarin plus initial heparin parental treatment. Compared with dabigatran, edoxaban produces cost savings of £38 and results in more QALYs, thus is considered dominant. Rivaroxaban dominates edoxaban, being less expensive and producing more QALYs than edoxaban.

1.5 ERG commentary on the robustness of the cost-effectiveness evidence submitted by the company

Model structure

The ERG found a lack of consistency in the approach followed by the company with regards to modelling specific VTE complications. Some of the model assumptions were also found to be clinically implausible. Specifically, the ERG is not convinced by the clinical plausibility of assuming that:

- For patients experiencing recurrent VTE events or MBs, their QoL is only impacted during 2 weeks, after which they return to the QoL experienced before the events. This issue is related with the decision to combine 2-week cycles with tunnel state structures;
- Patients return to their original anticoagulation therapy after a recurrent event (even though it is likely that the original therapy was not effective in preventing recurrence);
- Patients experiencing recurrent VTE after (or at) 12 months do not receive anticoagulation treatment for more than 2 weeks. In clinical practice, patients off anticoagulation treatment who experience a recurrent VTE event will be given anticoagulation therapy (whether returning to their original therapy regimen or a new one) and are in fact likely to need anticoagulation therapy for the reminder of their lives;
- The fact that CTEPH and stroke were considered treatment-related complications. The ERG's clinical experts advised that CTEPH is not an adverse event associated with anticoagulation therapy, but is instead a VTE complication. Therefore, patients in the model should be at risk of CTEPH at all times. The same applies for ischaemic strokes. Patients experiencing CTEPH discontinue anticoagulation treatment. Patients with CTEPH need anticoagulation therapy as recurrence might be catastrophic in these patients;
- Patients are at risk of developing PTS only in the on treatment and off treatment health states. PTS is a VTE-related complication and as such patients should be at risk of it at all times.
- The ERG is not clear why the model depicts a rare event like HIT in a separate health state but simplifies the increase in risk while receiving anticoagulation treatment for serious adverse events like ICH.
- The ERG is not clear why ischaemic strokes were included in the model when the company decided to exclude other cardiovascular events such as MI, as it believed that the type of anticoagulation therapy does not impact these events.

Treatment effectiveness

The ERG is concerned with the modelled effectiveness of edoxaban (and the other NOACs) in preventing recurrent VTE. The main issues identified are:

- The underlying assumption of proportional hazards across the Hokusai-VTE statistical analysis, the NMA and the economic analysis does not seem to be valid when visual inspection of Kaplan-Meier (KM) curves is undertaken. Furthermore, this assumption wasn't justified or validated by the company.
- Analysis of the phase-specific trial data for risk of recurrence with edoxaban does not seem to agree with the modelled risk of recurrence for edoxaban. Overall the risk of recurrence for edoxaban used in the model (and obtained through the NMA estimates) seems to be underestimated.

Treatment effectiveness – bleeding events

Visual inspection of the KM curves for bleeding events indicate the proportional hazards assumption could hold for CRNMB and MB when considered together. The ERG is concerned with the following issues with regards to the estimation of bleeding events in the model:

- Given that the phase-specific analysis was used for the estimation of the recurring events, the same approach should have been taken for the estimation of bleeding events. Using these different analyses for the estimation of recurrent VTE events and treatment adverse events bias the analysis as second (and potentially third) recurrent events are being included in the analysis whilst only first bleeding events are being considered, resulting in an underestimation of bleeding events.
- The company has not provided any justification why the phase-specific data were not used in the economic analysis (given they were available) and given that using the phase-specific data would have enriched the time-dependent analysis.
- When comparing the difference in the number of events occurring in the model and in the time-to-event analysis it seems that the potential bias in CRNMBs and MBs works in different directions, with the difference in CRNMBs favouring edoxaban and the difference in MBs favouring warfarin.

Other clinical input parameters

The ERG is concerned about the way the stroke health state was modelled. The probability of stroke used in the model and taken from Hokusai-VTE and reflects the probability of ischaemic and intracerebral haemorrhage (ICH) events in the trial. These two events are different and clinical opinion sought by the ERG clarified that after an ischaemic stroke patients are likely to stop anticoagulation treatment for a few weeks but most likely will go back on anticoagulation treatment. Conversely, after an ICH the patient is likely to stop receiving anticoagulation treatment forever. Therefore ICH events should have been modelled separately. In addition, this would have avoided the

double-counting of ICH in the stroke and MB states and would have allowed the analysis to capture the appropriate costs and benefits related to ICH, which are underestimated in the MB state.

Even though ICH has a catastrophic impact on a patient's wellbeing (which is not reflected in the MB state), the number of strokes (both ICH and ischaemic) events in the model is very low (0.63% over one year in both arms of the trial, respectively) and the number of stroke events in the warfarin and the edoxaban arms is not statistically different (HR 1.00; 95% CI: 0.58 to 1.72). Therefore the ERG acknowledges that even though the inclusion of a stroke health state in the company's model is methodologically flawed, it is unlikely to have a substantial impact on the final ICER.

The relevance of the HIT state in the overall analysis is also questionable, and similarly to other VTE-related events in the model, the inclusion of this health state doesn't have a substantial impact on the final ICER.

The company does not provide any justification as to why CTEPH data from Hokusai-VTE were not used to model these events in the economic analysis (or acknowledges the existence of these data). This should have been reported more transparently, together with the rationale behind why trial data were not used in the analysis. Even though the impact on the economic analysis is unlikely to be relevant, the ERG disagrees with the company assumption that CTEPH is a treatment-related adverse event as CTEPH is a VTE-related condition.

The company does not provide any justification for why PTS data from Hokusai-VTE were not used to model these events in the economic analysis (or acknowledges the existence of these data). This should have been reported more transparently, together with the rationale behind why trial data were not used in the analysis. Clinical experts to the ERG advised that PTS events reported in Hokusai-VTE are less prevalent than it would be expected in clinical practice. This seems to be the case with other events (e.g. CTEPH). The ERG notes that because the probability of PTS is the same across the different treatment arms, increasing the prevalence of PTS in the model would unlikely impact the final ICER.

Similarly to CTEPH, PTS is a VTE-related condition and as such it is clinically implausible that PTS can only occur in the on treatment and off treatment health states.

Patient populations

The average age of patients in the Hokusai-VTE trial is 56 years. Clinical opinion sought by the ERG informed that this reflects a younger population than the average VTE population presenting in the UK. Around 43% of the study population were women and 59% of patients presented with index DVT only. Clinical opinion to the ERG indicated that this broadly reflects clinical practice. Another population characteristic which hasn't been directly included in the economic model but is worth

mentioning is the reduced number of UK patients in the trial. In the warfarin arm of Hokusai-VTE, there are 1.6% of UK patients whilst in the edoxaban arm there, 1.1% of patients are from the UK.

Overall, for the baseline characteristics simulated in the economic model, it seems that the respective values were not dissimilar across intervention and comparator studies (i.e. Hokusai-VTE compared to other NOAC studies for VTE). However the proportion of patients with DVT (alone) was slightly higher in the RE-COVER trials than in Hokusai-VTE. Nonetheless, study populations varied significantly with respect to other characteristics. For example, the proportion of Asian patients in the study populations was around 3% in the RE-COVER trial and 21% in the RE-COVER II trial.

Parenteral therapy

Clinical opinion sought by the ERG advised that the proportion of patients receiving different types of LMWH (25% dalteparin, 25% tinzaparin and 25% enoxaparin) is not reflective of current clinical practice as enoxaparin is the most commonly used LMWH, with dalteparin and tinzaparin use combined being similar (or slightly higher) to the use of enoxaparin. Nonetheless, the proportion of the different types of LMWH in the model as this is unlikely to carry any relevant impact in the final ICER.

The company assumed that 25% of patients receive unfractionated heparin in the economic analysis; however the ERG's clinical experts indicated that less than 5% of patients receive this drug in clinical practice. The company did not include fondaparinux in their economic analysis (which is consistent with Hokusai-VTE).

In the economic model, the lead-in parenteral therapy duration is different for warfarin and the NOACs. Patients in the warfarin arm of the model receive 8.5 days of heparin treatment while patients in the other arms of the model (edoxaban and dabigatran) receive heparin for the initial 5 days of anticoagulation treatment. The duration of heparin treatment for the warfarin and edoxaban arms of Hokusai-VTE was 7.5 days and 8.5 days, respectively. Clinical opinion sought by the ERG explained that the blinding procedures in the trial were likely to have led to an increase in the heparin treatment duration when compared with clinical practice. It was also noted that 6.5 days is the most common period for overlapping parenteral therapy with warfarin and that the edoxaban licence defines a minimum of 5 days of heparin lead-in treatment. The company did not present any justification for the choice of different heparin treatment durations for the warfarin and the edoxaban (and dabigatran) arms of the model.

Edoxaban and warfarin therapy

In Hokusai-VTE, all patients received a minimum of 3 months of treatment. After 3 months, the remaining duration of treatment was at the physician's discretion, up to a maximum of 12 months.

The company mentions that, "*this flexibility in treatment duration is uncommon in clinical trials, and potentially empowers the trial to reflect clinical practice more than do other studies of VTE treatment and secondary prevention"* (CS, pg 44). Clinical opinion sought by the ERG agreed that the flexibility in the treatment duration in the edoxaban trial is more reflective of "real-life" practice than other studies where the treatment duration is fixed.

In the model, the base-case treatment duration was 12 months. Scenario analysis was undertaken to reflect treatment regimens of 3 months, 6 months and lifelong treatment. In Hokusai-VTE around 60% of patients received more than 6 months of therapy whilst 40% of the total number of trial patients carried on to receive 12 months (or longer periods) of treatment.

The company reports that the recommended dose for edoxaban is 60mg once daily, or 30mg in patients with moderate or severe renal impairment (CrCI 15–50 mL/min), patients with low body weight ≤60 kg or patients receiving concomitant P-gp inhibitors (cyclosporine, dronedarone, erythromycin or ketoconazole).

In the economic model there were no assumptions made with regards to the dose of edoxaban administered to patients. The company mentions that the daily cost of edoxaban is assumed to be £2.10, based on the assumption [redacted] . Therefore the dose of edoxaban in the economic analysis is not explicitly stated (or costed).

Mortality

The ERG is satisfied with the data and methodology used to model gender and age-related mortality in the model. The ERG has some concerns regarding the disease-specific mortality included in the model. These are related to the data used but also with the methodology employed. More specifically, the ERG raises the following issues:

- The analysis set taken from Hokusai-VTE to model mortality. The safety analysis set (on-treatment study period) should have been used instead of the mITT analysis set (overall study period).
- The mortality data analysed in Hokusai-VTE (on-treatment study period) is based on recurrent VTE mortality and not on index VTE mortality, therefore these data should have been used by the company to model recurrent VTE related mortality instead of index VTE mortality.
- The mortality associated with recurrent VTE in the model is overestimated. Even in the case where the safety analysis set (on-treatment study period) is used to model the mortality associated with recurrent VTE, there seems to be an overestimation of death

events compared to clinical reality. This is likely to be related to the high number of "unexplained deaths where VTE cannot be ruled out" reported in the trial. These account for 91% of the VTE-related deaths reported in Hokusai-VTE.

- The mortality probability associated with stroke does not include ICH deaths. Given that the probability of stroke in the model includes ICH, there is clearly a disconnection between the probability of stroke and the stroke-related mortality. This reinforces the ERG comments on the inconsistency and lack of transparency in the estimation of several model inputs in the economic analysis.
- Overall survival in the model seems to be overestimated despite the fact that recurrent VTE-related mortality is overestimated in the model.

Health-related quality of life

The ERG is reasonably satisfied with the estimation of patients' QoL in the model. Even though there are some methodological issues in the company's approach these are unlikely to carry a considerable impact on the final ICER. The main issue identified was the underestimation of the impact of recurring and MB events in patients' wellbeing. The ERG points to the lack of transparency in the identification and selection of the QoL sources used in the model.

Costs

The ERG is concerned with the lack of clinical plausibility of some of the assumptions underlying the cost estimation in the model. The ERG also disagrees with the monitoring resources assumed for warfarin and the NOACs. The issues identified by the ERG can be summarised as:

- The company assumed 100% of patients would receive inpatient care for their index DVT or PE event. Clinical opinion sought by the ERG advised that approximately 30% of patients with proximal DVT and 50% of patients with PE are likely to be treated as inpatients in UK clinical practice. Clinical experts also advised that all patients would receive diagnostic tests (not 50% of patients as assumed in the company's base case) and that the tests received would not be the same for DVT and PE events.
- The company assumed that patients experiencing a recurrent event go back to their original anticoagulation therapy after the event, even if the regimen hasn't been effective in preventing recurrence. The company also assumes that after 12 months, recurring patients only receive 2 weeks of anticoagulation therapy. Clinical opinion sought by the ERG indicates that both assumptions are highly implausible.
- It is likely that the company is overestimating the monitoring regimen required for warfarin patients and underestimating the monitoring regimen for edoxaban (and the other NOACs) patients.

Analysis

The ERG is concerned with the relevance and robustness of the OWSA. The choice of the input parameters to be varied wasn't justified by the company and, in some cases, reflects clinically implausible scenarios. The three inputs identified as being the key model drivers for edoxaban vs warfarin (probability of stroke and CTEPH with NOACs and probability of stroke with warfarin) are based on the assumption that the probability of these events might be different depending on the treatment received. As would be expected, when the probability of CTEPH or stroke is varied just in one arm of the economic model, the ICER changes substantially as these are expensive and serious conditions. However, varying the probability of these events in only one arm of the model doesn't have face validity, as there is no clinical rationale for CTEPH or stroke to be linked to the type of treatment received. By changing implausible parameters in the sensitivity analysis (but which have a substantial impact on the ICER), and by presenting only the eight most influential parameters in the model, the company rendered their OWSA largely irrelevant.

Additionally, there is a lack of transparency in the OWSA reported. Not only have the tornado diagrams not been provided in the model, but the macros running the OWSA do not work. Furthermore, the ERG manually ran the scenario where the probability of VTE recurrence with edoxaban was changed to its upper limit on the 95% Confidence Interval range (1.174) and obtained an ICER of £7,181. This hasn't been reported in the list of inputs with "noteworthy" impact, which included ICERs from around £10,000 to around £5,000.

The ERG is equally concerned with the validity of the PSA results. The company's decision not include key clinical parameter estimates from the NMA considerably removes the usefulness of the PSA.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths of the clinical evidence

The ERG considers that the large sample of patients included in the Hokusai-VTE trial analysis produces strong clinical evidence that edoxaban is non inferior to warfarin in the treatment and prevention of VTE in adults managed world-wide. The evidence for a non-inferior effect of edoxaban on the secondary outcomes of major bleeding and non clinically relevant major bleeding is also strong. The Hokusai-VTE trial appears to have been well conducted and the ERG considers the data are valid.

1.6.2 Strengths of the economic analysis

The company's analysis was based on Hokusai-VTE, a high quality randomised controlled trial. The formulae within the economic model are generally sound.

The company conducted subgroup analyses for PE patients and for different treatment durations which are relevant within NICE final scope.

1.6.3 Weaknesses and areas of uncertainty in the clinical analysis

Although the baseline characteristics of the patients in the two arms of the Hokusai-VTE trial are similar, the population is slightly atypical of those who require treatment in UK;

- a high proportion of individuals from Asian countries,
- younger and
- took the study drugs for longer.

There was some evidence of poorer outcomes in certain geographical regions but the ERG is unable to comment on the relevance of this to the UK. The ERG notes a potential key advantage of NOACs as stated in the CS is the lack of need for routine monitoring. The ERG is uncertain as to the exact monitoring arrangements that would be required for edoxaban in clinical practice, especially because the dose of edoxaban is related to variable patient factors. Clinicians will therefore be required to at least periodically weigh patients, measure their CrCl and monitor their use of Permeability-glycoprotein (P-gp) medication.

Evidence for the effect of edoxaban on people with active cancer is not presented by the company in its submission. A systematic review of NOACs (edoxaban, dabigatran, rivaroxiban and apixaban) versus LMW heparins in the management and prevention of VTE recurrence in people with cancer was published after the company completed the submission. The review concluded the NOACs seem to be as effective and safe as the LMW heparins for people with active cancer.

1.6.4 Weaknesses and areas of uncertainty in the economic analysis

The ERG considers that more transparency should have been employed in the selection and presentation of data inputs. Important data such as CTEPH and PTS data collected in Hokusai-VTE were not reported (or acknowledged) in the CS.

The ERG is concerned with the lack of clinical validity of some of the assumptions made in the economic model. The ERG's main concerns are related to:

- The modelled effectiveness of edoxaban (and the other NOACs) in preventing recurrent VTE. Analysis of Hokusai-VTE for the risk of recurrence with edoxaban does not seem to agree

with the modelled risk of recurrence for edoxaban. Overall the risk of recurrence for edoxaban seems to be underestimated in the economic analysis.

- Given that phase-specific data were used for the estimation of the recurring events, the same approach should have been taken for the estimation of bleeding events. Using different analyses sets for the estimation of recurrent VTE events and treatment adverse events bias the analysis, resulting in an underestimation of bleeding events.
- When comparing the difference in the number of events occurring in the model and in the time-to-event analysis it seems that the difference in CRNMBs and MBs works in different directions, with the difference in CRNMBs favouring edoxaban and the difference in MBs favouring warfarin.
- The mortality associated with recurrent VTE in the model is overestimated. Even in the case where the safety analysis set (on-treatment study period) is used to model the mortality associated with recurrent VTE, there seems to be an overestimation of death events compared to clinical reality. This is likely to be related to the high number of "unexplained deaths where VTE cannot be ruled out" reported in the trial. These account for 91% of the VTE-related deaths reported in Hokusai-VTE.
- It is likely that the company is overestimating the monitoring regimen required for warfarin patients and underestimating the monitoring regimen for edoxaban (and the other NOACs) patients.

The ERG is concerned that uncertainty in the model and respective outputs hasn't been properly explored by the company. The relevance and robustness of the OWSA and PSA are flawed and these analyses are unlikely to have truly captured the uncertainty around the final ICER.

The final ICER is considerably sensitive to minor changes in the monitoring schedules of warfarin and edoxaban.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The scenario analyses undertaken by the ERG are the following:

1. The ERG changed the odds ratio (OR) comparing the probability of recurrence for edoxaban with the probability of recurrence for warfarin used in the economic analysis to one to reflect not only the lack of statistical significance in the difference of recurring VTE events in the NMA and Hokusai-VTE but also to reflect clinical expert opinion.

2. The ERG used the company's phase-specific data to model the baseline probability of bleeding events with warfarin, instead of the time-to-event data used by the company in the base case analysis.
3. The ERG changed the OR comparing the probability of MB for edoxaban with the probability of MB for warfarin used in the economic analysis to 1 to reflect not only the lack of statistical significance in the difference of MB events in the NMA and Hokusai-VTE but also to reflect clinical expert opinion.
4. The ERG conducted a scenario analysis using the phase-specific data for recurrent VTE-related mortality obtained in Hokusai-VTE.
5. The ERG conducted a scenario analysis using the recurrent VTE-related mortality estimate used in TA 327, where the probability of dying of recurrence for dabigatran is reported as 3%.
6. The ERG increased the duration of the decrement in a patient's QoL after recurring VTE and MB in the model.
7. The ERG increased the duration of the decrement in a patient's QoL after recurring VTE and a MB in the model using the values reported in Cohen *et al*. 2014 to model recurrent VTE.
8. The ERG considered a scenario where the disutility associated with CRNMBs was removed from the economic analysis.
9. The number of INR monitoring visits for warfarin patients was reduced from 24 visits in the first year to 18 visits, to reflect three visits per quarter after the first 9 visits over the initial three months, instead of five visits per quarter.
10. A revised 5mg/day warfarin cost using PCA 2014 for all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg) was used in the model.
11. The treatment duration of heparin was changed to reflect the Hokusai-VTE trial (i.e. 7.5 days for edoxaban and 8.5 days for warfarin).
12. The treatment duration of heparin was changed to reflect clinical experts' advice (i.e. 6.5 days for warfarin and 5 days for edoxaban).
13. The ERG assumed that 30% of recurrent DVT cases and 50% of recurrent PE cases require hospitalisation.
14. Index and recurrent VTE diagnostic costs were applied to 100% of patients and according to the type of VTE event: DVT, £143.23; PE, £307.23.
15. The ERG conducted a scenario analysis in which the NICE CG92 estimate for the LT-CTEPH cost was applied in the model (£1,280 at 2014 price-year), combined with anticoagulation treatment costs.
16. The ERG removed the utility decrement associated with warfarin from the economic analysis.
17. The ERG removed the stroke health state from the economic model.

18. The ERG conducted scenario analysis to reflect different options for NOAC monitoring. As clinical opinion advised that this likely varies across clinical practice, the ERG undertook three scenarios, in accordance to the clinical advice received:
    a. Most conservative scenario: patients on NOACs have an annual appointment with their GP where they receive no tests;
    b. Average scenario: patients on NOACs receive an annual visit where they receive U&E;
    c. Less conservative scenario: patients receive biannual visits where they receive U&E.
19. The number of INR monitoring visits for warfarin patients was reduced from 24 visits in the subsequent years of treatment (for the company's scenario analysis of lifelong treatment) to 10 visits per year.

The scenario analyses conducted by the ERG showed that the number of INR monitoring visits required by patients on warfarin and edoxaban are the main key drivers of the economic analysis. The six main drivers of the economic analysis identified by the ERG are as follows:

- Number of INR monitoring visits assumed for warfarin. The ERG notes that assuming two less visits per quarter in the final three quarters of the year lead to an increase in the final ICER from £2,451 to £18,953 per QALY gained.
- The level of monitoring assumed for patients on NOACs. Even though the company assumed that no monitoring is required for patients on NOACs above the standard of care for VTE patients, clinical expert opinion advised the ERG that some monitoring takes place to assess a patient's kidney function. Depending on the level of monitoring assumed, the ICER comparing edoxaban to warfarin ranges from £4,780 to £7,315.
- The utility loss associated with warfarin treatment. When the ERG assumed that warfarin treatment does not have an impact in patients QoL the ICER for edoxaban compared with warfarin increased to £6,902 per QALY gained.
- The duration of the parental heparin treatment given before or simultaneously with edoxaban and warfarin respectively.
- The effectiveness of edoxaban compared with warfarin with regards to the probability of recurrence. In the model this is translated in the OR for recurrent VTE used in the analysis.
- The data used to model VTE-related mortality in the model.

The ERG notes that in all the scenario analyses, rivaroxaban dominates edoxaban. With regards to dabigatran, the two key model inputs impacting the final ICER for edoxaban vs dabigatran are the OR used to model the probability of recurrence for dabigatran compared with warfarin and the data used

to estimate the VTE-related mortality in the model. When the data from TA327 are used for VTE-related mortality in the model, the ICER for edoxaban vs dabigatran goes from dominant to £28,116.

Given the uncertainty in the NMA results and due to it being derived from a direct comparison in a randomised controlled trial (Hokusai-VTE), the ERG's alternative base case ICER incorporates all the Hokusai-VTE estimates available in the model. More specifically, the ERG incorporated scenario analyses 2,4,6,8,9,10,11,13,14,15,17 and 18b listed above. The final alternative base case ICER obtained by the ERG is £26,028 per QALY gained.

The ERG notes that the alternative base case ICER reflects a lead-in heparin regimen of 7.5 days for edoxaban. Changing this assumption in the model to reflect 5-days lead-in of heparin for edoxaban decreases the final ICER to £23,766. The ERG also notes that the alternative base case ICER presented incorporates the underlying proportional hazards assumption made in the Hokusai-VTE data analysis. However the ERG does not have access to the individual patient-level data necessary to model the trial without the use of ORs.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The Evidence Review Group (ERG) notes that the focus of this single technology appraisal (STA) is for the use of edoxaban 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 company's submission (hereafter referred to as CS), the company provides an overview of the key aspects of venous thromboembolism (hereafter referred to as VTE, a composite outcome of DVT and PE) and edoxaban tosylate relevant to the decision problem (CS; Section 2).

All information presented in the following sections that appear in boxes is taken directly from the CS unless otherwise stated and the references have been renumbered. The CS contains a description of the natural history of VTE (Box 1).

Box 1 (CS pg 19)

VTE is a vascular disease characterised by the formation of a blood clot (thrombus) in a vein. VTE consists of two clinical entities: DVT and PE. DVT is the formation of a thrombus in the deep veins of the extremities. PE is an obstruction of a pulmonary artery, caused by a deep vein thrombus that breaks off, migrates to the pulmonary arterial system and occludes a pulmonary artery by a blood clot that has formed in the venous system of the extremities and migrated to the lungs.[1, 2]
Abbreviations used in the box: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

The ERG group considers the natural history section of the company submission (Box 1) could more fully explain the prognosis for each clinical entity. PE is fatal if the thrombus blocks the blood supply to the lungs but there are several differential diagnoses and it can be mistaken for myocardial infarction and pneumothorax, in particular. Quick and accurate diagnosis and treatment are imperative to avoid death but PE can be difficult to diagnose based on clinical exam and patient history alone. It is estimated that only 25% of patients who present with the symptoms of PE do in fact have the condition.[3, 4] DVT can also be fatal if it leads to a PE. The ERG notes that in addition to the veins of the legs, blood clots can also arise in the vessels of the arms and pelvis.[5] These 2 clinical entities of VTE are associated with distinct additional complications. These are discussed in the complications section below.

The clinical manifestations of VTE presented in the CS are shown in Box 2.

Box 2 Clinical manifestations (CS; pg 19)

DVTs are asymptomatic for more than 50% of patients.[6] In symptomatic DVTs, the symptoms are non-specific as they overlap with other conditions (i.e., muscle strain or skin infection) [1] and include swelling, erythema, tenderness, soreness, and pain in the affected leg. The clinical presentation of PE is mostly non-specific and heterogeneous, ranging from asymptomatic to acute presentation with obstructive shock, dyspnoea, syncope or death.
Abbreviations used in the box: DVT, deep vein thrombosis; PE, pulmonary embolism

The ERG would add that DVT and PE share the same pathological process. One study has shown that 40% of patients with DVT also had PE detected on lung scans.[5] Pulmonary emboli can be incidental and clinically unimportant or can cause unexplained, sudden-onset, respiratory symptoms and chest pain for which patients will seek health care in emergency settings.[7] It has been estimated that for 25% of people with PE the first presentation is sudden death.[8] In a cohort of patients identified using data linkage techniques the proportion of people with VTE who died after first presentation was 15%.[9]

The ERG considers the company has summarised the epidemiology well (CS; pg 19) and would only add the association of VTE with gender and also the rate of mortality. The mortality rate from PE is high; studies in the US suggest 3-month mortality from PE ranges from 10% to 17.5% with men having higher fatality rates than women.[5]

The CS contains information about risk factors for VTE, as presented in the CS are shown in Box 3.

Box 3 Risk factors of VTE (CS; pg 20)

VTE can arise spontaneously (i.e. idiopathic or unprovoked), but in 50 to 70% of cases VTE is associated with acquired or inherent risk factors (i.e. provoked).[10, 11] PE and DVT share the same risk factors.[2, 11] VTE is considered to be 'provoked' in the presence of a temporary or reversible risk factor within the last 6 weeks to 3 months before diagnosis, and 'unprovoked' in the absence thereof.[12] Reversible risk factors include surgery (the risk being highest during the first two post-operative weeks, but remaining elevated for two to three months), trauma, immobilisation, pregnancy, oral contraceptive use or hormone replacement therapy.[12] Other main factors include age over 60 years, overweight, active cancer or cancer treatment (with varying risks for different types of cancer), inflammatory bowel disease, hip fractures, fractures of the lower extremities and proximal femur.[12, 13] Age has been identified as a strong risk factor for first VTE in several epidemiological studies.[13-15] For instance, a UK retrospective study reported that the incidence rate for first VTE events rises exponentially with age[13] This could be explained by both the accumulation of risk factors and the

biology of ageing.[16]
Abbreviations used in the box: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

The ERG considers these risk factors to be incomplete. The National Institute for Health and Care Excellence (NICE) Clinical Guideline on "Reducing the risk of venous thromboembolism in patients admitted to hospital"[17] identifies the following additional risk factors for VTE:

- critical care admission;
- dehydration;
- known thrombophilias;
- 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;
- varicose veins with phlebitis.

Importantly the ERG notes the CS does not include ethnicity as a risk factor for VTE. The is a significantly higher incidence among Caucasians and African Americans than among Hispanic persons and Pacific Islanders. White *et al.*[18] 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 ERG clinical experts concur that Asians have significantly lower incidence of VTE compared with the white population (spontaneous or unprovoked VTE is lower in Asians but they experience a similar risk of provoked VTE, post surgery) which could impact on the overall VTE incidence. The Asian population is also thought to be at a lower risk of recurrence but they are unaware of published data in support of this.

The company summarises the risk of recurrence by combining PE and DVT as the outcome VTE. NICE guideline[3] states that "compared with a DVT, a pulmonary embolism (PE) is a stronger predictor of a future PE, and therefore initial presentation is likely to be a factor in the decision to offer long-term oral anticoagulation". The CS presents details of VTE recurrence as presented in the CS are shown in Box 4 below.

Box 4 VTE recurrence (CS; pg 21)

There is a high rate of recurrence after a first VTE event. The risk of recurrence varies with time, with the highest risk occurring within the first year after the index event. During the early period, active cancer and failure to rapidly achieve therapeutic levels of

anticoagulation appear to independently predict an increased risk of recurrence.[19, 20] Based on historical data, the recent ESC guidelines [12] indicate the cumulative proportion of patients with early recurrence of VTE (on anticoagulant treatment) amounts to 2.0% at 2 weeks, 6.4% at 3 months and 8% at 6 months. The cumulative proportion of patients with late recurrence of VTE (after 6 months, and in most cases after discontinuation of anticoagulation) has been reported to reach 13% at 1 year, 23% at 5 years, and 30% at 10 years.[16]
Abbreviations used in the box: ESC, European Society of Cardiology; VTE, venous thromboembolism

The ERG notes that in terms of prognosis, DVT has a higher probability of recurrence compared with PE, but the recurrent DVT is less likely to lead to a PE, the more serious event: In a study by Murin *et al*.[21] 86% of recurrent events after DVT were DVT, whereas 66% of recurrent events after PE were PE. Martinez *et al*.[9] found the recurrence of VTE to be 13%. Clinical expert advice to the ERG confirms PE patients more likely to be on long term prevention and the risk of further PE and fatality from PE is higher than from DVT.

The complications of VTE can lead to long term morbidities or mortality and as such they have implications for health care systems. The details of VTE complications as presented in the CS are shown in Box 5 below.

Box 5 VTE Complications (CS; pg 21)

In addition to recurrence, VTE is associated with complications, including post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).[1] PTS is a chronic complication of DVT, and affects 20% to 50% of patients within 2 years of the first DVT event.[22] It is caused by venous hypertension, resulting either in a residual venous obstruction or valvular reflux. PTS is characterised by persistent or intermittent pain, swelling, itching, tingling or cramping in the limb and skin ulceration. PTS is severe in 5% to 10% of cases, and often manifests as venous ulceration.[23] Moreover, recurrent DVT in the same leg is a strong risk factor for development of PTS (HR 6.4; 95% CI 3.1 to 13.3).[22] CTEPH is a serious long-term complication of PE. It is characterised by an increase of blood pressure in the pulmonary artery, and can cause right ventricular heart failure. Several studies produced estimates of the proportion of patients with PE affected by CTEPH ranging from 0.4% to 8.8%.[24-30] The most recent one estimated a rate of 5.4%.[30]
Abbreviations used in the box: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism

The ERG is aware that CTEPH 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*.,[24] 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.

2.2 Critique of company's overview of current service provision

The company's overview of current service provision included an overview of the management of VTE, (diagnosis, Box 6 and Figure 1 and an overview of how edoxaban fits into the current diagnostic pathway, Box 7). The CS provides a Table of all guidance issued by NICE for VTE (CS; Table A4, pg 23). The ERG received the following clarification response about the monitoring arrangements for the Hokusai-VTE trial as presented in Box 8. In addition, the company outline the numbers of patients in England and Wales who would be eligible treatment with edoxaban and explain the basis of their calculations, Box 9.

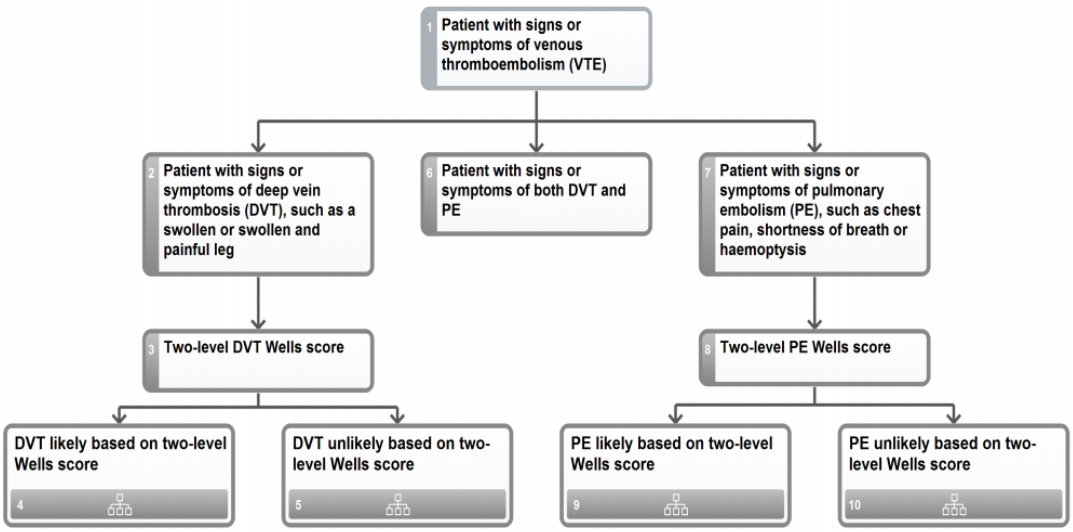
Box 9, together with factors relating to the estimated resource cost associated with (edoxaban) use in VTE, Box 10.

The company's submission includes part of the current clinical pathway recommended for the diagnosis of VTE in the UK (CS; pg 23). The ERG agrees that there are several differential diagnoses for VTE and this can make accurate diagnosis difficult, For example, the symptoms of PE can be similar to myocardial infarction or pneumothorax.

Box 6 Diagnosis (CS; pg 24)

Because symptoms are mostly non-specific, and DVT and PE are often asymptomatic (50-80% of cases), diagnosis is usually challenging and cannot be based only upon clinical examination.[1, 31] Patients with signs or symptoms of VTE are screened for signs or symptoms of DVT and/or PE. When signs of DVT and/or PE are found, an assessment of the patient's general medical history and a physical examination are carried out, to exclude other causes. Then a clinical and risk factors standardised assessment is used to determine the need for further diagnostic testing.[12, 32, 33] If DVT is suspected, the two-level DVT Wells score should be used to estimate the clinical probability of DVT (2 points or more indicates the DVT is likely), and an interim therapeutic dose of anticoagulation therapy for suspected DVT is given. If PE is suspected, the two-level PE Wells score is used to estimate the clinical probability of PE (more than 4 points indicated the PE is likely), and an interim therapeutic dose of anticoagulation therapy for suspected PE is given.
Abbreviations used in the box: DVT, deep vein thrombosis; PE, pulmonary embolism

Figure 1 Diagnosis pathway for VTE in primary, secondary and tertiary, as provided by NICE guidance (reproduced from Figure A1, CS pg 24)



The ERG believes this is incomplete and lacks some important aspects of the current diagnostic VTE pathway which have cost implications. Only part of the flow diagram of the diagnostic pathway from the current NICE guideline on the management of venous thromboembolic diseases and the role of thrombophilia testing is presented in the company's submission. (CS figure A3, pg 24,[3]). The diagnostic pathway is completely described in Appendix C in NICE CG 144.[3]

In summary, if a patient presents with suspected PE a general medical history, physical examination and a chest x-ray are all recommended to exclude other causes. Wells scores are then calculated to assess for the risk of PE and the patient also receives a D-dimer test, a laboratory assay which detects the level of the naturally-present blood protein D-dimer in a sample taken from the patient. Patients with symptoms of PE and a low risk Wells score but a positive D-dimer test are referred for a ventilation perfusion (V/Q) scan or Computerised Tomography Pulmonary Angiography (CTPA). Patients with a high risk Wells score may not receive a D-dimer test but can be directly referred for CTPA or V/Q scanning if locally available. Patients suspected of having PE may be offered anticoagulation treatment prior to the CTPA scan if they are either classed as high risk by the Wells score or have a positive D-dimer test.[3, 4, 34]

DVT patients with a Wells score of 2 may not have a D-dimer test but have an ultrasound scan and patients suspected of having DVT who have a Wells score of 1 or less but have a positive D-dimer test are also recommended to undergo ultrasound scanning within four hours. Patients may be offered anticoagulation treatment prior to the ultrasound if rapid access to ultrasound is not available and they are either classed as high risk by the Wells score or have a positive D-dimer test. Patients with a positive D dimer but whose US scan is negative are recommended to have a second US scan 6-8 days later.[3, 4, 34]

The ERG is aware that most patients suspected of having a VTE have their risk calculated using a Wells score but a number of other clinical prediction rules do exist. The Charlotte rule, the Geneva score, 2 and 3-level Wells score can all be used in clinical practice.[35]

The CS provides an overview of how edoxaban fits into the current treatment pathway for VTE and the disadvantages of VKA drugs, most commonly warfarin, as being of slow onset of action, drug-food and drug-drug interactions and a narrow therapeutic window requiring monitoring.

Box 7 Overview of how edoxaban fits into the current treatment pathway (Reproduced from CS; pg 24)

Anticoagulant pharmacotherapy forms the basis of VTE treatment, and is central to the prevention of recurrence.[12, 36, 37] It includes parenteral and oral therapies, as shown in Table A 1.

Table A 1. Current anticoagulant pharmacotherapy for treatment of VTE and prevention of recurrent VTE in UK

Type of therapy	**Pharmaceutical class**	**Name**
Parenteral therapies	Heparin group	Unfractionated heparin (UFH) (eg, calciparin)
		Low-molecular-weight heparin (LMWH) (eg, enoxaparin)
	Factor Xa inhibitors	Fondaparinux
Oral therapies	Vitamin K antagonists (VKA)	Warfarin, acenocoumarol, phanocoumarol and fluindione
	Non VKA oral anticoagulants (NOACs)	Direct thrombin inhibitors (dabigatran)
		Direct factor Xa inhibitors (rivaroxaban)

The standard treatment consists of LMWH followed by VKA.[38]

According to NICE guidelines [3], patients with confirmed proximal DVT or PE should be treated with LMWH or fondaparinux, according to comorbidities, contraindications and drug costs, with the following exceptions:

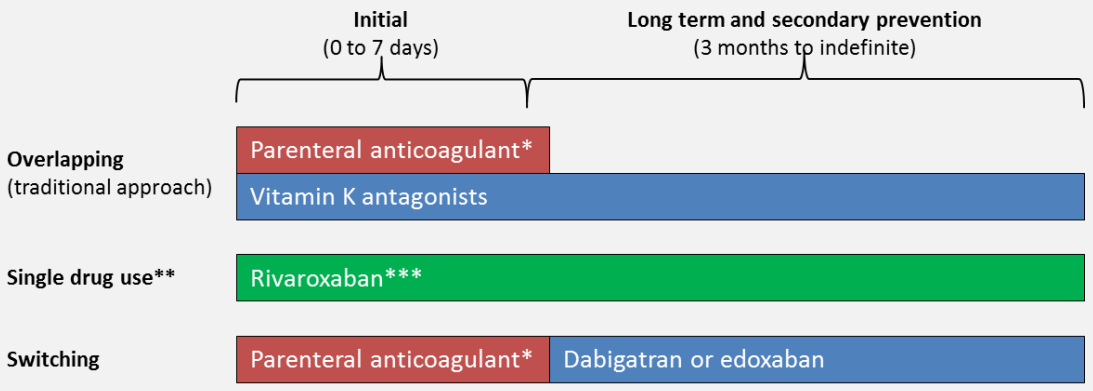
VKA are offered to patients with confirmed proximal DVT or PE within 24 hours of diagnosis.[3] This treatment should continue for 3 months, after what the risks and benefits of continuing VKA treatment is to be assessed:

VTE treatment approach has been evolving in recent years with the entry of NOACs. NOACs have proven efficacy and safety in large clinical trials and are indicated for use in VTE. Their advantages include rapid onset of action, a short half-life, no need for routine anticoagulation monitoring, and few drug-drug or drug-food interactions.

Summary of anticoagulation treatment approach

Figure A 1 summarises the anticoagulation treatment approach.

Figure A 1. Anticoagulation approach[39]



* UFH, LMWH, fondaparinux
** No NICE guidance on apixaban at the time of submission
*** Initiation dose different to maintenance dose

ESC also provides recommendations about NOACs[12], for acute phase treatment of pulmonary embolism. As alternatives to the combination of parenteral anticoagulation with a VKA, the following are recommended:

rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily)

apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily)

In addition, as an alternative to VKA treatment, the following are recommended:

dabigatran (150 mg twice daily, or 110 mg twice daily for patients >80 years of age or those under concomitant verapamil treatment) following acute phase parenteral anticoagulation

edoxaban following acute-phase parenteral anticoagulation

In the ESC guidelines[12], NOACs (rivaroxaban, apixaban, dabigatran, edoxaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min

Abbreviations used in the box: CrCl, Creatinine Clearance; DVT, deep vein thrombosis; ESC, European Society of Cardiology; NOAC, novel oral anticoagulant; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin k antagnosit; VTE, venous thromboembolism

The ERG notes that the company highlighted the need for oral anti coagulation with simple dosing guidance (CS; pg 27) and that edoxaban doses can be adjusted from 60mg to 30mg for patients with a creatinine clearance of 30 to 50 ml per minute or a body weight below 60kg (Summary of Product Characteristics (SmPC) CS, Annex 1, pg 5).

The ERG notes that the company states there is no general need for anti-coagulation monitoring of patients on edoxaban over and above usual clinical practice as recommended by NICE (CS; pg 18) and would expect a reduction in monitoring compared to INR monitoring associated with warfarin use. However, the ERG also notes rivaroxaban and dabigatran, which are already approved by NICE in this indication also do not require INR monitoring.

In addition, the SmPC for the use of edoxaban states that edoxaban is subject to additional monitoring and, “although treatment with edoxaban does not require routine monitoring, the effect on

anticoagulation can be qualitatively evaluated by an anti-Factor Xa assay which may help to inform clinical decisions in particular situations as e.g. overdose and emergency surgery" (SmPC pg 7). Also, "periodic hepatic monitoring is recommended for patients on Lixiana treatment beyond 1 year". The ERG notes that renal impairment is not a contraindication for treatment with warfarin, whereas severe renal impairment is a contraindication for treatment with edoxaban, rivaroxaban and dabigatran. Clinical experts report that baseline assessment of renal function is usually conducted prior to commencement of treatment with warfarin as renal function influences warfarin dosing. The ERG considers that assessment and monitoring of renal function is potentially a requirement in the treatment pathway for edoxaban. The ERG has received clarification from the company about the type and frequency of monitoring performed in the Hokusai-VTE trial but remains uncertain as to the level of monitoring required for edoxaban in routine clinical practice[40] (See section 4).

The ERG received the following clarification response about the monitoring arrangements for the Hokusai-VTE trial as presented in Box 8.

Box 8 Company's clarification reponse to clarification question A6; Please clarify the type and frequency of monitoring performed in the Hokusai-VTE trial? (e.g. were patients weighed at each visit?)

Starting with the Day 30 visit, subjects will return to the clinic monthly (every 30 days ± visit window shown in Appendix 17.4) until the Month 12 visit or study drug interruption/discontinuation. During study drug interruptions and after study drug discontinuation, subjects will be followed for primary and secondary efficacy and safety endpoints and SAEs by visit or telephone contact every 3 months until the Month 12 visit or until study drug treatment (and regularly scheduled protocol-specified visits) is resumed.

At these monthly on-site visits, INR assessments will be done using the POC device provided by the Sponsor (or back-up method as described in Section 5.4) for adjustment of warfarin (or placebo-to-match warfarin) doses. Additional interim visits may be scheduled, at the Investigators discretion, for INR monitoring.

At specified visits per the visit schedule in Appendix 17.4, the following will be performed:

• Record concomitant medications.
• Count unused study drug tablets.
• Record vital signs (sitting BP and heart rate) and weight.
• Record 12-lead ECG.
• Take PK samples and record date/time of the last dose of study drug taken prior to sampling, as well as the date/time of the last meal prior to each PK sample collection (See Appendix 17.8 and Study Laboratory Manual for further instructions).
• Take samples for PD analyses (D-dimer, anti-FXa activity, and exploratory biomarkers) and record date/time of the last dose of study drug taken prior to sampling and the PD sample collection

(Appendix 17.8 and Study Laboratory Manual for instructions).

• Take blood samples for the following laboratory tests:

− Liver function tests [ALT, AST, TBL, and ALP] at all monthly visits,

− Other serum chemistry analytes at identified visits,

− Hematology at identified visits,

− Samples should be sent to the central laboratory.

• Urinalysis at identified visits.

− Samples should be sent to the central laboratory.

In preparation for the Month 3 visit, subjects will be instructed to do the following:

• Record date/time of the last study drug dose taken before the Month 3 visit,

Record date/time of the last meal taken before the Month 3 visit,

• Not to take the study drug dose on the day of the Month 3 visit until administered the dose at the clinic.

During the Month 3 visit, blood samples for PK and PD will be taken. This involves the following procedures:

• Record date/time of the last study drug dose and last meal taken before the visit,

• Collect a PK sample and three PD samples (2 plasma and 1 serum) prior to in clinic study drug administration,

• Administer and record date/time of study drug given in the clinic,

• Collect an additional PK and an additional PD sample 1 to 3 hours after study drug administration,

• Refer to Appendix 17.8 for sample collection, processing, and storage instructions.

During the Month 12 visit, blood samples for PK and PD will be taken. This involves the following procedures:

• Record date/time of the last study drug dose and last meal taken before the visit,

• Collect a PK sample and PD samples at anytime during the visit,

• Refer to Appendix 17.8 for sample collection, processing, and storage instructions.

At PK and PD sampling visits other than Month 3 (Appendix 17.8), the PK and PD samples can be taken without in-clinic study drug administration. Date/time of last dose before the PK and PD sampling will be recorded along with date/time of both the PK and the PD sample collection. In case of an event (VTE or major or clinically relevant nonmajor bleeding), every attempt will be made to collect one PK and two PD samples (including date/time of sample) along with the date/time of last study drug dose before the PK and PD sampling.

At study drug dispensing visits specified in the visit schedule in Appendix 17.4:

• Collect unused study drug tablets,

• Call the IXRS to get new study drug kit numbers,

• Dispense study drug and record amount (number of tablets) dispensed.

All used/unused study drug supplies should be retrieved from subject at the monthly visits and new supplies dispensed. Study drug may be retrieved/dispensed at unscheduled visits if needed, e.g., due to warfarin dose changes.
Abbreviations used in the box: ECG, electrocardiogram; INR, international normalised ratio; POC, point of care; SAE, serious adverse event; VTE, venous thromboembolism

The company provides estimates of the number of patients for which edoxaban is indicated in England and Wales, Box 9.

Box 9 Estimated number of patients eligible for edoxaban (CS; pg 21)

The manufacturer has estimated that the following numbers of patients are covered by the indication described in section 1:1 and would be potentially eligible for treatment with edoxaban according to its SmPC.	
Year 1	60,453 patients
Year 2	61,410 patients
Year 3	62,624 patients
Year 4	63,764 patients
Year 5	64,844 patients

The company based their estimates of the number of patients in England and Wales who would be eligible for treatment with Non-VKA Oral Anticoagulants (NOACs) according to a study by Martinez *et al.*[9], a data linkage study. Data relating to a cohort of patients included in the Clinical Research Practice Data link (CRPD), Hospital Episode Statistics (HES), the Office for National Statistics (ONS) were used to calculate incident VTE in the UK. Patients were identified and followed up until a time point which could be one of a number of events including an incident VTE, death or the end of the 10 year study period, in October 2011. The ERG is unable to validate these calculations due to restrictions of time.

Box 10 Resource use (CS; pg 30)

The main resource use to the NHS associated with edoxaban is the acquisition cost of the drug. No additional costs are anticipated to arise based on location of care, staff usage, administration costs, monitoring or tests. As INR monitoring is unnecessary with edoxaban, a reduction in INR monitoring required with warfarin treatment is expected.
Abbreviations used in the box: INR, international normalised ratio

3. CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

The company provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE; CS, pg 34-35), together with the rationale for any deviation from the decision problem Table 1.

Table 1 Summary of decision problem as outlined in the company's submission (reproduced from CS; Section 5; pg 34 and 35)

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	**People with DVT and/or PE**	**As per NICE scope**	**Not applicable**
Intervention	Edoxaban tosylate	As per NICE scope	Not applicable
Comparator(s)	Initial treatment with a LMWH or fondaparinux and continued VKA Rivaroxaban Dabigatran For people for whom a VKA is unsuitable: LMWH or fondaparinux alone Rivaroxaban Dabigatran	As per NICE scope Note: no evidence available for edoxaban in patients for whom VKA is unsuitable	Not applicable
Outcomes	The outcome measures to be considered include: Mortality VTE recurrence Complications following DVT or PE, 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	As per NICE scope	Not applicable
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 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 Personal Social Services perspective.	As per NICE scope	Not applicable
Subgroups to be considered	If evidence allows, subgroups will be considered by type of VTE (PE or DVT). The analysis should consider both those	As per NICE scope Notes:	Not applicable

	who require a limited period of anticoagulation (3-6 months) and those who require long-term anticoagulation (usually lifelong). If evidence allows, the analysis should also consider people for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered. If the evidence allows, the analysis should consider separately people with active cancer and include any effect on the person's cancer or cancer treatment.	duration of anticoagulation can be varied in the model but no specific subgroups were aligned with different treatment durations patients for whom need for long-term anticoagulation is uncertain: no evidence available active cancer: no evidence available from our pivotal trial	
Special considerations, including issues related to equity or equality	Not applicable	Not applicable	Not applicable
Abbreviations used in the table: DVT, deep vein thrombosis; LMWH, low molecular weight heparin; NICE, National Institute of Health and Care Excellence; PE, pulmonary embolism; VKA, vitamin k antagonist			

The ERG notes the company's decision problem does not incorporate all the elements of the PICO in the final scope from NICE. Importantly it does not include certain sub group populations; people in whom a limited or long term need for anti coagulant therapy is uncertain, those with active cancer and those for whom a Vitamin K antagonist is unsuitable. The ERG notes the company's rationale that no evidence is available for edoxaban in patients for whom VKA is unsuitable.

Population

The company presents evidence in the CS from an evaluation of edoxaban in one phase III RCT, Housaki-VTE.[40] Housaki-VTE was an "event driven, double-dummy, parallel-group, multi centre, multi-national, non-inferiority study designed to evaluate the benefits and risks of edoxaban in reducing the risk of symptomatic recurrent VTE in patients with documented acute symptomatic DVT and/or PE" (CS pg 43).

While the final scope from NICE states the population of interest is people with DVT and or PE and no age restrictions are mentioned, the ERG notes the population inclusion/exclusion criteria for the company's pivotal trial was more restrictive and that one of the Hokusai-VTE trial inclusion criteria was that subjects had to be older than the minimum legal adult age (country specific) and in this regard the pivotal trial does not match the population in the final scope in that regard.

The ERG notes that the inclusion criteria for the Hokusai-VTE trial were confined to DVT presenting in the proximal vessels. These are defined as those involving the popliteal or femoral or iliac veins which resulted in the exclusion of people with 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 distal DVT. The ERG is thus unable to comment further on the safety or efficacy of edoxaban for treatment or prevention of distal DVT. The term DVT will be used to refer only to proximal DVT.

The CS reports that "patients with active cancer for whom long-term treatment with LMW heparin is anticipated" were excluded from the Hokusai-VTE trial (CS pg 123).[40]The ERG notes that patients with active cancer (n=208) were recruited to the trial ([40], supplementary appendix) anfd the CS reports a sub group analysis for these data were planned (pg 59). However, no sub-group analysis of these data is reported in the CS. The ERG is unsure of the company's definition of active cancer but note that in the Hokusai-VTE trial report patients with active cancer in whom loing term 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.

3.1. Intervention

The intervention that is the subject of this STA is edoxaban tosylate (Lixiana®). Edoxaban is orally administered and is a highly selective direct inhibitor of Factor Xa. By inhibiting Factor Xa, edoxaban disrupts conversion of fibrinogen to fibrin during the coagulation cascade and thus prevents the formation of a clot. Edoxaban acts rapidly and a dose of edoxaban has been found to maintain effective anticoagulation for up to 24 hours (CS pg 13). The CS reports edoxaban has no current requirement for routine coagulation monitoring.

Edoxaban does not have UK marketing authorisation (CS, pg 14). The company reports that edoxaban "*for preventing stroke and systematic embolism in people with atrial fibrillation"* was submitted to the European Medicines Agency (EMA) for regulatory approval use in treatment and prevention of recurrent VTE on [redacted]. CHMP positive opinion was anticipated in [redacted] and EMA marketing authorisation in [redacted]. However the final scope for this STA pertains to edoxaban for the treatment of people with DVT/PE. The ERG therefore requested clarification from the company about the details in section 1.3, page 14 of the CS for the UK marketing authorisation of edoxaban for its use in the treatment and secondary prevention of DVT and PE and received the following response, Box 11.

Box 11 Company's clarification to the ERG question about the indication for edoxaban.

This has been amended to state: "Edoxaban tosylate does not currently have a UK marketing authorisation for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults."

The company reported that edoxaban has already gained US FDA regulatory approval (January 2015) for use in the treatment of DVT and PE following 5-10 days of initial therapy with a parenteral anticoagulant and was also was approved in Japan in April 2011 for the prevention of VTE after major orthopaedic surgery (CS pg 16).

In January 2015 the company submitted data to NICE for the appraisal of edoxaban for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. Guidance on this indication is expected in September 2015 (CS, pg 17).

The company report explains edoxaban is available in 15mg, 30mg and 60mg film-coated tablets (CS pg 17). The dose duration is at least 3 months. (SmPC). The anticipated standard daily dose of edoxaban is 60mg taken once daily including those with mild to moderate hepatic impairment.

A dose reduction to 30mg once daily is recommended for the following groups (SmPC, pg 3)

- patients with moderate or severe renal impairment (CrCL 15-50mL/min);
- Low body weight≤60kg;
- Concomitant use of P-gp Inhibitors: cyclosporine, dronedarone, erythromycin, ketoconazole;
- In patients with mild renal impairment (CrCL>50-80mL/min).

The CS states edoxaban should be avoided in the following groups:

- In patients with end stage renal disease (ESRD) CrCL>15mL/min or on dialysis;
- Patients with gastritis, esophagitis or gastroesophageal reflux;
- Other patients at increased risk of bleeding;
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk;
- Patients with elevated liver enzymes (ALT/AST>2 x ULN) or total bilirubin ≥1.5 x ULN were excluded in clinical trials. Therefore edoxaban should be used with caution in this population prior to initiating edoxaban liver function tests should be performed;
- In patients with severe hepatic disease edoxaban.

The evidence for effectiveness of edoxaban in the CS comes from a single RCT, Housaki-VTE. The primary objective of this non-inferiority RCT (n=8240) was to compare initial low molecular weight heparin (LMWH) or unfractionated heparin followed by edoxaban (LMWH/edoxaban) to initial LMWH overlapping with warfarin, followed by warfarin alone (LMWH/warfarin) (CS, pg 43). Edoxaban was taken orally, once daily. The standard dose used was 60 mg. The dose of edoxaban was halved to 30 mg for patients perceived to be at higher risk for overexposure (and therefore increased risk of bleeding). Dose adjustment was permitted at randomisation and at any point during the study; dose adjustment after randomisation is a unique feature of Hokusai-VTE trial compared with trials of other NOACs for VTE. The ERG notes this fundamental difference in study design makes comparison with the findings of other NOAC trials difficult. The criteria for dose adjustment can be found in Table 2 below.

Table 2 Criteria for dose adjustment (adapted from CS, Table B3, pg 44)

At randomisation	During study
Moderate renal impairment (CrCl ≥30 mL/min and ≤50 mL/min as calculated using the Cockroft-Gault formula) Low body weight (≤60 kg) Concomitant potent P-glycoprotein (P-gp) inhibitor use (quinidine, verapamil)*	Moderate renal impairment (CrCl ≥30 mL/min and ≤50 mL/min as calculated using the Cockroft-Gault formula) and >20% drop from baseline Low body weight (≤60 kg) and >10% drop from baseline Concomitant potent P-gp inhibitor use (verapamil, dronedarone, quinidine, erythromycin, azithromycin, clarithromycin, ketoconazole or itraconazole)*

The type of LMWH used in the Hokusai-VTE trial was subcutaneous enoxaparin in doses of either 1 mg/kg BD or 1.5 mg/kg OD, or UFH. The ERG notes that fondaparinux, which was included the final scope from NICE was not a option for parenteral anticoagulant in the Hokusai-VTE study and the ERG is uncertain as to what effect, if any, this may have had on the trial outcomes (CS, pg 44).

The ERG notes this flexible duration of treatment is another key feature of the Housaki-VTE trial particularly regarding its comparability with other NOAC trial (Box 12). It does make interpreting the Hokusai-VTE trial in light of the NICE final scope subgroups of people who require acute treatment and people needing long term treatment difficult: Other NOAC studies have been conducted as short term studies and/or separate long term studies.

Box 12 Flexible treatment duration on Hokusai-VTE trial ((3) and CS pg 44).

All patients were to receive a minimum of 3 months treatment, consistent with clinical guidelines; after 3 months, the remaining duration of treatment was at the physician's discretion, up to a maximum of 12 months. Regardless of the total duration of treatment actually received, efficacy and safety data were collected on all patients during the entire 12-month period following randomisation. This

flexibility in treatment duration is uncommon in clinical trials, and potentially empowers the trial to reflect clinical practice more than do other studies of VTE treatment and secondary prevention.
Abbreviations used in the box: VTE, venous thromboembolism

To summarise, the ERG considers the intervention in the decision problem to be consistent with the anticipated licence and adheres to the NICE final scope for this STA.

3.2 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; or
- dabigatran.

The company presented data for acute parenteral treatment with heparin (either LMWH or unfractionated heparin [UFH] (but not 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 company 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.

Enoxaparin was the only LMW heparin parenteral therapy available to trial participants for parenteral therapy. The ERG is unsure of what effect, if any, the initial parenteral therapy would have on the overall safety and efficacy of edoxaban as no data for this is provided within the CS. It is therefore assumed within this report that the drugs used for initial parenteral therapy (i.e. prior to edoxaban or warfarin therapy) have equal efficacy.

The comparators in the company definition of the decision problem differ slightly from the NICE final scope. The ERG notes the company includes initial treatment for a minimum of 5 days with LMWH or fondaparinux alone and continued VKA, rivaroxaban or dabigatran as comparators in the CS. However, the CS does not include direct, *head-to-head*, comparisons of edoxaban with rivaroxaban, or dabigatran because there is an absence of suitable direct randomised evidence for these NOACs. In addition, evidence for people in whom VKA's are unsuitable is not presented in the CS due to the absence of comparable data for edoxaban.

In order to compare the NOACs drugs, the CS includes a network meta-analysis (NMA) including data from trials of edoxaban, rivaroxaban, dabigatran and apixaban versus VKA's (CS, pg 94). In the

absence of head-to-head trial data, the ERG considers the company's decision to synthesise relative treatment effects using NMA methods to be appropriate.

The ERG notes that apixiban was a comparator in the draft scope for this STA but is not included in the final scope from NICE, possibly because apixaban was the subject of an STA at the time the final scope was issued. Apixaban is therefore not considered further in this ERG report. The ERG's critique of the company's NMA is provided in Section 4.

The ERG notes the company reports the absence of data about the effect of edoxaban in patients for whom VKA is unsuitable and consequently no direct comparisons are available for LMWH, fondaparinux, rivaroxaban or dabigatran.

In summary, the ERG considers the company has included all of the key comparators in the decision problem but no data are presented for the subgroup of people unsuitable for VKAs.

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 and chronic thromboembolic pulmonary hypertension;
- adverse effects of treatment (particularly bleeding, including intracranial and gastrointestinal bleeding);
- health-related quality of life.

The primary efficacy endpoint of the Hokusai-VTE trials presented in the CS was the incidence of adjudicated symptomatic recurrent VTE in the mITT analysis set.[40] The principal safety endpoint was the incidence of adjudicated clinically relevant bleeding which is defined as the composite of major clinical bleeding or CRNM bleeding. Clinical advisors to the ERG indicate that this is suitable for addressing the outcomes in the NICE final scope of VTE recurrence. All outcomes are presented in Box 13.

Box 13 Outcomes in the Hokusai-VTE trial (CS pg 57)

The primary efficacy outcome was incidence of symptomatic recurrent VTE (composite of recurrent DVT, new non-fatal symptomatic PE, and fatal PE) during the 12-month study period. The primary safety outcome was clinically relevant bleeding (i.e., composite of major bleeding or

CRNM bleeding) which occurred during treatment or within 3 days after interrupting or stopping study drug. All bleeding events were adjudicated by the Clinical Events Committee. Major bleeding: overt bleeding (with one or more of a fall in haemoglobin ≥2 g/dL; leading to a transfusion of ≥2 units of packed red blood cells or whole blood; occurring in a critical site [intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal]; contributing to death CRNM bleeding: overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with any other discomfort such as pain, or impairment of activities of daily life) The secondary efficacy endpoint was the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period. The secondary safety endpoint was cases with pre-defined criteria suggesting hepatic dysfunction were evaluated and adjudicated by hepatic specialists in a blinded manner. Other safety assessments included all bleeding, clinical laboratory assessments, vital signs, physical examinations, AEs, SAEs, deaths, and other cardiovascular events. Additional endpoints included net clinical outcome (defined as the composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, major bleeding, and all-cause mortality) and net clinical benefit (defined as the composite of symptomatic recurrent VTE or major bleeding). All efficacy and safety endpoints were suitable for evaluating a treatment in this indication, recommended by relevant and authoritative bodies, measured in appropriate ways so as to assure internal validity and remove potential for bias.
Abbreviations used in the box: AE, adverse event; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism; SAE, serious adverse event; VTE, venous thromboembolism

The ERG notes that the CS does not present data for about the incidence of PTS or CPTH in the Hokusai-VTE population.

The ERG is aware that HRQoL data are discussed in the clinical sections and a search of HRQoL literature was performed and described in the cost-effectiveness sections of the CS (pg, 81 and pg 148t The patients in the Hokusai-VTE trial were asked to complete the EQ-5D, a self-administered utility instrument assessing patients' health status. The results from this HRQoL assessment are presented within the clinical effectiveness results in the CS (CS pg 81).

In summary, the ERG considers that the outcomes used by the company to address the decision problem issued by NICE are appropriate.

3.3 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 duration of treatment in the Hokusai-VTE trial was flexible; patients could receive edoxaban or warfarin for up to a period of one year with all patients receiving a minimum of 3 months treatment with edoxaban. After 3 months the remainder of the treatment duration was at the discretion of a physician and treatment could be extended up to a maximum of 12 months.

The actual exposure to the study drug in the double dummy phase (i.e. during the period when both study drugs [warfarin and edoxaban placebo or warfarin placebo and edoxaban] were taken was presented in the CS (Table B6, pg 56). The majority of trial patients received either edoxaban or warfarin for more than 6 months, with more than 35% receiving treatment for 12 months.

In patients with DVT alone almost 43% received study drugs for 12 months. The ERG was advised by its clinical experts that patients with DVT usually receive acute treatment for 3 months but treatment could be up to 6 months. By contrast patients with PE tend to receive anticoagulation for longer periods. The ERG considers that while those patients still taking drugs at 12 months can be considered a proxy group for life-long therapy, the long-term safety and efficacy data for edoxaban are limited by the 12 month duration of Housaki-VTE.

3.4 Other relevant factors (other considerations)

The ERG also notes that data are not available or presented in the CS for edoxaban use in the subgroup of people in whom the need for long-term anticoagulation is uncertain, and aspirin or no preventative treatment might be considered. The ERG notes that this subgroup was specified only if evidence allowed according to the NICE final scope and thus considers its omission from the CS to be legitimate.

The ERG notes that the company does not consider there to be equity or equality issues regarding the use of edoxaban. (CS pg 31 and 35). The clinical advisors to the ERG and the ERG agree that there do not appear to be any major equality issues to be considered. Nor is the ERG is aware of any ongoing Patient Access Scheme application.

4. CLINICAL EFFECTIVENESS

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

The company 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 both randomised and non-randomised evidence on the efficacy and safety of edoxaban and relevant comparators for treatment and secondary prevention of VTE from the published literature. The interventions of interest were the new oral anticoagulants (NOACs): direct thrombin inhibitors, (i.e. dabigatran, and factor Xa inhibitors, i.e. edoxaban, rivaroxaban, apixaban) and vitamin K antagonists (VKAs), e.g. warfarin.

The ERG is aware of a recent systematic review and meta-analysis to compare the effectiveness of New Oral Anticoagulants (NOACs) with warfarin for patients with active cancer.[41] The meta-analysis includes data from 6 trials, including those from the Hokusai-VTE trial. The results show no statistically significant differences in the numbers of recurrent VTEs, bleeding events or Clinically Relevant Major Bleeds (CRNMB) between NOACs and comparator anticoagulants. However, the ERGs clinical experts have confirmed that standard practice in the UK is for patients with active cancer to receive LMW heparin and therefore the relevance of these analyses to routine clinical practice is unclear.

The ERG recognises that although apixaban was a comparator in the draft scope from NICE it was not retained in the final scope and this may explain why the company included this NOAC in the search strategy. As discussed in Section 3.3, apixaban is not considered further in this ERG report.

The ERG notes that all of the interventions and comparators in the final scope from NICE are included in the search strategy with the exception of the parenteral anticoagulant, LMW heparin or fondaparinux. The ERG considers this omission is unlikely to have caused key studies to be missed.

4.1.1 Description and critique of company's search strategy

The company provided two search strategies in the CS for the review of clinical effectiveness, one for head to head RCTs which is also the source of trials for a network meta-analysis (NMA). The second search strategy is designed to identify non-RCTs (CS Appendix 1, pg 2, 7 and 12).

In the CS it is reported that the following databases were searched:

- MEDLINE and MEDLINE In-Process (using OVID platform);
- Embase (using OVID 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.

The company reported that the initial search of electronic databases was conducted from inception until May 2014 and updated in 1st December 2014.

The company used a combination of free-text search terms and Medical Subject Heading (MESH) terms covering the following (Appendix 2):

- population of interest: adults ≥ 18 years old requiring treatment or secondary prevention of DVT and PE;
- interventions of interest: edoxaban, dabigatran, rivaroxaban, warfarin, or Vitamin K antagonists.
- study types: RCTs and non-randomised studies;
- exclusions: case report, letters, historical article, studies were limited to studies in humans.

There was no restriction based on language applied in the database search strategies used by the company. The ERG considers the company to have conducted comprehensive searches using a variety of different electronic medical databases. In addition, the company reports scrutinising bibliographic reference lists of included studies and systematic reviews reports for relevant studies. The ERG considers the company's approach to searching for relevant studies to be appropriate for the systematic review. 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 CS Table B1, pg 38)

PICOS	Description	Justification
Inclusion criteria		
Population (P)	Adults (≥18 years) with DVT or PE	Consistent with scope
Interventions (I)	NOACs: direct thrombin inhibitors, i.e. dabigatran NOACs: Factor Xa inhibitors, i.e. apixaban, rivaroxaban, edoxaban Coumarins/ VKA, i.e. warfarin	Consistent with scope

Comparators (C)	All the interventions listed above	Consistent with scope
Outcomes (O)	Mortality Recurrent VTE Complications following DVT or PE, including post thrombotic syndrome, heart failure and chronic thromboembolic pulmonary hypertension Adverse effects of treatment including bleeding events, intracranial and gastrointestinal bleeding	Consistent with scope
Study design (S)	For RCT studies: RCTs Systematic review of clinical trials: Meta-analyses For non-RCT studies Non-RCTs	Consistent with scope
Exclusion criteria		
Population (P)	Subjects <18 y and subjects at risk of VTE after surgery	Consistent with scope
Interventions (I)	Studies not investigating edoxaban or relevant comparator	Consistent with scope
Comparators (C)	Studies not investigating edoxaban or relevant comparator	Consistent with scope
Outcomes (O)	Studies not reporting the outcomes listed in the scope	Consistent with scope
Study design (S)	Designs not listed in inclusion criteria	Consistent with scope
Abbreviations used in the table: DVT, deep vein thrombosis; NOAC, new oral anticoagulant; PE, pulmonary embolism; RCT, randomised controlled; VKA, vitamin k antagonist; VTE, venous thromboembolism		

4.1.2 Details of studies included in the review of clinical effectiveness

After de-duplication, the company's searches yielded 7216 articles from the search for RCTs for the clinical effectiveness systematic review. Following abstract and full text screening of 181 publications, a total of 2 reports of a single trial (n=1) were included in the review. The included trial was Hokusai-VTE (NCT00986154).[40] As before, the trial was designed to compare edoxaban (60mg or 30mg daily) and warfarin (target INR 2.0 to 3.0) for a flexible dosing period of 3 to 12 months. (CS, pg 38)

The ERG notes that no observational studies (non-RCTs) were identified for inclusion from the company's searches for the systematic review of clinical effectiveness.

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

4.1.3 Critique of data extraction

The company reported that data were extracted from full-text versions of studies or clinical study reports, where available. The company also reported that quality-control procedures for the data extraction included verification of all extracted data with their original sources by a second researcher; "relevant information was abstracted into the STA template into a pre-defined Microsoft Word® document by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion" (CS, Appendix pg 5). The ERG considers contemporaneous, duplicate, data extraction by 2 reviewers, each blind to the judgement of the other, to be the gold standard method of data extraction. The ERG notes the company reports items from the CONSORT statement (2010) within the text of the CS (pg 43-81).

4.1.4 Quality assessment

The company conducted a quality assessment for the trial included in the systematic review of RCTs using a QA tool that seems to be based on the Cochrane risk of bias tool. A summary of the company's quality assessment for the Hokusai-VTE trial reported within the CS are presented in Table 4.

Table 4 Summary of company's quality assessment for Hokusai-VTE (reproduced from Table B8 of the CS pg 62)

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

The ERG considers the company's approach to quality assessment (QA) for the Hokusai-VTE trial to meet with standard practice for the assessment of bias in RCTs and agrees with the quality assessment ratings.

Based on the methods outlined in the CS, the ERG considers that the company followed standard systematic review processes and considers the company's approach to the selection of studies and data extraction for the systematic reviews to be reasonable.

4.2 Summary and critique of submitted clinical effectiveness evidence: Hokusaki-VTE

The company's systematic review identified one trial (Hokusai-VTE), evaluating the effectiveness of edoxaban in the treatment and prevention VTE. Hokusai-VTE trial was a phase III, event driven, randomised, double blind, double dummy, parallel group, multi national, multi centre, non-inferiority study.

Hokusai-VTE population

The main characteristics of Hokusai-VTE are presented in Table 5 below.

Table 5 Main characteristics of Hokusai-VTE trial (adapted from Table B2, CS, pg 40)

Population	Intervention	Comparator
Adults aged ≥18 years with either Objectively diagnosed, acute, symptomatic DVT involving the popliteal, femoral, or iliac veins Objectively diagnosed, acute, symptomatic PE (with or without DVT)	Heparin/edoxaban Initial heparin plus placebo warfarin Heparin stopped once target INR reached, subject started edoxaban (60 mg OD*) and continued placebo warfarin.	Heparin/warfarin Initial heparin plus warfarin Heparin stopped once target INR reached, subject started placebo edoxaban (60 mg OD*) and continued warfarin
Abbreviations used in the table: CrCl, creatine clearance; DVT, deep vein thrombosis; INR, international normalised ratio; OD, once daily; P-glycoprotein, permeability glycoprotein; PE, pulmonary embolism *Reduced to 30mg if patients had one or more of the factors associated with edoxaban over exposure including body weight ≤60kg, CrCl between 30mL/min and 50mL/min, concomitant use of the P-glycoprotein inhibitors.		

Hokusai-VTE was conducted in 439 clinical centres in 37 different countries. A total of 8,292 patients were recruited. The ERG notes that there were a large number of exclusion criteria but based on the advice of clinical experts considers them to be appropriate for the population and therapies under investigation. Randomisation in the Hokusai-VTE trial was performed following the confirmed diagnosis of a VTE. The diagnosis of the VTE event at baseline was made based on the diagnostic criteria presented in Box 14.

Box 14 Diagnosis criteria for the index VTE event in Hokusai-VTE (CS, pg 50)

Diagnosis for the index DVT event required one of the following:
a non-compressible vein on ultrasonography
an intraluminal filling defect on venography
an intraluminal filling defect on spiral/contrast computed tomography (CT) of the legs

Diagnosis for the index PE event required one of the following:
an intraluminal filling defect on spiral CT or pulmonary angiography
cut-off of contrast material in a vessel more than 2.5 mm in diameter on pulmonary angiography
a perfusion defect involving at least 75% of a defect, with corresponding normal ventilation

a non-diagnostic lung scan accompanied by documentation of new DVT by ultrasonography or venography
Abbreviations used in the box: CT, computarised tomography; DVT, deep vein thrombosis; PE, pulmonary embolism

Randomisation was performed using a computer-generated randomisation scheme with variable block sizes, stratified according to the specific index event at presentation (PE or DVT without symptomatic PE) and the presence or absence of active cancer. Randomisation took place between January 2010 and October 2012 with a total of 8292 patients recruited. In Hokusai-VTE eligible patients were stratified according to the index diagnosis (DVT or PE with or without DVT) and other baseline risk factors including provoked VTE (immobilisation, recent surgery, trauma), and the need for a dose reduction before randomisation according to a 1:1 design (CS, pg 43). The ERG is aware that these are prognostic factors associated with the recurrence of VTE and as such stratification by these risk factors is appropriate.

Details of the mechanism used to maintain blinding for trial patients and those collecting patient outcomes regarding the treatment allocation are not presented in the CS. However, the published report of Hokusai-VTE explains that all patients in the trial had INR measurements taken with a point-of-care-device that that provided an actual INR value for patients receiving warfarin and a sham value for patients receiving warfarin placebo and edoxaban. The ERG acknowledges these arrangements as sufficient to maintain blinding amongst participants.

The company reported that, "demographic and baseline characteristics were comparable between the treatment groups including age, gender, race, presenting diagnosis, and risk factors". No measures of statistical significance were reported in the CS and so the ERG was unable to validate this statement. However, the ERG notes that based on the numerical data provided by the company, the treatment groups appear similar at baseline. The baseline characteristics of the patients included in Hokusai-VTE are presented in Table 6.

Table 6 Baseline characteristics of patients in Hokusai-VTE (adapted from CS, Table B6, pg 55).

Characteristic	**Warfarin (N=4122)**	**Edoxaban (N=4118)**	**DVT only**		**PE ± DVT**	
			Warfarin (N=2453)	**Edoxaban (N=2468)**	**Warfarin (N=1669)**	**Edoxaban (N=1650)**
Mean age (years±SD)	55.9±16.2	55.7±16.3	54.9±15.9	54.7±16.0	57.4±16.5	57.1±16.6
Age ≥75 years, n (%)	544 (13.2)	560 (13.6)	273 (11.1)	282 (11.4)	271 (16.2)	278 (16.8)
Male sex, n (%)	2356 (57.2)	2360 (57.3)	1481 (60.4)	1497 (60.7)	875 (52.4)	863 (52.3)
Weight, n (%)						
≤60 kg	519 (12.6)	524 (12.7)	304 (12.4)	320 (13.0)	215 (12.9)	204 (12.4)

Characteristic	Warfarin (N=4122)	Edoxaban (N=4118)	DVT only		PE ± DVT	
			Warfarin (N=2453)	Edoxaban (N=2468)	Warfarin (N=1669)	Edoxaban (N=1650)
>100 kg	654 (15.9)	611 (14.8)	379 (15.5)	360 (14.6)	275 (16.5)	251 (15.2)
Creatinine clearance, n (%), 30–50 mL/min	273 (6.6)	268 (6.5)	153 (6.2)	152 (6.2)	120 (7.2)	116 (7.0)
Patients dosed with 30 mg edoxaban (or placebo) at randomization, n (%)	719 (17.4)	733 (17.8)	411 (16.8)	425 (17.2)	308 (18.5)	308 (18.7)
Race, n (%)*						
Caucasian	2895 (70.2)	2867 (69.6)	1727 (70.4)	1695 (68.7)	1168 (70.0)	1172 (71.0)
Asian	861 (20.9)	866 (21.0)	544 (22.2)	561 (22.7)	317 (19.0)	305 (18.5)
Black or African-American	144 (3.5)	156 (3.8)	84 (3.4)	99 (4.0)	60 (3.6)	57 (3.5)
Other	215 (5.2)	220 (5.3)	97 (4.0)	109 (4.4)	118 (7.1)	111 (6.7)
Country, n (%)						
United Kingdom	67 (1.6)	44 (1.1)	-	-	-	-
Causes of DVT or PE, n (%)						
Unprovoked	2697 (65.4)	2713 (65.9)	1655 (67.5)	1666 (67.5)	1042 (62.4)	1047 (63.5)
Temporary risk factor†	1140 (27.7)	1132 (27.5)	655 (26.7)	655 (26.5)	485 (29.1)	477 (28.9)
History of cancer	393 (9.5)	378 (9.2)	205 (8.4)	209 (8.5)	188 (11.3)	169 (10.2)
Active cancer	99 (2.4)	109 (2.6)	-	-	-	-
Previous VTE	736 (17.9)	784 (19.0)	414 (16.9)	416 (16.9)	322 (19.3)	368 (22.3)
Anatomical extent of qualifying event‡, n (%)						
Limited	-	-	596 (24.3)	603 (24.4)	123 (7.4)	128 (7.8)
Intermediate	-	-	773 (31.5)	795 (32.2)	682 (40.9)	679 (41.2)
Extensive	-	-	1049 (42.8)	1035 (41.9)	778 (46.6)	743 (45.0)
Not assessable	-	-	35 (1.4)	35 (1.4)	86 (5.2)	100 (6.1)
Baseline NT pro-BNP, n (%)	-	-	-	-	1505 (90.2)	1484 (89.9)
≥500 pg/ml	-	-	-	-	484 (29.0)	454 (27.5)
Right ventricular dysfunction§, n/N (%)	-	-	-	-	179/504 (35.5)	172/498 (34.5)
Concomitant DVT, n (%)	-	-	-	-	404 (24.2)	410 (24.8)
Actual duration of treatment with study drug, n (%)						
3 months	528 (12.8)	485 (11.8)	306 (12.5)	299 (12.1)	222 (13.3)	186 (11.3)
>3 to ≤6 months	1084 (26.3)	1076 (26.1)	602 (24.5)	600 (24.3)	482 (28.9)	476 (28.9)
>6 months	2510 (60.9)	2557 (62.1)	1545 (63.0)	1569 (63.6)	965 (57.8)	988 (59.9)
12 months	1659 (40.2)	1661 (40.3)	1048 (42.7)	1054 (42.7)	611 (36.6)	607 (36.8)
Duration of study drug, mean days±SD /median	248.4±112.6 / 261	250.3±111.8 / 265	254.3±111.9 / 282	253.9±112.9 / 278	239.8±113.2 / 214	244.9±109.8 / 236

Characteristic	Warfarin (N=4122)	Edoxaban (N=4118)	DVT only		PE ± DVT	
			Warfarin (N=2453)	Edoxaban (N=2468)	Warfarin (N=1669)	Edoxaban (N=1650)
Total patient-years on study drug	2804	2822	1708	1716	1096	1107
Total patient-years of follow-up off study drug	994	970	559	565	436	405
Abbreviations used in the table: DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism						

As previously stated, the ERG notes that Hokusai-VTE recruited relatively few patients from the UK (n=111/8240 [1.34%]) (CS, pg 108). Furthermore clinical experts have highlighted that the proportion of Asian patients in Hokusai-VTE (n=21%) is higher than the proportion of Asian patients who present in UK clinical practice (Hokusai-VTE 2013, supplementary appendix) and for whom edoxaban is indicted in the UK. As reported in Section 2 of this ERG report, one study in the USA found the incidence of VTE events was significantly lower among Asians/Pacific Islanders compared to Caucasians (29/100,000/yr, p<0.001).[18] The ERG clinical experts advise that spontaneous (unprovoked) VTE is thought to be lower in Asians but provoked VTE (e.g. post surgery) incidence similar and thus may impact on the overall incidence. The Asian population is also generally believed to be at a lower risk of recurrence but the ERG clinical expert advisors were unaware of any published UK data to support this.

The ERGs clinical experts also commented that the mean baseline age in Hokusai-VTE is lower than would be typically expected for the UK population for whom treatment with edoxaban for VTE is indicated. The mean baseline age in the Hokusai-VTE trial was 56 years of age and the percentage over the age of 75 years of age, as reported in the CS is <14% (pg 55) The clinical experts to the ERG advised 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. However, the ERG is aware that the mean baseline ages of patients in other trials of oral anticoagulants recruited similarly aged populations of patients. (Section 3.3).

Regarding the baseline index event, the ERG's clinical experts consider the distribution of DVTs and PEs within the edoxaban trial to be consistent with typical UK clinical practice.

Interventions and comparisons

The primary objective of Hokusai-VTE was to compare outcomes of patients receiving initial LMWH (or unfractionated heparin) followed by edoxaban alone with LMWH overlapping with warfarin followed by warfarin alone for the treatment and prevention of recurrence of acute symptomatic VTE. Patients were randomised to receive open label LMWH or UFH plus placebo warfarin and edoxaban

(the group allocated to edoxaban) or placebo edoxaban and warfarin (the group allocated to warfarin). Warfarin was adjusted-dose warfarin (target INR ≥2 on two separate measurements). Edoxaban was taken orally once daily for a minimum of 5 days, the standard dose used was 60mg but the dose could be adjusted (halved) to 30mg for patients perceived to be at higher risk of over exposure and therefore increased risk of bleeding. This dose adjustment could take place at randomisation and at any point during the trial. The criteria used for dose adjustments are presented in Table 7.

Table 7 Criteria for dose adjustment (adapted from Table B3, CS, pg 44)

At randomization	During study
Moderate renal impairment (CrCl ≥30 mL/min and ≤50 mL/min as calculated using the Cockroft-Gault formula) Low body weight (≤60 kg) Concomitant potent P-glycoprotein (P-gp) inhibitor use (quinidine, verapamil)*	Moderate renal impairment (CrCl ≥30 mL/min and ≤50 mL/min as calculated using the Cockroft-Gault formula) and >20% drop from baseline Low body weight (≤60 kg) and >10% drop from baseline Concomitant potent P-gp inhibitor use (verapamil, dronedarone, quinidine, erythromycin, azithromycin, clarithromycin, ketoconazole or itraconazole)*
Abbreviations used in the table: CrCl, creatine clearance; P-glycoprotein, permeability glycoprotein	

The ERG notes that patients with low body weight (≤ 60kg), moderate renal impairment or concomitant potent P-gp inhibitor use are recommended to take the lower 30mg dose of edoxaban. The ERG requested details on the frequency and nature of monitoring in Hokusai-VTE during the clarification stage and remains uncertain as to whether the monitoring arrangements used in the trial would be required for edoxaban in clinical practice. The ERG is aware that a potential key advantage of NOACs as stated in the CS (pg 29) is the lack of need for routine monitoring. The ERG notes that the dose of edoxaban is related to variable patient factors and the ERG thus considers that clinicians will be required to at least periodically weigh patients, measure their CrCl and monitor their use of Permeability-glycoprotein (P-gp) medication.

The ERG notes that relevant appendices of the CSR were not made available to the ERG despite clarification about monitoring in Hokusai-VTE being sought. However, the company did provide details in their response on the type and frequency of monitoring used in Hokusai-VTE (Box 15).

Box 15 Part of the company's response to ERG request for clarification about monitoring in Hokusai-VTE

Starting with the Day 30 visit, subjects will return to the clinic monthly (every 30 days ± visit window shown in Appendix 17.4) until the Month 12 visit or study drug interruption/discontinuation. During study drug interruptions and after study drug discontinuation, subjects will be followed for primary and secondary efficacy and safety endpoints and SAEs by visit or telephone contact every 3 months until the Month 12 visit or until study drug treatment (and regularly scheduled protocol-specified visits) is resumed.

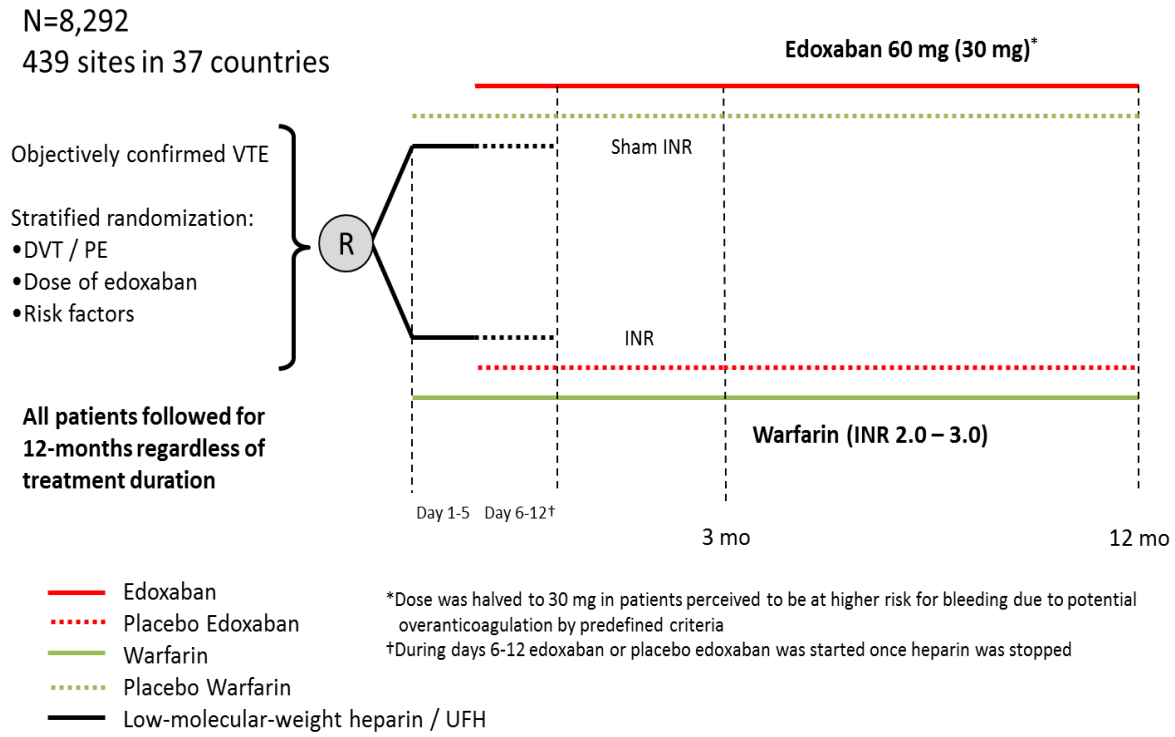
At these monthly on-site visits, INR assessments will be done using the POC device provided by the Sponsor (or back-up method as described in Section 5.4) for adjustment of warfarin (or placebo-to-match warfarin) doses. Additional interim visits may be scheduled, at the Investigators discretion, for INR monitoring. At specified visits per the visit schedule in Appendix 17.4, the following will be performed: • Record concomitant medications. • Count unused study drug tablets. • Record vital signs (sitting BP and heart rate) and weight. • Record 12-lead ECG. • Take PK samples and record date/time of the last dose of study drug taken prior to sampling, as well as the date/time of the last meal prior to each PK sample collection (See Appendix 17.8 and Study Laboratory Manual for further instructions). • Take samples for PD analyses (D-dimer, anti-FXa activity, and exploratory biomarkers) and record date/time of the last dose of study drug taken prior to sampling and the PD sample collection (Appendix 17.8 and Study Laboratory Manual for instructions). • Take blood samples for the following laboratory tests: − Liver function tests [ALT, AST, TBL, and ALP] at all monthly visits, − Other serum chemistry analytes at identified visits, − Hematology at identified visits, − Samples should be sent to the central laboratory. • Urinalysis at identified visits. − Samples should be sent to the central laboratory.
Abbreviations used in the box: ECG, electrocardiogram; INR, international normalised ratio; PE, pulmonary embolism; POC, point of care; SAE, serious adverse event

Treatment duration

The duration of Hokusai-VTE was 12 months with patients planned to receive treatment for a minimum of 3 months and a maximum of 12 months at the discretion of the physician. The ERG's clinical experts have advised that in routine clinical practice treatment for PE acute treatment is more likely to be six months unless requiring ongoing treatment or secondary prevention in which case treatment will also be lifelong. The treatment of acute DVT is likely to be three months but could be up to six months unless the patient requires ongoing treatment or secondary prevention in which case treatment will also be lifelong.

Figure 2 summarises the treatment pathways in Hokusai-VTE.

Figure 2 Hokusai-VTE design (adapted from CS Figure B 1.pg 46)



Hokusai-VTE outcomes

The primary efficacy outcome in the Hokusai-VTE trial was incidence of symptomatic recurrent VTE (composite of recurrent DVT, new non-fatal symptomatic PE, and fatal PE) during the 12-month study period.

The primary safety outcome, clinically relevant bleeding was a composite of major bleeding and clinically relevant non-major bleeding (CRNMB) which occurred during treatment or within 3 days after interrupting or stopping study drug. Major bleeding was defined as overt bleeding with one or more of a fall in haemoglobin ≥2 g/dL, leading to transfusion of ≥ 2 units of packed red cells or whole blood, occurring in a critical site (intracranial, intraspinal, intra ocular, pericaridial, intra articular, intra muscular with compartment syndrome or retroperitoneal) or contributing to death. CRNMB was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with with a physician (temporary) cessation with study treatment or associated with any other discomfort such as pain or impairment of activities with daily life (CS, pgs 57, 58).

The secondary efficacy outcome in Hokusai-VTE was the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period. Other outcomes included net clinical outcome (a composite of symptomatic recurrent

DVT, non-fatal symptomatic recurrent PE, major bleeding and all-cause mortality) and net clinical benefit (defined as the composite of symptomatic recurrent VTE or major bleeding).

Other safety outcomes included hepatic dysfunction, all bleeding, other clinical laboratory assessments, vital signs, physical examinations, AEs, SAEs, deaths, and other cardiovascular events.

In addition, the ERG acknowledges that data on the outcome of HRQoL, specified in the final scope issued by NICE, were collected in Hokusai-VTE and reported in the CS.

The ERG considers the outcomes in Hokusai-VTE are highly relevant to the management and prevention of VTE. They are the most conventionally collected patient outcomes in trials of anticoagulants for VTE and reflect those contained in the NICE final scope. (Robertson 2013, Testroote 2014) The ERG notes that the CS does not contain information about the ways in which the outcomes were measured. However, the ERG notes that all bleeding events were adjudicated by the Clinical Events Committee and that the company reported that all efficacy and safety endpoints were, "measured in appropriate ways so as to assure internal validity and remove potential for bias" (CS, pg 57).

The CS reports the primary analysis was based on an mITT which 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. (CS pg 47) 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 mITT and safety set populations were the same size.

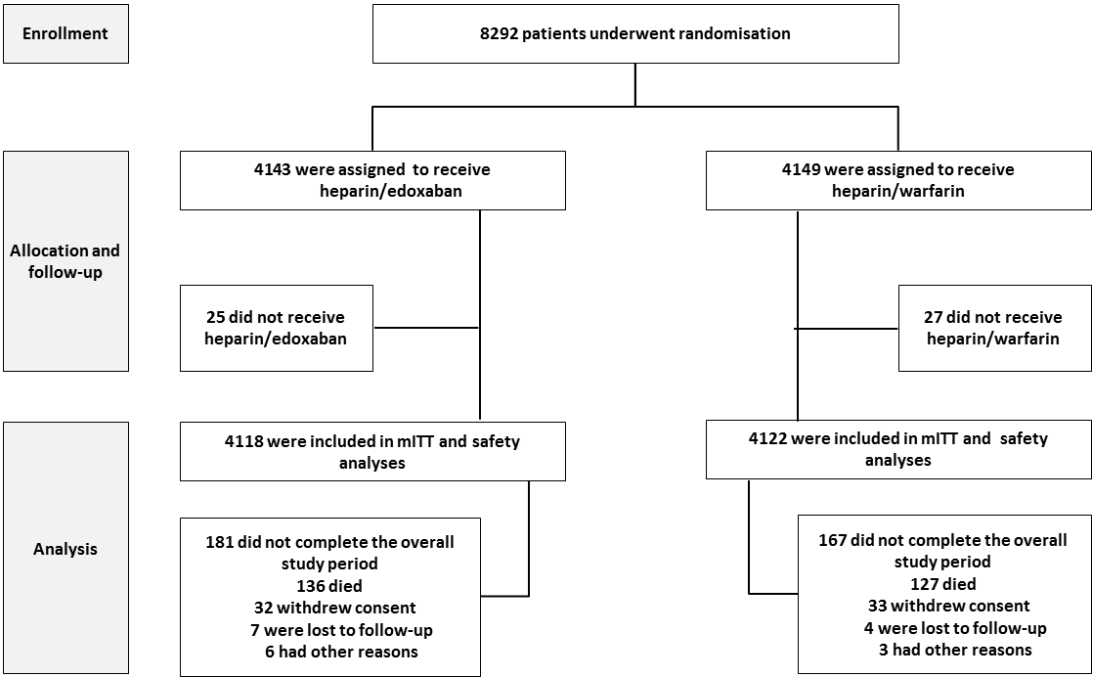
The duration of study treatment could vary in the Hokusai-VTE trial based on physicians discretion. The ERG is advised by the clinical experts that acute DVT typically is treated with anticoagulation for 3 months, but this could be extended up to 6 months unless the patient requires on-going treatment for secondary prevention, in which case treatment will be lifelong. In PE, acute treatment is more likely to be for 6 months and similarly, if patients require secondary prevention it will be life long. The ERG received clarification from the company about the number of patients who were still on treatment at 6 months, 5674/8230 (69%) of study patients. The ERG notes the company is aware that this high proportion of trial patients who received longer-than-usual durations of treatment indicates the Hokusai-VTE study population is high-risk and consequently may not reflect the population of patients routinely seen in UK clinical practice.

Table 8 provides data for the duration of treatment with the study drug.

Table 8 Duration of treatment, total patient years on study drug, total patient years of follow-up off study drug. (Adapted from CS Table B16, pg 72 and Table B6 pg 55)

Characteristics	Warfarin	Edoxaban	DVT only		PE +/- DVT	
			Warfarin	Edoxaban	Warfarin	Edoxaban
Actual duration of treatment with study drug, n (%)						
3 months	528 (12.8)	485 (11.8)	306 (12.5)	299 (12.1)	222 (13.3)	186 (11.3)
>3 to ≤6 months	1084 (26.3)	1076 (26.1)	602 (24.5)	600 (24.3)	482 (28.9)	476 (28.9)
>6 months	2510 (60.9)	2557 (62.1)	1545 (63.0)	1569 (63.6)	965 (57.8)	988 (59.9)
12 months	1659 (40.2)	1661 (40.3)	1048 (42.7)	1054 (42.7)	611 (36.6	607 (36.8)
Duration of study drug, mean days±SD /median	248.4±112.6 / 261	250.3±111.8 / 265	254.3±111.9 / 282	253.9±112.9 / 278	239.8±113.2 / 214	244.9±109.8 / 236
Total patient-years on study drug	2804	2822	1708	1716	1096	1107
Total patient-years of follow-up off study drug	994	970	559	565	436	405
Total number of days exposed to study drug						
Mean (days ±SD)	248.4 (112.61)	250 (111.75)	-	-	-	-
Median (days)	261,0	265.0	-	-	-	-
Abbreviations used in the table: DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism						

Figure 3 Flow chart of participants in Hokusai-VTE (reproduced from CS, pg 61)



4.2.1 Subgroup analyses

Subgroup analyses were conducted based on the following variables:

Primary outcome;

- Presenting diagnoses; DVT/PE/severe PE;
- Centre level INR-Time in Therapeutic Range (TTR);

Safety outcome;

- Bleeding events by anatomical location;
- Fragile status, age and history of cancer;
- Presenting diagnosis;
- Centre level ING-TTR.

Follow –up

Trial patients were followed up for 12 months after randomisation. The ERG clinical experts advise that this length of follow-up period is sufficient to capture recurrant events.

4.2.2 Description and critique of statistical approaches used in Hokusai-VTE

Hokusai-VTE was planned as a non-inferiority study to determine the efficacy (recurrence) and safety (bleeding) of edoxaban 60mg OD compared with warfarin in patients with symptomatic VTE, assessed using hazard ratios (HRs) and risk differences (RD).

A total of 8230 patients were recruited to the trial and 130 (3.2%) patients in the edoxaban group and 146 (3.5%) patients in the warfarin group experienced the primary outcome. The HR in the Hokusai-VTE trial was calculated based on the time to first occurrence of any component of the primary endpoint (recurrent symptomatic VTE and deaths related to PE) using the Cox (regression) proportional hazard model. The model terms included treatment group and stratification factors (index event, provoked/unprovoked index event and the need for dose reduction).

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 Hokusai-VTE trial was defined as 1.5 (two-sided α=0.05) for the HR. LMW heparin/edoxaban was considered non-inferior if the upper limit of the two-sided 95% CI for the hazard ratio was less than 1.5. If non-inferiority was achieved then secondary efficacy was set at 0.01 for superiority. (CS, pg 59). The ERG is aware that non-inferiority trial designs use one, not two-sided significance tests, the statistical difference of interest being in one direction only.[42] The study was powered for the accumulation of 220 primary efficacy events (recurrent VTE) in the mITT analysis set – the incidence of recurrent VTE was reckoned to be 3% - based on previous trials of VTE. Assuming equal efficacy of edoxaban and warfarin 220 events would give a power of 85% at the 5% level to demonstrate that LMW heparin/edoxaban is non-inferior to LMW heparin/warfarin.

The ERG notes 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.[43] 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.[44]

In total three data analysis sets were considered for the Hokusai-VTE trial; these were the modified Intent-to-Treat set (mITT) (n=8240), the per-protocol set (PP) (edoxaban n=3937 and warfarin n=3955) (CS figure B5, pg 61) and the safety analysis set (n=8240), The CS reports two study periods; an overall study period which was defined as the time from the reference date (randomisation date initial dose of study drug date) to the last follow-up visit and the on-treatment period the time period the subject was taking the study drug up to 3 days after their last dose.

The mITT was composed of all randomised patients who were documented to have taken at least one dose of study drug and were assigned to the randomised treatment groups for the analysis regardless of the actual study drug taken.

It was intended that the safety analysis set was comprised of all randomised subjects who received one dose of the study drug. Analyses were based on the randomised treatment, unless a subject inadvertently received the incorrect drug during the entire study, when they were analysed according to the treatment they actually received. However, the CS reports there were no treatment mis-allocations (CS, pg 61) therefore the number of patients allocated to each treatment group for the mITT and Safety Analysis Set SAS are the same (n=4118 in the edoxaban arm and n=4122 in the warfarin arm). The CS reports that 52 patients were randomised to receive a study drug but did not receive a single dose of the allocated drug (n=25 in the edoxaban arm and n=27 in the warfarin arm).

The ERG notes that in addition to conducting an analysis of the primary outcome for the overall study period the company report conducting a sensitivity analysis for the "on treatment period" only (the time during which patients were receiving the study drug or within 3 days after the study drug was stopped or interrupted). The "on treatment period" could be as short as 3 months but could be up to 12 months after randomisation.

Analyses of data for the primary and secondary efficacy endpoints, and of HRQoL, in Hokusai-VTE were based on the mITT set analysis.

In general, the ERG considers the company's approach to the statistical analysis of the data in the Hokusai-VTE trial to be appropriate.

4.2.3 Summary statement

For this STA, one RCT (Hokusai-VTE) was included in the clinical effectiveness section of the CS to provide clinical data on edoxaban for the acute treatment of VTE.[40]

The ERG considers that the inclusion and exclusion criteria of Hokusai-VTE trial were acceptable to address the trial's objectives. In addition, the ERG notes that the baseline characteristics of the randomised population of the Hokusai-VTE trials appeared to be well balanced between trial arms. The intervention was edoxaban, which is the focus of this STA, and the comparator warfarin. However the ERG has concerns about the small number of UK patients (n=111) included in the Hokusai-VTE trial which makes the generalisability of the trial findings to the UK population unclear.

In terms of follow-up and statistical data analysis, the ERG considers that the sample size was justuified and adequate to prove non-inferiority, the duration of follow-up in Hokusai-VTE was

acceptable for the outcomes assessed. The ERG also considers that the statistical analysis plan was appropriate.

4.3 Summary of results of Hokusai-VTE

4.3.1 Hokusai-VTE treatment compliance and discontinuations

In total, 8240 patients were enrolled in Hokusai-VTE with 8240 patients randomised to either edoxaban (4118 patients) or warfarin (4122 patients). However, 52 patients (0.63%) out of the 8240 did not receive a single treatment with any study drug and their outcomes were not included in any dataset. Twenty five patients received no treatment after allocation to the edoxaban group (0.60%) and 27 patients received no treatment after allocation to the warfarin group (0.65%). The number of patients who completed the study was high with [redacted] and [redacted] patients in the edoxaban and warfarin groups, respectively. Overall around 4% of patients did not complete the study period and this was mainly due to death. The company reports (CS pg 65) that more VTE events occurred after the discontinuation of the study drug when the overall period is compared with the on-treatment period.

Full details on the flow of patients through the study period are presented in Figure 3.

4.3.2 Hokusai-VTE treatment effectiveness results

The results of Hokusai-VTE with respect to the primary efficacy endpoints for the overall study period based on the mITT dataset are presented in Table 9. The ERG notes that the company reports that edoxaban 60mg OD demonstrated non-inferiority to adjusted-dose warfarin for the primary efficacy outcome (HR, 0.89 95% CI: 0.703 to 1.128) However, following the attainment of non-inferiority, superiority was tested for, but was not reached.

Table 9 Hokusai-VTE efficacy outcome results (adapted from Table B9, CS, pg 64)

	Edoxaban	**Warfarin**
All subjects with recurrent VTE, n (%)	130/4118 (3.2)	146/4122 (3.5)
HR Edoxaban vs Warfarin	0.89 (0.703 to 1.128)	
p-value (for non-inferiority)	<0.0001	
p-value (for superiority)	0.3362	
Type of first recurrent VTE, n (%)		
PE with/without DVT	73 (1.8)	83 (2.0)
PE-related deaths	24 (0.6)	24 (0.6)
Fatal PE	4 (<0.1)	3 (<0.1)
Unexplained deaths (and VTE cannot be ruled out)	20 (0.5)	21 (0.5)
Non-fatal PE	49 (1.2)	59 (1.4)
with DVT	2 (<0.1)	2 (<0.1)
without DVT	47 (1.1)	57 (1.4)
DVT only	57 (1.4)	63 (1.5)

Abbreviations used in the table: DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism

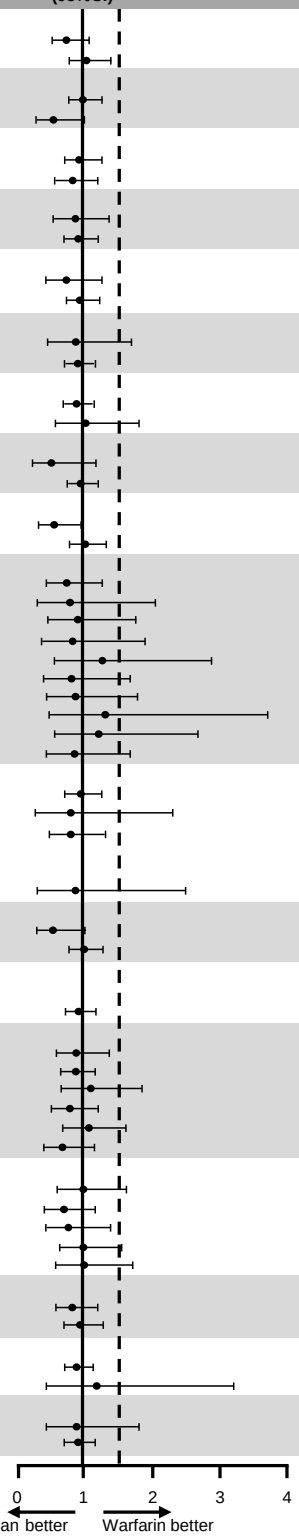
An analysis (Kaplan-Meier) of the cumulative event rate of study drugs using the mITT analysis set, in the overall study period found the edoxaban group experienced more VTE in the first 30 days than the warfarin group. The company reports this effect was mainly observed in the DVT population, 21 of whom experienced the primary outcome event compared with 15 in the warfarin arm. The absolute number of people with PE who experienced a recurrence for VTE during the overall treatment period was 9 in the edoxaban arm and 7 in the warfarin arm (CS, pg 65).

The company reports the findings from a sensitivity analysis of recurrent VTE in the "on treatment period". In this analysis 66/4118 (1.6 %) in the edoxaban arm experienced a recurrent VTE compared to 80/4122 (1.9%) patients in the warfarin group, hazard ratio 0.82; 95% CI: 0.60 to 1.14 ($p \leq 0.001$) for non-inferiority.

The CS contained a forest plot of subgroup analyses based on mITT analysis set for the overall study period for the primary outcome recurrent VTE (Figure 4).

Figure 4 Forest plot of subgroup analyses based on mITT analysis set for the over all study period

Subgroup	Edoxaban 60 mg (30 mg dose adj) n/M (%/yr)		Warfarin n/M (%/yr)		Hazard ratio with warfarin (95%CI)	P-value for interaction
Presenting diagnosis						
PE with/without DVT	47/1650	(2.8)	65/1669	(3.9)		0.1772
DVT only	83/2468	(3.4)	81/2453	(3.3)		
Age group						
<75 years	116/3558	(3.3)	119/3578	(3.3)		0.0586
≥75 years	14/560	(2.5)	27/544	(5.0)		
Gender						
Male	82/2360	(3.5)	87/2356	(3.7)		0.5810
Female	48/1758	(2.7)	59/1766	(3.3)		
Baseline risk factors						
Temporary factors	32/1132	(2.8)	38/1140	(3.3)		0.8274
All others	98/2986	(3.3)	108/2982	(3.6)		
Need for 30 mg edoxaban dose at randomisation						
Yes	22/733	(3.0)	30/719	(4.2)		0.4217
No	108/3385	(3.2)	116/3403	(3.4)		
Body weight at randomisation (IXRS)						
≤60 kg	15/524	(2.9)	18/519	(3.5)		0.8714
>60 kg	115/3594	(3.2)	128/3603	(3.6)		
Body weight at randomisation						
≤100 kg	108/3495	(3.1)	123/3455	(3.6)		0.6335
>100 kg	22/611	(3.6)	23/654	(3.5)		
Creatinine clearance at randomisation (IXRS)						
30-50 mL/min	8/268	(3.0)	16/273	(5.9)		0.1581
>50 mL/min	122/3850	(3.2)	130/3849	(3.4)		
Fragile						
Yes	18/715	(2.5)	34/706	(4.8)		0.0408
No	112/3403	(3.3)	112/3416	(3.3)		
Region						
Western Europe	22/680	(3.2)	30/679	(4.4)		0.9818
Central Europe	7/468	(1.5)	9/464	(1.9)		
Southern Europe	16/586	(2.7)	18/590	(3.1)		
Eastern Europe	10/483	(2.1)	12/485	(2.5)		
Nordic	12/174	(6.9)	10/180	(5.6)		
China/Japan	13/349	(3.7)	16/344	(4.7)		
Other Asian	14/501	(2.8)	16/503	(3.2)		
Australia/New Zealand	8/145	(5.5)	6/145	(4.1)		
South Africa/South America	13/316	(4.1)	11/312	(3.5)		
USA/Canada	15/416	(3.6)	18/420	(4.3)		
Race						
Caucasian	91/2867	(3.2)	98/2895	(3.4)		0.8264
Black or African American	6/156	(3.8)	7/144	(4.9)		
Asian	27/866	(3.1)	34/861	(3.9)		
American Indian or Alaska native	0/0	(0.0)	0/0	(0.0)		
Native Hawaiian or other Pacific Islander	0/0	(0.0)	0/0	(0.0)		
Other	6/220	(2.7)	7/211	(3.3)		
Medical history: cancer						
History of cancer	14/378	(3.7)	28/393	(7.1)		0.0734
No history of cancer	116/3740	(3.1)	118/3729	(3.2)		
Active cancer at randomisation						
Active cancer	4/109	(3.7)	7/99	(7.1)		-
No active cancer	126/4009	(3.1)	139/4023	(3.5)		
Centre-level INR percent time in therapeutic range for warfarin subjects						
<60%	38/1199	(3.2)	45/1271	(3.5)		0.9136
≥60%	89/2876	(3.1)	101/2845	(3.6)		
<25th percentile (55.82%)	28/713	(3.9)	27/748	(3.6)		0.4678
≥25th to <50th percentile (64.03%)	35/1329	(2.6)	44/1291	(3.4)		
≥50th to <75th percentile (70.41%)	41/1115	(3.7)	42/1180	(3.6)		
≥75th percentile	23/918	(2.5)	33/897	(3.7)		
Initial heparin treatment duration on or after randomisation						
0-5 days	34/870	(3.9)	24/583	(4.1)		0.4984
6 days	23/922	(2.5)	27/717	(3.8)		
7 days	18/726	(2.5)	25/749	(3.3)		
8-9 days	34/885	(3.8)	40/1011	(4.0)		
≥10 days	21/715	(2.9)	30/1062	(2.8)		
Initial heparin treatment duration						
<Median (7 days)	57/1792	(3.2)	51/1300	(3.9)		
≥Median (7 days)	73/2326	(3.1)	95/2822	(3.4)		
Initial type of heparin treatment received						
Enoxaparin	122/3958	(3.1)	138/3956	(3.5)		
UFH	8/148	(5.4)	7/151	(4.6)		
Concomitant aspirin use						
Yes	14/368	(3.8)	15/346	(4.3)		0.9779
No	116/3750	(3.1)	131/3776	(3.5)		



The CS reports a reduction in risk of recurrent VTE of 25%, HR 0.52 (95% CI 0.274 to 0.996) for those ≥75 years. The CS also reports a reduction in risk of recurrent VTE of 47% for those of fragile status. The ERG notes only one of the tests of interaction is statistically significant in these subgroup analyses; fragile status. The company states treatment with edoxaban resulted in a relative risk reduction of VTE in those patients with a history of cancer of whom reported *active cancer*) (208/771 (27%)) (CS pg 68). The ERG note that the 95% CI for this estimate includes 1 and the effect is therefore not statistically significant.

Depending on the index diagnosis the CS presents estimates for the following groups of patients with DVT or PE, and patients with severe PE: Of 4921 patients with an index DVT alone, 2468 were randomised to edoxaban and 2453 to the warfarin group. For the overall study period these data produced an HR of 1.02 (95% CI: 0.750 to 1.384) and HR of 0.96 (95% CI: 0.64 to 1.42) in the analysis of the on treatment period. In patients with PE (n= 3,319, edoxaban n=1650 and warfarin n=1669) analyses of the overall study period produced an HR 0.73 (0.502 to 1.062), and the on-treatment period HR 0. 60 (95% CI 0.34 to 1.08) (CS, pg 69). The ERG notes these all indicate edoxaban is non-inferior to warfarin.

Analyses of the effect of edoxaban on the primary outcome in patients with severe PE showed non-inferiority for;

- an extensive event (multiple lobes with ≥25% of the entire vasculature) HR = 0.84 (95% CI: 0.489 to 1.432);

- right ventricular dysfunction (the ratio of right ventricular diameter to left ventricular diameter) HR 0.42 (95% CI 0.146 to 1.199).

For right ventricular dysfunction (NT-proBNP level ≥500pg/mL) HR 0.52 (95% CI: 0.28 to 0.98) the company reports a statistically significant reduction in those treated with edoxaban (48% p≤0.5).

In the CS the company reports data for the International Normalised Ratio (INR) (Table 10). Time in therapeutic range (TTR) was 63.5 % at INR 2.0 to 3.0 and for INR of 1.8 to 3.2 the observed TTR for warfarin was 77.1%. The subgroup analysis based on centres with different levels of TTR was reported to show no statistically significant differences. The company interpretation of these data is that the performance of edoxaban is not related to suboptimal therapy with warfarin (CS, pg 70).

Table 10 Primary efficacy endpoint by centre level INR-TTR (mITT analysis set, overall study period) (reproduced fromTable B14, CS, pg 70)

TTR Subgroups	Warfarin	Edoxaban	HR, edoxaban vs warfarin (95% CI)
Centres with TTR <60%	45/1271 (3.5%)	38/1199 (3.2%)	0.89 (0.574–1.364)
Centres with TTR ≥60%	101/2845 (3.6%)	89/2876 (3.1%)	0.87 (0.653–1.153)
Centres with TTR <25th percentile (55.82%)	27/748 (3.6%)	28/713 (3.9%)	1.09 (0.641–1.848)
Centres with TTR ≥25th to <50th percentile (55.82%–64.03%)	44/1291 (3.4%)	35/1329 (2.6%)	0.77 (0.496–1.205)
Centres with TTR ≥50th to <75th percentile (64.03%–70.41%)	42/1180 (3.6%)	41/1115 (3.7%)	1.05 (0.681–1.610)
Centres with TTR ≥75th percentile	33/897 (3.7%)	23/918 (2.5%)	0.66 (0.384–1.129)
Abbreviations used in the table: TTR, time in theraputic range			

In this subgroup analysis the Centres with TTR ≥25th to <50th percentile (55.82%–64.03%) produce an HR of 1.09; 95% CI: 0.641, 1.848 and Center-Level INR-TTR for Warfarin subjects ≥ 50 < 75% Percentile (70.41%): HR: 1.05; 95% CI: 0.681, 1.610 CS (pg 70). The ERG agrees with the company that there are no significant differences in the primary efficacy endpoint by centre level INR-TTR. However, given the magnitude of uncertainty in the individual estimates (as illustrated by the wide 95% CIs), there is insufficient evidence to establish that TTR has no impact on the relative efficacy of edoxaban compared to warfarin (Box 16).

Box 16 Summary of the results from subgroup analyses and those favouring warfarin (CSR, pg 106)[45]

Overall, of the 55 subgroup comparisons presented, 45 favored edoxaban, 3 had no Hazard Ratio calculated, and 7 favored warfarin (Figure 11.4, Table 14.2.5.1, and Table 14.2.5.7). Favoring Warfarin: 1. Presenting diagnosis DVT only: HR: 1.02; 95% CI: 0.750, 1.384 2. Region: Nordic: HR: 1.26; 95% CI: 0.547, 2.892 3. Region: Australia/New Zealand: HR: 1.31; 95% CI: 0.461, 3.734 4. Region: South Africa/South America: HR: 1.21; 95% CI: 0.544, 2.677 5. Center-Level INR-TTR for Warfarin subjects < 25% Percentile (55.82%): HR:1.09; 95% CI: 0.641, 1.848 6. Center-Level INR-TTR for Warfarin subjects ⩾ 50 < 75% Percentile (70.41%): HR: 1.05; 95% CI: 0.681, 1.610 7. Initial Heparin Type = UFH: HR: 1.17; 95% CI: 0.425, 3.213.
Abbreviations used in the box: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; INR, international normalised ratio; TTR time in therapeutic range; UFH, unfractionated heparin

The ERG notes that the number of patients who experienced a recurrent VTE and all cause mortality was not statistically significantly different between the two study drugs HR 1.00 (95% CI 0.832 to 1.20) (CS, pg 71). The company reported in the CS (pg 64) that there was [redacted] by treatment group in the rate of any of the secondary endpoints.

The CS reports a total of [redacted] patients in Hokusai-VTE completed EuroQol-5 Dimensions (EQ-5D) questionnaires. The geographical distribution of the health-related quality of life (HRQol) data (Table B 25, CS, pg 80) shows they were mostly [redacted]. The ERG is uncertain as to [redacted]. The ERG notes the company reports the trial was underpowered for an analysis of the effect of edoxaban and warfarin on HRQoL and consequently no estimate of the relative effect that study drugs have on HRQoL is presented in the CS (Table B28, CS, pg 81).

4.3.3 Efficacy conclusions

Edoxaban was shown to be non-inferior to warfarin for the primary efficacy endpoint of symptomatic recurrent VTE in a the main outcome analysis in the Hokusai-VTE trial.

The baseline characteristics of the patients in the two arms of the Hokusai-VTE trial are similar. However, the population is atypical of those who requiring treatment in UK, having a high proportion of individuals from Asian countries, being younger and taking the study drugs for longer periods. There was some evidence of poorer outcomes in certain geographical regions but the ERG is unable to comment on the relevance of this to the UK.

The ERG notes a non-statistically significant difference in recurrent endpoint events for patients with index DVT taking edoxaban in the first 30 days of the trial (21 edoxaban versus 15 warfarin). This effect was much less marked in the index PE group (9 edoxaban and 7 warfarin) (CS pg 65).

4.3.4 Hokusai-VTE safety and adverse events

Adverse events

An overview of the number of adverse events (AEs) that occurred during the Hokusai-VTE trial is presented in Table 11.

Table 11 Treatment duration and study drug exposure (safety analysis set) in Hokusai-VTE (reproduced from CS, pg 72 Table B17)

	Edoxaban N=4118	**Warfarin N=4122**
Total Number of Subjects Completing Study Drug Treatment	3423 (83.1)	3404 (82.6)
Total Number of Subjects with Permanent Study Drug Discontinuations	695 (16.9)	718 (17.4)
Reason For Permanent Study Drug Discontinuation		
Suspected Endpoint/Adverse Event	364 (8.8)	367 (8.9)
Suspected Endpoint	138 (3.4)	158 (3.8)
Adverse Event	233 (5.7)	222 (5.4)
Elective Surgery	17 (0.4)	18 (0.4)
Concomitant Use of Prohibited Study Medication	4 (<0.1)	2 (<0.1)
Subject Withdrew Consent	21 (0.5)	22 (0.5)
Subject Lost to Follow-up	2 (<0.1)	3 (<0.1)
Pregnancy	8 (0.2)	4 (<0.1)
Protocol Violation	22 (0.5)	22 (0.5)
Other	255 (6.2)	279 (6.8)

As stated previously the CS reports the majority of of study participants received treatment for more than 6 months and more than 40% of patients received treatment for longer than 12 months. The company report that the percentage of patients who discontinued the study for any reason was comparable between the edoxaban and warfarin treatments groups (16.9% and 17.4% respectively). These data were also comparable for for study drug permanent discontinuation for the 3, 6 and 12 month internded treatment sub-groups. Discontinuation based on the composite of suspected endpoint/adverse event was 8.8% and 8.9% in the edoxaban group and the warfarin group, respectively (CS, pg 72).

The ERG notes that the overall number of AEs was similar between the treatment groups. The ERG notes that in Hokusai-VTE, 695 (16.9%) patients in the edoxaban group had an AE that led to treatment discontinuation, compared to 718 (17.4%) patients in the warfarin group, not statistically significantly different. The ERG notes that the CS does not explicitly state the nature of the most frequently recorded AEs in Hokusai-VTE in the CS.

The primary safety endpoint was major bleeding events. Analysis of the safety analysis set for the on treatment study period is shown in Table 12.

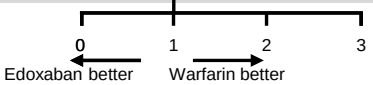
Table 12 Primary safety endpoint: adjudicated bleeding events (safety analysis set – on-treatment study period) (adapted from Table B18, CS, pg 73)

	Edoxaban N=4118	**Warfarin N=4122**
Major and CRNM Bleeding, n (%)	349 (8.5)	423 (10.3)
HR Edoxaban vs. Warfarin (95% CI)	0.81 (0.705, 0.936)	
p-value	0.004	
Major Bleeding, n (%)	56 (1.4)	66 (1.6)
HR Edoxaban vs. Warfarin (95% CI)	0.84 (0.592, 1.205)	
p-value	0.3521	
Fatal, n (%)	2 (<0.1)	10 (0.2)
CRNM Bleeding, n (%)	298 (7.2)	368 (8.9)
HR Edoxaban vs. Warfarin (95% CI)	0.80 (0.68–0.93)	
p-value	0.004	
All Bleeding, n (%)	895 (21.7)	1056 (25.6)
Abbreviations used in the table: CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio		

In Hokusai-VTE fewer patients in the edoxaban group had major and clinically relevant non-major bleeds (CRNMBs) compared to the warfarin group and this difference was statistically significant (Table 12). However, the statistical significance of this composite outcome is driven by the significant reduction for CRNMB (HR 0.80, 95% CI: 0.68 to 0.93) and no statistically significant difference exists for major bleeding. The CS reports edoxaban also had numerically fewer major bleeds than warfarin (56 (1.4%) vs 66 (1.6%)), but this was not statistically significant (CS, pg 73). The ERG notes the number of fatal bleeds in the two groups was 2 (<0.1%) in the edoxaban group and 10 (0.2%) in the warfarin group.

Figure 5 Forest plot of safety by subgroup (safety analysis set, on treatment study period) (CS, pg75)

Subgroup	Edoxaban 60 mg (30 mg dose adj) n/M (%/yr)		Warfarin n/M (%/yr)		Hazard ratio with warfarin (95%CI)	P-value for interaction
Presenting diagnosis						
PE with/without DVT	166/1650	(10.1)	187/1669	(11.2)		0.3463
DVT only	183/2468	(7.4)	236/2453	(9.6)		
Age group						
<75 years	279/3558	(7.8)	341/3578	(9.5)		0.9305
≥75 years	70/560	(12.5)	82/544	(15.1)		
Gender						
Male	144/2360	(6.1)	215/2356	(9.1)		0.0041
Female	205/1758	(11.7)	208/1766	(11.8)		
Baseline risk factors						
Temporary factors	110/1132	(9.7)	125/1140	(11.0)		0.5176
All others	239/2986	(8.0)	298/2982	(10.0)		
Need for 30 mg edoxaban dose at randomisation						
Yes	58/733	(7.9)	92/719	(12.8)		0.0695
No	291/3385	(8.6)	331/3403	(9.7)		
Body weight at randomisation (IXRS)						
≤60 kg	39/524	(7.4)	64/519	(12.3)		0.1111
>60 kg	310/3594	(8.6)	359/3603	(10.0)		
Body weight at randomisation						
≤100 kg	294/3495	(8.4)	368/3455	(10.7)		0.1470
>100 kg	54/611	(8.8)	54/654	(8.3)		
Creatinine clearance at randomisation (IXRS)						
30-50 mL/min	28/268	(10.4)	39/273	(14.3)		0.5926
>50 mL/min	321/3850	(8.3)	384/3849	(10.0)		
Fragile						
Yes	79/715	(11.0)	97/706	(13.7)		0.8759
No	270/3403	(7.9)	326/3416	(9.5)		
Region						
Western Europe	63/680	(9.3)	65/679	(9.6)		0.4667
Central Europe	29/468	(6.2)	34/464	(7.3)		
Southern Europe	56/586	(9.6)	55/590	(9.3)		
Eastern Europe	18/483	(3.7)	28/485	(5.8)		
Nordic	10/174	(5.7)	13/180	(7.2)		
China/Japan	31/349	(8.9)	47/344	(13.7)		
Other Asian	43/501	(8.6)	74/503	(14.7)		
Australia/New Zealand	19/145	(13.1)	17/145	(11.7)		
South Africa/South America	25/316	(7.9)	32/312	(10.3)		
USA/Canada	55/416	(13.2)	58/420	(13.8)		
Race						
Caucasian	236/2867	(8.2)	253/2895	(8.7)		0.0266
Black or African American	15/156	(9.6)	17/144	(11.8)		
Asian	75/866	(8.7)	125/861	(14.5)		
American Indian or Alaska native	0/0	(0.0)	0/0	(0.0)		
Native Hawaiian or other Pacific Islander	0/0	(0.0)	0/4	(0.0)		
Other	23/220	(10.5)	27/211	(12.8)		
Medical history: cancer						
History of cancer	47/378	(12.4)	74/393	(18.8)		0.1533
No history of cancer	302/3740	(8.1)	349/3729	(9.4)		
Active cancer at randomisation						
Active cancer	20/109	(18.3)	25/99	(25.3)		0.6544
No active cancer	329/4009	(8.2)	398/4023	(9.9)		
Centre-level INR percent time in therapeutic range for warfarin subjects						
<60%	83/1199	(6.9)	139/1271	(10.9)		0.0175
≥60%	265/2876	(9.2)	284/2845	(10.0)		
<25th percentile (55.82%)	47/713	(6.6)	92/748	(12.3)		0.0231
≥25th to <50th percentile (64.03%)	117/1329	(8.8)	140/1291	(10.8)		
≥50th to <75th percentile (70.41%)	95/1115	(8.5)	109/1180	(9.2)		
≥75th percentile	89/918	(9.7)	82/897	(9.1)		
Initial heparin treatment duration on or after randomisation						
0-5 days	82/870	(9.4)	63/583	(10.8)		0.6078
6 days	65/922	(7.0)	77/717	(10.7)		
7 days	56/726	(7.7)	84/749	(11.2)		
8-9 days	77/885	(8.7)	91/1011	(9.0)		
≥10 days	69/715	(9.7)	108/1062	(10.2)		
Initial heparin treatment duration						
<Median (7 days)	147/1792	(8.2)	140/1300	(10.8)		
≥Median (7 days)	202/2326	(8.7)	283/2822	(10.0)		
Initial type of heparin treatment received						
Enoxaparin	333/3958	(8.4)	403/3956	(10.2)		
UFH	16/148	(10.8)	18/151	(11.9)		
Concomitant aspirin use						
Yes	55/368	(14.9)	55/346	(15.9)		0.4628
No	294/3750	(7.8)	368/3776	(9.7)		



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The CS reports that 49 of the subgroup comparisons favoured edoxaban for the principal safety outcomes. However the ERG notes the results of only 18 subgroup analyses were presented graphically only (i.e. without explicit hazard ratios and 95% CIs) in Figure 3 (CS pg 74). The CS reports the rates of bleeding were numerically lower with edoxaban than warfarin in the following groups associated with a higher risk of bleeding; age ≥75 years, fragile status, (age≥ 75years and or body weight ≤50kg, and or CrCl 30-50 mL/min) concomitant aspirin use. The ERG interprets only the following subgroups as being statistically significantly different according to the tests for interaction; female gender, Asian race and centre level INR percentage time in TTR for <60% TTR and ≥25th to 50th percentile (64.03%).

The ERG notes bleeding was reported in a number of anatomical sites in patients in both arms of the Hokusai-VTE trial (Table B19, CS, pg 76) and the CS reports the bleeding events in the edoxaban group were lower or equal to that of the warfarin group at all sites except for the gastro intestinal tract and vagina. The ERG notes the absence of results from tests of statistical significance provided for these data.

The subgroup analyses for fragile status was defined as:

- age ≥75 years of age;
- body weight of ≤50kg;
- CrCl 30-50 mL/min;
- history of cancer.

The CS reports 1421 patients met these criteria and fewer fragile patients in the edoxaban group experienced bleeding events when compared to the warfarin group. The CS states this led to a relative risk reduction of 21% which was not statistically significantly. This is consistent with the hazard ratio presented in Table B 20 of the CS (pg 77) (HR 0.79 95% CI 0.589 to 1.068).

The ERG notes the number of bleeding events in the subgroup analysis based on the index diagnosis at trial entry was reported in the CS to be [redacted] (CS, pg 77). For those with an index PE the data showed [redacted].

A sub group analysis of the primary safety outcomes stratified according to centre-level INR TTR for warfarin was reported in the CS (pg 77 Table B22). The overall TTR (INR 2.0 to 3.0) across all patients in the study was reported to be 63.5% with 18.9% <2.0 and 17.6% > 3.0. The ERG notes these sub group analyses produced outcomes consistent with those reported for the primary efficacy

outcome (recurrent VTE) (i.e. centres with an TTR <25th percentile (55.82%) demonstrated a statistically significant difference in favour of edoxaban for the primary safety outcome (major and CRNM bleeding) HR = 0.52 (95% CI 0.366 to 0.738)).

The CS reports secondary safety end points for all bleeding, major adverse cardiac events death based on analysis of the safety analysis set for the on-treatment study period.

Bleeding events

There were 828 (20.1%) investigator-confirmed bleeding events in the edoxaban group compared to 980 in the warfarin group (23.8%). The CS reports a trend of fewer bleeds that met serious criteria in the edoxaban group, and similarly for life threatening bleeds and bleeds that led to hospitalisation Table 13. The ERG notes the numbers of bleeds leading to study discontinuation appears much higher in the warfarin arm than the edoxaban arm and considers the lack of tests of statistical significance for these analyses to be an important omission.

The CS reports the number of intracranial bleeds was lower in edoxaban vs warfarin groups (6 vs 18 respectively). The same effect was observed for retro peritoneal bleeding (0 vs 4 patients for edoxaban and warfarin respectively) (CS, pg 78). The CS reports the absolute numbers of bleeding events for both study drugs (Table 13).

Table 13 Investigator confirmed bleeding events (safety analysis set, on treatment) (reproduced from Table B 23, CS pg 78)

	Edoxaban (n=4118)	**Warfarin (n=4122)**
Any Investigator-confirmed Bleed	828 (20.1)	980 (23.8)
Met Serious Criteria (SAE)	111 (2.7)	132 (3.2)
Fatal	6 (0.1)	6 (0.1)
Life-threatening	5 (0.1)	11 (0.3)
Required/Prolonged Hospitalization	101 (2.5)	119 (2.9)
Led to Study Drug Interruption	121 (2.9)	213 (5.2)
Led to Study Drug Permanent Discontinuation	58 (1.4)	57 (1.4)

Major adverse cardiac events (MACE)

Major adverse cardiac events were defined as non fatal MI, non-fatal stroke non fatal SEE and cardiovascular death). These occurred in 1.2 % of the edoxaban group and 1.0% of the warfarin group. An analysis of this secondary safety endpoint produced an HR of 1.22 (95% 0.804 to 1.854; p=0.35). The ERG notes the [redacted] of edoxaban compared to warfarin for major adverse cardiac events. (CS pg 78).

Death

The CS reports that all cause mortality was comparable between the two groups; 35 (0.8%) in the edoxaban group and 33 (0.8%) in the warfarin group (Table 14). Although the CS refers to data for the overall study period the ERG notes the data in Table 10 relates to the study on-treatment period only. (CS pg 78).

Table 14 Ajudicated primary cause of death (safety analysis set, on-treatment study period) (Reproduced from CS, Table B 24, pg 79)

	Edoxaban (n=4118)	**Warfarin (n=4122)**
All Causes	35 (0.8)	33 (0.8)
VTE-Related Death	13 (0.3)	10 (0.2)
PE	2 (<0.1)	0 (0.0)
Unexplained Death (and VTE cannot be ruled out)	11 (0.3)	10 (0.2)
Cardiovascular Death	6 (0.1)	3 (<0.1)
Myocardial infarction	1 (<0.1)	2 (<0.1)
Ischemic stroke	2 (<0.1)	0 (0.0)
Systemic embolic event	0 (0.0)	0 (0.0)
Other Cardiac Death [a]	3 (<0.1)	1 (<0.1)
Other Known Cause	16 (0.4)	20 (0.5)
Cancer	4 (<0.1)	7 (0.2)
Bleeding (including Haemorrhagic Stroke)	2 (<0.1)	5 (0.1)[b]
Infectious Disease	7 (0.2)	4 (<0.1)
Other [b]	3 (<0.1)	4 (<0.1)

Abbreviations used in the table: PE, pulmonary embolism; VTE, venous thromboembolism
Data are n (%).
[a] Other cardiac deaths were postoperative tamponade, heart failure, ruptured aortic aneurysm (edoxaban) and arrhythmia (warfarin).
[b] Three fatal edoxaban cases (perforated bowel, acute respiratory distress, and suicide) and four fatal warfarin cases (respiratory failure, MVA, suicide, and homicide).

Safety conclusions

Edoxaban is reported as being superior to warfarin for the principal safety end point (composite of major and CRNM bleeding). The ERG notes edoxaban was not superior to warfarin for major bleeds.

Edoxaban demonstrated broadly consistent bleeding profile across pre specified sub groups. In subgroups typically associated with high risk of bleeding the edoxaban was associated with numerically lower rates of bleeding than warfarin. The ERG notes that the estimates for only 18 categories of subgroups analyses are presented in the CS.

The company's assertion that there was no difference between edoxaban and warfarin with regards to additional safety endpoints, including major adverse events and with regards to all cause mortality is not explicitly demonstrated statistically.

4.4 Description and critique of the network meta-analysis

4.4.1 Methods

The company conducted network meta-analyses (NMAs) to provide relative treatment effect estimates between different NOACs using warfarin as a common comparator regarding efficacy and safety for the treatment and secondary prevention of VTE. The company used a Bayesian Markov Chain Monte Carlo (MCMC) simulation approach to the NMA, using OpenBUGS software to carry out the NMA. The OpenBUGS code used was supplied to the ERG in the company's response to clarification questions. The ERG validated the results generated by the company using the OpenBUGS code supplied for a sample of outcomes.

The same searches used to identify trials were used as those described above in Section 3. However, the inclusion/exclusion criteria for the study selection described in Section 6.2.1 of the CS were different from the criteria for study selection for the NMA. The inclusion criteria for the NMA are detailed in Table 15.

Studies were included if they met the criteria for the population, comparators and design as well as including at least one of the interventions and outcomes of interest. In addition, only full-text publications were included and there were no language restrictions.

Table 15 PICOS criteria (reproduced from CS Table B 29)

PICOS	Inclusion
Population	VTE patients, including DVT and PE patients Patients must have been included in the study for a newly treated VTE episode (treated for <1 month) Subgroup analysis: PE patients only
Interventions	Primary interventions of interest were NOACs, including direct factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban) and direct thrombin inhibitors (dabigatran) with or without initial treatment with one of the following approved parenteral anticoagulants LMWHs (certoparin, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, tinzaparin) UH Indirect factor Xa inhibitors (fondaparinux, idraparinux, idrabiotaparinux, SR123781A) Secondary interventions of interest included the following standard therapies: VKA (acenocoumarol, fluindione, phenindione, phenprocoumon, and warfarin) plus initial treatment with one of the above approved parenteral anticoagulants; and aspirin with or without one of the above approved parenteral anticoagulants.
Comparators	Eligible comparators included placebo or any active therapy providing: indirect or direct evidence for comparisons of primary interventions of interest Or direct evidence for comparisons of secondary interventions to one another or to primary interventions of interest For the following drug classes, comparators were required to be from a different drug class (comparisons of different drug types, dosages, or administrations within drug classes were not allowed).

	UH LMWH Indirect factor Xa inhibitors Aspirin
Outcomes of interest	Recurrent VTE (DVT, PE) Major bleeding CRNM bleeding VTE-related mortality All-cause mortality Total adverse events Post-thrombotic syndrome Discontinuations Anticoagulant-induced clotting Cardiovascular outcomes (e.g. myocardial infarction) Chronic thromboembolic pulmonary hypertension
Study Design	RCTs Phase II or Phase III RCTs (including open-label studies) Follow-up duration of at least 3 months
Abbreviations in the table: CRNM, Clinically Relevant Non-Major; DVT, deep vein thrombosis; LMWH, Low Molecular Weight Heparin; NOAC, Non-VKA Oral Anticoagulants; PE, pulmonary embolism; RCT, randomized controlled trial; UH, Unfractinated Heparin; VKA, Vitamin K Antagonist; VTE, venous thromboembolism	

The methods used for abstract appraisal, study inclusion, data extraction and quality assessment were the same as those reported in Section 3.

Figure B 11 in the CS (pg 84) showed the flow diagram of studies for inclusion in the NMA. After de-duplication 7216 records remained, abstract and full text articles were assessed and a total of 9 RCTs from a total of 181 were included. The ERG notes that the company refined the inclusion criteria of studies for the NMA further, deciding to include only those that reported data to evaluate a fixed-treatment duration of 6 months. The company stated that, "in order to reduce heterogeneity between studies, after careful review of the different designs, and discussion with clinicians, it was decided to carry out the indirect treatment comparison using fixed treatment duration of 6 months." The ERG notes that if the trials had similar designs, it may have been more appropriate to use the latest available time point (typically 12 months) and assuming that the relative treatment effect holds irrespective of all time points. However, as the Hokusai-VTE trial used a different study design compared to the other trials, it seems reasonable to use the 6-month data for all outcomes.

Six trials reported data to evaluate fixed-treatment duration of 6 months. As previously mentioned, the ERG has excluded the trial of apixaban[39] from the critique as this is subject to an on-going appraisal by NICE in this indication. Therefore, only five RCTs are considered in the critique of the NMA: RE-COVER, RE-COVER II, EINSTEIN-PE, EINSTEIN-DVT.[40, 46-49]

RE-COVER[46] and RE-COVER II[47] include a fixed treatment duration of 6 months. EINSTEIN-DVT[48] and EINSTEIN-PE[49] are designed with fixed treatment durations of 12 months, but the company extracted 6-month data from the Kaplan Meier curves. The company conducted a *post-hoc* analysis of Hokusai-VTE to provide 6-month endpoints for the on-treatment population. Further details on treatments in these trials are presented later in section 4.8.3 of this ERG report.

There were no head-to-head trials identified comparing NOACs and so the company conducted NMA (also known as mixed treatment comparison [MTC]) 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 company chose to use NMA to estimate the relative efficacy and safety of edoxaban compared with all treatments of interest and stated that, "an advantage of this technique is that it allows for indirect comparisons to be made between pairs of treatments that have not been compared directly in clinical trials. Indeed, no RCTs comparing NOACs have been conducted." The company also stated that, "Bayesian NMA models were used to simultaneously synthesize the results of the included studies for each outcome of interest and to obtain relative treatment effects [50-53]". The ERG notes that the company used methods that are broadly in-line with the NICE Decision Support Unit.[54] The company conduced analyses in VTE population and secondary analyses in PE population.

4.4.2 Outcomes reported in the NMA

The company conducted NMAs on the following outcomes (CS pg 90-91):

- Efficacy endpoints;
  - VTE recurrence;
- Safety endpoints;
  - Composite bleeding (major and clinically relevant non major bleeding);
  - Major bleeding;
  - Clinically Relevant Non Major bleeding;
  - VTE-related death;
- Other endpoint;
  - Net clinical benefit (composite of VTE recurrence and major bleeding).

4.4.3 Studies included in the analyses

Table 16 shows a summary of the trials that were used to conduct the NMA. The rivaroxaban trials included in the analysis for acute treatment of DVT and PE, (Einstein-DVT[48] and Einstein-PE[49]), 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 these rivaroxaban 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, all initial parenteral treatments (e.g. LMWH) were assumed to have equal efficacy in the NMA.

The dabigatran trials RE-COVER[46] and RE-COVER II[47] were both double blinded phase III trials. In RE-COVER[46] patients were initially treated with parenteral anticoagulation therapy for a median of 9 days and in RE-COVER II[47] treated with low molecular weight or unfractionated heparin for 5 to 11 days. Initial treatment was followed by either dabigatran (150 mg twice daily) or warfarin that was dose-adjusted to achieve an international normalized ratio of 2.0 to 3.0, for the treatment of recurrent acute symptomatic VTE. Treatment duration was 6 months.

Table 16 Summary of the trials used to conduct the NMA (adapted from CS Table B 30)

Study (primary ref)	Intervention	Blinding	Patient population	No randomised patients	Trial length
Edoxaban study					
Hokusai-VTE[40]	LMWH + edoxaban LMWH + VKA	Double blinding (initial therapy with LMWH was open-label)	VTE	8292	3-12 months
Comparator studies					
RE-COVER[46]	LMWH + VKA LMWH + dabigatran	Double blinding	VTE	2564	6 months
RE-COVER II[47]	LMWH + VKA LMWH + dabigatran	Double blinding	VTE	2568	6 months
EINSTEIN-DVT[48]	LMWH + VKA Rivaroxaban	Open-label, blind adjudication of outcomes	DVT	3449	3, 6, or 12 months
EINSTEIN-PE[49]	LMWH + VKA rivaroxaban	Open-label blind adjudication of outcomes	PE	4833	3, 6 or 12 months
Abbreviations in the table: DVT, deep vein thrombosis; LMWH, Low Molecular Weight Heparin; PE, pulmonary embolism; VKA, Vitamin K Antagonist; VTE, venous thromboembolism					

The ERG notes that the initial parenteral therapy used was similar at baseline between the dabigatran and warfarin groups in the RE-COVER trials. 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, though the ERG has no audit data on their use in the UK. The ERG also acknowledges that the

RE-COVER trials, in common with the Hokusai-VTE trial, 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 company conducted quality assessments for each of the trials of which a summary is provided in Table 17. The ERG considers the quality assessments that were reported in the CS to be mostly adequate. The ERG notes that in general the company assessed the trials to be of reasonable or unclear quality.

Table 17 Summary of companys quality assessment for Hokusai-VTE, EINSTEIN-DVT, EINSTEIN-PE, RE-COVER, RE-COVER II[40, 46-49] (adapted from CS Appendix 5)

Study question reference	Domain	Hokusai-VTE	EINSTEIN-DVT	EINSTEIN-PE	RE-COVER	RE-COVER II
1	Random sequence generation (selection bias)	Low risk	Low risk	Low risk	Low risk	Low Risk
2	Allocation concealment (selection bias)	Low risk	High risk	High risk	Low risk	Low Risk
3	Blinding of participants and personnel (performance bias)	Low risk	High risk	High risk	Low risk	Low risk
4	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Unclear risk	High risk	High risk	Unclear risk	High risk
5	Blinding of outcome assessment (detection bias) (Mortality)	Unclear risk	High risk	High risk	Low risk	
6	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk	Low Risk	Low Risk	Unclear	Low risk
7	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Low risk	Low Risk	Low Risk	High risk	Low risk
8	Selective reporting (reporting bias)	Low risk	Low Risk	Low Risk	Low risk	Low risk

The company judged the EINSTEIN trials at a high risk of bias for allocation concealment, blinding of participants, personnel and outcome assessment, which was caused by the open-trial design used in the trials. The ERG considers this to be less of a concern for objective outcomes, for example mortality or recurrent VTE.

In addition, the company judged the RE-COVER-II[47] trial to be at high risk of bias for "Blinding of outcome assessment (detection bias) (patient-reported outcomes)" for which the company provided in appendix 5 a quote from the original trial paper, "We had not planned for independent central adjudication of acute coronary syndromes, but this decision was revised by the steering committee and performed at the end of the trial, after database lock but while the committee was still blinded to

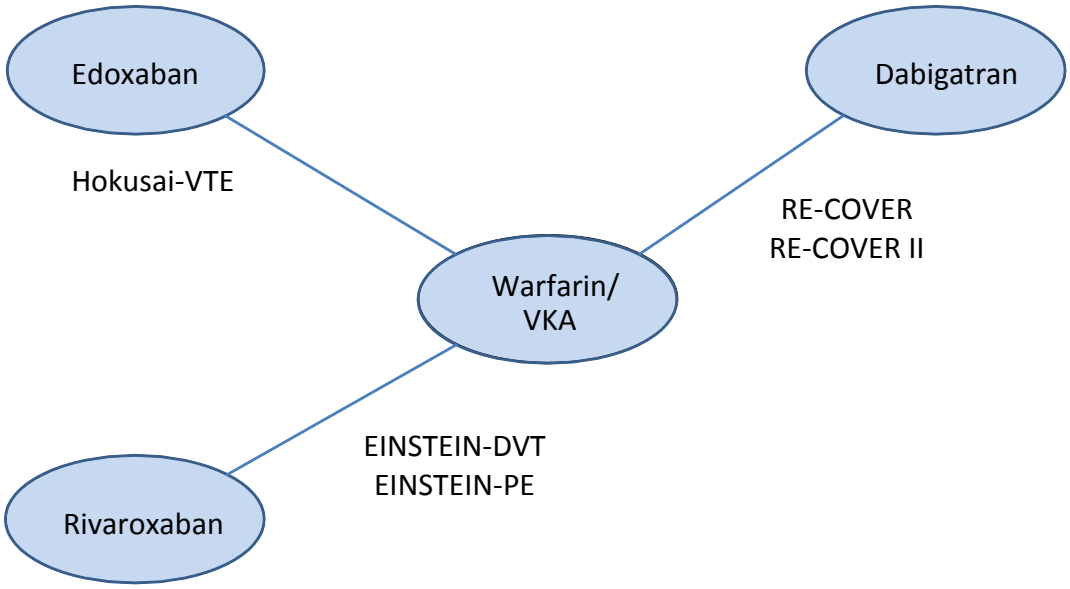
the treatment allocation." The ERG notes that this quote was not accompanied by a rationale from the company and the ERG is unsure about the link between this quote and detection bias for patient-reported outcomes. The ERG concludes that here is insufficient reason to judge the RE-COVER-II trial to be at high risk of bias for blinding of outcome assessment of patient-reported outcomes. The judgement for "Blinding of outcome assessment (detection bias) (Mortality)" for RE-COVER-II is missing in the CS Appendix 5. The ERG considers the risk of bias for both of these domains to be low as blinding of outcome assessment appears to have taken place in the RE-COVER II trial as in the original trial paper is stated, "A central adjudication committee, whose members were unaware of the treatment assignments, classified all suspected outcome events, bleeding events, and deaths."Also as previously mentioned, blinding is less of a concern for objective outcomes.

Furthermore, the company judged the RE-COVER[46] trial to be at high risk of bias for "Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks)". The company provided a quote from the original trial paper, "The study drug was stopped before 6 months in 204 patients (16.0%) in the dabigatran group (126 because of an adverse event, 21 because of nonadherence, 9 because of loss to follow-up, 39 because of withdrawal of consent, and 9 for other reasons) and in 183 patients (14.5%) in the warfarin group (102 because of an adverse event, 35 because of nonadherence, 6 because of loss to follow-up, 36 because of withdrawal of consent, and 4 for other reasons)." However, the ERG considers the risk of bias for incomplete outcome data for the RE-COVER trial to be at low because the number of attritions, the numbers in each intervention group and reasons for attrition were reported. Also the proportion of patients in which the study drug was stopped was reasonable and comparable between the groups (16.0% in the dabigatran group and 14.5% in the warfarin group).

Figure 6 shows the network diagram for the NMA. The trial network created by the company forms a "radiating star", [55] in which warfarin is the treatment that links the other treatments together. The impact of which is that as there are no "cross-links" and only the separate NOAC studies vs warfarin inform the treatment effect of each comparator in the network. A consequence of which is that the NMA results of each comparison vs warfarin should be identical to that reported in the underlying studies. The key comparisons presented by the company to address the NICE final scope for treatment and secondary prevention of VTE in patients with VTE and/or PE were:

- edoxaban vs rivaroxaban via warfarin; and
- edoxaban vs dabigatran via warfarin.

Figure 6 Network diagram: treatment and secondary prevention of VTE in patients with VTE



4.4.4 Heterogeneity

The company did not quantitatively investigate the heterogeneity between studies due to the nature of the network: a low number of studies having a similar design and similar comparators (maximum of two for dabigatran and rivaroxaban).

The company did not fit a random effects models due to the lack of information for estimating the between-study variance. The company stated that, "An alternative would have been to consider an informative prior for between-study variance but this kind of prior has not been found in the literature review."

The ERG asked the company to provide the Deviance Information Criterion (DIC) and a comparison of the residual deviance with the number of unconstrained data points for each outcome when using a fixed and random effects model for the NMA. The DIC presented by the company (clarification letter response A13) shows that both the fixed or random effects models are an equally good fit. However, given the small number of studies populating the network, and in particular the lack of any studies creating "loops" connecting treatments, the ERG considers the company's use of the results from fixed effects analyses to be reasonable.

The company undertook a qualitative exploration of heterogeneity and found that the studies differed in a number of aspects outlined in Box 17.

Box 17 Heterogeneity (reproduced from CS, pg 101)

The studies were found to differ in a number of aspects such as: "Blinding: most studies were double-blind except for the two EINSTEIN studies that were open-label; Heparin lead-in: in the RE-COVER and Hokusai-VTE studies, not in AMPLIFY and EINSTEIN; Duration of treatment: 6 months in RE-COVER and AMPLIFY studies, pre-specified 3, 6, or 12 months in EINSTEIN, flexible 3 to 12 months in Hokusai-VTE; Proportion of extensive PE patients: from 24% in EINSTEIN-PE to 46% in Hokusai-VTE". These heterogeneous aspects raised the question of the appropriateness of conducting a mixed-treatment comparison. After discussion with clinicians, efforts were made to try to at least align the duration of treatment which was thought to be a driver of efficacy and safety.

The ERG considers this approach to be a pragmatic but would have preferred the company had gone further and performed two separate analyses based on index event (DVT or PE), which would have resolved another potential source of clinical heterogeneity. The ERG requested this at clarification and the company's response was (clarification letter response B 11), "The primary objective of the network meta-analysis was to derive estimates of the relative effect of edoxaban versus the other NOACs and warfarin on efficacy and safety outcomes in patients with VTE. As a secondary objective, we evaluated the subgroup of patients with PE, where a) the unmet clinical need remains high, and b) sufficient data to compare a number of agents are available. Thus, the DVT-only subgroup was outside the scope of the NMA and a full analysis across the class would not have been possible." While the ERG appreciates that time is limited in the response to clarification, it does not believe this request to be unreasonable as the subgroup analysis requested was in the NICE scope and Hokusai-VTE was pre-specified by index VTE event. Moreover, this analysis can be done as raw data for both the VTE population and PE subgroup were presented by the company and the difference between these two groups represents the DVT subgroup. The ERG conducted DVT subgroup analysis and presents the results in in section 4.11.5 of this ERG report.

The company stated to have not identified any of the trials as a source of inconsistency. The ERG notes that there was no evidence of large differences in patients' baseline characteristics between the trials (Appendix 6, Table 90, Table 91 and Table 92).

4.4.5 Results from the NMA

Table 18 provides a summary of treatments and endpoints of interest of the five trials that were included in the analyses.

Table 18 Summary of treatments and endpoints of interest of trials included in analyses

	Treatments of Interest				**Endpoints of Interest**		
Trial	Edoxaban	Dabigatran	Rivaroxaban	Warfarin	Recurrent VTE	Clinically Relevant Bleeds	Major Bleeds
Hokusai-VTE[40]	x			x	x	x	x
RE-COVER[46]		x		x	x	x	x
RE-COVER II[47]		x		x	x	x	x
EINSTEIN-DVT[48]			x	x	x	x	x
EINSTEIN-PE[49]			x	x	x	x	x

The results of the equivalent NMA analysis are presented in Table 19. As a validation of the company's NMA, the ERG performed it's own analysis of the dataset provided by the company producing very similar results.

Table 19 NMA estimates of relative treatment effects (data from CS Table B 41- B 50)

Outcome (treatment analysis)	**Population**	**Edoxaban vs VKA regimen/Warfarin**	**Edoxaban vs Dabigatran**	**Edoxaban vs Rivaroxaban**
		OR (95% CrI)	**OR (95% CrI)**	**OR (95% CrI)**
VTE recurrence	Whole population	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
	Patients with PE	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Composite of Major or Clinically Relevant Non Major Bleedings	Whole population	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
	Patients with PE	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Major Bleeding	Whole population	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
	Patients with PE	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Clinically Relevant Non Major Bleeding	Whole population	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
	Patients with PE	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
VTE related death	Whole population	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])

Net clinical benefit (composite of VTE recurrence events and major bleeding events)	Whole population	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Abbreviations in Table: CrI, Credible Interval; OR, Odds Ratio; ND, no data; PE, pulmonary embolism; VKA, vitamin k antagonist; VTE, venous thromboembolism				

Base case: patients with VTE

The results show that edoxaban has a similar risk profile as other NOACs (and warfarin) for VTE recurrence, major bleeding, VTE-related death and net clinical benefit (composite of VTE recurrence events and major bleeding events). The ERG notes that the result for net clinical benefit (composite of VTE recurrence events and major bleeding events) is not available for dabigatran. The ERG also considers that the non-inferiority design of the original studies has limited the opportunity for any NOAC in the network to have demonstrated a significant difference from any other treatment in the network, should one exist for prevention of VTE recurrence.

Other findings of interest are:

- Edoxaban has a [redacted];
- Edoxaban has a [redacted]

The company stated that, "Based on qualitative assessment, the NMA results for each NOAC versus warfarin are in general consistent with the direct evidence from the original pivotal trials, supporting the validity of the analysis."

As previously mentioned, the ERG notes that the NMA results of each comparison vs warfarin should be identical to the underlying studies. Having compared the results, the ERG concludes that the results of NMA for edoxaban, dabigatran and rivaroxaban versus warfarin were consistent with the results of the individual trials.

Subpopulations: patients with PE and DVT

The company stated that, "VTE recurrence in the PE population is defined as in the overall VTE population, including fatal or non-fatal PE and/or DVT."

The company stated that edoxaban showed a trend to have lower VTE recurrence in PE population compared to all the NOACs and warfarin. The ERG notes that the 95% Credible Intervals for the risk

of VTE recurrence in patients with PE are wide indicating a large amount of uncertainty in the estimates. Therefore, the evidence suggests that [redacted].

Edoxaban has a [redacted].

Edoxaban has a [redacted].

As previously mentioned, the ERG conducted a subgroup analysis for the DVT population. Table 20 shows the results of the ERG NMA for DVT together with the company's results for PE.

Table 20 Estimates of relative treatment effects for PE and DVT population (*data from CS Table B 47- B 50)

Outcome (treatment analysis)	**Population**	**Edoxaban vs Warfarin**	**Dabigatran vs Warfarin**	**Rivaroxaban vs Warfarin**
		OR (95% CrI)	**OR (95% CrI)**	**OR (95% CrI)**
VTE recurrence	Patients with PE*	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
	Patients with DVT	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Composite of Major or Clinically Relevant Non Major Bleedings	Patients with PE*	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
	Patients with DVT	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Major Bleeding	Patients with PE*	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
	Patients with DVT	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
Clinically Relevant Non Major Bleeding	Patients with PE*	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])
	Patients with DVT	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])	[redacted] ([redacted] to [redacted])

Abbreviations in Table: CrI, Credible Interval; OR, Odds Ratio; ND, no data; PE, pulmonary embolism; VTE, venous thromboembolism

Numbers in **Bold** would be considered statistically significant at the 5% threshold for significance.

When comparing each of the NOACs with warfarin, there are no large differences in treatment effects for the outcomes between the different NOACs in the PE and DVT populations. The findings must be interpreted in the light of the relatively small number of events in these subgroups.

Rivaroxaban has a [redacted]. Edoxaban and dabigatran have a significantly lower risk on MB and CRNMB, and CRNMB alone in the DVT population. None of the NOACs had a significant effect on MB in the PE or DVT population.

These findings indicate that there is no clear trend showing that a particular NOAC has better results compared to other NOACs. Although some of the ORs appear to show a significant effect compared to warfarin, the Credible Intervals are wide and approach 1. The ERG concludes that the differences between the different NOACs are likely to be modest with [redacted].

4.5 Conclusions of the clinical effectiveness section

- The company presented data for the safety and efficacy of edoxaban 60mg OD (or 30mg OD for frail, elderly or patients with poor liver or kidney function) in the treatment and prevention of VTE based on one randomised controlled trial, Hokusai-VTE.

- The ERG considers Hokusai-VTE, presented in the CS for this STA, to be a well conducted, multi-centre international, double-blind, randomised controlled trial appropriately powered to demonstrate non-inferiority at the pre-specified margin.

- The primary efficacy endpoint of Hokusai-VTE was recurrent symptomatic VTE for which edoxaban was proven to be non-inferior to warfarin based on a pre-specified non-inferiority margin.

- The analysis of data for the trial safety endpoint, major bleeding, also showed edoxaban was also non-inferior to warfarin. Tests of statistical significance proved superior for the composite endpoint of major bleeding and CRNMB.

- The Hokusai-VTE trial design was different from other trials evaluating NOACs for this condition in that patients could have their drug dose altered at the beginning and during the conduct of the study depending on the presence of characteristics of frailty and poor kidney or liver or liver function.

- It was also possible for physicians to alter the dose during the conduct of the trial and extend treatment until the trial ended (12 months). The relevance of this design is that the Hokusai-

VTE study patients would potentially be treated with the study drugs for longer than they would in routine clinical practice.

- The poor external validity of the patient population recruited into Hokusai-VTE to the UK VTE population is also a concern. However, trials of other NOACs have similarly included patients with demographic profiles which differ from those seen in UK clinical practice.

- The degree of monitoring that is required to ensure patients do not require a dose reduction from 60mg to 30mg of edoxaban is unclear from the CS. The ERG's clinical experts advised that regular monitoring is required to ensure patients do not develop moderate to severe renal impairment, a change in body weight ≤60kg, or concomitant use of selected P-gp inhibitors.

- Subgroup data according to index VTE event (i.e. PE or DVT) demonstrated no significant difference in the efficacy of edoxaban in relation to preventing the recurrence of VTE.

- The results of the subgroup analyses for the efficacy of edoxaban in reducing VTE recurrence compared with warfarin indicate more favourable results with the use of edoxaban for people considered to be in fragile health (i.e. age ≥75 years and/or body weight ≤50 kg and/or CrCl 30–50 mL/min). Subgroup analyses for the safety analysis found more favourable outcomes for edoxaban in men, Asians and centres which reported TTR less than 60%.

- The ERG notes that PTS and CTEPH were listed as outcomes of interest in the final scope issued by NICE but data were not presented in the clinical effectiveness section of the CS. These data were collected during in Hokusai-VTE and have been used to inform the ERG economic model.

- There is an absence of robust long-term HRQoL data for edoxaban in the treatment and secondary prevention of VTE. While HRQoL data were collected in Hokusai-VTE, the small number of respondents severely limits their usefulness.

- The limited data provided within the CS for those with a diagnosis of active cancer recruited to the trial was not subject to analysis, possibly because of the small number of patients with the diagnosis who experienced an event.
- The ERG is aware of a recent systematic review and meta-analysis published in 2015 by Vedovati and colleagues to compare the effectiveness of NOACs with warfarin for patients with active cancer.[41] The results show no statistically significant differences in efficacy or safety endpoints between NOACs and comparator anticoagulants. However, the ERGs clinical experts have confirmed that standard practice in the UK is for patients with active cancer to

receive LMWH and therefore the relevance of these analyses to routine clinical practice is unclear.

- There are currently no direct head-to-head randomised controlled trials comparing edoxaban with other NOACs and so the ability to draw conclusions about their relative efficacy is limited by the uncertainty in the NMA.
- The results from Hokusai-VTE show that edoxaban has a similar risk profile as other NOACs (and warfarin) for VTE recurrence, major bleeding, VTE-related death and net clinical benefit (composite of VTE recurrence events and major bleeding events) in the VTE population.
- When comparing each of the NOACs with warfarin, the results for the two subgroups (PE and DVT) are largely consistent with the results for the overall population.
- The ERG concludes that the differences between the different NOACs are subtle and that the effects are likely to be caused by random chance in the PE and DVT population.

4.6 SUMMARY OF CLINICAL RESULTS

Data from a single RCT shows edoxaban is non-inferior to warfarin for prevention of recurrent symptomatic VTE and deaths related to VTE, and was proven to be superior to warfarin for major and CRNM bleeding in one RCT.

However, the generalisability of the results from the trial is uncertain as only 111 UK patients were recruited onto the trial and the patient demographics differ from the UK population who are indicted for treatment with for VTE. The ERG clinical experts advise that patients recruited to NOAC trials are slightly younger than those managed in UK clinical practice. In the Hokusai-V-TE trial there were more males than females recruited which does not reflect the increased VTE incidence experienced by females especially for provoked VTE. The trial also has a high proportion of Asians recruited and this is a concern as the Asian race is considered to have a much lower risk of VTE than the caucasians population.

The degree of monitoring that is required to ensure patients do not require a dose reduction from 60mg to 30mg is unclear. Some form of monitoring is required to ensure patients do not develop moderate to severe renal impairment, a body weight ≤60kg, or concomitant use of selected P-gp inhibitors. Edoxaban has a similar risk profile as other NOACs (and warfarin) for VTE recurrence, major bleeding, VTE-related death and net clinical benefit (composite of VTE recurrence events and major bleeding events).

Active cancer was not defined by the investigators of the Hokusai-VTE trial and active cancer was a trial exclusion criteria. Despite being an outcome in the original NICE scope, active cancer patients were recruited but no analysis was performed for these data and consequently little is known about the outcomes for this group of patients.

There are currently no direct head-to-head data to compare edoxaban with other NOACs and so the ability to draw conclusions about their relative efficacy is limited by the uncertainty around the indirect effect estimates generated from the NMA.

The results show that edoxaban has a similar risk profile as other NOACs (and warfarin) for VTE recurrence, major bleeding, VTE-related death and net clinical benefit (composite of VTE recurrence events and major bleeding events) in the VTE population. When comparing each of the NOACs with warfarin, there are no large differences in treatment effects for the outcomes between the different NOACs in the PE and DVT populations.

Edoxaban has a higher risk of composite (major or clinically relevant non major) bleeding than dabigatran, but a similar risk profile for composite bleeding as warfarin and rivaroxaban;

Edoxaban has a lower risk for clinically relevant non major bleeding compared to warfarin and rivaroxaban and a similar risk for dabigatran.

4.7 Clinical issues

- [UK marketing authorisation is not currently held for the use of edoxaban, however positive opinion from the EMA was adopted on 23rd April 2015;
- Edoxaban is non-inferior to warfarin for the treatment and prevention of recurrent symptomatic VTE, but edoxaban was not proven to be superior to warfarin;
- Edoxaban is non-inferior to warfarin with regard to a composite outcome of major bleeds and Clinically Relevent Non Major Bleeding (CRNMB);
- Absence of an analysis of clinical trial data to assess the safety and efficacy of edoxaban in the treatment and prevention of VTE in people with active cancer;
- Lack of robust H-RQoL data for people taking edoxaban for the treatment and prevention of VTE;
- PTS and CTEPH were listed as outcomes of interest in the final scope issued by NICE but were not presented as outcomes in the clinical effectiveness data of the CS;
- Absence of direct comparative data from a randomised controlled trial comparing edoxaban with dabigatran and rivaroxaban.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and of the *de novo* economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© EXCEL-based economic model. Table 21 summarises the location of the key economic information within the company's submission (CS).

Table 21: Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	
Population	
Model structure	
Technology	
Treatment continuation rules	
Clinical parameters and variables	
Measurement and valuation of health effects and adverse events	
Resource identification, valuation and measurement	
Sensitivity analysis	
Results	
Validation	
Subgroup analysis	
Interpretation of economic evidence	
Strengths and weaknesses of economic evaluation	
Abbreviation used in table: MS, company's submission.	

5.2 Summary of the company's key results

In the base-case analysis, the company presented deterministic and probabilistic results for the comparisons of edoxaban tosylate (hereafter referred as edoxaban) versus warfarin, dabigatran and rivaroxaban in the VTE population for a treatment duration of 12 months. In scenario analyses, further comparisons were made for treatment duration periods of 3 and 6 months and lifetime treatment and for PE patients only. A summary of the ICERs presented by the company in the base case analysis is provided in Table 22, for ease of reference.

Table 22. A summary of the ICERs presented by the company for acute treatment and treatment and secondary prevention

Edoxaban versus >>	Warfarin	Dabigatran	Rivaroxaban
Deterministic			
ICER	£2,451	Edoxaban dominant (less costly, more effective)	Edoxaban dominated (more costly, less effective)
Probabilistic			
ICER	£2,278	Dominated	Dominant
Probability of edoxaban being considered cost-effective at a threshold of £20,000 versus selected comparator	73.65%	74.80%	7.40%
Treatment and secondary prevention (deterministic)			
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LMWH, low-molecular-weight heparin, MS, company's submission; SW, south-west.			

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic review of the economic literature to identify cost-effectiveness publications relevant to the use of edoxaban for the acute treatment and secondary prevention of DVT and PE. Details of the search strategy (CS, Appendix 10, pages 18-20) and inclusion and exclusion criteria (CS, Table B 53, page 111) were provided within the appendices and submission, respectively.

The following electronic databases were searched: Medline; Embase; EconLit; and the Cochrane Library (NHS EED). The search was carried out in May 2014 and updated in December 2014. Search terms captured the condition of interest (DVT / PE), a range of interventions (edoxaban, dabigatran, rivaroxaban, apixaban and warfarin) and economic evaluation studies; no limits on the date of publication were applied.

In addition to database searches, bibliographies of systematic reviews articles were examined to obtain additional references and bibliographies of accepted references were also reviewed to identify other potentially relevant references (CS, Appendix 10, page 20).

A total of 12 cost-effectiveness analyses were identified from the original search (4 studies) and the updated search (8 studies). None of the studies included edoxaban. These considered the cost-effectiveness of apixaban, dabigatran, rivaroxaban or warfarin against at least one comparator. Of the 12 studies, six were performed in the UK; however, none of those six studies have been published in a peer-reviewed journal which potentially reduces their credibility. The company extracted data from these studies and presented these within the submission (CS, Table B 54, pages 114-122). The

company also undertook a study quality assessment for each of the 12 studies within the appendices (CS, Appendix 11, pages 21-32).

The ERG considers that the search terms used by the company to identify economic evaluations were comprehensive and appropriate; moreover, the economic filters were comparable to those recommended by SIGN.[56] However, the ERG notes that searches were not performed in the Health Technology Assessment (HTA) database, which may have resulted in the omission of relevant publications. During clarification the ERG asked the company the rationale for not searching the HTA database. The company's response is presented in Box 18.

Box 18: Company's justification for not searching the HTA database to identify cost-effectiveness studies or studies that measured and valued health effects (Company's response to clarification question, C1 and C2)

> The specifications for our literature search included only the NHS Economic Evaluations Database [NHS EED] within the Cochrane library. This was an oversight on our part. We checked the bibliography of our literature search and found that all of the studies identified from the search strategy specified in the dabigatran submission were also identified in our searches. Therefore, this does not seem to have resulted in a material difference to the search results.

The ERG found a discrepancy between search dates reported in the main body of the submission with Appendix 10. According to Appendix 10of the CS, the search was conducted in December 2014 alone, whereas the submission presents the article selection process using an initial (May 2014) and updated search (December 2014). The ERG requested further clarification from the company on these inconsistencies. The company's stated "The statement presented in Appendix 10 is incorrect… All initial searches were performed in May 2014, and all updates were conducted in December 2014." For completeness the ERG has reproduced the initial and updated search strategies provided by the company during clarification in the Appendix.

The inclusion and exclusion criteria applied are considered to be reasonable, with the exception of the choice of included interventions. The company restricted included studies to those which evaluated at least one of the following treatments: apixaban, dabigatran, edoxaban, rivaroxaban and warfarin. Economic analyses and cost studies comparing low molecular weight heparin (LMWH), and unfractionated heparin (UFH) that did not evaluate apixaban, dabigatran, edoxaban, rivaroxaban or warfarin were not formally included in the review.

To assess if relevant cost-effectiveness studies were missed during the company's search, the ERG reviewed economic evaluation studies included within the systematic review for three related STAs, TA261[57] (an STA appraising the use of rivaroxaban for the treatment of acute DVT and secondary

prevention of DVT and PE), TA287[58] (an STA appraising the use of rivaroxaban for the treatment of acute PE and secondary prevention of DVT and PE) and TA327[59] (an STA appraising the use of dabigatran for the treatment and secondary prevention of DVT and PE). As a consequence of this limit on interventions, the company omitted data from a number of studies which considered only LMWH or UFH, and which were included in TA261 or TA287 (Gomez-Outes *et al.*[60]; Drantisaris *et al.*[61]; Perlroth *et al.*[62]; Perez de Llano *et al.*[17]). However none of these studies were used to inform the economic analysis within TA261 or TA287.

In addition, the ERG notes that Marchetti *et al.*[63] was identified and included in the review for all three related STAs; this study reports a decision tree analysis comparing LMWH with warfarin over 3-months for the prevention of DVT recurrence. It is unclear why this study was not identified or included in the review, but later used by the company to inform the utility decrement for warfarin treatment. The inclusion of Marchetti *et al.*[63] to inform health related quality of life (HRQoL) data is discussed further in Section 5.4.7.

Although the search strategy adopted by the company appears generally appropriate, the ERG considers that a number of relevant NICE publications were omitted from the company's included studies because the company did not search the HTA database. In particular, the company did not include HTA reports TA261, TA287 and TA327.[57-59] In addition, NICE clinical guideline CG144, a guideline relating to the management of venous thromboembolic diseases, was not identified or included.[3]

The ERG considers that cost-effectiveness evidence within these NICE publications are of relevance for this STA; therefore the ERG summarised the data within these studies in Table 23 for completeness.

Table 23. Summary of cost-effectiveness evidence contained within TA261[57], TA287[58], TA327[59] and CG144[3]

Intervention and comparators	Model overview	Costs	Benefits	ICER
TA327 Dabigatran for the treatment and secondary prevention of DVT and PE, 2014[59]				
• Initial treatment with heparin (LMWH or UF for 5 days) followed by dabigatran 150mg twice a day (or 110mg twice a day for patients aged 80 years or patients who receive concomitant verapamil). • Initial treatment with heparin (LMWH or UF) with continued VKA (warfarin). • Rivaroxaban (15mg twice a day for 21 days followed by 20mg daily). • For cancer patients, LMWH treatment (dalteparin; 200 IU/kg for 1 month, followed by 150 IU/kg for remainder of treatment).	• 60 year (lifetime) Markov model from the NHS/PSS perspective, with 1-month cycle length; • cost-utility analysis; • 9 health states in the base case: on-treatment for index event; recurrent DVT; recurrent PE; ICH; MBE; CRNMB; severe PTS; CTEPH; off-treatment; death; • additional 3 health states in sensitivity analysis: MI; UA; dyspepsia.	Costs included: • daily drug acquisition costs; • INR monitoring; • costs of VTE events; • cost of bleeding; • cost of cardiovascular events (included in sensitivity analysis); • management of ICH, PTS, CTEPH, MI and UA. Unit costs were taken from the NHSRC 2012/13, the Unit costs for Health and Social care 2011, MIMS (March – May 2014) and published literature specifically for CTEPH (pulmonary endarterectomy), MI, UA and dyspepsia. Costs inflated to 2014 values using the Hospital and Community Health Services (HCHS) pay & prices index. Costs were discounted at 3.5% per annum after year one.	HRQoL was modelled relative to a baseline using Prescott-Clarke *et al.*[64]. Disutility associated with an initial and recurrent DVT and PE was estimated using EQ-5D scores collected within RE-COVER I and II. Disutility estimates for ICH, MBE, CTEPH, PTS, MI, UA and dyspepsia were taken from a systematic review of the literature. Treatment related utilities were taken from Marchetti *et al*., 2001[63]. Benefits were discounted at 3.5% per annum after year one.	**Full population** **Acute treatment phase, 6 month treatment duration:** • dabigatran versus warfarin, ICER of £862; • dabigatran versus rivaroxaban, dabigatran dominant. Appraisal Committee most plausible ICER: • dabigatran versus warfarin, ICER of £18,240 • dabigatran versus rivaroxaban, dabigatran dominant. **Acute treatment and secondary prevention:** • dabigatran versus warfarin, ICER of £8,319; • dabigatran versus rivaroxaban, dabigatran dominant; Appraisal Committee most plausible ICER: • dabigatran versus warfarin, ICER of £35,768; • dabigatran versus rivaroxaban, rivaroxaban

				extendedly dominated. **Population with cancer** Acute treatment phase: • dabigatran versus LMWH, SW quadrant (dabigatran is less costly and less effective) Acute treatment and secondary prevention: • dabigatran versus LMWH, dabigatran dominant. Appraisal Committee most plausible ICER: not estimated.
TA287 Rivaroxaban for treating PE and preventing recurrent VTE, 2013[58]				
• 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	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, the Unit costs for Health and Social care 2011 and the BNF 64. 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 using Kind *et al*.[65]. Estimates were taken from a systematic review of the literature. Treatment related utilities were taken from Marchetti *et al*.[63] 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 lifelong 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.

	whole surviving cohort.			
TA261 Rivaroxaban for the treatment of DVT and prevention of recurrent DVT and PE, 2012[57]				
• 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). • For cancer patients, LMWH treatment (dalteparin) at UK licensed dose.	• 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 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.	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 2009/10, the Unit costs for Health and Social care 2010, and MIMS. 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 using Kind *et al*.[65] Estimates were taken from a systematic review of the literature. Treatment related utilities were obtained from Marchetti *et al*. [63] Benefits were discounted at 3.5% per annum after year one.	**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** 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[3]				
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 (45 years) Markov model from the perspective of the UK NHS/PSS, with a 1-year cycle length; • cost-utility analysis; • 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.	HRQoL was modelled relative to a baseline for PE, MBE and stroke using Kind *et al*.[65] Estimates were taken from a systematic review of the literature. Benefits were discounted at 3.5% per annum after year one.	**No long-term strategy versus long-term strategy:** Initial unprovoked PE ICER: £9,981 Initial unprovoked DVT ICER: £83,310 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; MI, myocardial infarction; 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; UA, unstable angina; VKA, vitamin-K antagonist; VTE, venous thromboembolism; WTP, willingness-to-pay.

5.4 *Summary and critique of company's submitted economic evaluation by the ERG*

5.4.1 NICE reference case checklist

Table 24 and Table 25 summarise the ERGs quality assessment of the company's economic evaluation. Table 24 summarises the ERGs appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3; Table 25 summarises the ERGs appraisal of the quality of the company's de novo economic model using the Philips checklist.[66]

Table 24. 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	Yes, however: • The company did not perform subgroup analyses for the following populations: patients with DVT; people for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered; people with active cancer. The ERG notes that the company had data available to undertake subgroup analysis for DVT patients, but not for the other subgroups; • The base case analysis assumed 12-month treatment duration, but the company presented subgroup analysis for patients who require a limited period of anticoagulation (3–6 months) and those who require long-term anticoagulation (lifelong). • Major bleeding events did not distinguish between intracranial and gastrointestinal bleeding in the model; • The company included stroke and HIT as adverse events that were not specified in the scope.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes. The comparators listed within the final scope were: • Initial treatment with a LMWH or fondaparinux and continued VKA; • Rivaroxaban; • Dabigatran The ERG notes the company only considered initial treatment with LMWH and not fondaparinux, and the specific VKA chosen by the company was warfarin.
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 a life time horizon (50 years) is long enough to capture the costs and consequences associated with treatment, but survival may be overestimated in model as 20% of

		VTE patients in the model survive until the age of 90.
Synthesis of evidence on outcomes	Systematic review	Yes, a systematic review was carried out. The ERG notes that the synthesis of the clinical data was carried out through a NMA described in Section 4. The ERG has concerns regarding the search strategies for cost-effectiveness studies and studies that report utility data; these are discussed in Sections 5.3 and 5.4.7.1.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes.
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	No. The company carried out deterministic (scenario, OWSA and subgroup) analysis and PSA, however the ERG has several concerns with the choice of parameters included in the OWSA and with the choice of a non-parametric distribution for the NMA ORs in the PSA. This is described in Section 5.4.10.
Abbreviations used in the table: CEACs, cost-effectiveness acceptability curves; ERG, evidence review group; HRQoL, health-related quality of life; LMWH, low molecular weight heparin; OWSA, one-way sensitivity analysis; QALYs, quality-adjusted life yeas; TTO, time trade-off; VKA, vitamin k agonist; WTP, willingness-to-pay		

Table 25. Philips checklist[66]

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	The company stated that expert opinion was obtained to validate the model structure.
S4: Structural assumptions	The ERG has several concerns with the clinical plausibility of some of the structural assumptions made in the economic model.
S5: Strategies/ comparators	The company considered heparin plus dabigatran, heparin plus warfarin, and

	rivaroxaban as comparators.
S6: Model type	Appropriate; cost-utility analysis.
S7: Time horizon	A life time horizon (50 years) is long enough to capture the costs and consequences associated with treatment, but survival may be overestimated in model as 20% of patients in the model survive until the age of 90.
S8: Disease states/pathways	The ERG has several issues related to different health states in the model. The CTEPH health state was considered to be a treatment complication by the company however clinical experts have advised the ERG that CTEPH is a complication of PE. The implications of this are discussed in Section 5.4.3. The inclusion of the HIT state in the model isn't totally justified or potentially relevant. There was a double counting of ICH events in the model as the stroke health state included ICH which was also included in the MB state. These issues are further discussed in Section 5.4.2.
S9: Cycle length	The ERG has some issues regarding the cycle length (2 weeks) in the model. The combination of the cycle length and the decision to model recurrent VTE and bleeding events as tunnel states is underestimating the impact of these events in patients' QoL. This si further discussed in Section 5.4.2. A half-cycle correction was applied, which is appropriate.
Data	
D1: Data identification	The company's literature searches for cost-effectiveness analyses, resource use and costs, and utilities were clearly described post clarification. However, the ERG notes the following: • The rationale for selecting identified data sources for the model was 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 always provided; • The literature review was not targeted to identify complications of treatment; • The company did not search the HTA database, as a result previous NICE guidance and technology appraisals were not identified in the literature searches.
D2: Pre-model data analysis	Not reported.
D2a: Baseline data	Baseline data were taken from the Hokusai-VTE trial. The average age of patients (56 years) is slightly below the average age of VTE patients in the UK. The proportion of females (43%) and the proportion of patients with DVT only (59%) portray the VTE UK population. The company omitted distal DVT from the analysis, but the ERG agrees this is not an important VTE event to capture. The ERG notes that only 2.7% of the trial patients were from the UK.
D2b: Treatment effects	The key measure of effectiveness modelled by the company was the probability of recurrent VTE. The company estimated the probability of recurrent VTE for each treatment using their phase-specific analysis (index event to 14 days, 15 days to 98 days 99 days to 364 days). The key measure of safety modelled by the company was the probability of MB and CRNMB. The company estimated the probability of MB and CRNMB separately for each treatment using their time-to-event analysis. The company did not justify why the phase-specific analysis was not utilised to model bleeding events when this was available. The ERG notes that phase-specific data would have enriched the time-dependent analysis for bleeding events. Using different analysis for the estimation of recurrent VTE and bleeding events bias the analysis as second (and potentially third) recurrent events are being included in the recurrent VTE

	analysis whilst only first bleeding events are being considered, resulting in an underestimation of bleeding events. Treatment effectiveness is discussed extensively in Section 5.4.3.
D2c: Costs	After clarification the company used the latest source of data available (NHS Reference Costs 2012/14[67], BNF[68] and Unit Costs for Health and Social Care 2013/14[69]) and inflated costs to the year 2014. The ERG believes the monitoring costs for warfarin are overestimated whilst the monitoring costs for edoxaban are potentially underestimated.
D2d: Quality of life weights (utilities)	The company applied a baseline utility value within the model to reflect patients' age and gender. The company then applied a utility decrement to this value according to whether the patient experienced recurrent VTE, MB, CRNMB, PTS, CTEPH, HIT or if the patient was treated with warfarin. The ERG has several concerns with the utility data used, especially for the index and recurrent VTE states.
D3: Data incorporation	Data incorporation in the model lacks transparency overall. After clarification the company provided helpful information to identify parameter sources however the company was not very transparent in justifying the selection of specific data sources when alternatives were available. This is described throughout Section 5 of the report.
Assessment of uncertainty	
D4a: Methodological	The company did not assess analytical methods in sensitivity analysis.
D4b: Structural	The company assessed structural assumptions relating to the duration of treatment, which is appropriate.
D4c: Heterogeneity	The company presented a scenario using ORs estimated from Hokusai-VTE rather than the NMA. Heterogeneity was also assessed through a PE (with or without DVT) subgroup.
D4d: Parameter	The company carried out deterministic (scenario, OWSA and subgroup) analysis and PSA however the ERG has several concerns with the choice of parameters included in the OWSA and with the choice of a non-parametric distribution for the NMA ORs in the PSA. This is described in Section 5.4.10.
Consistency	
C1: Internal consistency	The model is generally sound with no obvious mathematical inconsistencies.
C2: External consistency	Expert opinion was sought by the company for external validation. A comparison of the results of the model with the results of Hokusai-VTE and previous STAs was provided.
Abbreviations used in table: CRNMB, clinically relevant non-major bleeding; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; ERG, evidence review group; HRQoL, health related quality of life; LMWH, low molecular weight heparin; MI, myocardial infarction; OR, odds-ratio; PE, pulmonary embolism; PTS, post thrombotic syndrome; QoL, quality of life; RR, risk ratio; rVTE, recurrent venous thromboembolism; VTE, venous thromboembolism.	

5.4.2 Modelling approach and model structure

In this section the ERG presents the economic model developed by the company. We begin by briefly describing the model and then discuss the modelling approach and the model structure in the next subsection.

The company developed a *de novo* cohort Markov model in Microsoft Excel®. The base case model assumes that patients receive treatment for 12 months, either with warfarin, edoxaban or other NOAC.

The company reports that the model captures both the treatment and management of VTE.

All VTE patients enter the model (presented in Figure 7) in the on treatment state. This health state also portrays the VTE index health state as all patients entering the model have been diagnosed with VTE (acute DT, with or without PE, or PE). Whilst on treatment, patients can experience a recurrent VTE event or suffer a treatment-related adverse event like heparin-induced thrombocytopenia (HIT), clinically relevant non-major bleeding (CRNMB) or a major bleed (MB). Patients on treatment can also develop chronic thromboembolic pulmonary hypertension (CTEPH), which can evolve to long-term CTEPH (LT-CTEPH), or experience a stroke. Patients who do not die from a stroke, move on to the post-stroke health state.

Patients experiencing a HIT event, a CRNMB, a MB, CTEPH or a stroke are assumed to stop anticoagulation treatment whilst experiencing the event.

After 12 months of anticoagulation therapy (with edoxaban or any of the comparator drugs), all patients (if alive) move to the off treatment state where they stay for the remaining 49 years of the analysis. During the initial 12 month treatment period patients can also move into the off treatment state if they experience events such as HIT, CRNM, MB and CTEPH. After moving to the off treatment state at 12 months, patients can still experience recurrent VTE however they do not receive any drug therapy after they move from the recurrent event health state.

Whilst in the on treatment and off treatment states, patients are at risk of developing post-thrombotic syndrome (PTS). Patients can die at any point in the model. Age-dependant mortality was included in the model, along with disease specific mortality. Events such as index VTE, VTE recurrence, MB, CTEPH (long-term or not) and stroke are assumed to be associated with an increased mortality risk. This is further explored in Section 5.4.6.

In their submission the company reports that the probability of VTE recurrence varies with time, with the highest risk of recurrent VTE occurring within the first year after the index event. It is stated that the model takes this into account by using 5 different time periods since the index event. These are the following:

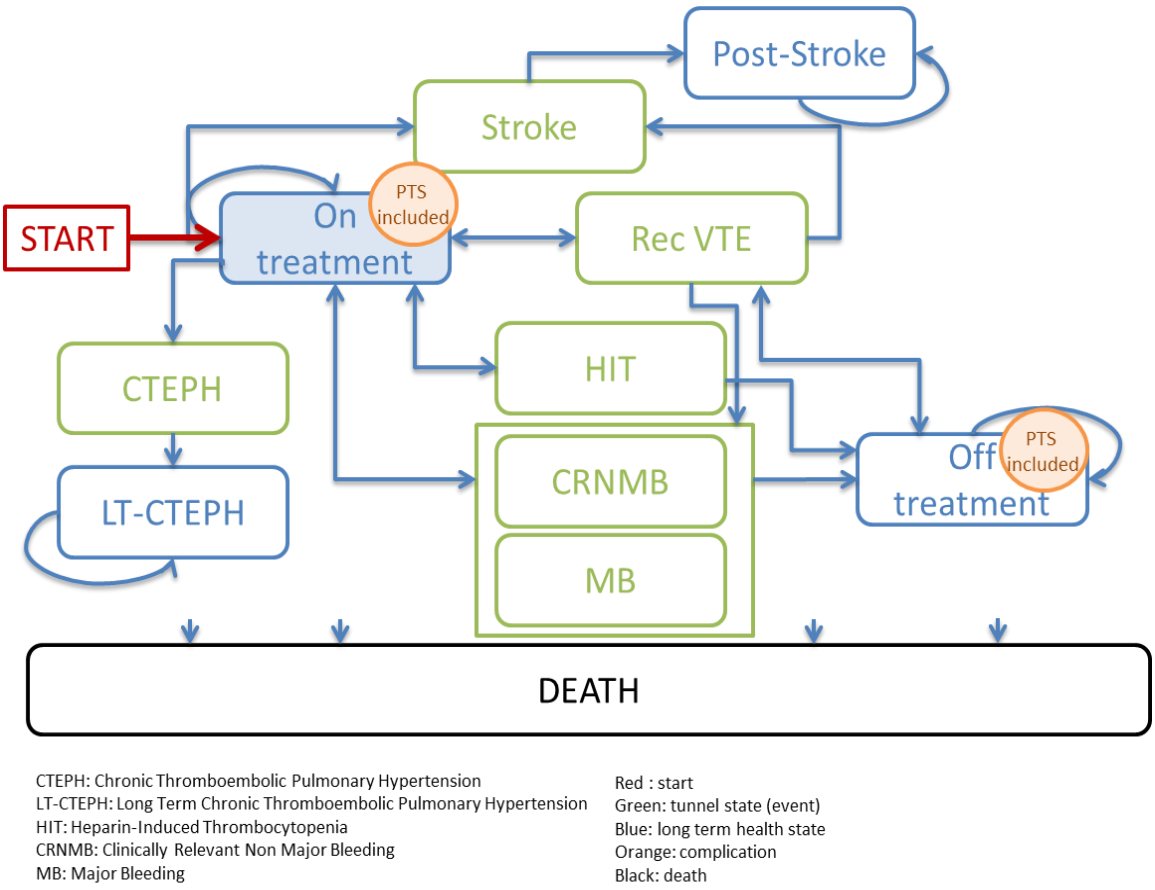
- Day 1 to day 14 – 1 cycle;
- Day 15 to day 98 (3 months) – 6 cycles;
- Day 99 (4 months) to Day 183 (6 months) – 6 cycles;
- Day 184 (6 months) to Day 364 (12 months) – 13 cycles;

- Day 365 (12 months) onwards.

Each time period has a corresponding transition matrix in the economic model which is reported to translate different probabilities of events occurring at different points in time after the index VTE event. This is explored in detail in Section 5.4.3.

The company provided a description of the different health states included in the model. This is presented in the CS (Table B55, pg 126). The ERG provides further detail on the different health states included in the model in Section 5.4.2.2.

Figure 7. Company model structure (CS; Figure B23, pg 124)



The cycle length in the economic model is 2 weeks (considered as 14 days) and a half-cycle correction was applied.

The time horizon considered in the economic model was lifetime (the model was run for 1300 cycles, the equivalent to 50 years).

5.4.2.1 ERG comments on the modelling approach and model structure

In this section the ERG discusses the different health states included in the economic model, the cycle length used in the model and finally the time horizon of the analysis. Upon the ERG request for clarification, the company has changed some of the assumptions in the economic model. Therefore we focused our appraisal on the updated model structure.

Health states included in the economic model

On treatment/index VTE state

Patients start the model in the on treatment state. This state also represents the index VTE state as all patients entering the model have experienced their index VTE event. This is appropriate and in line with the Hokusai-VTE trial. Whilst in this state, patients receive edoxaban or any of the comparator drugs for 12 months, unless they die or discontinue treatment for any reason (for example a MB).

Two points relating to the index VTE state deserve further attention:

- *Switching therapies*

Clinical opinion sought by the ERG explained that patients on anticoagulation therapy who suffer a recurrent event will have their therapy adjusted after the event occurs as the original therapy is not effectively preventing recurrence. Anticoagulation therapy varies quite significantly across clinical practice and is highly dependent on patient characteristics but in general, if patients are originally on warfarin when they experience a recurrent VTE event, they will either get a higher dose of warfarin to increase their INR or switch to a NOAC after the event. For patients on edoxaban (or other NOACs), after recurrence occurs, patients will most likely be switched to warfarin. All patients would also receive a lead-in heparin treatment after their recurrence. However, in the economic model, patients experiencing a recurrent event are assumed to return to their original anticoagulation therapy (after they received the heparin treatment for 2 weeks). Upon request for clarification, the company reported that clinical experts consulted by the company indicated that it would be appropriate to re-initiate patients on the same therapy they were previously receiving. Nonetheless, the ERG believes that allowing patients to adjust or switch their original anticoagulation therapy after a recurrent event would be more realistic and in line with clinical practice.

- *Aggregation of DVT and PE events in the on treatment state*

The company decided not to specify the type of index VTE (i.e. DVT or PE) that patients experienced. Previous STAs have split the type or index event and also the type of recurrence. Upon a request for clarification from the ERG the company mentioned that the primary efficacy outcome in the Hokusai-VTE trial was the composite outcome of VTE recurrence and thus this was used in the economic model. The ERG finds this argument potentially justifies why both types of recurrent events

were modelled together, but not why the same approach was taken for the index events. Hokusai-VTE trial data would have allowed the split in these populations to be modelled.

Nonetheless, subgroup statistical analysis undertaken by the company showed that the presenting type of VTE was not a statistically significant predictor of the primary efficacy endpoint in the Hokusai-VTE trial (p-value 0.1772). This indicates that the type of index VTE event (PE with/without DVT and DVT alone) did not have an impact on recurrence of VTE in the Hokusai-VTE trial.

From a statistical and quantitative point of view, it seems that aggregating DVT and PE index events is a reasonable simplification however from a methodological point of view, splitting the type of index VTE event could have added transparency to the model structure.

Recurrent VTE state

In the economic model, patients on and off treatment are at risk of suffering recurrent VTE events. However, recurrent VTE was modelled as a tunnel state, which means that patients cannot stay in this state for more than 1 consecutive cycle. As the cycle duration chosen for the economic model is 2 weeks, this effectively means that patients experience the recurrent VTE event (together with respective costs and benefits) for 2 weeks only. During these 2 weeks, patients are hospitalized, and receive treatment for their recurrent event. After this period, they can return to the on treatment state, where they will continue to receive their original anticoagulation treatment, they can also experience a CRNMB, a MB, a stroke or discontinue treatment if the recurrent event happens at (or after) 12 months.

In their original model, the company assumed that patients would not receive anticoagulation therapy during these 2 weeks. However, upon the ERG's request for clarification the company changed this assumption and patients in the recurrent VTE state were assumed to receive anticoagulation therapy, including the heparin treatment. This is why, even though Figure 7 doesn't show it, patients in the recurrent VTE health state can also experience a HIT event in the company's updated model.

Two points relating to the recurrent VTE state deserve further attention:

- *The duration of recurring events*

Given that the company decided to choose 2-week cycles for their economic analysis, the fact that the recurrent VTE state was modelled as a tunnel state raises some issues. Clinical opinion sought by the ERG advised that several of the events considered in the economic model as tunnel states would impact patients' QoL for periods longer than 2 weeks. In the case of recurrent PE and DVT, it was mentioned that these events can easily impact the patients' QoL for 1 month as the lungs and/or legs can remain symptomatic over weeks or months.

However in the economic model, patients' QoL is only impacted for 2 weeks, after which it returns to the QoL patients experienced before the recurrent event. Clearly this is an underestimation of the impact that recurrent VTE has on patients' wellbeing.

This could have been solved by either lengthening the cycle duration in the model, or by modelling the recurrent VTE state in a different way. The recurrent VTE state could have been modelled as a "normal" state (i.e. not a tunnel state) thus allowing patients to remain in this health state for longer, accruing the respective costs and QALYs, or alternatively a "post-recurrent VTE" state could have been created in addition to the recurrent VTE state, where patients could move after experiencing VTE recurrence.

This issue is further explored in Section 5.4.7, where the ERG discusses the QoL of VTE patients. The cycle length used in the model is discussed further below in this section of the report.

- *Aggregation of DVT and PE events in the recurrent VTE state*

Similarly to the modelling approach taken in the on treatment state, the company decided not to specify the type of recurrence (i.e. DVT or PE) that patients experienced.

However it should be noted that specific modelled events are dependent to the type of recurrence. This is the case with CTEPH, for example, which is assumed to only occur in PE patients. Other aspects of DVT and PE make these events quite distinct. For example, they impact the QoL of patients differently and they have different mortality risks. The consequences of these events are therefore different, as it is shown by CTEPH, a rather serious condition only present in patients with PE.

As per the company clarification, the primary efficacy outcome in the Hokusai-VTE trial was the composite outcome of VTE recurrence therefore assumptions were made to allow the estimation of the DVT- and PE-specific events aforementioned. The baseline proportion of presenting DVT (59%) and PE (41%) was assumed to be the same as the proportion of recurrent DVT and recurrent PE, respectively.

Clinical opinion informed the ERG that it is reasonable to assume that the type of treatment is not relevant in predicting the type of VTE event avoided, that is, the type of treatment is relevant in preventing recurring VTE overall, but not necessarily in preventing DVTs or PEs specifically. If we accept this, then splitting the type of recurrence in the model doesn't add much value to the analysis.

Nonetheless, and given that the proportion of recurrent DVTs and PEs had to be considered in the model in order to model subsequent events and outcomes (like for example CTEPH), the company

could have split the type of index VTE and recurring event in the model. This could have added transparency to the model structure, but would not be likely to change the model final results.

Off treatment state

Patients discontinue treatment for 3 reasons in the economic model:

- After the end of the 12 months treatment;
- After an adverse event (or a complication) or when they die.

After patients discontinue treatment they are never allowed back on the treatment.

The ERG is concerned with the fact that once patients discontinue treatment they do not receive any further anticoagulation treatment, even in the case of a recurrent VTE event. Therefore the different reasons for treatment discontinuation considered in the economic model are now discussed:

- *End of treatment period*

The base case model assumed 12-month treatment duration. In clinical practice treatment duration is highly determined by the type of VTE (i.e. provoked or unprovoked). Whilst some patients will only receive 3 or 6 months of anticoagulation therapy (generally patients with provoked DVT), most patients in need of 12 months of therapy are likely to remain on anticoagulants forever.

Irrespective of treatment duration, the fact that patients experiencing recurrent VTE after (or at) 12 months do not receive any kind of anticoagulation treatment is highly implausible and unrealistic from a clinical point of view. Patients off anticoagulation treatment who experience a recurrent VTE event will be given anticoagulation therapy (whether returning to their original therapy regimen or a new one) and are in fact likely to need anticoagulation therapy for the reminder of their lives (depending if the recurrent event was provoked or unprovoked).

- *Adverse events or other complications*

In the model structure described in Figure 7, patients who experience bleeding events (CRNMB or MB) or HIT have a probability of discontinuing treatment. This is coherent with clinical practice.

However, what is not explicitly shown in the model structure is that patients experiencing a CTEPH or a stroke also discontinue treatment. The ERG requested clarification from the company as to why this assumption was made. The company stated that although patients with CTEPH could receive life-long anticoagulation therapy, the costs of this wouldn't have an impact on the model given the other substantial costs of CTEPH.

Clinical opinion sought by the ERG advised that patients with long term CTEPH will remain on anticoagulants as a VTE recurrence would be catastrophic in these patients and that CTEPH is a good indication for requiring lifelong anticoagulation. With regards to stroke, this would depend on the type of stroke (this is discussed in the next subsections).

In light of this, it seems clinical implausible that patients experiencing CTEPH would discontinue anticoagulation therapy. Nevertheless, the ERG acknowledges that allowing CTEPH patients to receive further anticoagulation treatment would have a very small impact on the final economic results. Not because the cost of anticoagulation treatment is not relevant, as suggested by the company, but because the probability of CTEPH across all arms of the economic model is the same. As the risk of CTEPH is not dependent on the type of treatment received, increasing the costs associated with CTEPH would not change the final ICER significantly, as the increase in costs is likely to cancel out across treatment arms.

Finally, once patients move to the off treatment state in the model, they are not allowed to experience CTEPH or stroke events. The plausibility of this assumption is discussed in the CTEPH and stroke sections, respectively.

CRNMB and MB states

Patients on anticoagulation therapy can also experience CRNMBs and MBs, after which they can discontinue or go back to treatment. This is appropriate as bleeding is a well-known side effect of anticoagulation treatment but not always leads to permanent treatment discontinuation.

Similarly to recurrent VTE, the CRNMB and the MB health states were modelled as tunnel states. Clinical opinion provided to the ERG advised that MB events can easily impact the patients' QoL for 1 month or more. CRNMBs were said to impact patients QoL for less than 2 weeks on average. Again, there seems to be an underestimation of the impact that MBs have on patients' wellbeing, and possibly an overestimation of the impact of CRNMBs. This is further explored in Section 5.4.7, where we discuss the QoL of VTE patients.

As previously discussed, this could have been solved by either lengthening the cycle duration in the model, or by modelling the bleeding states in a different way.

HIT state

Patients receiving initial intraperitoneal doses of heparin (in the on treatment and recurrent VTE states) are at risk of suffering from a HIT event.

In the CS it is mentioned that the inclusion of HIT in the model was discussed with the company's clinical experts and that the decision to include HIT, even if deemed uncommon, was taken to demonstrate consideration of all possibilities.

Clinical opinion sought by the ERG advised that the risk of HIT is indeed minor and that this health state didn't need to be included, especially as patients only received one dose of heparin at the beginning of their anticoagulation therapy, and that such low dose would be extremely unlikely to result in HIT events.

To note is that the risk of HIT in the model was estimated to be 0.02% over two weeks, which reflects the low likelihood of the event occurring. Furthermore, the probability of experiencing HIT was considered to be the same across all treatment arms. Even though the risk of HIT is associated with the probability of recurrence (as patients need a new heparin dose after recurrence) and the probability of recurrence is different across treatment arms, the risk of HIT is extremely low, therefore the inclusion of this health state in the model doesn't have a significant impact on the final ICER.

CTEPH and long-term CTEPH states

Patients on anticoagulation therapy can also experience CTEPH, after which they discontinue treatment. After CTEPH, patients can also move into the LT-CTEPH state. As previously discussed in this section the assumption that patients with CTEPH and LT-CTEPH would discontinue anticoagulation therapy is unrealistic from a clinical point of view. Despite this, the impact of changing this assumption in the model is not likely to change the final ICER.

Similarly to recurrent VTE, CRNMB and the MB health states, CTEPH was modelled as a tunnel state. Clinical opinion provided to the ERG advised that CTEPH can impact the patients' QoL for 1 month or more. However, since the company included an additional state of LT-CTEPH in the model, there are no issues of underestimation of the duration of the impact of this event in patients' QoL.

Finally, patients were considered to be at risk of CTEPH only when receiving anticoagulation therapy. Patients discontinuing treatment or terminating the 12 months anticoagulation therapy were not at risk of CTEPH anymore. Upon request for clarification from the ERG, the company explained that CTEPH (and stroke) were considered to be treatment-related complications and therefore, once patients were off treatment they were not at risk of experiencing these events anymore.

The ERG's clinical experts advised that CTEPH is not an adverse event associated with anticoagulation therapy, but instead a VTE complication. Therefore, patients in the model should be at risk of CTEPH at all times. Nonetheless, given that the probability of CTEPH in the model is 0.035% and the same across treatment arms, allowing patients to experience CTEPH after 12 months would be unlikely to substantially impact the final ICER.

Once patients are on the LT-CTEPH state they cannot experience any other event in the model (except death). The fact that patients on the LT-CTEPH state cannot experience PTS and stroke (ischaemic stroke) is not realistic from a clinical point of view, especially with PTS which is a VTE-related complication.

Stroke and post-stroke states

Patients on treatment can also experience a stroke. Patients who do not die from a stroke move on to the post-stroke health state. As previously mentioned, and even though it is not explicitly shown in the model structure, patients who experience a stroke discontinue anticoagulation treatment.

The ERG is concerned about the inclusion of the stoke health state in the model. The issues associated with this are now discussed in turn.

- *Double counting of haemorrhagic strokes and exclusion of other cardiovascular events*

One of the issues related to the inclusion of the stroke health state in the model is that it includes intracerebral haemorrhages (ICHs). These were also included in the MB health state as these are effectively bleeding events. This leads to a double counting of events in the economic analysis. The ERG has requested clarification from the company about the decision to include a discrete stroke health state and clarify if any adjustments were made to account for the apparent double counting of haemorrhagic strokes in the model. The company's response is presented in Box 19 below.

Box 19: Company's justification for including the stroke health state in the model (response to clarification question, B1j)

Stroke was included as a health state because anticoagulant treatment affects stroke outcomes in patients who receive these agents. The double counting issue as it applies to bleeding and haemorrhagic strokes is a commonly raised issue in this field, and studies of all anticoagulants have the same issue. Disambiguation or adjustments for the different stroke types is difficult. We did not adjust for this, and made the assumption that all anticoagulants included in the analysis are affected to a similar degree. Therefore there may be some systematic over-representation of haemorrhagic stroke but this should not affect the comparative analyses presented here. Furthermore this is likely a conservative assumption in the case of edoxaban, which demonstrated significant reductions in haemorrhagic stroke compared with warfarin in the ENGAGE study.

As the company decided to include the stroke health state in the model, and given that the Hokusai-VTE trial reported data on other cardiovascular events like myocardial infarction (MI) and systemic embolic events, the ERG also requested clarification as to why these other events were not considered in the model. The company's reply in presented in Box 20 below.

Box 20: Company's justification for not including other cardiovascular events in the model (response to clarification question, B1k)

Stroke was included in order to capture the effect of anticoagulants on intracranial haemorrhage. Other cardiovascular events have not been shown to occur at different rates using warfarin or other NOACs and therefore would not have a significant impact on the model.
Abbreviations used in the box: NOAC, novel oral anticoagulant

After the clarification provided by the company, the ERG confirmed that the stroke state in the model includes, but is not limited to, ICH events. In fact, the probability of stroke used in the model and taken form the Hokusai-VTE trial, reflects the probability of ischaemic and ICH events in the trial.

Clinical opinion sought by the ERG clarified that after an ischaemic stroke patients are likely to stop anticoagulation treatment for a few weeks but most likely will go back on anticoagulation treatment. Conversely, after an ICH the patient will stop receiving anticoagulation treatment forever.

In light of this, the following considerations need to be made:

- ICHs events should not be considered twice in the economic model. The justification provided by the company that the double counting issue related to IHCs is a common issue and that this would not impact the final ICER as there is a systematic over-representation of haemorrhagic stroke across all treatment arms is not a very satisfying one. From a methodological point of view it would have been fairly straightforward to avoid the double counting of IHCs in the model:
    - An alternative and separate health state could have been created to take into account ICH. The problem with including ICH in the major bleed state is that, according to clinical opinion provided to the ERG, ICH has a 40% mortality risk and 60% disabling risk. The MB state currently considered does not take into account the true impact of ICH in patients' quality of life.
    - The MB state should not include ICH events for the reason aforementioned. This would be relatively easy to implement as the Hokusai-VTE trial data provided bleeding events data with enough granularity.
    - If a stroke state was to be included in the model, this should have only included ischaemic strokes. However, for a matter of consistency, if ischemic strokes were considered in the model, other cardiovascular events should have been included in the analysis.

- As mentioned before, if only ICH are considered, then suffering a stroke will always lead to treatment discontinuation. But, if stroke includes ICH and ischaemic stroke, as it is the case for the economic model, then assuming all patients would discontinue anticoagulation treatment is not clinically plausible as patients suffering from ischaemic stroke are likely to go back to anticoagulation treatment after a few weeks.

- Finally, patients discontinuing treatment or terminating the 12 months anticoagulation therapy were no longer considered at risk of stroke in the model. Upon request for clarification from the ERG, the company explained that stroke was considered a treatment-related complication and therefore, once patients were off treatment they were not at risk of experiencing these events anymore. As discussed above, VTE patients are always at risk of suffering from ICH (even if treatment helps to prevent the event). Ischaemic stroke is not a treatment-related event.

Once patients are in the post-stroke state they cannot experience any other event in the model (except death). The fact that patients in this state cannot experience PTS and CTEPH is not realistic from a clinical point of view, as there are VTE-related complications.

Post-thrombotic syndrome (PTS)

PTS was not originally included as an explicit health state in the economic model. After the clarification stage, the company decided to include the PTS health state in the model as per the ERG's recommendation. Patients at risk of developing PTS in the model are patients in the on treatment and off treatment states. This means that patients in all the tunnel states (CTEPH, CRNMB, MB, HIT, recurrent VTE and stroke) and patients in the LT-CTEPH and post-stroke states cannot experience PTS.

As previously mentioned, PTS is a VTE-related condition and can occur at any time and so should not be restricted to the on or off treatment states. Clinical opinion provided to the ERG suggested that the majority of patients presenting with PTS will do so in the first 2 years after a VTE event. It was also mentioned that PTS is more prevalent in DVT than PE patients, but since patients with a PE may have undiagnosed DVT, is reasonable to assume PTS can occur in the entire VTE population.

In light of this, assuming that only patients in the on treatment and off treatment states are at risk of PTS seems to be clinically implausible especially for the LT CTEPH and post stroke states, where patients could spend up to around 50 years.

Cycle length

The cycle length in the economic model is 2 weeks (considered as 14 days). A half-cycle correction was applied, which is appropriate.

As mentioned in this section, the combination of the cycle length and the decision to model recurrent VTE and bleeding events as tunnel states raises some concerns as this is likely to be underestimating the decrement in patients' QoL associated with these events. The company explained that the 2-week cycle length was chosen to reflect the acute timeframe in which VTE events occur. Box 21 provides the full company's response.

Box 21: Company's justification for selection of cycle length (response to clarification question, B1a)

The 2 week cycle length was chosen for a number of reasons. Firstly, the effect of the heparin lead-in and the initial treatment phases of the various comparators could be more accurately modelled with a shorter cycle. Moreover, this choice allowed the risk of HIT and the risk of VTE recurrence after the index event to be more accurately captured. The risk of HIT exists only after the administration of heparin/LMWH, which should not be longer than 2 weeks. Furthermore all of the studies of NOACs in this indication have shown that the risk of VTE recurrence decreases markedly with time after the VTE index event, so it was considered more accurate to consider a short cycle. We note that there is no loss of accuracy by using a shorter cycle length. If anything, the model provides more granularity by using a 2-week cycle. Finally, this was validated by UK experts in the advisory board, held in February 2014.[a] This cycle length was said to be "relevant to capture most of the relevant events associated with anticoagulant therapies".
Abbreviations used in the box: HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin; NOAC, novel oral anticoagulant; VTE, venous thromboembolism.

The ERG understands that shorter cycle lengths can be favourable to capture rapidly changing and acute conditions. Indeed, we agree that a short cycle length can add granularity and flexibility to an economic model. However, and as mentioned before, when shorter cycles are used, then the use of tunnel states needs to be carefully considered as these can potentially underestimate the impact of certain events on patient's QoL and respective costs.

Clinical opinion sought by the ERG advised that several of the events considered in the economic model would impact patients' QoL for periods longer than 2 weeks. This is the case for recurring VTE events, MBs and PTS which can impact patients' wellbeing for several weeks or even months.

This issue could have been solved by either lengthening the cycle duration in the model, or by modelling the crucial health states in a different way, as explained above.

[a] Clinical experts that contributed to this advisory board: Prof. Martin Buxton (Chair); Dr Ameet Bakhai; Dr Ander Cohen; Mrs Pippa Anderson; Dr Jonathan Belsey

Time horizon

The time horizon considered in the economic model was lifetime. The model was run for 1300 cycles, the equivalent to 50 years, by which time 99.9% of simulated patients had died.

Given that patients enter the model with an average age of 56 years, it would be expected that all patients would be dead before 50 years, when they would be 106 years. Nonetheless, 35 years after the beginning of the model 80% of patients are still alive. This implies that 20% of VTE patients would virtually survive until the age of 90. This indicates that survival is potentially overestimated in the economic model. This is discussed in Section 5.4.6 of the report.

Perspective and discounting

The company 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.

In conclusion, the ERG finds that there is lack of consistency in the approach followed by the company with regards to modelling specific VTE complications. Some of the model assumptions were also found to be clinically implausible. The approach undertaken raises the following concerns:

- The ERG is not convinced by the clinical plausibility of assuming that:
    - For patients experiencing recurrent VTE events or major bleeds, their QoL is only impacted during 2 weeks, after which they return to the QoL experienced before the events. This issue is related with the decision to combine 2-week cycles with tunnel state structures;
    - Patients return to their original anticoagulation therapy after a recurrent event (even though it is likely that the original therapy was not effective in preventing recurrence);
    - Patients experiencing recurrent VTE after (or at) 12 months do not receive anticoagulation treatment for more than 2 weeks. In clinical practice, patients off anticoagulation treatment who experience a recurrent VTE event will be given anticoagulation therapy (whether returning to their original therapy regimen or a new one) and are in fact likely to need anticoagulation therapy for the reminder of their lives;

Superseded see erratum

- The fact that CTEPH and stroke were considered treatment-related complications. The ERG's clinical experts advised that CTEPH is not an adverse event associated with anticoagulation therapy, but instead a VTE complication. Therefore, patients in the model should be at risk of CTEPH at all times. The same applies for ischaemic strokes;
- Patients experiencing CTEPH discontinue anticoagulation treatment. Patients with CTEPH need anticoagulation therapy as recurrence might be catastrophic in these patients;
- Patients are at risk of developing PTS only in the on treatment and off treatment states. PTS is a VTE-related complication and as such patients should be able to experience it at all times.

- The ERG is not clear why the model depicts a rare event like HIT in a separate health state but simplifies the increase in risk while receiving anticoagulation treatment for serious adverse events like ICH.
- The ERG is not clear why ischaemic strokes were included in the model when the company decided to exclude other cardiovascular events such as MI, as it believed that the type of anticoagulation therapy does not impact these events.

5.4.3 Treatment effectiveness within submission

Treatment effectiveness within the model is implemented through transition probabilities between the different health states presented in the previous section. In this section the ERG describes and discusses how transition probabilities between health states were estimated within the different arms of the economic model.

Clinical inputs used in the economic model were taken from the Hokusai-VTE trial, the NMA and literature.

In the model, treatment effectiveness impacts patients' transition from the on treatment (i.e. VTE index event) to the recurrent VTE state. It also impacts the probability of patients experiencing CRNMB and MB and discontinuing treatment thereafter. This means that in the economic analysis, the type of anticoagulation therapy the patient receives (warfarin or NOACs) determines the likelihood of a patient experiencing a recurrent VTE event (acute DVT, with or without PE, or PE), a bleeding event (CRNMB or MB) and discontinuing treatment after bleeding. All other transition probabilities are assumed independent of the type of anticoagulation therapy given to patients.

All transition probabilities after 1 year were assumed to be equal to the respective probability between the 99th day and the 364th day.

The ERG begins by presenting and discussing how VTE recurrence was estimated in the model, then presents and discusses how the treatment adverse events were estimated, and finally looks into VTE-related complications.

5.4.3.1 Treatment effectiveness within submission

The probability of recurrence in the intervention arm of the model (and in the dabigatran and rivaroxaban arms) was estimated by taking the probability of recurrence for warfarin estimated in the Hokusai-VTE trial and then applying the six-month odds rations (ORs) obtained through the NMA, comparing warfarin to the other NOACs.

Table 26 presents the probability of experiencing recurrent VTE in the warfarin arm of the model. The ORs for VTE recurrence are presented in Table 27. The ERG identified several discrepancies between the ORs presented in the CS (Table B58, pg 132) and the estimates used in the economic model (also reported in the NMA Section 4.4.5). Therefore the ERG corrected these and presents the values used in the economic analysis in the tables below.

Table 26. Probability of recurrent VTE on warfarin- Hokusai-VTE, safety population, on-treatment period

Time period	N	n	Probability	2-week probability used in the model	95% Confidence interval
From index event to 14 days	4,122	23	0.56%	0.558%	0.331% to 0.785%
From 15 days to 98 days	3,972	43	1.083%	0.181%	0.761% to 1.404%
From 99 days to 364 days	3,578	16	0.447%	0.024%	0.229% to 0.666%

Table 27. NMA odds ratios for NOACs compared with warfarin for VTE recurrence at 6 months

Treatment	Time period	Odds ratio*	95% Credible interval*
Edoxaban	From index event to 14 days	[redacted]	[redacted]
Edoxaban	From 15 days to 98 days	[redacted]	[redacted]
Edoxaban	From 99 days	[redacted]	[redacted]
Rivaroxaban	From index event to 14 days	[redacted]	[redacted]
Rivaroxaban	From 15 days to 98 days	[redacted]	[redacted]
Rivaroxaban	From 99 days	[redacted]	[redacted]
Dabigatran	From index event to 14 days	[redacted]	[redacted]
Dabigatran	From 15 days to 98 days	[redacted]	[redacted]
Dabigatran	From 99 days	[redacted]	[redacted]
*values in bold were corrected by the ERG			

In order to use the ORs obtained through the NMA and apply these to the warfarin estimates thus obtaining the final probability of recurrent VTE for edoxaban (and other NOACs), some additional calculations were made. The company reports that ORs were converted into relative risks (RRs) so these could be then applied to the warfarin estimates. The equation used to convert ORs into RRs is as follows:

$$RR = OR/(1-P_{ref})+(P_{ref}*OR)$$

where OR are the odd ratios obtained from the NMA and P_{ref} is the probability of reference (i.e. warfarin) for the odd ratio and the RR.

The company reports that the final probability of recurrent VTE for edoxaban, dabigatran and rivaroxaban was then obtained by applying the following formula:

$$P_{edoxaban} = 1-(1-((1-(1-P_{warfarin})^{1/t})*RR))^{t}$$

where $P_{edoxaban}$ is the probability of the event occurring in the edoxaban arm of the model during period t and $P_{warafarin}$ is the probability of the event occurring the warfarin arm of the model during period t.

The estimated probability of recurrent VTE experienced by patients on edoxaban, dabigatran and rivaroxaban, respectively, is presented in Table 28.

Table 28. Probability of recurrent VTE on edoxaban estimated with NMA odd ratios

Treatment	Probability*	2-week probability used in the model
Edoxaban	0.473%	0.473%
Dabigatran	0.919%	0.154%
Rivaroxaban	0.379%	0.020%
*calculation undertaken by the ERG		

The probability of VTE recurrence for warfarin and edoxaban (and the other NOACs) required an adjustment to reflect the model cycle length (2 weeks). The company adjusted the raw probability of recurrence for warfarin taken from Hokusai-VTE to reflect 2-week cycles and then applied the ORs as previously described, thus obtaining 2-week estimates for the probability of recurrence for edoxaban, dabigatran and rivaroxaban. The formula used to adjust the raw probability was as follows:

$$p_{cycle}=1-(1-p)\text{^}(1/nc)$$

where p_{cycle} is the probability relative to the cycle length, p is the probability available in the clinical trial or literature and nc is the number of cycles on which this probability is based (for example, for annual probability, number of cycles = 26).

ERG comments on the treatment effectiveness within submission

The company used the probability of VTE recurrence for warfarin as the baseline effectiveness in the model. The NMA ORs were then applied to these data to estimate the probability of recurrence in the other arms of the economic model. The formulae used by the company to convert the ORs into RRs and then estimate the probability of recurrence with the obtained RRs is appropriate, nonetheless more complex than usual. For example, the equation:

$$P_{edoxaban} = 1-(1-((1-(1-P_{warfarin})^{1/t})*RR))^{t}$$

could have been replaced simply with:

$$P_{edoxaban} = P_{warfarin}*RR$$

This would have reduced the complexity of the formulae used in the model and increased transparency. Regardless of this, from a methodological point of view the formulae are equivalent.

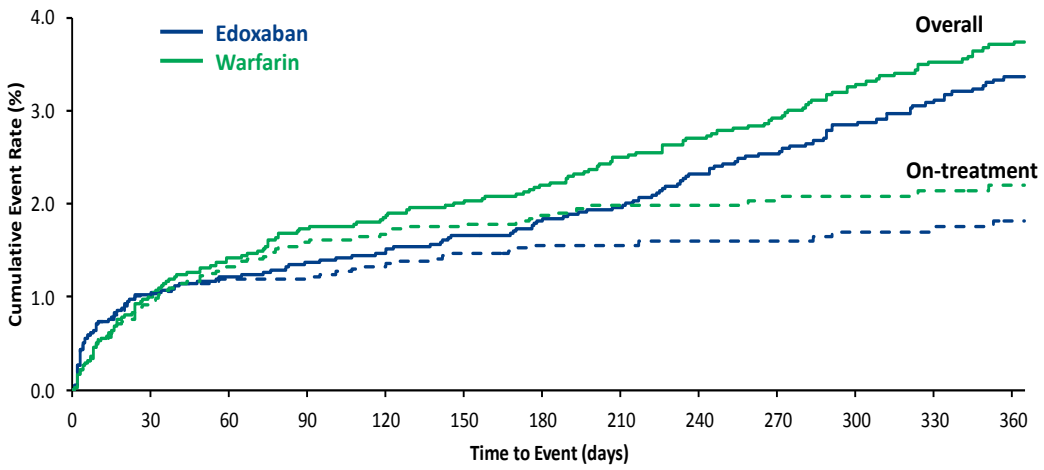
The probability of VTE recurrence for warfarin and edoxaban (and the other NOACs) required an adjustment to reflect the model cycle length (2 weeks). The ERG is satisfied with the formulae used to adjust the probabilities, however, from a methodological point of view, it would have been more appropriate to first apply the ORs to the warfarin raw probability and then adjust the final estimates to reflect the correct cycle length then the other way around, which was the methodology followed by the company. Nonetheless, given that the probability of recurrence is low in the model, using the more robust method would not carry a substantial impact (final results only varied by the centesimal value).

The company reports that in order to reflect the change in risk patients face over time the model incorporates five transition matrices, covering different time periods. However, as can be observed from Table 27 the ORs obtained with the NMA are constant across the different time periods. This means that, with regards to recurring VTE, the time dependency incorporated in the model comes from the baseline warfarin estimates. This implicitly assumes that the risk trend over time for warfarin is the same for edoxaban, dabigatran and rivaroxaban. In other words, the company assumed proportional hazards (PHs) across all treatment arms. Therefore, the assumption that the risk of recurrent VTE for warfarin varies across time in a similar fashion as for edoxaban (and other NOACs) should have been validated and such validation should have been presented by the company.

Figure 8 presents the Kaplan Meier (KM) curves for the primary endpoint (adjudicated symptomatic recurrent VTE) for the mITT analysis set for overall and on-treatment periods. It can be observed that in both analysis sets, the risk of recurrence with edoxaban seems to be higher than the risk of recurrence with warfarin during the initial period of analysis and then around 30 days later, the risk of recurrence with warfarin becomes greater than the risk of recurrence with edoxaban.

Based on the KM curves presented in Figure 8 it seems that the PHs assumption doesn't hold in this case. More statistical analysis would have to be conducted in order to ascertain if the PH assumption can be verified, however this would require patient-level data, which the ERG does not have.

Figure 8. KM curves for VTE recurrence for the overall and on-treatment periods



Number at Risk:													
Edoxaban Overall	4118	4050	4024	4002	3985	3974	3959	3885	3692	3524	3358	3190	2918
Warfarin Overall	4122	4055	4023	4001	3992	3975	3962	3864	3683	3519	3367	3184	2936
Edoxaban On-tx	4118	3892	3793	3724	3539	3478	3200	2320	2169	2029	1890	1769	1308
Warfarin On-tx	4122	3893	3791	3703	3499	3423	3170	2305	2140	2015	1880	1740	1306

In light of this, another important validation of the recurrent VTE estimates used in the model is the comparison between the estimated VTE recurrence and the observed recurrence for edoxaban in the Hokusai-VTE trial.

In Table 29 the ERG presents the Hokusai-VTE estimates of recurrent VTE for edoxaban, while in Table 30 the probability of VTE recurrence estimated in the economic model is provided. Finally in Table 31 the ERG presents the difference in the number of events estimated in the model and the number of events observed in the trial.

Looking at the tables below it can be noted that there is a slight underestimation of VTE recurrence in the initial 14 days, an overestimation during the 15 – 98 days of analysis and then finally no miss

estimation during the last period up to 1 year. This is demonstrated by the results presented in Table 31, which also show that the total difference in estimated vs actual number of recurrences amounts to a total number of 6 extra events estimated overall in the first year. However, it should be noted that the time intervals are not proportional, i.e whilst the first time interval reflects a 14-day period, the second time period of the analysis reflects 2.5 months. Therefore, while the overall number of events is similar it is likely that the distribution of VTE recurrence over the different time periods will underestimate the consequences of VTE.

Table 29. Probability of recurrent VTE on edoxaban- Hokusai-VTE, safety population, on-treatment period

Time period	N	n	Probability	2-week probability used in the model	95% Confidence interval
From index event to 14 days	4118	30	0.729%	0.729%	0.469 to 0.988
From 15 days to 98 days	3967	21	0.529%	0.088%	0.304 to 0.755
From 99 days to 364 days	3614	17	0.470%	0.025%	0.247 to 0.693

Table 30. Probability of recurrent VTE on edoxaban obtained with NMA odd ratios

Time period	Probability	2-week probability used in the model
From index event to 14 days	0.473%	0.4731%
From 15 days to 98 days	0.919%	0.1537%
From 99 days to 364 days	0.379%	0.0200%

Table 31. Difference in the number of observed and estimated recurrent VTE events

Time period	Observed	Estimated	Difference
From index event to 14 days	30	19	-11
From 15 days to 98 days	21	38	17
From 99 days to 364 days	17	17	0
Total	68	74	6

It should also be mentioned that all transition probabilities after 1 year were assumed to be equal to the respective probability between the 99th day and the 364th day. If one assumes the same would happen in “real life”, i.e. if one assumes that if the Hokusai-VTE trial had continued the recurrent events observed in the last period of analysis would be constant over time, this would mean that the favourable difference in the number of observed and estimated recurrent events for edoxaban is maintained throughout the rest of the analysis. This implies that for the remaining 49 years of the analysis, every year there would be an additional 3 events estimated, compared with the observed events. This would amount to a total of 147 additional events, which is quite significant. The ERG is unclear why the company did not attempt to extrapolate the trial data and estimate the recurrence of

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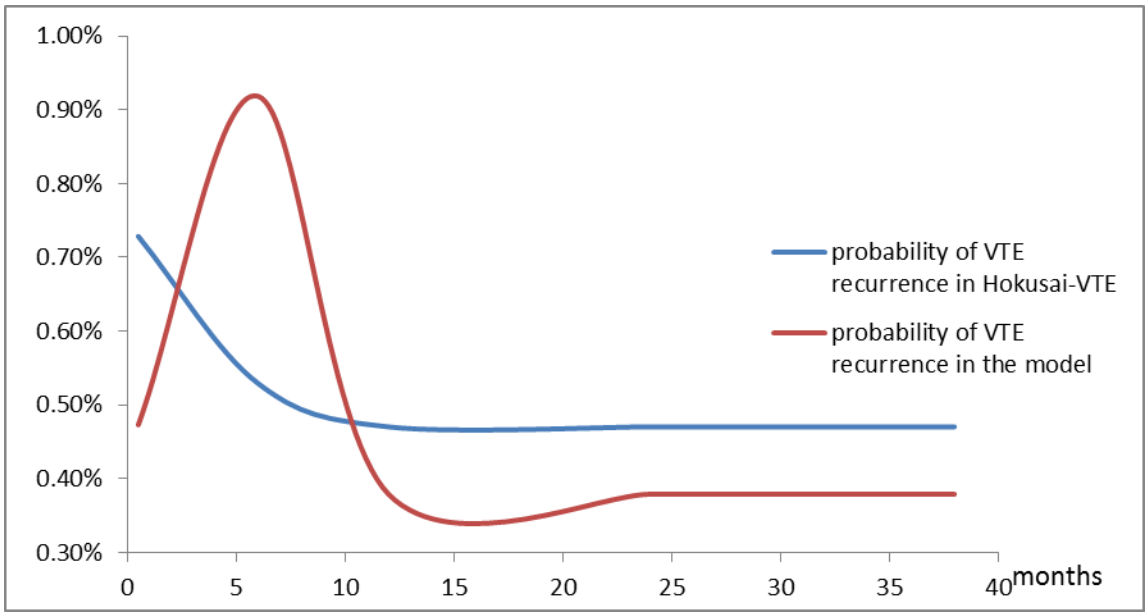
VTE in the following years of the model. Furthermore, no clinical justification was provided by the company to support the assumption that the risk of recurrence would be maintained after 12 months. Nevertheless, if this assumption is valid, then this would lead to a number of nearly 150 overestimated recurrent events.

Figure 9 below illustrates the issues reported in this subsection. It can be observed how the probability of recurrent VTE for edoxaban is underestimated during the initial (short) period of the analysis, then peaking at around 6 months and finally how the difference in the probability of recurrence after 1 year is maintained in the economic model, favouring edoxaban, when compared with the hypothetically observed events in the trial.

Figure 9. Difference in observed and estimated probability of recurrent VTE for edoxaban (produced by the ERG)



The combination of the issues raised is better explained by analysing Figure 10 and Figure 11 below. In Figure 10 the estimated recurrent VTE for warfarin and edoxaban can observed. As previously explained, the recurrence trend in warfarin was used as the baseline, and then the ORs obtained through the NMA (constant over time) were applied to obtain the recurrent VTE in the edoxaban arm. The consequence of this is that the curves are symmetrical and that there is a proportional difference in the risk throughout time (as PHs were assumed). However when we look at Figure 11, we can see the observed recurrence of VTE in the Hokusai-VTE trial for the warfarin and edoxaban arms of the trial. Not surprisingly, Figure 11 resembles Figure 9 as the probability of VTE recurrence in the model for edoxaban was modelled based on the probability of recurrence in the trial for warfarin.

The discrepancy between Figure 10 and Figure 11 is rather significant and casts doubt on the validity and the clinical plausibility of the modelled edoxaban arm in the economic model. This problem is

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related to the PH assumption made not only in the economic analysis but also in the Hokusai-VTE underlying statistical analysis and ultimately in the NMA.

Figure 10. VTE recurrence in the economic model (produced by the ERG)

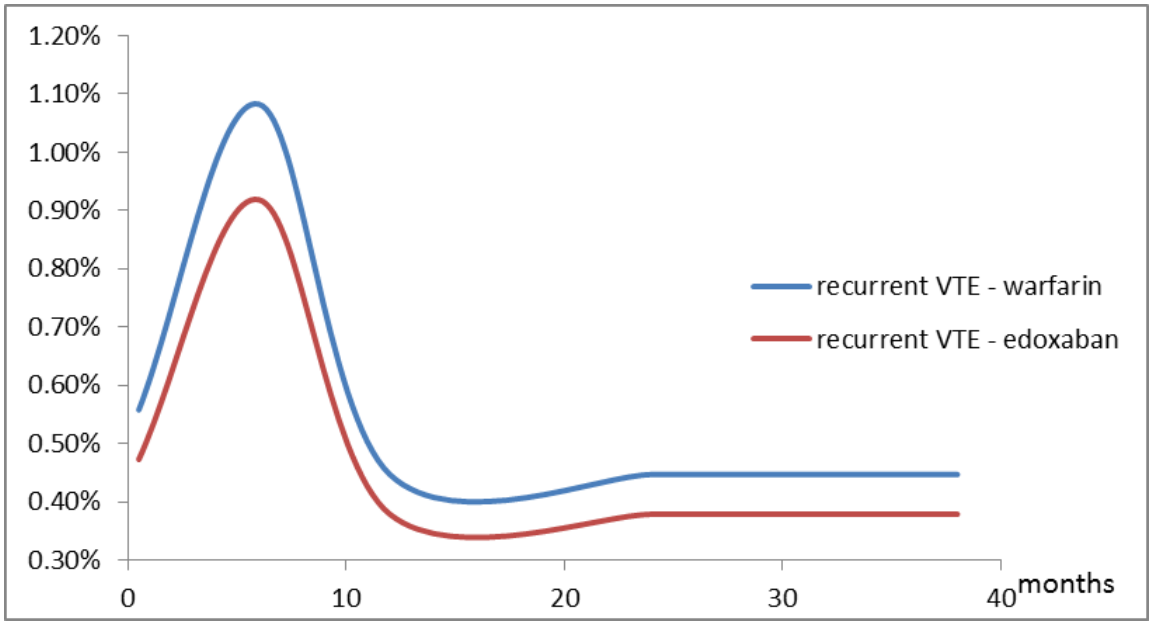
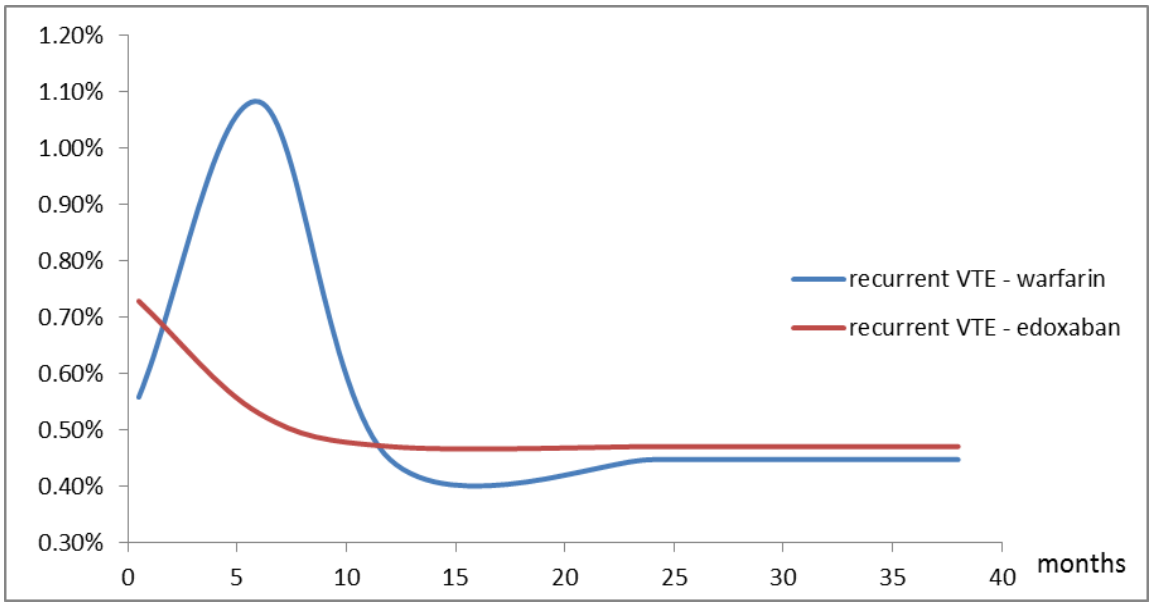


Figure 11. VTE recurrence in the Hokusai-VTE trial (produced by the ERG)



NMA estimates

The ORs estimates obtained from the NMA are calculated based on results at 6-months but are used in the economic model across the different time periods. As there is no significant difference in risk of

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recurrence between any of the NOACs and warfarin at 6-months, this could be interpreted as all of the NOACs having the same risk as warfarin over time.

The ERG considers that the non-inferiority design of the original trials included in the NMA has limited the opportunity for any NOAC in the network to have demonstrated a significant difference from any other treatment in the network, should one exist for prevention of VTE recurrence. In the individual studies, each NOAC was found to be non-inferior to warfarin and the findings of the NMA reflect these results. Nonetheless, as reported in several occasions throughout the CS, the benefit of edoxaban compared with warfarin is not that it results in significantly fewer recurrent VTE events.

In light of these findings, the ERG believes that an informative scenario analysis would be to set the ORs for recurring events across all treatments in the economic analysis to 1 to reflect not only the lack of statistical significance in the difference of recurring VTE events in the NMA and the Hokusai-VTE trial but also to reflect clinical expert opinion. The ERG has conducted this analysis and presents the results in Section 6.2.

In summary, the ERG is concerned with the modelled effectiveness of edoxaban (and the other NOACs) in preventing recurrent VTE. The main issues identified are:

- The underlying assumption of PH across the Hokusai-VTE statistical analysis, the NMA and the economic analysis does not seem to be valid when visual inspection of KM curves is undertaken. Furthermore, this assumption wasn't justified or validated by the company.

- Analysis of the phase-specific trial data for risk of recurrence with edoxaban does not seem to agree with the modelled risk of recurrence for edoxaban. Overall the risk of recurrence for edoxaban used in the model (and obtained through the NMA estimates) seems to be underestimated.

5.4.3.2 Adverse events of treatment

The company accounted for the following adverse events within the economic model:

- CRNMB and MB
- HIT
- Stroke

These are now explored in turn.

Bleeding events (CRNMB and MB)

The probability of bleeding in the intervention arm of the model (and in the dabigatran and rivaroxaban arms) was estimated by taking the probability of bleeding while on warfarin, estimated in

the Hokusai-VTE trial, and then applying the six-month ORs derived through the NMA to the warfarin baseline estimates.

Table 32 presents the probability of experiencing bleeding events in the warfarin arm of the model. The odds ratios for the risk of MB and CRNMB are presented in Table 33. The ERG identified some discrepancies between the odds ratios presented in the CS (Table B61, pg 133) and the estimates used in the economic model (also reported in the NMA Section 4.4.5). Therefore the ERG corrected these and presents the values used in the economic analysis in the tables below.

Table 32. Probability of bleeding on warfarin – Hokusai-VTE trial, safety population, on-treatment period

Type of bleed	N	n	Probability	2-week probability used in the model	Confidence interval
CRNMB	4,122	368	8.93%	0.359%	8.06% to 9.80%
MB	4,122	66	1.60%	0.062%	1.22% to 1.99%
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; MB, major bleed					

Table 33. NMA odds ratios for NOACs compared with warfarin for bleeding events at 6 months

Treatment	Event	Odds-ratios*	Confidence interval*
Edoxaban	MB	[redacted]	[redacted]
Edoxaban	CRNMB	[redacted]	[redacted]
Rivaroxaban	MB	[redacted]	[redacted]
Rivaroxaban	CRNMB	[redacted]	[redacted]
Dabigatran	MB	[redacted]	[redacted]
Dabigatran	CRNMB	[redacted]	[redacted]
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; MB, major bleed *values in bold were corrected by the ERG			

The ORs obtained through the NMA were applied to the warfarin estimates to estimate the final probability of CRNMB and MB for the edoxaban, dabigatran and rivaroxaban arms of the model using the same method employed for the estimation of recurrent VTE, described in the previous section. The estimated probability of CRNMB and MB experienced by patients on edoxaban, dabigatran and rivaroxaban, respectively, is presented in Table 34.

Table 34. Probability of bleeding on edoxaban estimated with NMA odd ratios

Treatment	Event	Probability*	2-week probability used in the model

Edoxaban	CRNMB	7.2%	0.28%
	MB	1.5%	0.06%
Dabigatran	CRNMB	5.4%	0.21%
	MB	1.2%	0.05%
Rivaroxaban	CRNMB	9.4%	0.38%
	MB	0.9%	0.04%
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; MB, major bleed *calculation undertaken by the ERG			

The probability of treatment discontinuation after a bleeding event while on warfarin or edoxaban was taken from the Hokusai-VTE trial. The probability of treatment discontinuation after CRNMB and MB with dabigatran and rivaroxaban were assumed the same as for edoxaban.

Table 35 and Table 36 present the probability of treatment discontinuation, dependant on anticoagulation therapy, for CRNMB and MB respectively.

Table 35. Probability of treatment discontinuation after CRNMB – Hokusai-VTE trial, safety population, overall treatment period

Treatment	N	n	Probability	2-week probability used in the model	Confidence interval
Warfarin	368	19	5.2%	5.2%	4.5% to 5.8%
Edoxaban	298	25	8.4%	8.4%	7.5% to 9.2%
Dabigatran, rivaroxaban	NA	NA	8.4%	8.4%	7.5% to 9.2%
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; NA, not applicable					

Table 36. Probability of treatment discontinuation after MB – Hokusai-VTE trial, safety population, overall treatment period

Treatment	N	n	Probability	2-week probability used in the model	Confidence interval
Warfarin	67	26	38.8%	38.8%	37.3% to 40.3%
Edoxaban	57	17	29.8%	29.8%	28.4% to 31.2%
Dabigatran, rivaroxaban	NA	NA	29.8%	29.8%	28.4% to 31.2%
Abbreviations used in the table: MB, major bleed; NA, not applicable					

The probability of bleeding for warfarin and edoxaban (and the other NOACs) required an adjustment to reflect the model cycle length (2 weeks). The company adjusted the raw probability of bleeding for warfarin taken from Hokusai-VTE to reflect 2-week cycles and then applied the ORs as previously described, thus obtaining 2-week estimates for the probability of bleeding for edoxaban, dabigatran and rivaroxaban. The formulae used to adjust the raw probability were the same as the ones used to adjust the VTE recurrence probabilities (described in the previous subsection).

ERG comments on bleeding events

The company took the probability of CRNMB and MB for warfarin, estimated in their time-to event analysis, as the baseline bleeding probability in the model. The NMA ORs were then applied to these data to estimate the probability of bleeding in the other arms of the economic model. The formulae used by the company to convert the ORs into RRs and then estimate the probability of bleeding with the obtained RRs was described in the previous section and the ERG is generally satisfied with the method used even though a simpler approach could have been taken.

The probability of VTE recurrence for warfarin and edoxaban (and the other NOACs) required an adjustment to reflect the model cycle length (2 weeks). The ERG is generally satisfied with the method used even though a more robust approach could have been taken, as described in the VTE recurrence section.

The company reports that their analysis aimed to reflect the change in risk which patients face over time. Therefore the ERG does not understand the company's decision to not use their post-hoc analysis, a phase-specific analysis that looked at the number of events occurring in the 3 time periods of relevance (day 1 to day 14, day 15 to day 98 and day 99 onwards) but instead using their time-to-event analysis. To note is that the recurrence of VTE in the model was estimated using the phase-specific analysis (as reported in the previous section). The company has not provided any justification why the phase-specific data were not used in the economic analysis (given they were available) and given that using the phase-specific data would have enriched the time-dependent analysis. The ERG presents the results of the phase-specific analysis in Table 37 and in Table 38 below for CRNMB and MB, respectively.

To note is that the following ERG comparative analysis of the phase-specific and time-to-event model estimates is made in terms of the 2-week probability estimates. This is because the unit of time needs to be the same across the estimates in order to conduct a comparative analysis, thus the ERG took the estimates provided by the company for the 2-week model cycles across all data sets.

Table 37. Probability of CRNMB on warfarin - Hokusai-VTE, safety population, on-treatment period (reproduced from Hokusai post-hoc analysis Table 1.4.3.4.2)[70]

Time period	N	n	Probability	2-week probability	95% confidence interval
From index event to 14 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
From 15 days to 98 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
From 99 days to 364 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 38. Probability of MB on warfarin- Hokusai-VTE, safety population, on-treatment period(reproduced from Hokusai post-hoc analysis Table 1.4.6.4.2)[70]

Time period	N	n	Probability	2-week probability	95% confidence interval
From index event to 14 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
From 15 days to 98 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
From 99 days to 364 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 12 and Figure 13 below present the probability of CRNMB and MB on warfarin estimated in the phase-specific analysis and the time-to-event analysis, whilst Table 39 and Table 40 report the difference in the number of events estimated and the number of events in the phase-specific and in the time-to-event analysis, respectively.

As it can be observed from Figure 12 and Figure 13, the probability of CRNMB and MB in the warfarin arm of the model (which is the same as the probability in the time-to-event analysis) is assumed to be constant over time. However, the phase-specific analysis shows that the 2-week probability of bleeding events decreases with time. Furthermore, analysis of Table 40 shows that the overall number of CRNMB events in the 2 analyses differs by [redacted] (with [redacted] events estimated in the phase-specific analysis) whilst the difference in terms of MB events is less significate, with [redacted] additional MB events reported in the phase-specific analysis.

This indicates that using the time-to-event analysis underestimates the number of CRNMB quite substantially, compared with the phase-specific analysis. The difference in these analyses was explained by the company during the clarification process. Essentially, the time-to-event analysis counted the number of first events experienced by a patient during the on-treatment period. A subject may have had multiple periods of study drug use if they temporarily interrupted and resumed study drug during the study. Contrastingly, the phase-specific (or post-hoc) analysis counted patients events multiple times (up to a maximum of 3) during the treatment period (plus 3 days). To note is that in each of the phases of the analysis (i.e. day 1 to day 14, day 15 to day 98 and day 99 onwards) only the first event of the patient would be counted but if the patient experienced an event in another phase of the analysis, then the event would be counted. This suggests that the additional 24 CRNMB events estimated in the post-hoc analysis were second (and possibly third) events experienced by patients in different treatment phases (who did not discontinue treatment permanently).

Given that the phase-specific analysis was used for the estimation of the recurring events, the same approach should have been taken for the estimation of bleeding events. Using these different analyses for the estimation of recurrent VTE events and treatment adverse events skews the analysis as second (and potentially third) recurrent events are being included in the analysis whilst only first bleeding events are being considered, resulting in an underestimation of bleeding events.

The same principle applies for MB events, even though the difference in the number of events in the warfarin arms of the time-to-event and post-hoc analysis is less substantial thus impacting the final analysis to a smaller extent.

The ERG notes that the smaller difference in the number of MB events in the time-to-event and post-hoc analysis is reasonable as in theory patients suffering a MB are more likely to permanently discontinue treatment than patients suffering a CRNMB event.

Figure 12. Probability of CRNMB on warfarin in the model (time-to-event analysis) and in the post-hoc analysis (phase-specific analysis) (produced by the ERG)

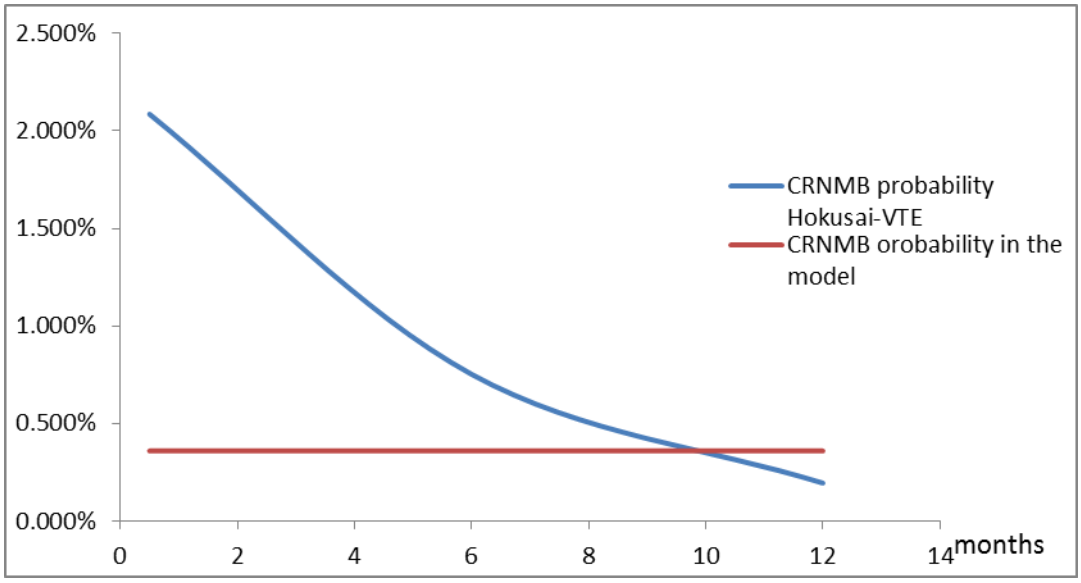

Figure 13. Probability of MB on warfarin in the model (time-to-event analysis) and in the post-hoc analysis (produced by the ERG)

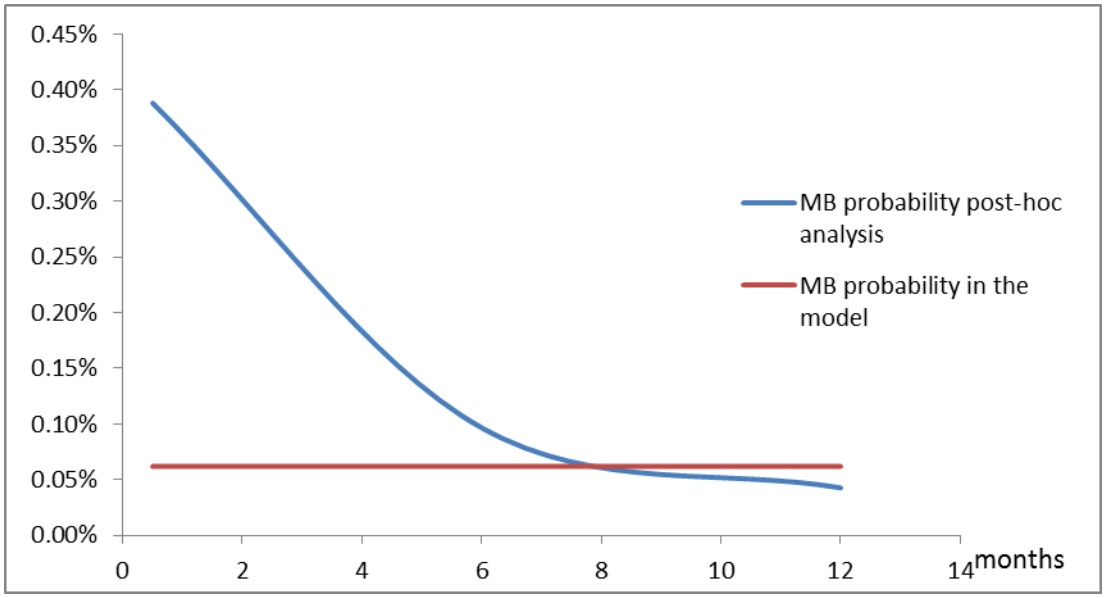

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Table 39. Number of CRNMB events observed in time-to-event and phase-specific analysis and number of events in the model in the first 12 months

Treatment	Time-to-event analysis	Phase-specific analysis	Difference (time-to-event minus phase-specific)	Estimated	Difference (estimated minus time-to-event)	Difference (estimated minus phase-specific)
Warfarin	368	392	-24	376	8	-16
Edoxaban	298	324	-26	296	-2	-28
Difference	-70	-68	-	-80	-	-

Table 40. Number of MB events observed in time-to-event and phase-specific analysis and number of events in the model in the first 12 months

Treatment	Time-to-event analysis	Phase-specific analysis	Difference (time-to-event minus phase-specific)	Estimated	Difference (estimated minus time-to-event)	Difference (estimated minus phase-specific)
Warfarin	66	68	-2	65	-1	-3
Edoxaban	56	58	-2	61	5	3
Difference	-10	-10	-	-4	-	-

Because the ORs are constant over time the difference in the estimated edoxaban and warfarin curves is symmetrical across time. Furthermore, because the probability of bleeding events occurring for warfarin was estimated as a constant across time, so was the probability of bleeding events in the edoxaban arm.

Similarly to recurrent VTE, the company assumed proportional hazards (PHs) across all treatment arms. Therefore, the assumption that the risk of CRNMB and MB for warfarin varies across time in a similar fashion as for edoxaban (and other NOACs) should have been validated and such validation should have been presented by the company.

Figure 14 presents the KM curves for the primary safety endpoint (adjudicated major/CRNM bleeding) for the safety analysis set for the on-treatment period. Visual inspection of the curves shows that the risk of bleeding with edoxaban seems to be lower than the risk of bleeding with warfarin throughout the analysis. However, it is important to note that these curves combine CRNMB and MB events together.

Based on the KM curves presented in Figure 14 it seems that the PHs assumption could be plausible. More statistical analysis would have to be conducted in order to ascertain if the PH assumption can be verified, however this would require patient-level data, which the ERG does not have.

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Figure 14. KM curves for adjudicated major it CRNM bleeding events, safety analysis set, on-treatment period (reproduced from CS, Figure B8)

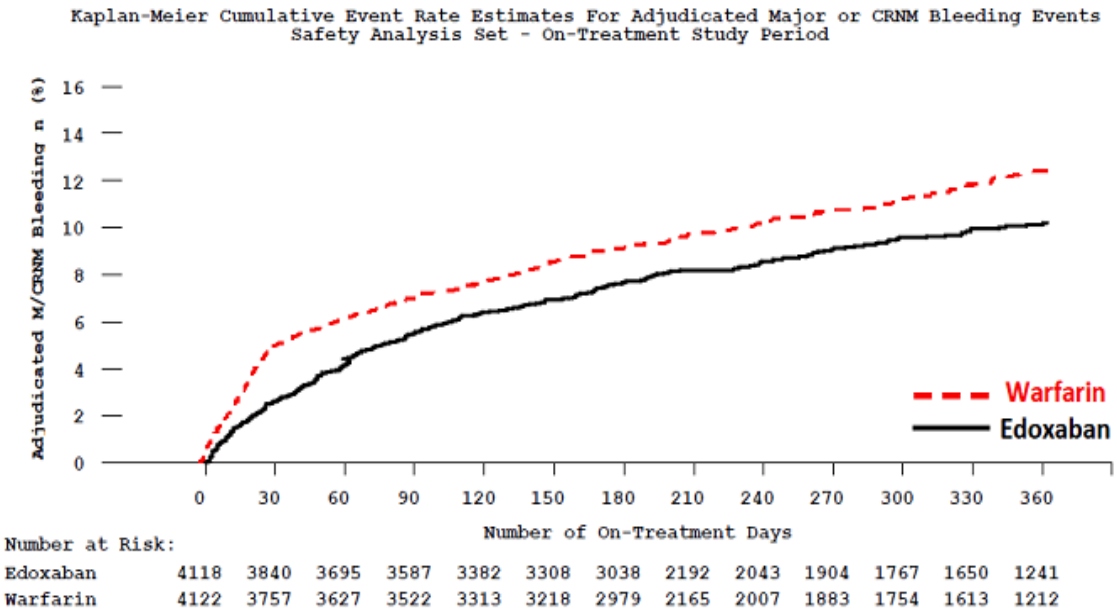


Figure 15 shows the difference in the CRNMB estimated curves for edoxaban and warfarin and the edoxaban and warfarin curves in the post-hoc analysis (phase-specific analysis). There is a substantial underestimation of the probability of CRNMB in the first 9 months of the analysis. After month 10, the probability of CRNMB is overestimated in the model. It can be observed how the post-hoc CRNMB curves seem to super-impose closer to 12 months. When comparing the difference in the number of estimated events between the warfarin and the edoxaban arms and the events observed in phase-specific analysis (Table 39) during the first 12 months of the analysis then this results in an overall underestimation of events in both arms (16 events in the warfarin arm and 28 events in the edoxaban arm). This difference comes from the difference in the phase-specific and the time-to-event analysis aforementioned.

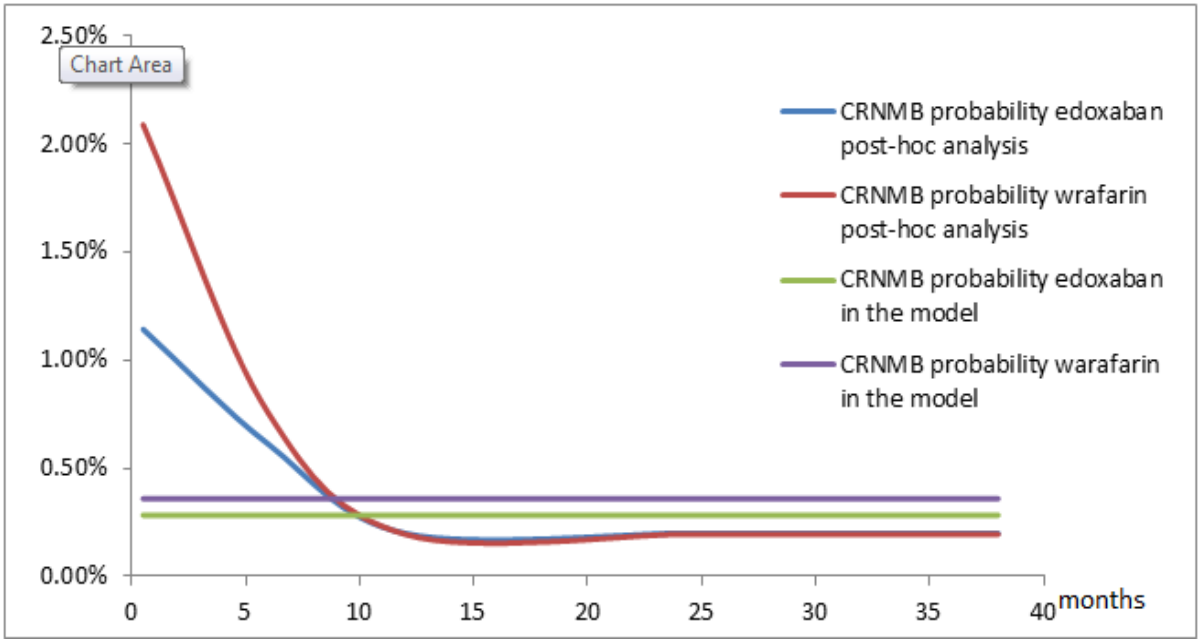
Figure 16 shows the difference in the MB estimated curves for edoxaban and warfarin and the difference in the edoxaban and warfarin curves in the post-hoc analysis (phase-specific analysis). To

note is that the post-hoc curves cross around month 9, with edoxaban presenting a higher risk of MB than warfarin until month 9, which then switches. This contradicts the KM curves presented in Figure 14. The nearly super-imposed model curves reflect the OR estimate of [redacted]. Similarly to CRNMB there is an underestimation of the probability of MB in the first 9 months of the analysis. After month 10, the probability of MB is overestimated in the model. More precisely, and according to

Table 39, there is in an underestimation of events in the warfarin arm of the model and an overestimation in the edoxaban arm of the model, exactly by the same number of events; 3 during the first 12 months of the analysis. This difference is linked to the difference in the phase-specific and in the time-to-event analysis aforementioned.

Nonetheless all transition probabilities after 1 year were assumed to be equal to the respective probability between the 99th day and the 364th day. If one assumes the same would happen in "real life", i.e. if one assumes that if the Hokusai-VTE trial had continued the bleeding events observed in the last period of analysis would be constant over time, then in the case of CRNMB events, there is a slight overestimation of the marginal effectiveness of edoxaban vs warfarin in terms of preventing bleedings and there is an overall overestimation in the total number of events; while in the case of MB, there is an underestimation of the marginal effectiveness (but an overestimation of the marginal effectiveness before 9 months) of edoxaban compared with warfarin after 12 months. In the case of bleeding events this is less relevant as after 12 months patients are only allowed to experience CRNMB and MB events when in the recurrent VTE state.

Figure 15. Probability of CRNMB in the model and in the post-hoc analysis (produced by the ERG)



Superseded see erratum

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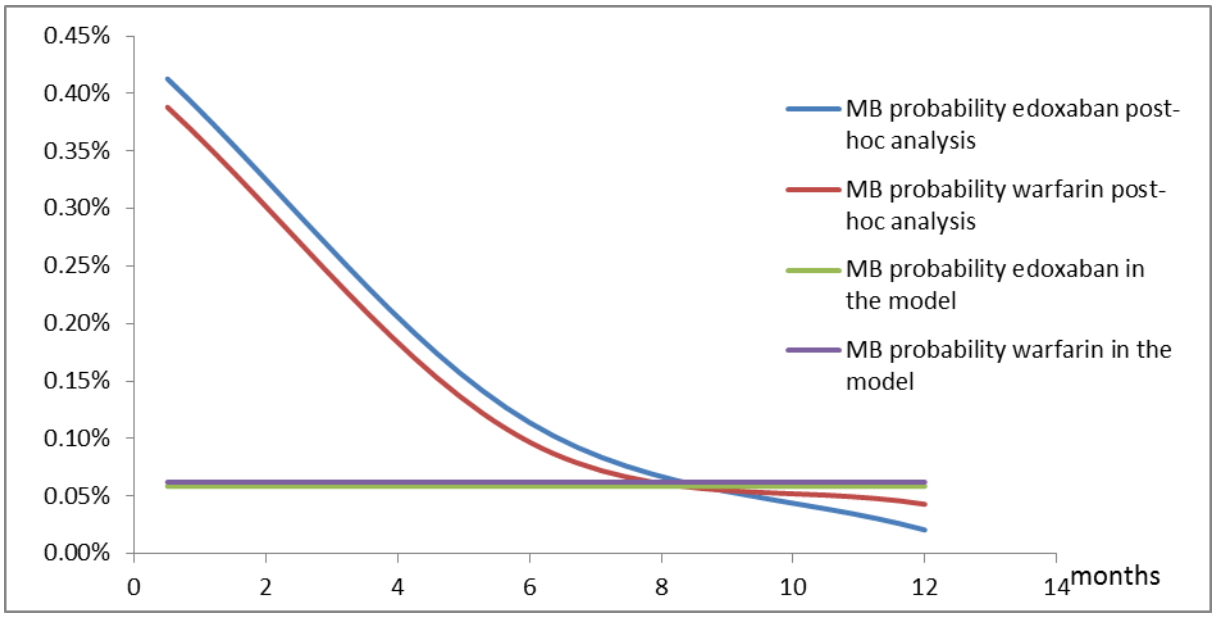
Figure 16. Probability of MB in the model and in the post-hoc analysis (produced by the ERG)



The difference between the KM curves and the post-hoc curves can be explained through several factors such as the fact that different methods of analysis were behind the curves (KM curves were derived by time-to-event analysis and the post-hoc curves were derived by phase-specific analysis) and the fact that the KM curves combine CRNMB and MB events, which seem to behave differently.

The discrepancy between the post-hoc curves and the estimated curves is substantial in the initial 9 months of the analysis. Given that the edoxaban curves were modelled using ORs applied to the warfarin curves, the reason for this difference is the discrepancy between the post-hoc and the time-to-event curves in the warfarin arms of the model.

When comparing the difference in the number of events occurring in the model and in the time-to-event analysis (Table 39) there are 8 additional CRNMB events estimated in the warfarin arm of the model (compared to the time-to-event analysis in the Hokusai-VTE trial) and there are 2 fewer events estimated in the model during the initial 12 months. This means that there is a total difference in the number of events of 10, introducing bias into the analysis in favour of edoxaban.

In terms of MB events, there are 5 additional events estimated in the edoxaban arm of the model (compared to the time-to-event analysis in the Hokusai-VTE trial) and there is1 less event estimated in the warfarin arm of the model. This means that there is a total difference in the number of events of 6, introducing bias into the analysis against edoxaban.

Therefore the difference in CRNMBs and MBs in the model and in the time-to-event analysis works in different directions, with the difference in CRNMBs favouring edoxaban and the difference in MBs favouring warfarin.

In summary, the ERG believes that the phase-specific analysis data should have been used to obtain the warfarin baseline data. Therefore the ERG conducted a scenario analysis using these data and presents the results in Section 6.2.

Finally, the company used the probability of treatment discontinuation after a bleeding event while on warfarin or edoxaban from the Hokusai-VTE trial. The probability of treatment discontinuation after CRNMB and MB with dabigatran and rivaroxaban was assumed the same as for edoxaban. Clinical opinion sought by the ERG indicated that the estimates used were generally reasonable, however the probability of discontinuation after a MB (30% for edoxaban and 39% for warfarin) was slightly lower, with the probability of discontinuation after MB being closer to 50%. The clinical advisors to the ERG revealed different opinions when assessing the probability of discontinuation differs across treatment arms in the model. Whilst it was mentioned that there is no reason for discontinuation to differ between the treatments (unless due to ICH), it was also stated that it made sense that the NOACs are associated with a greater probability to discontinue than warfarin.

NMA estimates

The ORs estimates obtained from the NMA are calculated based on results at 6-months but are used in the economic model across the different time periods. As there is no significant difference in risk of MB between any of the NOACs and warfarin at 6-months, this could be interpreted as all of the NOACs having the same risk as warfarin over time.

The ERG considers that the non-inferiority design of the original trials included in the NMA has limited the opportunity for any NOAC in the network to have demonstrated a significant difference from any other treatment in the network, should one exist for prevention of VTE recurrence. In the individual studies, each NOAC was found to be non-inferior to warfarin and the findings of the NMA reflect these results. Nonetheless, as reported in several occasions throughout the CS, the benefit of edoxaban compared with warfarin is not that it results in significantly fewer bleeding events.

In light of these arguments, and consistently with the approach taken for recurrence, the ERG believes that an informative scenario analysis is to set the ORs for bleeding events across all treatments in the

economic analysis to 1 to reflect the lack of statistical significance in the difference of recurring MB events in the Hokusai-VTE trial and to reflect clinical expert opinion provided to the ERG. The ERG has conducted this analysis and presents the results in Section 6.2.

In the Hokusai-VTE trial, there was a statistically significant difference in CRNMB between edoxaban and warfarin As such the ERG conducted a scenario analysis were the OR for MB equals 1 but the OR for CRNMB is kept as modelled in the base case model.

In conclusion, the ERG is concerned with the following issues with regards to the estimation of bleeding events in the model:

- Given that the phase-specific analysis was used for the estimation of the recurring events, the same approach should have been taken for the estimation of bleeding events. Using these different analyses for the estimation of recurrent VTE events and treatment adverse events skews the analysis as second (and potentially third) recurrent events are being included in the analysis whilst only first bleeding events are being considered, resulting in an underestimation of bleeding events.

- The company has not provided any justification why the phase-specific data were not used in the economic analysis (given they were available) and given that using the phase-specific data would have enriched the time-dependent analysis.

- When comparing the difference in the number of events occurring in the model and in the time-to-event analysis it seems that the difference in CRNMBs and MBs works in different directions, with the difference in CRNMBs favouring edoxaban and the difference in MBs favouring warfarin.

5.4.3.3 HIT events

In the model, the risk of HIT has only been considered in the first 2 weeks of anticoagulation treatment given that this event is related with heparin treatment. Therefore, patients experiencing index VTE or VTE recurrence are at the risk of experiencing HIT as they receive heparin with (or before) warfarin, edoxaban or dabigatran. Patients receiving rivaroxaban do not require initial treatment with heparin; therefore these patients are not at risk of HIT in the model.

The probabilities of HIT with edoxaban and warfarin were taken from Hokusai-VTE; for edoxaban the 2-week probability was reported as 0.024% (1 patient out of 4,118) and for warfarin 0.024% (1 patient out of 4,122). The risk of HIT associated with dabigatran and warfarin was assumed to be the

same as with edoxaban (CS, Table B 62); hence the resultant probability applied in the first cycle of the model was 0.024%, (Table 41).

Patients experiencing a HIT event have a 40% probability of discontinuing heparin treatment. This estimate was based on a company assumption.

Table 41: Probability of HIT applied in the model

Intervention	Baseline probability (95% confidence interval)	Source	Resultant probability in the first cycle
Warfarin	0.024% (0.00% - 0.07%)	Hokusai-VTE	0.024%
Edoxaban			
Dabigatran		**Assumption**	
Abbreviations used in the table: HIT, heparin induced thrombocytopenia; VTE, venous thromboembolism			

ERG comment on HIT events

As discussed in Section 5.4.2, the relevance of the HIT state in the overall analysis is questionable. Clinical opinion sought by the ERG advised that the risk of HIT is indeed minor and that it would have been reasonable to have excluded this health state, especially as patients only received one dose of heparin at the beginning of their anticoagulation therapy, and at such a low dose it would be extremely unlikely to result in HIT events. The ERG notes that only 2 patients experience HIT in the Hokusai-VTE trial.

However, and similarly to other VTE-related events in the model, the inclusion of this health state in the model doesn't have a significant impact on the final ICER.

With regards to heparin discontinuation, clinical opinion provided to the ERG advised that patients experiencing a HIT event would be switched from heparin to fondaparinux, and not just discontinue heparin treatment. Again, for the reasons explained before, changing this is the model would not impact the final ICER.

5.4.4.3 Stroke events

The probability of stroke in the economic analysis was modelled with Hokusai-VTE data. The definition of stroke reported in the Hokusai-VTE trial protocol is presented in Box 22.

Box 22: Definition of stroke taken from the Hokusai-VTE trial protocol

A stroke is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit in the distribution of a single brain artery that is not due to an identifiable nonvascular cause (i.e. brain tumor or trauma), and that either is associated with symptoms lasting more than 24 hours or that results in death within 24 hours of symptom onset or if symptoms last <24 hours a clear matching

lesion on CT or MRI […] All strokes will be sub-classified as “ischemic “or “primary hemorrhagic” based on imaging data, if available, or “uncertain cause” if imaging data is not available according to the definitions below. In addition, ischemic stroke will be further sub-classified by presence or absence of haemorrhage […] A TIA as an abrupt onset over minutes to hours of a focal non-fatal, neurological deficit in the distribution of a single brain artery that lasts less than 24 hours and that does not satisfy the definition of stroke above.
Abbreviations used in the box: CT, computerised tomography; MRI, magnetic resonance imaging; TIA, transient ischaemic attack

Patients on treatment (during their index VTE or recurring VTE event) are at risk of stroke in the economic model. Patients who do not die from a stroke move on to the post-stroke health state. As previously mentioned, and even though it is not explicitly shown in the model structure, patients who experience a stroke discontinue anticoagulation.

The probability of stroke with warfarin and edoxaban was taken from Hokusai-VTE; for edoxaban this was reported as 0.63% (26 patient out of 4,118) and for warfarin 0.63% (26 patients out of 4,122).

The risk of stroke associated with dabigatran and rivaroxaban were assumed to be the same as with edoxaban (CS, Table B 63). The estimated probability of stroke is presented in Table 42.

Table 42: Probability of stroke applied in the model

Intervention	Baseline probability (95% confidence interval)	Source	Resultant probability per cycle
Warfarin	0.63% (0.39%-0.87%)	Hokusai-VTE	**1- (1- 0.63%)^(1/26) =** 0.02%
Edoxaban			
Dabigatran		Assumption	
Rivaroxaban			

ERG comment on stroke

The ERG is concerned about the way the stroke health state was modelled, as per the discussion presented in Section 5.4.2. At the clarification stage, the company confirmed that the stroke health state includes, but is not limited to, ICH events. In fact, the probability of stroke used in the model and taken form the Hokusai-VTE trial, reflects the probability of ischaemic and ICH events in the trial. These two events are rather different and clinical opinion sought by the ERG clarified that after an ischaemic stroke patients are likely to stop anticoagulation treatment for a few weeks but most likely

will go back on anticoagulation treatment. Conversely, after an ICH the patient will stop receiving anticoagulation treatment forever.

Therefore, from a methodological point of view, ICH events should have been modelled separately. This would have avoided the double-counting of ICH in the stroke and MB states and would have allowed the analysis to capture the appropriate costs and benefits related to ICH, which are underestimated in the MB state.

Similarly to other estimates in the model, the probability of stroke in the analysis is the same across all treatment arms. Even though the event can be experienced whilst on recurrence (and the probability of recurrence is not the same across all treatment arms), the combination of the low probability of stroke and the fact that patients are only allowed to stay in the recurrent state for 2 weeks leads to a very low number of stroke events while on recurrence.

Even though ICH has a catastrophic impact on a patient's wellbeing (which is not reflected in the MB state), the number of strokes (both ICH and ischaemic) events in the model is extremely low (0.63% over 1 year in both arms of the trial, respectively) and the number of stroke events in the warfarin and the edoxaban arms is not statistically different (HR 1; 95% CI: 0.58 to 1.72).

In light of these arguments, the ERG undertook a scenario analysis where the stroke health state is removed from the model to avoid double counting of ICH events and to be consistent with the company's decision to not include other cardiovascular events in the analysis. The ERG acknowledges that even though the inclusion of a stroke state is methodologically flawed, this is is unlikely to impact the final ICER. Finally the ERG notes that even though the MB state underestimates the impact of ICH events, there are no reasons to believe that the number of ICH events is different across treatment arms hence the impact of ICH events in the analysis is silent.

5.4.3.4 CTEPH and LT CTEPH

The ERG discusses the CTEPH health state separately as the company considered this a treatment-related complications in the model (company's response to clarification, question B1) but the ERG disagrees with this categorisation. In fact CTEPH is a VTE-related complication, as per confirmation provided by the ERG's clinical experts.

In the economic model, and as described in Section 5.4.2, only patients with an index PE in the on treatment and recurrent VTE health states were at risk of CTEPH. The company assumed that acute pulmonary hypertension needed to be present for at least three months before a diagnosis of CTEPH could be made. As a consequence, CTEPH was only modelled from day 99 to lifetime, where the probability of CTEPH after 364 days was assumed to be equal to the probability between the 99th day

and the 364th day. The probability of CTEPH was assumed to be equal regardless of the anticoagulation treatment received.

Once patients experienced CTEPH they were assumed to discontinue anticoagulation treatment for the rest of the analysis. Patients who survived their CTEPH and were not cured transferred to the LT-CTEPH health state.

CTEPH data were obtained from literature. Nonetheless, the Hokusai-VTE trial captured CTEPH data, even though the company does not report this in the CS. In fact, only 1 patient (on edoxaban) suffered from CTEPH during the 12-month trial period.

The ERG identified a reporting error in the submission, which identified the data source for CTEPH data as Pengo *et al*.[24], when the economic model reported this source to be Guérin *et al*.[30]. During clarification stage the company explained that Guérin *et al*.[30] was the source used in the economic analysis. In Guérin *et al*.[30] 146 patients were analysed and 8 patients (5.4%) had suspected CTEPH during a median follow-up of 26 months. CTEPH was confirmed using right heart catheterisation in 7 cases (4.8%; 95% CI: 2.3 to 9.6) and ruled-out in one.

In order to estimate the probability of CTEPH in the model, the company multiplied the probability of PE (4.8%) taken from Guérin *et al*.[30] by the proportion of PE patients in the total population ([redacted] from Hokusai-VTE. This produced a CTEPH probability of [redacted], which was then adjusted to reflect the cycle length in the model (Table 43).

Table 43: Probability of CTEPH applied in the model

Intervention	Baseline probability	Source	Resultant probability per cycle
Warfarin	[redacted]	Guérin *et al*, 2014[30]	[redacted]
Edoxaban			
Dabigatran			
Rivaroxaban			

The probability of LT-CTEPH was based on the assumption that 33% of CTEPH patients move into the long-term state, regardless of the initial anticoagulant treatment.

ERG comment on CTEPH

Following consultation with clinical experts, and after review of the systematic review of cost-effectiveness evidence carried out by the company, the ERG considers that CTEPH is a relevant albeit rare complication associated with VTE. Therefore, patients in the model should be at risk of CTEPH

at all times. However given that the probability of CTEPH in the model is the same across treatment arms, allowing patients to experience CTEPH after 12 months would be unlikely to substantially impact the final ICER.

Similarly, the assumption that patients with CTEPH and LT-CTEPH would discontinue anticoagulation therapy is unrealistic from a clinical point of view (as discussed in Section 5.4.2). Despite this, the impact of changing this assumption in the model is not likely to change the final ICER.

Even though the impact on the economic analysis is unlikely to be relevant, the ERG disagrees with the company assumption that CTEPH is a treatment-related adverse event. Furthermore, the company's assumption that the probability of CTEPH is the same regardless of the treatment received is contradictory to their assumption that this is a treatment-related complication. The ERG's clinical experts agreed that CTEPH is a complication associated specifically to PE and that it is reasonable to assume that CTEPH diagnosis is confirmed only after 3 months of the PE index event.

The Hokusai-VTE trial captured CTEPH data, even though this information is not provided in the CS. The post-hoc analysis undertaken identified [redacted] occurring in the edoxaban arm of the trial over the 12-month follow-up period.[70]

The company used Guérin *et al*. to inform the probability of CTEPH in the model.[30] is the ERG notes that the company did not report how this was identified or selected in the CS and in the clarification stage. Nonetheless, the study is a good quality study, with generally robust statistical analysis. Clinical experts agreed that the CTEPH probability of 5% over 2 years presented in the study is reasonable.

It should be noted that the population in the Guérin *et al*. study who suffered from CTEPH was, on average, 75 years old.[30] Age is a well-established predictor factor of VTE, in fact the company's subgroup analysis indicated that being 75 years or older in the trial was a statistically significant prognostic factor of recurrent events. The average age in Guérin *et al*.[30] was 61 years old, while the average age in the Hokusai-VTE trial was 56. The slightly younger VTE population in the Hokusai-VTE trial and the fact that only around 13% of the trial patients were 75 years or older, might explain the lower prevalence of CTEPH in the trial.

Table 44 compares the annual probability of CTEPH and the number of CTEPH events after 1 year in the model and in the Hokusai-VTE trial. Even though there is a significant overestimation of the number of events predicted by the model, the impact on the final ICER is negligible since the number of estimated events is the same across treatment arms.

Table 44. Annual estimation of CTEPH in the model and in Hokusai-VTE

Treatment	Annual probability of CTEPH in the model	Annual probability of CTEPH in Hokusai-VTE trial[70]	Number of CTEPH events in the model	Number of CTEPH events in the Hokusai-VTE trial[70]
Edoxaban	[redacted]	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; VTE, venous thromboembolism				

The ERG notes that all patients in the Guérin *et al*. study who suffered a CTEPH event remained on anticoagulation treatment (VKA regimen).[30] Only 2[b] of the 7 patients with CTEPH were deemed appropriate to undertake surgery. That is, 29% of patients were eligible for surgery. This compares to the 57% of patients receiving surgery in the economic model.

Similarly, 4 of the 7 patients received bosentan (together with VKA), amounting to 57% of CTEPH patients requiring additional drug therapy. This is broadly in line with the proportion of CTEPH patients receiving drug therapy (other than anticoagulation) in the model.

Two patients did not need further therapy, and remained on their anticoagulation therapy. If it is assumed that patients who undergo surgery are successfully treated for their CTEPH, this suggests that 3 patients (43%) would be considered as LT-CTEPH patients. The proportion of LT-CTEPH in the model was slightly lower at 33%.

In light of this, it is not clear why the company did not use Guérin *et al*. to model the LT-CTEPH in the model.[30] This source could have provided all the information needed to estimate the probabilities used in the model. Instead the company used different literature sources (see Section 5.4.3.4) and assumptions to derive model inputs. Again, the impact of this in the final ICER is not relevant as CTEPH and LT-CTEPH was modelled in a similar fashion across treatment arms.

The ERG notes that the probability of CTEPH does not change with the number of recurrent VTE events. The ERG consulted with clinical experts who advised this is not reflective of clinical practice because the recurrence of VTE increases the probability of experiencing CTEPH. The ERG

[b] Even though 2 patients were eligible for surgery, only 1 patient agreed to undergo the procedure

acknowledges that for this to be considered, a different model structure would be necessary, where successive recurrent VTE events would be modelled separately.

5.4.3.5 Complications associated with VTE events included in the model

Despite not being explicitly modelled, PTS was considered a VTE-related complication in the economic analysis.

The company assumed that the entire VTE population (i.e. those with index PE and DVT) are at risk of PTS while in the on treatment and off treatment health states. Published literature was used to inform model inputs for PTS events in the model. Even though this information was not provided in the CS, the Hokusai-VTE trial also captured data on PTS events.

The probability of experiencing PTS was taken from Prandoni *et al*. 1997 which reported an incidence of 2.7% PTS severe cases in the first year and 5.4% over the following 4 years, for severe episodes.[71] The probability of PTS was assumed to be equal regardless of the anticoagulation treatment received. The probabilities applied in the model for the first year and subsequent years are presented in Table 45.

Table 45: Probability of PTS applied in the model

Intervention	Source	Annual probability	Resultant probability per cycle during the first year	Resultant probability per cycle in subsequent years
Warfarin	Prandoni *et al*. 1997[71]	First year, 2.7%; subsequent years, 5.4%	1- (1- 2.7%) ^ (1/26) = 0.0011	1- (1- 5.4%)^(1/104) = 0.0055
Edoxaban				
Dabigatran				
Rivaroxaban				

ERG comment on complications associated with VTE

Following consultation with clinical experts, and after review of the systematic review of cost-effectiveness evidence carried out by the company, the ERG considers that PTS is a relevant complication associated with VTE. Therefore, patients in the model should be at risk of PTS at all times.

As previously mentioned, PTS is a VTE-related condition and as such it is clinically implausible that PTS can only occur in the on treatment and off treatment states. Clinical opinion to the ERG suggested that the majority of patients presenting with PTS will do so in the first 2 years after a VTE event. It was also mentioned that PTS is more prevalent in DVT than PE patients, but since patients with a PE may have undiagnosed DVT, is reasonable to assume PTS can occur in the entire VTE population.

The ERG is concerned with the lack of transparency in the selection of the data source used to model PTS. Not only the CS does not report that PTS was analysed in the Hokusai-VTE model, but during clarification stage the company mentions that, “No cases of PTS were recorded in the Hokusai-VTE clinical trial” (Company’s response to clarification, B2). Nonetheless, the post-hoc analysis provided by the company reports the phase-specific analysis of the PTS events in the trial.[70] This is reported in Table 46. There were a total of [redacted] reported in the Hokusai-VTE trial ([redacted] in the edoxaban arm and [redacted] in the warfarin arm of the trial).

Table 46. Frequency distribution on number of patients with a non-adjudicated PTS event separately by MAPI phase and treatment group-Safety Analysis Set (reproduced from Hokusai-VTE post-hoc analysis Table 1.4.12.4.2)[70]

		Heparin/warfarin						**Heparin/edoxaban**						**Total**					
Phase		N	n	p	SE (p)	95% CI		N	n	p	SE (p)	95% CI		N	n	p	SE (p)	95% CI	
Start day	**Stop day**					Lower limit	Upper limit					Lower limit	Upper limit					Lower limit	Upper limit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: CI, confidence interval; N, number of subjects in analysis set; n, number of subjects meeting event criteria; SE, standard error

a.“N” is the absolute number of patients who are on study treatment at start of the phase

b.“n” / “p” is the absolute/percentage number of patients with the specific event of interest within a specific phase

c.The 95% CI has been calculated using the normal approximation

d.Within a specific phase, only the first event of a patient is taken into account

e.Patients with events in different phases will be counted in each of these phases as having an event

The company took the probability of severe PTS from Prandoni *et al*. 1997 when probabilities for mild and moderate PTS were also reported.[71] The overall PTS probability reported in the study is 18% after 1 year and 6.5% over the following 4 years. Clinical experts informed the ERG that 18% in the first year is more reasonable than 2.7%, but that 18% is still low compared to clinical practice. Moreover, experts advised that up to 40% of patients can have PTS in some form and for moderate or severe PTS this could be 25 to 30%. During clarification the ERG asked the company why the probability for severe cases was used in the economic model, the company's response is presented in Box 23.

Box 23 Company's rationale for using the probability associated with severe PTS (Company's response to clarification, B2)

No cases of PTS were recorded in the Hokusai-VTE clinical trial. Published evidence suggests that mild PTS had little detrimental effect on quality of life[72]; therefore, the model includes only severe PTS. A similar assumption was mentioned in the dabigatran submission.
Note reference re-numbered by ERG Abbreviations used in the box: PTS, post thrombotic syndrome; VTE, venous thromboembolism

In summary, it seems that the PTS events reported in the Hokusai-VTE trial are less prevalent than it would be expected in clinical practice. This seems to be the case with other events (e.g. CTEPH). Nonetheless, the company does not provide any justification as to why the trial data were not used to model these events in the economic analysis (or acknowledges the existence of these data). This should have been reported more transparently, together with the rationale behind why trial data were not used in the analysis.

The ERG notes that because the probability of PTS is the same across the different treatment arms, increasing the prevalence of PTS in the model would be unlikely to impact the final ICER.

Finally, the ERG notes that the probability of PTS does not change with the number of recurrent VTE events. The ERG consulted with clinical experts who advised this is not reflective of clinical practice because the recurrence of VTE increases the probability of experiencing PTS. The ERG acknowledges that for this to be considered, a different model structure would be necessary, where successive recurrent VTE events would be modelled separately.

5.4.3.6 Probability of recurrent VTE off treatment

The company used Coleman *et al.*[73] to model the probability of recurrent VTE for patients off anticoagulation treatment. Coleman *et al.*[73] compared the extended use of anticoagulation therapy with rivaroxaban for an additional 6–12 months of therapy with patients on placebo. Patients off anticoagulation treatment reported a probability of recurrence of 5.6% at the end of the first year and 3.5% after two years. The company took these estimates to model the probability of recurrence for patients off treatment for one year and after two years, respectively.

ERG comment on complications associated with VTE

The source used by the company to model the probability of recurrent events for patients off treatment is based on a robust analysis, which used EINSTEIN-Extension trial data comparing rivaroxaban 20 mg once daily with placebo in patients who completed their standard treatment course of anticoagulation (3–12 months in duration) after an index VTE. Nonetheless, the ERG notes that the company could have presented this analysis using the Hokusai-VTE trial data. As seen in Figure 8, the KM curves for the overall treatment and the on treatment analyses differ substantially, suggesting that the overall treatment curves, which report higher rates of recurrence compared with the on treatment curves, are representative of the recurrence rates in patients off anticoagulation treatment. The estimated difference between these curves could have been used by the company to model (or validate) the probability of recurrence when patients are off treatment in the economic analysis.

In conclusion, the ERG is concerned with the lack of clinical validity of some of the assumptions made in the economic model. The ERG also considers that more transparency should have been employed in the selection and presentation of data inputs. The ERG's main concerns are related to:

- The modelled effectiveness of edoxaban (and the other NOACs) in preventing recurrent VTE. Analysis of the phase-specific trial data for risk of recurrence with edoxaban does not seem to agree with the modelled risk of recurrence for edoxaban. Overall the risk of recurrence for edoxaban used in the model (and obtained through the NMA estimates) seems to be underestimated.

- Given that phase-specific data were used for the estimation of the recurring events, the same approach should have been taken for the estimation of bleeding events. Using different analyses sets for the estimation of recurrent VTE events and treatment adverse events skews the analysis, resulting in an underestimation of bleeding events.

- When comparing the difference in the number of events occurring in the model and in the time-to-event analysis it seems that the difference in CRNMBs and MBs works in different

directions, with the difference in CRNMBs favouring edoxaban and the difference in MBs favouring warfarin.

- The relevance of the HIT state in the overall analysis is questionable however, and similarly to other VTE-related events in the model, the inclusion of this health state in the model doesn't have a significant impact on the final ICER.

- The company does not provide any justification as to why CTEPH trial data were not used to model these events in the economic analysis (or acknowledges the existence of these data). This should have been reported more transparently, together with the rationale behind why trial data were not used in the analysis.

- Even though the impact on the economic analysis is unlikely to be relevant, the ERG disagrees with the company assumption that CTEPH is a treatment-related adverse event as CTEPH is a VTE-related condition.

- It is not clear why the company did not use Guérin *et al.* to model the LT-CTEPH in the model.[30] This source could have provided all the information needed to estimate the probabilities used in the model. Instead the company used different literature sources.

- The company does not provide any justification for why PTS trial data were not used to model these events in the economic analysis (or acknowledges the existence of these data). This should have been reported more transparently, together with the rationale behind why trial data were not used in the analysis.

- PTS events reported in the Hokusai-VTE trial are less prevalent than it would be expected in clinical practice. This seems to be the case with other events (e.g. CTEPH). The ERG notes that because the probability of PTS is the same across the different treatment arms, increasing the prevalence of PTS in the model would unlikely impact the final ICER.

- As previously mentioned, PTS is a VTE-related condition and as such it is clinically implausible that PTS can only occur in the on treatment and off treatment states.

5.4.4 Population

5.4.4.1 Population considered in the economic analysis versus the NICE final scope

The population considered by the company for this STA comprised adults with DVT and/or PE. The company presented results for the overall VTE population.

Scenario analysis included patients who require a limited period of anticoagulation (3 and 6 months) and those who require lifelong treatment. This 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)[74].

NICE scope also included people for whom a VKA is unsuitable; however this was not considered in the economic analysis. The company reports that there were no data available from Hokusai-VTE that allowed this analysis to be undertaken.

The population considered by the company is largely in adherence with requirements of the NICE final scope for this STA. The company 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 company was reasonable; proximal DVT and PE are considered to be the most important VTE events to capture within this STA.

5.4.4.2 Generalizability of modelled population

The model population characteristics were based on the Hokusai-VTE trial population. The baseline patient characteristics used were not reported in the CS but are presented in Table 47. Patient characteristics considered relevant for the economic model were:

- Mean age
- Gender
- Proportion of patients with DVT only

Table 47. Baseline population in the economic model – all treatment arms

Parameter	Mean values used in the model
Age	55.8
Gender (female)	43%
Proportion of patients with DVT only	59.3%
Abbreviations used in the table: DVT, deep vein thrombosis	

ERG comment

Hokusai-VTE population

The average age of patients in the Hokusai-VTE trial is 56 years. Clinical opinion sought by the ERG informed that this reflects a younger population than the average VTE population presenting in the UK. Around 43% of the study population were women and 59% of patients presented with index DVT only. Clinical opinion to the ERG indicated that this broadly reflects clinical practice.

Another population characteristic which hasn't been directly included in the economic model but is worth mentioning is the reduced number of UK patients in the trial. In the warfarin arm of the Hokusai-VTE trial, there are 1.6% of UK patients whilst in the edoxaban arm there, 1.1% of patients are from the UK.

Clinical experts advising the ERG pointed to the high percentage of Asian patients in the Hokusai-VTE trial population (21%). Asian patients have significantly lower incidence of VTE compared with other races as spontaneous (unprovoked) VTE is lower in less observed in these patients (even though they have a similar risk of provoked VTE, for example, due to surgery). This may impact on the overall VTE incidence in the Hokusai-VTE trial. Clinical opinion also advised that Asian patients are thought to be at a lower risk of recurrence however there are no published data in support of this.

Comparator studies' populations

The comparator studies included in the NMA were the RE-COVER and RE-COVER II trials, which look at the effectiveness of dabigatran compared to warfarin and the EINSTEIN-DVT and EINSTEIN-PE which analyse the effectiveness of rivaroxaban compared with warfarin in DVT and PE patients, respectively.

The average baseline age in the RE-COVER and RE-COVER II trials is 55 years and in the EINSTEIN-DVT and EINSTEIN-PE trials is 56 and 58 years, respectively.

The gender distribution across all trials is in favour of males. The proportion of women in the RE-COVER and RE-COVER II trials is 42% and 39%, respectively whilst in the EINSTEIN-PE and EINSTEIN-DVT trials the homonymous estimates are 47% and 43%.

In the RE-COVER trial 69% of patients presented with an index DVT event. Amongst the RE-COVER II population, 68% of patients had an index DVT event. The rivaroxaban trials (EINSTEIN-DVT and EINSTEIN-PE) cannot be compared with the other studies with regards to the proportion of patients presenting with index DVT only, as the 2 studies were split according to the type of VTE event patients experienced (i.e these were split according to PE and DVT populations) thus the proportions of type of VTE in these studies are not indicative of general clinical practice.

Overall, for the baseline characteristics simulated in the economic model, it seems that the respective values were not dissimilar across intervention and comparator studies. However the proportion of patients with DVT (alone) was slightly higher in the RE-COVER trials than in the Hokusai-VTE trial.

Nonetheless, study populations varied significantly with respect to other characteristics. For example, the proportion of Asian patients in the study populations was around 3% in the RE-COVER trial population and a 21% in the RE-COVER II trial.

5.4.5 Interventions and comparators

5.4.5.1 Comparison with the NICE scope

The NICE final scope for this submission considered edoxaban tosylate for people with DVT and/or PE.[74]

The CS reports that currently edoxaban does not have a UK marketing authorization, which is expected to be granted in May 2015. The expected indication for edoxaban is for the treatment of VTE, including DVT and PE and prevention of recurrent VTE in adults. It is also mentioned that in January 2015, the US FDA approved edoxaban for the treatment of DVT and PE following 5-10 days of initial therapy with a parenteral anticoagulant.

The company states that the recommended dose for edoxaban is 60 mg once daily, or 30 mg in specific patient groups. These consist of people with moderate or severe renal impairment (CrCI 15-50 mL/min), patients with low body weight ≤60 kg or patients receiving concomitant permeability - glycoprotein (P-gp) inhibitors (cyclosporine, dronedarone, erythromycin or ketoconazole). A 15mg dose is also considered in the draft SmPC for patients switching from edoxaban to a VKA.

The comparators included in the scope were as follows:

- Initial treatment with a LMWH or fondaparinux and continued VKA;
- Rivaroxaban;
- Dabigatran;
- For people for whom a VKA is unsuitable:
    - LMWH or fondaparinux alone;
    - Rivaroxaban;
    - Dabigatran.

ERG comment

The intervention drug considered in the economic model matches the NICE final scope.[74] Even though the expected indication for edoxaban reported in the CS does not explicitly state the expected edoxaban dose, the 60 mg and the 30 mg used in the economic analysis seem to reflect clinical practice and the Hokusai-VTE trial treatment regimen.

With regards to the comparators included in the economic analysis:

- Initial parenteral therapies considered in the economic analysis were LMWH (dalteparin, tinzaparin and enoxaparin) and UFH. The inclusion of LMWH is appropriate and consistent with the NICE final scope, even though the types of LMWH included might not be reflective of current clinical practice. This is discussed in the next subsection.
- UFH was also included in the economic analysis, even though it is not explicitly mentioned in the NICE final scope. The company assumed that 25% of patients receive UFH in the economic analysis however the ERG's clinical experts indicated that less than 5% of patients receive this drug in clinical practice.
- Fondaparinux was not included in the economic analysis. This is reflective of clinical practice and also reflects the Hokusai-trial treatment regimens.
- The VKA regimen included in the analysis was warfarin. This is consistent with clinical practice and the Hokusai-VTE trial.
- Rivaroxaban was included as an alternative to the combination treatment of parenteral and VKA anticoagulation, which is appropriate.
- Dabigatran was included in the economic analysis as an alternative to VKA and to edoxaban, which is appropriate. Dabigatran was considered together with an initial anticoagulation parenteral therapy.
- People for whom a VKA treatment regimen is unsuitable were not considered in the economic analysis as data were not available to model this scenario.

5.4.5.2 Modelled treatment regimens

The treatment regimens modelled for edoxaban and the included comparators are outlined in Table 48.

Table 48. Interventions and comparators modelled in the company's economic analysis

	Treatment duration	Daily dose
Intervention		
Edoxaban	12 months	Edoxaban at a dose of 60mg once daily, as per EMA filing and Hokusai-VTE design.
Comparators		
Warfarin	12 months	5mg twice daily.^
Dabigatran	12 months	300 mg taken as one 150 mg capsule twice daily.
Rivaroxaban	12 months	15 mg twice daily for 21 days followed by 20 mg once daily for the remaining duration of anticoagulation treatment.
Heparin*	Edoxaban regimen: 5 days lead-in	Dalteparin (LMWH): 15,000-unit (0.6-mL) syringe.

	Warfarin regimen: 8.5 days overlapping Dabigatran regimen: 5 days lead-in Rivaroxaban regimen: 0 days	Tinzaparin (LMWH): 0.7-mL (14,000-unit) syringe. Enoxaparin (LMWH): 100-mg (1-mL, 10 000-units) syringe. Unfractioned heparin: 5,000 units/mL:5-mL amp.
* Proportion of patients receiving different drugs in the model: 25% dalteparin, 25% tinzaparin, 25% enoxaparin, 25% unfractionated heparin. ^ Inferred from the economic model as the company did not specify this in the CS. Abbreviations used in table: LMWH, low-molecular-weight heparin; mg, milligrams; mL, millilitres.		

ERG comment

In this section the ERG discusses:

- The parenteral therapy modelled
- The treatment duration of edoxaban, warfarin and heparin
- The dose of edoxaban modelled

Parenteral therapy

Edoxaban, warfarin and dabigatran were modelled together with the initial heparin parenteral therapy described in Table 48. Clinical opinion sought by the ERG advised that the proportion of patients receiving different types of LMWH (25% dalteparin, 25% tinzaparin and 25% enoxaparin) is not reflective of current clinical practice as enoxaparin is the most commonly used drug, with dalteparin and tinzaparin use combined being similar (or slightly higher) to the use of enoxaparin.

The company assumed that 25% of patients receive UFH in the economic analysis however as previously mentioned the ERG's clinical experts indicated that less than 5% of patients receive this drug in clinical practice. The Hokusai-VTE study includes patients receiving UFH however the ERG could not find data on how many patients in the trial were given the drug. In the RE-COVER trials, 12% of patients received UFH as part of their initial parental anticoagulation treatment.

Finally it should be mentioned that even though the company did not include fondaparinux in their economic analysis (which is consistent with the Hokusai-VTE trial), around 4% of patients in the RE-COVER trials received the drug as part of their initial parental anticoagulation treatment regimen.

The ERG did not conduct any scenario analysis to vary the proportion of the different types of LMWH in the model as this is unlikely to carry any relevant impact in the final ICER.

Treatment duration – Edoxaban and warfarin

In the Hokusai-VTE trial, all patients received a minimum of 3 months of treatment. After 3 months, the remaining duration of treatment was at the physician's discretion, up to a maximum of 12 months. The company mentions that, "*this flexibility in treatment duration is uncommon in clinical trials, and*

potentially empowers the trial to reflect clinical practice more than do other studies of VTE treatment and secondary prevention" (CS, page 44).

Clinical opinion sought by the ERG agreed that the flexibility in the treatment duration in the edoxaban trial is more reflective of "real-life" practice than other studies where the treatment duration is fixed. Table 49 presents the mean and median duration of treatment in the Hokusai-VTE trial, along with the proportion of patients in the different treatment duration categories.

In the model, the base-case treatment duration was 12 months. Scenario analysis was undertaken to reflect treatment regimens of 3 months, 6 months and lifelong treatment. The results of this analysis are presented in Section 6.2. The ERG's clinical experts' opinion is that patients receiving 12 months of anticoagulation treatment are those likely to need anticoagulation therapy for the rest of their lives or until the risk of a VTE event no longer outweighs the risk of a treatment-related adverse event. Therefore, whilst a 12-month treatment scenario might be more realistic than shorter treatment scenarios considered in previous TAs, the lifelong treatment scenario is likely to be the one closer to reality (in the case of patients kept on treatment for 12 months of therapy). The ERG notes that treatment duration is highly dependent on the type of VTE (i.e. provoked or unprovoked), so for some patients 3 months of anticoagulation therapy might be suitable.

As shown in Table 49, around 60% of patients received more than 6 months of therapy whilst 40% of the total number of trial patients carried on to receive 12 months (or longer periods) of treatment. Unfortunately the duration of treatment is not reported according to whether the VTE event was provoked an unprovoked.

Finally, and as discussed in Section 5.4.2 the ERG is concerned with the fact that after 12 months of treatment patients cannot receive any further anticoagulation therapy, even if they experience a recurrent VTE event.

Table 49. Treatment duration and study drug exposure, safety analysis set (CSR, pg 124, Table 12.1)[45]

Treatment duration and study drug exposure	Edoxaban N=4118	Warfarin N=4122
Duration of Actual Treatment (days) [a,b]		
Mean (SD) Duration, days	251.9 (112.04)	250.3 (113.01)
Median Duration, days	267.0	266.0
≤3 Months, n (%) [b,c]	485 (11.8%)	528 (12.8%)
>3 to ≤6 Months, n (%)	1076 (26.1%)	1084 (26.3%)
>6 Months, n (%)	2557 (62.1%)	2510 (60.9%)
≥12 Months, n(%)	1661 (40.3%)	1659 (40.2%)
Total Number of Days Exposed to Study Drug [d]		
Mean (SD), days	250.3 (111.75)	248.4 (112.61)
Median, days	265.0	261.0

Abbreviations: N, number of subjects in analysis set; n, number of subjects meeting event criteria; SD, standard deviation.

[a] Duration of Actual Treatment Period = date of last dose - date of first dose +1 day.

[b] <= 3 months was <= 95 days, >3 to < =6 Months was > 95 to <= 185 days, > 6 Months was > 185 days, and >= 12 months was >= 353 days.

[c] [redacted]

[d] Study Drug Exposure is the total number of days the subject takes study drug during the Overall Study Period, with interruptions not included in the interval of time. Number of Days Exposed = date of last dose - date of first dose +1 day - periods of interruptions

Note: Median number of days for study drug interruption is derived by subtracting Median days exposed (days) from Median treat duration (days).

Source: Table 14.1.5.5

Treatment duration – heparin

In the economic model, the lead-in parenteral therapy duration is different for warfarin and the NOACs. Patients in the warfarin arm of the model receive 8.5 days of heparin treatment while patients in the other arms of the model (edoxaban and dabigatran) receive heparin for the initial 5 days of anticoagulation treatment.

Table 50 presents the duration of heparin treatment for the warfarin and edoxaban arms of the Hokusai-VTE trial. It can be observed that the mean heparin treatment duration for edoxaban was 7.5 days (median 7 days) and that for warfarin the mean treatment duration was 8.5 days (median 8 days). Clinical opinion sought by the ERG explained that the blinding procedures in the trial were likely to have led to an increase in the heparin treatment duration when compared with clinical practice. It was also noted that 6.5 days is the most common period for overlapping parenteral therapy with warfarin and that the edoxaban licence defines a minimum of 5 days of heparin lead-in treatment. The company did not present any justification for the choice of different heparin treatment durations for the warfarin and the edoxaban (and dabigatran) arms of the model.

The study protocol for the Hokusai-VTE trial indicates a minimum of 5 days of heparin treatment. For edoxaban this was meant to be a lead-in treatment and for warfarin the treatment with heparin could happen simultaneously.

Therefore, the ERG modelled the following options:

- Modelling the treatment duration of heparin to reflect the Hokusai-VTE trial (i.e. 7.5 days for edoxaban and 8.5 days for warfarin); or
- Modelling the treatment duration with heparin according to clinical expert opinion provided to the ERG of 6.5 days of heparin together or before warfarin and the licensed 5 days of lead-in heparin for edoxaban.

Results of this scenario analysis are presented in Section 6.2.

In terms of the potential impact of the heparin treatment duration in effectiveness estimates, subgroup analysis undertaken in the Hokusai-VTE trial revealed that the difference in initial heparin duration categories in the trial was not statistically significant with regards to the primary effectiveness outcome (the composite endpoint of DVT, non-fatal PE and fatal PE).

Therefore the approach taken by the company is not consistent and is likely to bias costs (this is further discussed in Section 5.4.8.2). The impact on the modelled effectiveness of edoxaban is unlikely to be substantial as subgroup analysis has shown that duration of initial heparin treatment is not a significant prognostic factor.

Table 50. Initial heparin treatment duration, safety analysis set (reproduced from CSR, pg 125, Table 12.2)[45]

Treatment duration and study drug exposure	Edoxaban N=4118	Warfarin N=4122
Initial Heparin Treatment Duration, days		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Minimum	[redacted]	[redacted]
Maximum	[redacted]	[redacted]
Number of Days, n (%)		
0-5 days	[redacted]	[redacted]
6 days	[redacted]	[redacted]
7 days	[redacted]	[redacted]
8 days	[redacted]	[redacted]
9 days	[redacted]	[redacted]
≥ 10 days	[redacted]	[redacted]
Abbreviations: N, number of subjects in analysis set; n, number of subjects meeting event criteria; SD, standard deviation. Source: Table 14.1.5.8.		

The dose of edoxaban

The company reports that the recommended dose for edoxaban is 60 mg once daily, or 30 mg in patients with moderate or severe renal impairment (CrCI 15-50 mL/min), patients with low body weight ≤60 kg or patients receiving concomitant P-gp inhibitors (cyclosporine, dronedarone, erythromycin or ketoconazole).

In the economic model there were no assumptions made with regards to the dose of edoxaban administered to patients. The company mentions that the daily cost of edoxaban is assumed to be £2.10, based on [redacted]. This is further explored in Section 5.4.8.2.

Therefore the dose of edoxaban in the economic analysis is not explicitly stated (or costed – see Section 5.4.8.2). Table 51 below shows the proportion of patients in the Hokusai-VTE trial who received 60 mg edoxaban and 30 mg edoxaban doses. It seems that at randomisation around 18% of patients were put on the 30 mg dose regimen, with only 2% of patients switching from the 60 mg regimen to the 30 mg one during the trial period. Ultimately, the estimate of effectiveness of edoxaban vs warfarin used in the economic analysis and taken from the Hokusai-VTE trial is a reflection of the drug doses presented in Table 51.

Table 51. Edoxaban dose summary, safety analysis set (reproduced from CSR, pg 126, Table 12.3)[45]

Edoxaban dose	Edoxaban N=4118 n (%)	Warfarin N=4122 n (%)
Number of Subjects With 60mg Dose at Randomisation	[redacted]	[redacted]
Number of Subjects With 30mg Dose at Randomisation	[redacted]	[redacted]
Number of Subjects With 30mg Dose After Randomisation	[redacted]	[redacted]
Reasons for 30mg Dose		
Weight Only (≤60kg)	[redacted]	[redacted]
CrCL Only (≤50mL/min and ≥30mL/min)	[redacted]	[redacted]
Quinidine and/or Verapamil Use Only	[redacted]	[redacted]
CrCL and Quinidine/Verapamil Use	[redacted]	[redacted]
Weight and CrCl	[redacted]	[redacted]
Weight and Quinidine/Verapamil Use	[redacted]	[redacted]
Weight and CrCl and Quinidine/Verapamil Use	[redacted]	[redacted]

Abbreviations: CrCL, creatinine clearance; N, number of subjects in analysis set; n, number of subjects meeting event criteria.

Note: Edoxaban dose at Randomization is derived from information recorded in the IXRS. Subjects randomized to study prior to Amendment 2 who were taking dronedarone concomitantly with study-drug were to be given the 30 mg edoxaban (or edoxaban placebo) dose allocation.

Note: Percentages for subjects with 30 mg edoxaban/edoxaban placebo after randomization are based on number of subjects with 60 mg edoxaban/edoxaban placebo 60 mg at randomization.

Source: Table 14.1.5.13.

5.4.6 Mortality

5.4.6.1 Mortality data used in the model

The company included disease-related death and other-cause mortality in their economic analysis. Disease-related mortality is associated with patients experiencing specific events, whilst other-cause mortality is age and gender dependent.

Disease-related mortality was estimated for the following events:

- VTE (index and recurring events);

- CRNMB;
- MB;
- HIT;
- Stroke.

The mortality associated with specific events in the model was estimated mainly with Hokusai-VTE data but also with data found in literature. Table 52 and Table 53 present the disease-related mortality estimates used in the economic model. Event-related mortality was assumed to not depend on the type of anticoagulation treatment received.

Table 52. Mortality estimates derived from Hokusai-VTE trial data

Event	N	n	Probability	2-week probability	Confidence interval	Analysis set
VTE-related death	8,240	48	0.58%	0.022%	0.35%-0.81%	mITT popoulation, overall study period
CRNMB related death	666	0	0%	0%	NA	Safety population, on-treatment period
MB related death	124	12	9.7%	9.7%	8.8%-10.6%	Safety population, on-treatment period
Stroke related death	52	2	3.85%	3.85%	0.0%-0.09%	Safety population, on-treatment period
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; MB, major bleed; mITT, modified intention-to-treat; NA, not applicable; VTE, venous thromboembolism						

Table 53. Mortality estimates derived from literature data

Event	Probability	2-week probability	Source
HIT-related death	1.74%	1.74%*	Joseph *et al.* 2014[75]
VTE recurrence-related death	13.7%	13.7%	Carrier *et al.* 2010[76]
*Corrected after clarification stage. Abbreviations used I the table: HIT, heparin induced thrombocytopenia; VTE, venous thromboembolism.			

Other-cause mortality was taken from UK life tables and is age-and-gender-dependent. The mortality estimates were adjusted to the proportion of females present in the baseline Hokusai-VTE population and are reported in Table B68 of the CS (pg 135).Age and gender-mortality is also independent of the type of anticoagulation treatment received.

ERG comment on the mortality data used in the model

The ERG has several concerns with the data used to estimate mortality in the model. In this subsection the ERG looks at the data used to model disease-related mortality for each event separately.

Index VTE and VTE recurrence mortality data

The company used trial data to model the mortality associated with index VTE and literature data to estimate the mortality associated with recurrent VTE events. Furthermore, the company used the mITT population, overall treatment study period analysis set to estimate the index VTE mortality in the model, whilst all the other mortality estimates obtained from Hokusai-VTE were modelled with safety, on-treatment data (Table 52).

During clarification, the company provided the rationale for using the mITT analysis set (overall study period) for the estimation of index VTE related death when the safety analysis set (on treatment period) was used for all the other estimates. The company's response is provided in Box 24.

Box 24: Company's response to why the mITT analysis set (overall study period) was used for the estimation of VTE related death (Company's response to clarification question, B3)

This is a conservative assumption specific to VTE-related mortality. The data clearly show that VTE recurrence increases when patients are off treatment (as evidenced by the divergence of the Kaplan Meier curves for the overall study period and on-treatment populations in the mITT analysis), and therefore VTE related death should follow the same pattern. However, VTE related deaths were adjudicated on an overall study period basis in Hokusai VTE, and these estimates provide more authoritative information on VTE as the cause of death. If VTE related deaths were adjudicated on an on-treatment basis, we would certainly have used this as a source. Our primary concern was to avoid misallocation of VTE as the causative factor in these deaths, and we believe that this is an acceptable and conservative trade-off in the case of this question.
Abbreviations used in the box: mITT, modified intention-to-treat; VTE, venous thromboembolism

The ERG is concerned with the response provided by the company given that the data referred to as non-existent (i.e. the adjudicated number of VTE-related deaths for the on-treatment period) were presented several times, in the CS and in the company post-hoc analysis. Additionally, the company acknowledges that these data are the most appropriate data to model the probability of index VTE death. The ERG presents the data reported in the CSR (Table 12.20, pg 153) and in the post-hoc analysis (Table1.4.9.6.2, pg 623) in Table 54 and Table 55, respectively.

As can be observed, the values presented in the figures below differ substantially from the values presented in Table 52. Whilst Table 52 reports a total of [redacted], Table 54 and Table 55, report a total of [redacted] VTE-related death respectively. The (negligible) difference in the values reported in Table 54 and Table 55 comes from the previously explained difference in the methodological approach in the time-to-event analysis (Table 54) and in the phase-specific analysis (Table 55).

Therefore the estimate used in the model should have been derived from the on-treatment analysis set and not from the overall treatment analysis set, as the overall treatment period analysis includes all the deaths occurring when patients were off treatment, which potentially skews the analysis and introduces inconsistency in the mortality estimates used in the economic analysis.

However, even though the ERG considers that the on-treatment analysis set is the correct one to be used in the analysis, the ERG disagrees that these data should be used to model the probability of mortality associated with index VTE events in the model. In fact these data should be used to model the mortality associated with recurrent VTE in the model. It seems unreasonable to use the data collected in the trial to model the mortality associated with index VTE when the analysis undertaken in Hokusai-VTE refers to VTE recurrence mortality, and not index VTE mortality, which was not specifically analysed in Hokusai-VTE. Looking at the mortality risk presented in Table 55 for each phase of the model, the recurrent VTE-related mortality is 12.1% at phase 1, 8.8% at phase 2 and 9.7% at phase 3 respectively.

Table 54. Adjudicated Primary Cause of Death, Safety Analysis Set – On-Treatment Study Period (reproduced from the CSR pg 153, Table 12.20)[45]

Cause of death	Edoxaban N=4118 n (%)	Warfarin N=4122 n (%)
All causes	[redacted]	[redacted]
VTE-Related Death	[redacted]	[redacted]
PE	[redacted]	[redacted]
Unexplained death (and VTE cannot be rules out)	[redacted]	[redacted]
Cardiovascular Death	[redacted]	[redacted]
MI	[redacted]	[redacted]
Iscehmic stroke	[redacted]	[redacted]
SEE	[redacted]	[redacted]
Other Cardiac Death [a]	[redacted]	[redacted]
Other Known Cause	[redacted]	[redacted]
Cancer	[redacted]	[redacted]
Bleeding (including Hemorrhagic Stroke) [b]	[redacted]	[redacted]
Infectious Disease	[redacted]	[redacted]
Other [c]	[redacted]	[redacted]

Abbreviations: MI = myocardial infarction, N = number of subjects in analysis set, n = number of subjects meeting event criteria, PE = pulmonary embolism, SEE = systemic embolic event, VTE = venous thromboembolism.

[a] Other cardiac deaths were postoperative tamponade, heart failure, ruptured aortic aneurysm (edoxaban) and arrhythmia (warfarin).

[b] Apparent discrepancy from Table 12.6 as follows: Subject had a bleed event on-treatment and subsequently dies off-treatment = CEC reports event as “fatal bleed” in Table 12.6; CEC reports the death off -treatment (in Table 12.21) but not on-treatment (not in Table 12.20 above).

[c] Three fatal edoxaban cases (perforated bowel, acute respiratory distress, and suicide) and four fatal warfarin cases (respiratory failure, MVA, suicide, and homicide).

Note: Subject narratives for subjects referred to in footnotes [a], [b], and [c] may be found in Section 14.3.3.

Note: Deaths are included in the On-Treatment Study Period if they occurred on or after the date of first dose of any study drug. Deaths that occurred after the third day following the calendar date of any “last dose” and before the date of the next “first dose” are not considered for the On-Treatment Study Period

Source: Table 14.2.6.1.

Table 55. Frequency distribution on the number of patients with an adjudicated confirmed fatal symptomatic recurrent VTE event starting within treatment period plus 3 days- Safety Analysis Set Set (reproduced from Hokusai-VTE post-hoc analysis Table 1.4.9.6.2)[70]

			Heparin/warfarin						**Heparin/edoxaban**						**Total**					
Phase			N	n	p	SE (p)	95% CI		N	n	p	SE (p)	95% CI		N	n	p	SE (p)	95% CI	
Mapi phase	**Start day**	**Stop day**					Lower limit	Upper limit					Lower limit	Upper limit					Lower limit	Upper limit
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: CI, confidence interval; N, number of subjects in analysis set; n, number of subjects meeting event criteria; SE, standard error

a.“N” is the absolute number of patients who are on study treatment at start of the phase

b.“n” / “p” is the absolute/percentage number of patients with the specific event of interest within a specific phase

c.The 95% CI has been calculated using the normal approximation

d.Within a specific phase, only the first event of a patient is taken into account

e.Patients with events in different phases will be counted in each of these phases as having an event

Clinical opinion sought by the ERG indicated that the mortality estimate of 13.7% (taken from Carrier *et al*.[76]) used for recurrent VTE events in the model is likely to be overestimating the probability of death after recurring events. It was mentioned that the PE mortality risk is expected to be 1% to 3% and that for DVT this would be even lower. It was added that recurrence may not be as likely to be fatal as index events as patients, having already had one event, are more likely to recognise signs of VTE and seek help earlier.

Comparing the on-treatment trial estimates with the clinical opinion provided, it seems that using the on-treatment set to estimate the probability of recurrent VTE would still result in an overestimation of the number of deaths. The ERG notes that out of the 23 deaths identified in Table 54, 21 (91%) are attributable to, "unexplained death and VTE cannot be ruled out". Clinical opinion sought by the ERG advised that, from the data provided in the CSR, it is impossible to tell whether these events were VTE related or not.

In light of the issues discussed here, the ERG concludes that:

- The mortality estimates used to model index VTE and VTE recurrence death are not appropriate;
- The safety analysis set (on-treatment study period) should have been used instead of the mITT analysis set (overall study period);
- Even in the case where the safety analysis set (on-treatment study period) is used to model the mortality associated with recurrent VTE, there seems to be an overestimation of death events compared to clinical reality.

Therefore, the ERG conducted two scenario analyses. One using the recurrent VTE-related mortality estimated in the Hokusai-VTE trial and the other using the recurrent VTE-related mortality reported in TA327, where the probability of dying of recurrence for dabigatran is 3%.[59] This estimate is consistent with clinical expert opinion.

Finally, the company considered that the mortality risk was the same across all treatment arms. This is consistent with clinical expert opinion sought by the ERG.

CRNMB and MB mortality data

The ERG is satisfied with the data used to calculate the mortality associated with CRNMB. With regards to the mortality associated with MB events in the model, the estimate used is likely to be underestimating the probability of death as the MB state includes ICH events. This is explored in the stroke mortality section that follows.

Stroke mortality data

As previously discussed, the ERG has several issues with the method used to estimate the risk of stroke in the model. The ERG believes that the stroke health state modelled in the analysis should not include ischaemic strokes and should only include ICH (and that ICH should have been excluded from the MB health state). As the current stroke state includes ICHs and ischaemic strokes, the mortality associated with this state (3.85%) underestimates the impact of ICH events, which according to clinical opinion have an associated mortality rate of 40%.

The ERG believes it is important to note that, *the company excluded ICH events from the analysis of the probability of mortality associated with the stroke state*.

The ERG produced Table 56, where it can be observed that the mortality currently used in the model is only representative of ischaemic strokes. Given that the probability of stroke in the model also includes ICH, there is clearly a disconnection between the probability of stroke and the stroke-related mortality. This reinforces the ERG comments on the inconsistency and lack of transparency in the estimation of several model inputs in the economic analysis.

It should also be noted that including the number of fatal ICH events in the final stroke mortality rate would still lead to an estimated mortality lower than that observed in clinical practice for ICH events.

Table 56. ICH and ischaemic events in Hokusai-VTE

Reason for mortality	Edoxaban	Warfarin	Total
Total number of strokes	26	26	52
Ischaemic events	21	8	29
ICH events	5	18	23
Proportion of ischaemic events	80.8%	30.8%	55.8%
Proportion of ICH events	19.2%	69.2%	44.2%
Fatal ischaemic	2	0	2
Fatal ICH	0	6	6
Proportion of fatal ischaemic events	9.5%	0.0%	**3.8%**
Proportion of fatal ICH events	0.0%	33.3%	11.5%
Total	2	6	8
Percentage	7.7%	23.1%	15.4%

Abbreviations used in the table: ICH, intracranial haemorrhage

For the purpose of estimating the number of ICH and ischaemic strokes the ERG assumed that these were the only two types of stroke considered in the Hokusai-VTE trial.

HIT mortality data

Originally, the company used Prandoni *et al*. 2005 to estimate the mortality associated with HIT.[77] However this study reported the probability of HIT patients developing thromboembolic

complications (VTE, ischemic stroke, MI and arterial embolism) compared with patients who did not experience HIT and not the probability of dying from HIT.
Therefore, after clarification, the company changed this in the model and used an alternative estimate from another study (Joseph *et al*.[75]). The ERG notes that by changing the sources used to model the mortality associated with HIT, the estimate decreased from 17% to 1.7%.

Clinical opinion sought by the ERG diverged in terms of validating the estimate, whilst one clinical expert considered that 17% was a reasonable estimate, another clinical expert considered this to be a significant overestimation. However as previously discussed in the report, it is unlikely that the HIT mortality used in the model substantially impacts the final ICER.

Other health states
Clinical opinion provided to the ERG advised that CTEPH should have been modelled along with an increase in the risk of mortality of about 20%. However, as mentioned before, including this in the model is unlikely to have a substantial impact in the final ICER.

Other-cause mortality
The ERG is overall satisfied with the data used to estimate the gender and age-related mortality in the model.

5.4.6.2 Estimated mortality

The probability of index VTE-related death was applied for the initial 12 months of the analysis. Therefore, everyone in the model experienced an increase in mortality related to their index VTE event, regardless of the heath state they were in, with the exception of patients experiencing recurrent events. For the other events associated with an increase in the mortality risk, the final mortality estimate is calculated additively. For example, a patient experiencing a MB event during the first 12 months of the analysis will have a risk of mortality of 0.022% (index VTE mortality) + 9.7% (MB mortality) = 9.722%.

After the end of the first year, the index VTE-related increment in mortality is removed from the model, so a patient experiencing a MB event will have a mortality risk of 9.77% after the first year of the analysis. The health states associated with an additional increase in mortality risk after 12 months are therefore VTE recurrence, HIT, MB and stroke.

Other-cause mortality was taken from UK life tables and is age-and-gender-dependent. The age and gender-related death is added to the disease-specific mortality in the model.

ERG comment on the estimated mortality

The ERG fundamentally disagrees with the method used to estimate disease-related mortality in the first 12 months of the analysis. Adding the index VTE-related mortality to the other event-specific mortality estimates for 12 months is not only inconsistent with the way that the costs and benefits of index VTE are estimated in the model, is also inconsistent with the way recurrent VTE-related death is estimated. Additionally this approach leads to a clinical implausible scenario which is now discussed.

Essentially this method assumes that a patient with an index VTE event (DVT alone or PE with our without DVT) will be exposed to an increased risk of death during the following 12 months of the event. This is despite of patient receiving treatment or not. There are several flaws in this approach:

- This is not consistent with the way cost and benefits associated with index VTE are estimated in the model. The impact of index VTE in patients' QoL is modelled during 2 weeks.
- This reflects an extremely implausible clinical reality, especially for patients with a provoked VTE who receive treatment and are cured at 3 or 6 months.
- It generates a considerable inconsistency with the way recurrent VTE is modelled, which again leads to an implausible scenario from a clinical point of view. The model structure implies that patients experiencing a recurrent VTE only suffer an increase in their mortality risk for 2 weeks (due to the recurrent VTE). It seems implausible that patients with an index VTE suffer an increase in their risk of dying for 1 year due to their index event but only experience an increase in their mortality risk for 2 weeks when it comes to recurring events.
- Finally, due to additive method employed in the analysis, this approach leads to an increase in the risk of death associated with MB, CRNMB, stroke and HIT during the 12 first months of the analysis. However, after 12 months, the probability of dying due to MB, CRNMB, stroke and HIT decreases, even if a patient experiences a subsequent event.

Therefore the ERG believes that the index VTE mortality should be applied for the 2 weeks only and that it should have the same value as the recurrent VTE mortality estimate. This assumption is unlikely to affect the final ICER as everyone starts the model with and index event, therefore the number of deaths due to index VTE is the same across different treatment arms.

Inspection of Figure 17, Table 57 and Table 58 indicates that overall, during the first 12 months of the analysis, survival in the model broadly reflects survival in the Hokusai-VTE trial. Nonetheless, it should be noted that survival in the warfarin arm of the model seems slightly higher.

Figure 17. Survival in the first 12 months of the analysis (produced by the ERG)

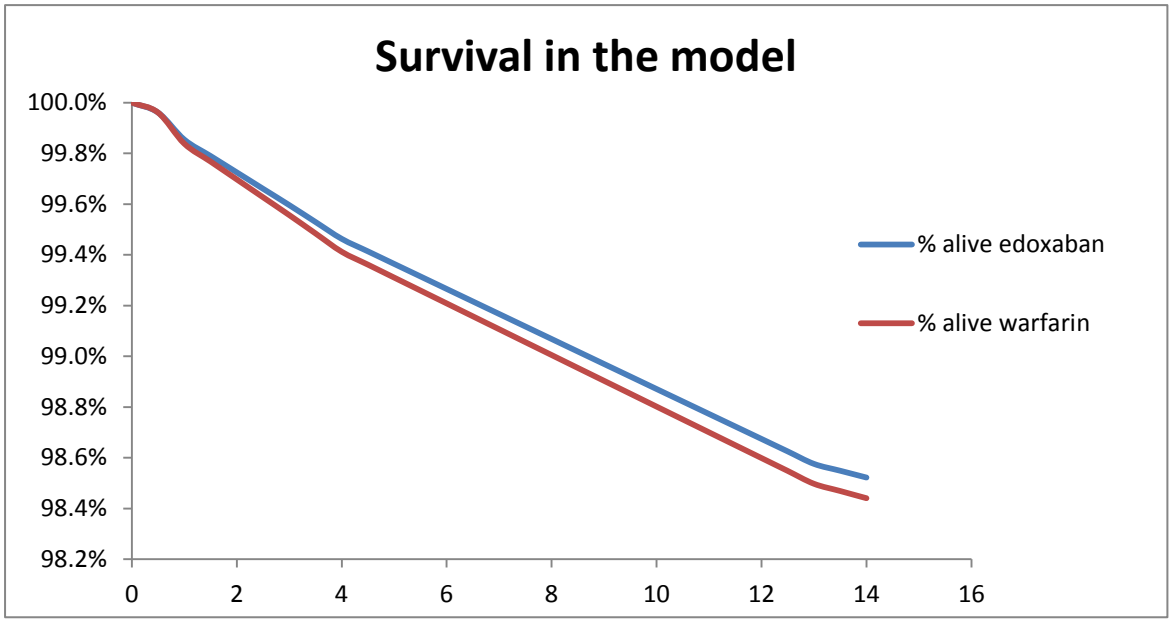


Table 57. Survival in the edoxaban arm of the Hokusai-VTE trial (post-hoc analyses, phase-specific analysis, on-treatment population, safety analysis set, Table 1.4.13.4.2)[70]

Time period	N	n	Probability
From index event to 14 days	[redacted]	[redacted]	[redacted]
From 15 days to 98 days	[redacted]	[redacted]	[redacted]
From 99 days to 364 days	[redacted]	[redacted]	[redacted]

Table 58. Survival in the warfarin arm of the Hokusai-VTE trial ((post-hoc analyses, phase-specific analysis, on-treatment population, safety analysis set, Table 1.4.13.4.2)[70]

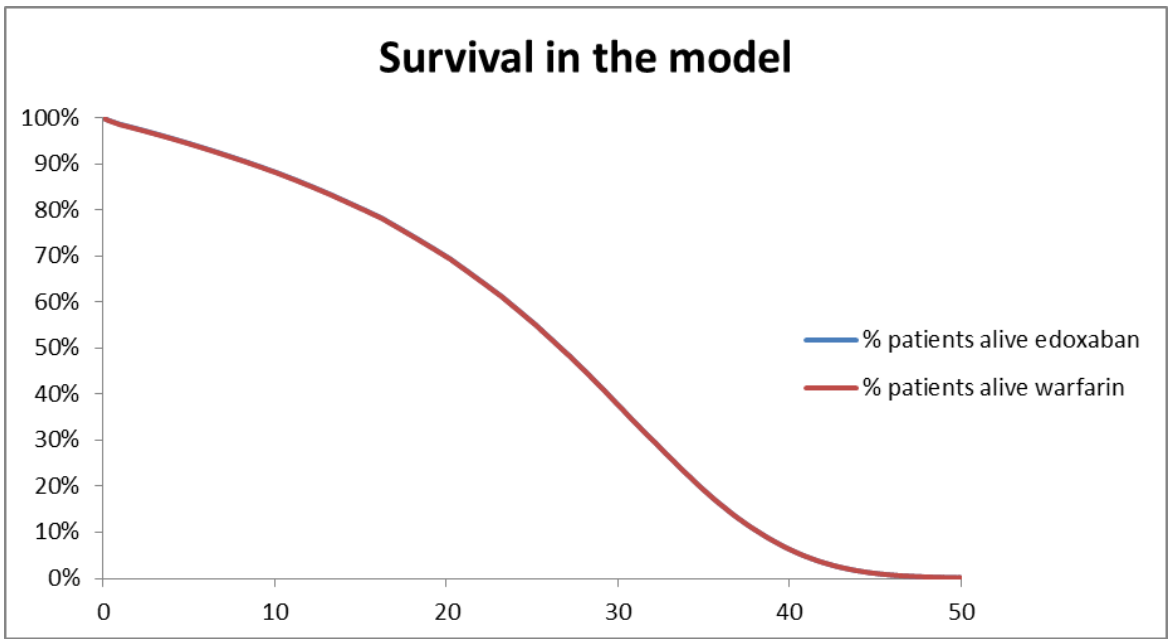
Time period	N	n	Probability
From index event to 14 days	[redacted]	[redacted]	[redacted]
From 15 days to 98 days	[redacted]	[redacted]	[redacted]
From 99 days to 364 days	[redacted]	[redacted]	[redacted]

Even though recurrent VTE mortality seems to be overestimated, the overall survival in the model seems to be overestimated. This is essentially due to the low number of patients relapsing. As the recurrent VTE-related mortality is overestimated but the probability of recurrent VTE in the model is low this is not sufficient to offset the overestimation of the overall survival.

As mentioned in Section 5.4.2, given that patients enter the model with an average age of 56 years, it would be expected that all patients would be dead before 50 years, when they would be 106 years.

Nonetheless, 35 years after the beginning of the model 80% of patients are still alive. This implies that 20% of VTE patients would virtually survive until the age of 90. This indicates that survival is potentially overestimated in the economic model. Figure 18 shows the survival estimated in the 50 years of analysis.

Figure 18. Survival estimated in the model across the time horizon (produced by the ERG)



In conclusion, the ERG is satisfied with the data and methodology used to model gender and age-related mortality in the model. The ERG has some concerns regarding the disease-specific mortality included in the model. These are related to the data used but also with the methodology employed. More specifically, the ERG raises the following issues:

- The analysis set taken from Hokusai-VTE to model mortality. The safety analysis set (on-treatment study period) should have been used instead of the mITT analysis set (overall study period).
- The mortality data analysed in Hokusai-VTE (on-treatment study period) is based on recurrent VTE mortality and not on index VTE mortality, therefore these data should have been used by the company to model recurrent VTE related mortality instead of index VTE mortality.

Superseded see erratum

- The mortality associated with recurrent VTE in the model is overestimated. Even in the case where the safety analysis set (on-treatment study period) is used to model the mortality associated with recurrent VTE, there seems to be an overestimation of death events compared to clinical reality. This is likely to be related to the high number of "unexplained deaths where VTE cannot be ruled out" reported in the trial. These account for 91% of the VTE-related deaths reported in Hokusai-VTE.
- The mortality probability associated with stroke does not include ICH deaths. Given that the probability of stroke in the model includes ICH, there is clearly a disconnection between the probability of stroke and the stroke-related mortality. This reinforces the ERG comments on the inconsistency and lack of transparency in the estimation of several model inputs in the economic analysis.
- Overall survival in the model seems to be overestimated despite the fact that recurrent VTE-related mortality is overestimated in the model.

5.4.7 Health-related quality of life (HRQoL)

5.4.7.1 Company systematic literature review for health-related quality of life data

The company carried out a systematic review to identify HRQoL studies relevant to the health states considered in the model. Details of the search strategy (CS, Appendix 12, pg 33-36) and inclusion and exclusion criteria (CS, Appendix 12, 1.1.27) were provided within the appendices of the CS.

The following electronic databases were searched: Medline; Embase; EconLit; and the Cochrane Library (NHS EED). The search was carried out in May 2014 and updated in December 2014. The company used terms to capture the health condition of interest (DVT / PE) and study type (HRQoL study).

In addition to database searches, bibliographies of systematic reviews articles were examined to obtain additional references. Bibliographies of accepted references were also reviewed to identify other potentially relevant references (CS, Appendix 12, pg 36).

A total of 15 studies that reported utility estimates were identified. The company extracted data from these studies and presented these within the submission (CS, Table B 78, pages 151-156). Of those 15 studies, only two (Cohen *et al*.[78] and Sullivan *et al*.[79]) evaluated utility values in line with NICEs preferred methods and both of those studies related to index or recurrent DVT or PE. Table 59 summarises the HRQoL data contained within Cohen *et al*.[78] and Sullivan *et al*.[79]

Table 59: HRQoL data contained within Cohen *et al*.[78] and Sullivan *et al*.[79]

Study; type	Study population	Methods of	Mean utility estimate (SD)

		elicitation and valuation	
Cohen *et al.* 2014[78]; prospective, observational, multicentre (seven European countries)	DVT or PE Baseline: 2790 1 month follow up:1453 3 month follow up: 1417 6 month follow up: 723 Mean age 61.3 53.2% male Patients received, heparin, heparin/VKA or NOAC treatment	Patients completed EQ-5D-5L Valuation method to produce utility values not reported	DVT, baseline: 0.71(0.26) DVT, 1 month: 0.79 (0.22) DVT, 3 months: 0.84 (0.19) DVT, 6 months: 0.85 (0.19) PE± DVT, baseline: 0.67 (0.32) PE± DVT, 1 month: 0.75 (0.24) PE± DVT, 3 months: 0.79 (0.22) PE± DVT, 6 months: 0.81 (0.23)
Sullivan *et al.* 2011[79] RCT, country NR	VTE Completed: 2299 Patients received dabigatran or warfarin treatment Age and gender characteristics not reported	Patient completed EQ-5D-3L Valued using UK weights	Decrement associated with recurrent DVT: -0.17 Decrement associated with recurrent PE: -0.06 Decrement associated with clinically relevant bleeding: -0.03
Abbreviations used in the table: DVT, deep vein thrombosis; PE, pulmonary embolism; RCT, randomised controlled trial; VTE, venous thromboembolism			

In addition to data identified for recurrent VTE events, the company considered that 6 of the 15 identified studies included relevant utility data for adverse events or complications of treatment, specifically:

- heparin administration (the impact on utility caused by administration of parenteral therapy) (Comerota *et al*.[80]);
- bleeding (Hogg *et al*. 2013[81] and Locadia *et al*.[82]);
- post thrombotic syndrome (PTS) (Enden *et al*.[83]; Lenert *et al*.[72]; Locadia *et al*.[82]; O'maera *et al*.[84]);
- stroke (Locadia *et al*.[82]; Hogg *et al*.[85]).

The search for HRQoL studies was restricted to a VTE population. The ERG believes this restriction would not sufficiently capture adverse effects of treatment such as HIT; or that complications associated with VTE including stroke and CTEPH would not be sufficiently captured in the search. This is confirmed by the fact that none of the included studies reported utility data for CTEPH or HIT. The ERG requested clarification from the company on how studies relating to these health states were identified. The company's response is presented Box 25.

Box 25: Company's intention to identify relevant studies whilst restricting the population to VTE (Company's response to clarification, C3)

As stated in the answer to question B26, the literature reviews performed for the purpose of retrieving inputs for the model were probably not targeted enough. Indeed, the search terms restricted the VTE population. This should be considered as a limitation of this submission.

As highlighted in the ERG comment on the cost-effectiveness search in Section 5.3, the ERG notes that searches were not performed in the Health Technology Assessment (HTA) database, which may have resulted in the omission of relevant publications. This was also acknowledged by the company as a further limitation of the search during clarification (Box 18).

5.4.7.2 Overview of utilities applied within the company's economic analysis

Within the model, all patients are assigned a baseline utility value adjusted by age according to the UK population norm taken from Kind *et al*. (Table 60).[65] Health state-related disutilities were then applied to patients' baseline utility value in each health state. For the majority of the health states, disutilities were applied multiplicatively whilst for VTE recurrence and HIT, the disutilities were applied additively.

Table 61 summarises the HRQoL values used within the company's economic analysis, the source of these data, and the company's stated justification for selection.

Table 60: Population utility norms taken from Kind *et al.*[65]

Age	Utility value
45-54	0.8203
55-64	0.7974
65-74	0.7732
75+	0.7366

Table 61: HRQoL data applied within the company's model (adapted from Table B79, CS)

Health state	Utility value	Confidence interval	Reference	Justification within the submission (Table B79)	Justification provided at clarification (Company's response to clarification, B27)
VTE events					
VTE index event	[redacted]	[redacted]	Hokusai-VTE substudy[86]	[redacted]	[redacted]
VTE index event, PE subgroup	[redacted]	[redacted]	Hokusai-VTE substudy[86]	[redacted]	
Recurrent VTE	**-0.1253***	-0.233;0.024	Sullivan *et al*, 2011[79]	Unweighted QALY decrement of recurrent DVT and recurrent PE	For the state "Recurrent VTE", Sullivan *et al*. [79] was identified from the systematic literature search, as the only source providing utility values from the EQ-5D approach using UK tariffs.
Treatment					
Treatment with warfarin	-0.0120*	-0.24 ; 0.000	Marchetti *et al*, 2001[63]	Well documented limitations of warfarin (frequent INR monitoring, numerous food and drug interactions, etc.)	For the state "Treatment with warfarin", no article retrieved from the systematic literature review was identified. Marchetti *et al*.[63] was identified from the dabigatran STA, checked for relevance in terms of available information, and selected as it presents well documented limitations of warfarin (frequent INR monitoring, numerous food and drug interactions, etc.)
Treatment with NOAC	0.0000*	NA	-	Set to 0 since Utility decrement from with warfarin estimated vs. NOAC.	For the state "Treatment with NOAC", no reference was used as the utility was set to 0.
Complications of VTE					
PTS	**-12%****	-24.45% ; -6.76%	Locadia *et al*, 2004[82]	Relative decrement estimated at 55 years of age from Locadia *et al*.[82] (**utility 0.82**)	For the state "PTS", Locadia *et al*.[82] was preferred to Enden *et al*. (2013) as the population of interest in Enden *et al.*[83] includes patients with DVT only. To better reflect the population of the model, the Locadia *et al.* values were selected, as based on a VTE population.
CTEPH	-30%**	-59.99% ; 0.45%	Meads *et al*, 2008[87]	Relative decrement estimated at 55 years of age from Meads *et al*.[87] (utility 0.56)	For the states "CTEPH" and "LT CTEPH", no relevant publication was found from the systematic literature review. Meads *et al*.[87] was identified, checked for relevance and selected.
LT CTEPH	-30%**	-59.99% ; 0.45%	Meads *et al*,	Relative decrement estimated at	

Health state	Utility value	Confidence interval	Reference	Justification within the submission (Table B79)	Justification provided at clarification (Company's response to clarification, B27)
			2008[87]	55 years of age from Meads *et al*.[87] (utility 0.56)	
Adverse effects of treatment					
HIT	-0.0712*	-0.14 ; -0.000	Gould *et al*, 1999[88]	The QALY decrement is 0.00274 (1 day of null utility over 1 year). Loss of QALY over one cycle only = 0.00274*26= 0.0712	For the state "HIT", Gould *et al*.[88] was selected as the only source available.
CRNMB	-19%**	-30.91% ; -6.56%	Locadia *et al*, 2004[82]	Relative decrement estimated at 55 years of age from Locadia *et al*.[82] (utility 0.648)	For the states "CRNMB" and "MB", values from Locadia *et al.*[82] were identified as the only source. In addition, this source was found to be one of the major references available. Although there were limitations in this study due, for example, to its elicitation of preferences from patients rather than the general public, this study provided time trade-off utilities for various states considered in the economic model submitted for dabigatran and rivaroxaban as sources for CRNMB and MB.
MB	**-31%****	-65.26% ; -10.83%	Locadia *et al,* 2004[82]	Relative decrement estimated at 55 years of age from Locadia *et al*.[82] (**utility 0.65**)	
Stroke	-59%**	-156.68 ; 39.45%	Locadia *et al,* 2004[82]	Relative decrement estimated at 55 years of age from Locadia *et al*.[82] (utility 0.33)	For the state "Stroke", Locadia *et al*.[82] was found to be the only source providing utilities. It should be noted that the reference was not well displayed in the submission (119 instead of 118), this has been corrected.
Post-stroke	-12%**	-21.11% ; 3.32%	Lunde, 2013[89]	Relative decrement estimated at 55 years of age from Lunde[89] (utility 0.70)	For the state "Post-stroke", no relevant publication was found from the systematic literature review. Lunde[89] was identified, checked for relevance and selected.

* Absolute utility decrement; ** relative utility decrement.

Note values in bold were the corrected values reported by the company during clarification.

Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; LT, long term; MB, major bleed; NOAC, novel oral anticoagulant; PE, pulmonary embolism; PTS, post thrombotic syndrome; QALY, quality adjusted life year; VTE, venous thromboembolism.

5.4.7.3 ERG comment on the utilities applied within the company's economic analysis

In this subsection The ERG discusses the utility data used to estimate the impact on patients' QoL related with:

- VTE events;
- complications associated with VTE events;
- treatment with warfarin;
- adverse effects of treatment .

The ERG notes that four of the studies used to inform health state disutilities were not identified in the company's review (Gould *et al*.[88]; Lunde[89]; Meads *et al*.[87] and Marchetti *et al*.[63]). During clarification the ERG asked the company to explain how those four sources were identified and selected. The company's response is presented in Box 26.

Box 26: Company's response to how studies not included in the systematic review were identified and selected (Company's response to clarification, B26)

The literature review performed for the purpose of retrieving measurement and valuation of health effects was probably not targeted enough. Indeed, the search terms used included "VTE", "DVT", "PE" and extensions of these key words, but did not include any term relative to "warfarin treatment", "HIT", "CTEPH" and "post-stroke", considered as complications of treatment. It was not abnormal that none of the included study reported utility value associated with warfarin treatment, with HIT, with CTEPH or with post-stroke. When necessary, additional targeted searches were conducted and other sources were checked, including the dabigatran STA. • In the dabigatran STA, Marchetti *et al*.[63] was used as the main source for utility decrement associated with warfarin treatment. • Gould et al. 1999[88], Meads et al. 2008[87] and Lunde 2013[89] were found via an additional targeted search on Medline These values were not found via the systematic literature search, nevertheless they were found to be relevant for this submission.
Note referenced re-numbered by ERG Abbreviations used in the box: CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; PE, pulmonary embolism; STA, single technology appraisal; VTE, venous thromboembolism

For completeness, Table 62 provides a summary of the data contained with these four studies that were not extracted by the company (studies included in the company's HRQoL review are presented within the CS, Table B78).

Table 62: HRQoL data contained within Gould *et al*.[88]; Lunde[89]; Meads *et al*.[87] and Marchetti *et al*.[63]

Study (country)	Study population	Methods of elicitation and valuation	Mean utility estimate
Gould *et al*. 1999[88] (US)	Cost-utility analysis of LMWH compared with UFH for treatment of acute DVT.	Decrements in utility for early clinical outcomes were expressed as days lost from quality-adjusted life expectancy because of hospitalisation.	Assumed 1 additional day of hospitalisation, taken from: HCIA, Inc. Length of Stay by Diagnosis, United States.1997.[90]
Lunde, 2013[89] (Norway)	345 stroke patients admitted to the stroke unit of a Norwegian hospital. Stroke defined as patients suffering from ischemic stroke, haemorrhagic stroke, and TIA. Mean age 68.7 years. 64% male.	Patients completed EQ-5D-3L. Valued using TTO UK tariff (Dolan 1997[91]).	0.70 (SD 0.3)
Meads *et al*. 2008[87] (UK)	308 patients with CTEPH. (Characteristics reported for the whole study population: 869 patients with pulmonary hypertension: 37% male; mean age 56.6 years).	Condition specific utility index, CAMPHOR QoL questionnaire. McKenna *et al.*[92] report the CAMPHOR QoL scale was used to create 36 health states that were valued by 249 representative members of the UK adult population, using TTO.	0.56 (SD 0.29)
Marchetti *et al*. 2001[63] (Italy)	Cost-utility of LMWH with that of oral anticoagulants in preventing recurrences after an episode of VTE. 48 patients who were receiving warfarin or LMWH. Mean age 57 years.	Patients completed a TTO questionnaire to determine if they would accept trading some days of life to avoid warfarin or LMWH treatment.	Treatment with warfarin: -0.012 (95% CI -0.008, -0.016) Treatment with LMWH: -0.008 (95% CI -0.005, -0.011).
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism;; SD, standard deviation; TIA, transient ischemic attack			

Overall the ERG is worried with the lack of transparency and coherence in the selection of the utility data used in the economic analysis. This is further discussed in the next subsections.

5.4.7.4 Disutility associated with VTE events

The utility associated with the index VTE event was derived from the Hokusai-VTE EQ-5D data. [redacted] (CS, pgs 78-80). For the full population and PE subgroup models, this was [redacted] and [redacted], respectively.

The disutility for a recurrent VTE was based on the disutilities reported in Sullivan *et al*. for a recurrent DVT (-0.17) and PE (-0.06) (Table 59).[79] As the company did not model DVT and PE events separately the resulting utility value for a recurrent VTE was estimated assuming 59.3% of patients presented with a DVT. This resulted in an absolute utility decrement of -0.1253, after the clarification stage, where the company corrected a mistake in the calculation of the utility decrement estimate identified by the ERG.

ERG comment on the disutility associated with VTE events

The ERG points to the lack of coherence in the company's approach with regards to [redacted] On page 147 of the CS, the company states that the utility substudy, "was considered as a small sample and therefore not appropriate for use in the cost-effectiveness analysis". Nonetheless, the company used this source to model the utility associated with the VTE index state in the model. The ERG is concerned that the company has chosen to use utility data in the model that they believe is unsuitable. The ERG also notes that the company did not explain the rationale for selecting the utility values from Hokusai-VTE rather than the studies identified in the review. During clarification the ERG asked the company to justify their selection. The company's rationale for this approach is presented in Box 27.

Box 27: Company's rationale for selecting the utility values for VTE from Hokusai-VTE (Company's response to clarification, B27)

> For the state "VTE index event", it was felt more appropriate to use the value from the Hokusai-VTE study rather than the value from Cohen et al. (2014)[78] which presented data from patients in the PREFER in VTE registry.

Furthermore, the ERG is unclear as to why the company weighted the utility associated with the "recurrent VTE" state by DVT and PE utility, when the health state "on treatment/index VTE" captures the overall VTE utility and does not distinguish between PE and VTE. The company's response is presented in Box 28.

Box 28: Company's rationale for not considering the proportion of DVT patients for the index event (Company's response to clarification, B4)

The decrement in utility associated with the "recurrent VTE" state is a weighted average of disutility. This estimate takes the decrements for DVT and PE and weights them according to the breakdown of index events in the Hokusai VTE study. This was done to accurately determine the disutility that accrued when a recurrent VTE event (the primary efficacy outcome in the Hokusai and other studies of NOACs in this indication) was experienced. We disagree that this is a splitting of the utility; rather, it is a weighted aggregate of utilities associated with two types of clinical manifestation of recurrence. As for the utility value taken from European Hokusai VTE patients for the "on treatment/index VTE", this is an average value taken from patients with DVT and PE±DVT. Therefore we see no inconsistency between the approaches used to produce these estimates.
Abbreviations used in the box: DVT, deep vein thrombosis; PE, pulmonary embolism; NOAC, novel oral anticoagulant; VTE, venous thromboembolism

As the proportion of DVT and PE patients used to weight the overall utility for recurrent events is taken from the baseline distribution of VTEs (i.e. DVT and PE) in Hokusai-VTE and so reflects the distribution of index events in the study, it would have been more consistent to also weight the utility value used for the index events. The Hokusai-VTE substudy also included the utility values for DVT and PE separately. This reflects the issue of lack of consistency in the estimation of model inputs, mentioned throughout the report.

The values for a recurrent DVT and PE reported in Sullivan *et al*.[79] appear to contradict what would be expected in clinical reality, as the decrement associated with PE is lower than the decrement associated with DVT. Clinical experts advised that the utility values reported in Sullivan *et al*. [79] look unexpected but could be plausible because patients with a DVT could be in more pain and discomfort than patients with a PE (even though this is a more serious condition).

Due to the reasons discussed in Section 1.4.12.3, the ERG believes that the same utility values should be used to model the impact of index VTE and recurrent VTE. Given that the Hokusai-VTE data is likely to be insufficiently robust, and the values in Sullivan *et al*.[79] seem to be contradictory to clinical reality, the ERG conducted a scenario analysis using the values reported in Cohen *et al*.[78] to model index and recurrent VTE.

The Cohen *et al*. study reported utility data separately for patients with a DVT or PE (with or without DVT) and it is based on the EQ-5D questionnaire completed by patients in the UK.[78] The size of the

population is as follows: baseline, 2790; 1 month follow up, 1453; 3 month follow up, 1417; 6 month follow up, 723. The utility values reported in Cohen *et al*. are 0.71 for a DVT and 0.67 for a PE.[78]

Finally, clinical opinion to the ERG advised that several of the events considered in the economic model as tunnel states would impact a patient's QoL for periods longer than 2 weeks. In the case of recurrent PE and DVT, it was mentioned that these events can easily impact a patient's QoL for one month as the lungs and/or legs can remain symptomatic.

The ERG believes that the impact of VTE on a patient's QoL is underestimated in the economic model; the ERG conducted a scenario analysis to reflect a QALY loss of 1-month duration after recurring VTE.

5.4.7.5 Utility of complications associated with VTE events

The company estimated the impact on a patient's QoL experiencing the following events:

- PTS;
- CTEPH;
- LT CTEPH.

The utility, source, and duration of the utility decrement applied within the model for each complication are presented in Table 63.

Table 63: Utility, source and duration of applied utility for complications of VTE events

Complication	Utility reported in the source	Source	Relative decrement estimated at 55 years of age applied in the model	Duration of disutility
PTS*	Median, 0.82; IQR 0.66 to 0.97	Locadia *et al*. 2004[82]	-12%	Lifetime
CTEPH	Mean, 0.56; SD, 0.29	Meads *et al*. 2008[87]	-30%	2 weeks
LT CTEPH	Mean, 0.56; SD, 0.29	Meads *et al*. 2008[87]	-30%	Lifetime
*Corrected values provided by the company during clarification Abbreviations used in table: CTEPH, chronic thromboembolic pulmonary hypertension; IQR, interquartile range; PTS, post-thrombotic syndrome; SD, standard deviation				

The utility applied by the company for PTS was obtained from Locadia *et al*.[82] This study used TTO techniques to elicit the preference valuations from 53 patients with a VTE, 48 of which had PTS. The study was conducted in the Netherlands and the resulting utility value reported for PTS was 0.82. This was based on a population aged 53 years (utility norm of 0.95 for patients without PTS). To adjust this utility value to the age of the population in the model (55.8 years) and to reflect the difference between the utility norms in Locadia *et al*.[82] and Kind *et al*[65], the following calculation was made:

0.82* 0.81/0.95 = 0.699

where 0.81 is the midpoint utility between 45-54 years and 55-64 years in Kind *et al.*[65]

The relative decrement was then estimated by calculating the percentage change from a patient with PTS (utility 0.699) to a patient aged 55.8 years without PTS (utility of general population in Kind *et al.*[65]is 0.7974): 0.699/0.7974 = 88%. To calculate the relative decrement this is subtracted from 100% to produce a relative utility decrement of 12%.

The utility estimates used by the company for CTEPH and LT-CTEPH were obtained from Meads *et al.*[87] A total of 308 patients with CTEPH completed the CAMPHOR QoL questionnaire; the CAMPHOR QoL states were then valued by members of the general population using the TTO technique. The authors reported a mean utility value of 0.56 which the company used to calculate the percentage change from a patient with CTEPH (utility 0.56) to a patient aged 55.8 years without CTEPH (utility of general population 0.7974): 0.56/0.7974 = 70%. To calculate the relative decrement this was subtracted from 100% to produce a relative utility decrement of 30%.

As described in Section 5.4.2, CTEPH is a tunnel state that patients experience for one cycle; hence, the disutility associated with CTEPH is applied for 2 weeks. In the case of LT-CTEPH, patients incur the disutility associated with LT-CTEPH for the rest of their lives.

ERG comment the disutility of complications associated with VTE events

The ERG notes the company identified and included an alternative source for PTS utility data by Enden *et al.*[83] This study considered 189 Norwegian patients with proximal DVT. The authors reported that, independent of treatment arms, patients with mild or severe 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.

These decrements (0.02 to 0.09) imply a higher utility for a patient with PTS than that estimated by the company. A decrement of 0.02 to 0.09 would produce a utility value of 0.7774 to 0.7074 for a 55 year old (population norm 0.7974) rather than a utility value of 0.7017 when the relative decrement (12%) is applied.

Given that the difference in the utility values is not large, the ERG considers the utility estimate used to be acceptable. Additionally, the duration of the decrement in a PTS patient's QoL is likely to be underestimated, nonetheless because patients have the same probability of experiencing PTS across the model the impact of this in the final ICER is unlikely to be relevant.

The ERG considers the duration of the CTEPH-associated disutility (2 weeks) to be reasonable due to the inclusion of a LT-CTEPH health state..

Clinical opinion to the ERG considered that the company's assumption that the utility associated with LT-CTEPH is equal to the utility associated with CTEPH is unrealistic as patients on treatment would have a better QoL than patients with untreated CTEPH.

5.4.7.6 Disutility associated with warfarin treatment

To estimate the disutility associated with warfarin treatment, the company subtracted the mean utility values presented within Marchetti *et al*. from perfect health (1.00 – 0.988 = 0.012).[63] The disutility was applied for the duration of warfarin treatment for patients in the on treatment health state of the warfarin arm of the model.

ERG comment on the disutility associated with warfarin treatment

Clinician opinion sought by the ERG suggested the disutility applied by the company was reasonable as patients who receive warfarin treatment will have to go through lifestyle changes such as regular INR monitoring and adjustments and monitoring of diet. The ERG therefore agrees that there may be cause to believe that warfarin treatment would be associated with a disutility.

However, the ERG is not confident in the utility estimates produced by Marchetti *et al*.[63] because of the small sample size and therefore generalizability 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 edoxaban. 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 edoxaban treatment being included in the study, it is difficult to determine whether edoxaban would also have been associated with a decrement.

The ERG notes that this study was used within TA261, TA287 and TA327 to estimate a disutility associated with warfarin and LWMH treatment.[57-59] Box 29 below presents the discussion at the Appraisal Committee meeting for TA327 surrounding the utility value for warfarin treatment.

Box 29: Committee deliberations for warfarin disutility taken from the final appraisal determination (FAD) for dabigatran, TA327[93]

> The Committee heard that qualitative research on warfarin treatment suggested that people were anxious about being in the appropriate INR therapeutic range and whether they were taking the correct dose of warfarin. They also found warfarin monitoring visits to be inconvenient, and the dietary considerations associated with taking warfarin had a detrimental effect on their quality of life. The Committee noted that in the company's model, the utility decrement associated with warfarin

was greater than that associated with injections of LMWH. It heard from the patient expert that this was reasonable, because people are willing to accept the negative effects of LMWH as a part of initial short-term treatment. In contrast, because warfarin is taken for a longer time, the cumulative effect on quality of life would likely be greater. The Committee concluded that warfarin treatment, particularly if life-long, could be expected to reduce quality of life but the extent to which it did so was uncertain. It further concluded that although the company's estimate of utility decrement was based on limited evidence, it was the best estimate available and had been accepted as reasonable in previous appraisals.
Abbreviations used in the box: INR, international normalised ratio; LMWH, low molecular weight heparin

Following this consensus the ERG believes that warfarin use impacts patients' QoL. Nonetheless, the quantification of this impact is challenging. The ERG undertook a scenario analysis was the utility decrement associated with warfarin use was removed from the analysis to assess the impact of this on the final ICER.

In light of the discussion within the FAD the ERG notes the company did not include a decrement for patients receiving LMWH. However the ERG considers the exclusion of this decrement to be reasonable if patients only receive LMWH for up to 8.5 days in the model; adjusting for this short-time frame would have a negligible impact on the ICER if a decrement was to be applied.

5.4.7.7 Disutility associated with adverse events of treatment

The company estimated the impact on patients' QoL experiencing the following events:

- HIT;
- MB;
- CRNMB;
- Stroke;
- Post-stroke.

The utility, source, and duration of utility applied within the model for each complication are presented in Table 64.

Table 64: Disutility, source and duration of applied disutility for adverse events of treatment

Complication	Utility reported in the source	Source	Relative decrement estimated at 55 years of age applied in the model	Duration of disutility
HIT	0.00274*	Gould *et al*. 1999[88]	NA	2 weeks

MB**	0.65	Locadia *et al*, 2004[82]	-31%	2 weeks
CRNMB	0.76	Locadia *et al*, 2004[82]	-19%	2 weeks
Stroke	0.33	Locadia *et al*, 2004[82]	-59%	2 weeks
Post-stroke	0.70	Lunde, 2013[89]	-12%	Lifetime
*QALY decrement equal to 1 day's loss **Corrected values provided by the company during clarification Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; HIT, heparin-induced thrombocytopenia; MB, major bleed;; QALY, quality adjusted life year				

As described in Section 5.4.2, "HIT", "MB", "CRNMB" and "Stroke" are tunnel states; hence these are assumed to impact a patient's HRQoL for only one cycle (2 weeks). However, the impact associated with "Post-stroke" is applied for the patient's lifetime.

For HIT events, a disutility was applied to the patient's baseline health state utility, and applied for the duration of the event. The disutility associated with HIT was estimated on the assumption patients are hospitalised for one day, which results in a loss of 0.00274 (1/365). The company then adjusted this to the duration of one cycle (2 weeks) resulting in an absolute utility decrement of 0.0712.

For CRNMB, MB and stroke a relative decrement was estimated. The utility values for each of these states were taken from Locadia *et al.* who defined these health states as "muscular bleeding", "gastro-intestinal bleeding", and "non-fatal haemorrhagic stroke", respectively.[82] This study used TTO techniques to elicit the preference valuations from 53 patients with VTE (23 patients with MB events and 48 patients with PTS) in the Netherlands.

Locadia *et al*. reported utility values of 0.65 for a MB, 0.76 for a CRNMB and 0.33 for stroke based on a population aged 53 years (utility norm of 0.95 for a healthy patient).[82] To adjust this utility value to the age of the population in the model (55.8 years) and to reflect the difference between the utility norms in Locadia *et al*.[82] and Kind *et al.*[65], the following calculations were made:

- MB: 0.65*0.81/0.95 = 0.554
- CRNMB: 0.76* 0.81/0.95 = 0.648
- Stroke: 0.33*0.81/0.95 = 0.281 (calculated by the ERG)

where 0.81 is the midpoint utility between 45-54 years and 55-64 years in Kind *et al.*[65]

The resulting utility values from Locadia *et al*.[82] for a patient aged 56 years are 0.554 for a MB, 0.648 for a CRNMB and 0.281 for stroke. The relative decrement for a patient experiencing a MB, CRNMB or stroke was then estimated by calculating the percentage change from a patient

experiencing a MB (utility 0.554), CRNMB (utility 0.648) or stroke (utility 0.281) to a patient aged 55.8 years with a utility of the general population (utility 0.7974):

- MB: 0.554/0.7974 = 69%
- CRNMB: 0.648/0.7974 = 81%
- Stroke: 0.281/0.7974 = 35% (calculated by the ERG)

To calculate the relative utility decrements this percentage change is subtracted from 100% to produce relative utility decrements of 31% for a MB, 19% for a CRNMB and 65% for stroke.

The company estimated the relative decrement for post-stroke by calculating the percentage change from a patient with stroke (utility 0.70) to a patient aged 55.8 years without stroke (utility of general population 0.7974): 0.70/0.7974 = 88%. To calculate the relative decrement this is subtracted from 100% to produce a relative utility decrement of 12%.

The utility value (0.70) used in the post-stroke state was taken from Lunde[89] who employed the EQ-5D to generate utility scores from 345 stroke patients admitted to the stroke unit of a Norwegian hospital; their health was then valued using the TTO UK tariff.[91]

ERG comment on the disutility associated with adverse events of treatment

The ERG is not convinced by the robustness of the methods used in Gould *et al.*, to derive the impact of HIT in a patient's QoL.[88] Although due to time constraints the ERG was unable to carry out a systematic review of the HRQoL literature to identify alternative HIT utility values, the ERG carried out a simplistic CEA Registry hosted by the Tufts Medical Center search for HIT. However, no relevant studies were identified. Clinical opinion sought by the ERG considered one day of hospitalisation to be a reasonable estimate. Nonetheless, the ERG identified a mistake in the estimation of the utility decrement associated with HIT in the model. The utility decrement was adjusted twice for the duration of the cycle length; once in the estimation of the utility decrement (presented in the previous subsection) and then again when the utility of HIT was multiplied by the number of patients in the state, and divided by 26. The ERG has corrected this in the model and presents the results in Section 6.1.

After reviewing the utility values applied for bleeding events within previous STAs (specifically TA261[57], TA287[58] and TA327[59]) the ERG has several comments on the application of disutilities for bleeding events.

Firstly, the company has applied a disutility for CRNMB states. In previous STAs for VTE, the assumption that CRNMB events cause a decrement in a patient's QoL has been critiqued. Clinical experts advised the ERG that CRNMBs may be serious enough to temporarily stop anticoagulation

treatment, but the majority of CRNMBs can be dealt with within hours and would not affect the patient for 2 weeks; i.e. a patient with a CRNMB would require medical attention but this would not affect their quality of life. During clarification the ERG asked the company to justify the rationale for including a disutility for CRNMB in the model. The company's response is presented in Box 30.

Box 30: Company's rationale for including a disutility for CRNMB (Company's response to clarification, B24)

We believe that these events have an impact of the utility of patients that is worth capturing in an economic analysis. The definition of CRNM bleeding, as per the Hokusai VTE protocol (available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1306638/suppl_file/nejmoa1306638_protocol.pdf) includes events not meeting the criteria for major bleeding, but associated with medical interventions, unscheduled contact with a physician, etc., and can also include events such as epistaxis leading to an intervention, haematuria, and intramuscular haematoma, all of which have direct cost implications and non-trivial impacts on health-related quality of life. In TA327, the manufacturer of dabigatran derived a decrement of 0.04 based on EQ5D data collected in the pivotal studies and applied it to the model, which had a cycle length of one month. The ERG raised concerns that the disutility associated with several categories of these bleeds would not last for the full duration of a one-month cycle. There were also concerns about the implementation of the disutility in the model engine. Furthermore, the submission to NICE from the manufacturers of apixaban includes a utility decrement of 0.0054 for clinically relevant non-major bleeds (see recent FAD for ID726), although the cycle length in this model is three months. Our model has a cycle length of two weeks, which allows the effect on utility to be captured at a greater level of granularity than in other models.
Abbreviations used in the box: CRNM, clinically relevant non-major; ERG, Evidence Review Group; FAD final appraisal determination; NICE, National Institute for Health and Care Excellence; TA, technology appraisal; VTE, venous thromboembolism

Similar to TA237[59], the ERG considered a scenario where the disutility associated with CRNMBs was removed from the economic analysis.

Secondly, (and as previously discussed) the ERG believes the company has underestimated the impact of MB on a patient's QoL. Clinical opinion sought by the ERG advised that MB events can easily impact a patient's QoL for 1 month or more. In line with previous STAs, the ERG conducted a

scenario analysis where the disutility for a MB is doubled within the cycle to reflect a 1-month duration period.

The ERG notes that the company failed to adjust the stroke utility value reported within Locadia *et al.*[82] (0.33) to a patient aged 55.8 years. Consequently the ERG has corrected this utility decrement from 59% to 65% using the methods described above. Results are presented in Section x.

The ERG notes that within Lunde, stroke was defined as patients suffering from ischemic stroke, haemorrhagic stroke, and TIA, but the proportion of patients suffering from each type was not reported in the study.[89] Clinical experts advised the ERG that including patients with TIA will increase the quality of life reported because TIA has no impact on quality of life and would be resolved within 24 hours. Within Hokusai-VTE, TIA was defined as, "an abrupt onset over minutes to hours of a focal non-fatal, neurological deficit in the distribution of a single brain artery that lasts less than 24 hours and that does not satisfy the definition of stroke above." (Hokusai-VTE Appendix, page 18). For this reason the ERG believes the utility value associated with the post-stroke in the model is likely to be slightly overestimated.

5.4.7.8 Methods used by the company to apply disutilities in the model

In this subsection the ERG discusses the methodological approach used to estimate the utility associated with the different heath states in the model.

There were two methods used to estimate the utility associated with the different health states, depending on the health state modelled. The ERG has reviewed these methods separately.

Index VTE (or on treatment), recurrent VTE, off treatment and HIT states

For the index and recurrent VTE, the off treatment and the HIT states, disutilities were applied additively. Furthermore, at entry in the model, for the index and recurrent VTE, the off treatment and the HIT states, all disutilities associated with these events were applied to an index VTE utility value (instead of the age-specific norm) for the duration of the first cycle of the model. The company states that this has no impact on the results since it was applied uniformly across treatment arms but improved face validity (CS, page 159).

After the first cycle, the utility associated index VTE is not used again, and the disutility values associated with the on treatment, recurrent VTE, off treatment and HIT states are applied to the age-specific norm.

Other health states

For the other health states in the model (CRNMB, MB, CTEPH, PTS and stroke) disutilities were applied multiplicatively. The percentage decrease in patient's QoL was estimated by dividing the absolute utility value associated with the specific health state by the utility value associated with the patient's age and gender. This relative impact was then applied to the age norm utility value.

The duration of utility values in the model are dependent on the type of health state (i.e, if the state was a tunnel state or not). Thus, utility estimates applied in tunnel states last for 2 weeks in the model (for example, recurrent VTE and MB), whilst utility values applied in the other health states impact patient's utility for as long as the patient stays in the specific health state. In summary:

- For VTE recurrence, MB, CRNMB, HIT, CTEPH and stroke the respective decrement in patients' wellbeing only lasts for 2 weeks;
- For the PTS, LT-CTEPH and post-stroke health states the respective decrement in patients' wellbeing only lasts for the remainder of patients' life (i.e. lifetime);
- For the on treatment state, the utility decrement associated with warfarin was assumed to last for 12 months, the same period as the treatment duration.

ERG comment on the methods used by the company to apply disutilities in the model

The baseline utility norms used in the model reflect an aging population, where the baseline utility keeps decreasing with age. The ERG notes this is the recommended method to estimate health state utilities from different sources according to the NICE DSU TS12, "to facilitate consistency and thus comparison of results we would recommend the multiplicative method, using adjusted baselines, is used".[94]

ERG comments on the method used to estimate the utility in the Index VTE (or on treatment), recurrent VTE, off treatment and HIT states

Disutilities associated with these health states were applied additively. As the original literature sources estimated the decrement in QoL of patients associated with the specific conditions this approach is reasonable. However, the ERG is not convinced by the use of the index VTE utility value in the first cycle of the model; instead of the age-specific norm should have been used to estimate the baseline utility, to which the QoL decrement could have been applied.

As illustrated in Table 65, when a patient enters the model in the on treatment health state they have a utility of [redacted] that relates to the index VTE. From there, and after 2 weeks, the patient can remain in the on treatment health state and experience the associated age-related utility value for the patient's age. As a result the patient's utility increases to 0.80 after only one cycle (2 weeks).

If a patient suffers a recurrent VTE, their quality of life drops from [redacted] (during the first 2 weeks, or 0.80 in the remaining cycles) to 0.43 (or 0.67, respectively). However, the patient only experiences this decrease for 2 weeks.

After reviewing Table 65, the ERG disagrees that including the index-VTE utility in the analysis adds face validty to the model. In fact, the ERG believes that this may decrease the validity of the model, given that:

- Patients in the on treatment state go from [redacted] to 0.80 in the space of 2 weeks. This is quite a radical change in a patient's wellbeing that is implausible from a clinical point of view. The same issue applies for patients off treatment.

- This approach implies that the impact of index VTE on a patient's wellbeing is considerably larger than the impact of recurrent VTE events throughout the model. That is, a patient with an index VTE experiences a utility of [redacted] in the first cycle of the model, but if the patient experiences a recurrent VTE event 2 weeks after this, his/her utility actually increases to 0.67. This is highly implausible. In fact, in reality, the impact of further recurrent events on a patient's wellbeing is likely to keep increasing or at least remain the same (but not decreaas suggested in the model).

- Finally, the company states that this doesn't have an impact to the final results as the same utilities were applied across all treatment arms. However, even though the utility values might be the same, the probability of patients experiencing recurrent events is not the same across different arms of the model. Despite this, the impact in the economic analysis is likely to be small, as it only happens in 1 cycle of the model and the number of recurring events is low.

Table 65: Utility values applied for each health state applied in the model

Age	On treatment	rVTE	Off treatment	HIT	CRNMB	MB	CTEPH	LT CTEPH	Stroke	Post stroke
55.80*	[redacted]	0.43	0.55	0.48	0.65	0.55	0.56	0.56	0.33	0.70
55.84	0.80	0.67	0.80	0.73	0.65	0.55	0.56	0.56	0.33	0.70
55.88	0.80	0.67	0.80	0.73	0.65	0.55	0.56	0.56	0.33	0.70

*Starting age in the model based on patients in the Hokusai VTE trial

Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; LT, long term; MB, major bleed; NOAC, novel oral anticoagulant; PE, pulmonary embolism; PTS, post thrombotic syndrome; QALY, quality adjusted life year; rVTE recurrent venous thromboembolism; VTE, venous thromboembolism

The same utility value, or utility decrement, should have been used to model the impact of index and recurrent VTE events. This would result in a conservative approach which assumes that the impact on

patient's wellbeing is the same with index and recurrent events. A less conservative approach, but perhaps a more realistic one would be to assume that a recurrent VTEs would have a bigger impact on patients' wellbeing than an index event.

ERG comments on the method used to estimate other utilities in the model

The ERG was concerned that the company did not take into account the study population age within the literature when the relative utility decrements were calculated. Within the model, the utility values were calculated as a relative decrement compared with the UK population norm at 55 years regardless of the age of study participants. The ERG requested clarification on this subject and the company's response is presented in Box 31.

Box 31: Company's rationale for calculating the relative utility decrement compared with the UK population norm at 55 years (Company's response to clarification, B25)

We have assumed that the baseline age is the 55-64 age range for all the studies, as this was the case in most of them. As examples: for the state "Treatment with warfarin", Marchetti *et al*. (2001)[63] interviewed patients aged 57±15 years (range, 23 to 78); for the states "CTEPH" and "LT CTEPH", Meads *et al*. (2008)[87] included patients aged 56.6±15.4 years (range 17.0–90.0). In addition, 55-64 years is likely to be very representative of the age of the population who experience a VTE, as shown in literature, and as reported in the baseline results of the Hokusai-VTE study, which was designed in order to show a high level of generalisability. Finally, we feel the impact of using a different population norm for utilities would be negligible in terms of total QALYs, as well as ICER.
Note references re-numbered by ERG Abbreviations used in the box: CTEPH, chronic thromboembolic pulmonary hypertension; ICER, incremental cost-effectiveness ratio; LT, long term; QALY, quality adjusted life year; VTE, venous thromboembolism

The ERG notes that despite the company's response, after clarification, the utility values seem to have been adjusted to reflect the correct population utility norm.

In conclusion, the ERG is reasonably satisfied with the estimation of patients' QoL in the model. Even though there were some methodological issues in the company's approach these are unlikely to carry a considerable impact on the final ICER. The main issue identified was the underestimation of the impact of recurring and MB events in patients' wellbeing.

The ERG points to the lack of transparency in the identification and selection of the QoL sources used in the model.

5.4.8 Resources and costs

In this section the ERG outlines the systematic review carried out by the company to identify resource use and cost evidence for use within the economic model. Sections 5.4.8.2 to 5.4.8.6 provide further detail on the cost estimates used in the economic analysis. More specifically, the ERG looks at:

- The intervention and comparator's costs (Section 5.4.8.2);
- The costs of index VTE (Section 5.4.8.3);
- The costs of recurrent VTE events (Section 5.4.8.4);
- The costs associated with the complications associated with VTE events (Section 5.4.8.5);
- The costs associated with adverse effects of treatment (Section 5.4.8.6).

The ERG notes that the company did not inflate all prices to the same year in their original submission, which was rectified after the clarification stage. The updated model uses either NHS Reference Costs for 2013/2014[67], the latest version of the BNF[68] for unit costs, or published literature. Prices were inflated using the PSSRU Hospital and Community Health Services index (HCHS)[69] to represent a 2014 cost year when costs were taken from the published literature.

The company reports that estimates of resource use were not validated externally. In general, clinical opinion sought by the ERG disagreed with some of the resource data reported in the submission.

5.4.8.1 Systematic review for resource use and costs

The strategies used to identify relevant resource and cost data for the UK used the same search terms used to identify cost-effectiveness studies, described previously in Section 5.3. Out of the 19 costing studies identified, none were set in the UK. The limitations of this search have been discussed previously in Section 5.3.

Similarly to the HRQoL search, the cost search strategy was restricted to a VTE population, which the ERG believes could potentially miss costs related with specific adverse effects of treatment including bleeding and heparin-induced thrombocytopenia (HIT); or complications associated with VTE including stroke and chronic thromboembolic pulmonary hypertension (CTEPH). As reported in Section 5.4.7.1, the company agreed with the ERG and reported that the search strategies were not targeted enough.

5.4.8.2 Intervention and comparator's costs

Heparin parenteral therapy

As discussed in Section 5.4.5.2, warfarin, edoxaban and dabigatran treatments are initiated following (or simultaneously in the case of warfarin) an initial parenteral treatment with heparin (LMWH or

UFH). The daily drug cost of heparin was estimated as the average cost of four different heparin products available on the market (dalteparin, tinzaparin and enoxaparin and UFH), with each product providing 25% of the market share.

The daily cost of administration of heparin was calculated using a weighted average of self-administration costs and the cost of administration by a district nurse. The cost of instructions on self-administration was considered only once.

The costs associated with heparin treatment are presented in Table 66.

Table 66. Heparin treatment costs

Item	Cost	Reference
Administration		
Instructions of self-administration of LMWH*	£37.00	NHSRC 2013-2014 [67]: N02AF "District Nurse, Adult, Face to face"
Administration of LMWH by professionals*	£37.00	NHSRC 2013-2014 [67]: N02AF "District Nurse, Adult, Face to face"
Proportion of patients self-administering vs. done by professional	92%	Assumption supported by STA for rivaroxaban[95]
Heparin acquisition		
Cost of dalteparin per day	£8.50	BNF[68] Price: £8.47, dose:15,000-unit (0.6-mL) syringe
Cost of tinzaparin per day*	£8.34	BNF[68] Price:£11.90, dose:20 000 units/mL:0.7-mL (14 000-unit) syringe
Cost of enoxaparin per day	£8.00	BNF[68] Price: £8.03,dose:100-mg (1-mL, 10 000-units) syringe
Cost of UFH per day	£7.60	BNF[68] Price: £7.58,dse:5000 units/mL:5-mL amp
Total heparin cost per day*	£8.11	Company assumed each heparin holds 25% market share
Duration of heparin		
Edoxaban	5 days lead in	Assumption of SmPC similar to dabigatran
Dabigatran	5 days lead in	Dabigatran SmPC
Warfarin	8.5 days overlapping	Hokusai-VTE CSR Table 12.2[45]: edoxaban 7.5 days (n=4,118), warfarin 8.5 days (n= 4,122)
Total cost of heparin applied for each drug in the first cycle		
Edoxaban	£89.37	Administration (£48.84) + acquisition (£40.53)
Dabigatran	£89.37	Administration (£48.84) + acquisition (£40.53)
Warfarin	£128.09	Administration (£59.20) + acquisition (£68.89)

*Updated heparin treatment costs provided during clarification

Abbreviations used in the table: BNF, British National Formulary; CSR, clinical study report; LMWJ, low molecular weight heparin; NHSRC, National Health Service Reference Costs; SmPC, summary of product characteristics; STA, single technology appraisal; UFH, unfractionated heparin

Warfarin and NOACs

Warfarin and NOACs do not have an associated administration cost as these are oral anticoagulants that are self-administered.

A summary of the daily drug costs per patient applied within the company's model is presented in Table 67. Table 48 in Section 5.4.5.2 presents the modelled drug doses in the economic analysis.

Table 67: Summary of the applied drug cost per patient, by intervention and comparator

Item	Resource use / cost	Reference
Warfarin		
Daily cost of warfarin*	£0.02	eMIT suggests the average ex-VAT price of 28 tab pack is £0.23; this would change the daily cost to £0.0164
Total cost of warfarin + heparin (first cycle)*	£128.32	Daily cost multiplied by 14 days in a cycle added to 8.5 days of heparin co-administration
Total cost of warfarin (following cycles)*	£0.23	Daily cost multiplied by 14 days in a cycle
Edoxaban		
Daily cost of edoxaban	£2.10	Daiichi Sankyo
Total cost of edoxaban + heparin (first cycle)*	£108.27	Daily cost multiplied by 14 days in a cycle added to 5 day heparin lead-in
Total cost of edoxaban (following cycles)	£29.40	Daily cost multiplied by 14 days in a cycle
Dabigatran		
Daily cost of dabigatran	£2.20	BNF[68] net price 150 mg 60-cap pack =£65.90 300 mg taken as one 150 mg capsule twice daily following treatment with a parenteral anticoagulant for at least 5 days
Total cost of dabigatran + heparin (first cycle)	£109.14	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. So we must have cost of heparin for 5 days, and cost of dabigatran for 9 days (twice daily). Cost per day: £2.197 (150 mg, 60-cap pack = £65.90)
Total cost of dabigatran (following cycles)	£30.76	BNF[68] net price 110 mg 10-cap pack = £10.98,dose:75 mg ,once daily, cost per day =10.98/10 = £1.098
Rivaroxaban		
Rivaroxaban (first cycle)	£73.50	15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE
Rivaroxaban (following cycles)	£29.40	14-tab pack = £29.40 dose:15 mg once daily, cost per day = 29.40/14 = £2.10
*Updated costs provided during clarification Abbreviations used in the table: BNF, British National Formulary; DVT, deep vein thrombosis; PE, pulmonary embolism; VAT, value added tax		

Warfarin was taken twice daily and was initiated in co-administration with heparin for 8.5 days. The daily cost of warfarin was estimated to be £0.02. As a result, the cost of treatment associated with warfarin was £128.32for the first cycle (14 days) and £0.23 for subsequent treatment cycles.

Edoxaban was considered to be started after 5 days of heparin treatment. The daily cost of edoxaban was assumed to be £2.10. The company reports that [redacted]. The cost of treatment associated with edoxaban during the first cycle was £108.27 and £29.40 in subsequent treatment cycles.

As edoxaban, dabigatran required a 5-day heparin lead-in. The daily cost of dabigatran was considered to be £2.20, resulting in a first-cycle cost of £109.14 and a following treatment cycle cost of £30.76.

Rivaroxaban has a 21-day twice-daily initiation dose (15mg twice daily); the subsequent maintenance dose is once-daily (20mg). The daily cost of rivaroxaban is therefore £4.20 during the first three weeks and £2.10 thereafter. The company simplified the application of these two regimens in the model by using the following calculation for the first cycle of the model:

(£4.20*14) + (£2.10*7)

The first term corresponds to the first two weeks of treatment, and the second term corresponds to the cost of the second daily dose during the third week of treatment. The cost of rivaroxaban was therefore artificially increased to £73.50 during the first cycle, and dropped to £29.40 during subsequent cycles.

ERG comment on acquisition and administration costs

Heparin parenteral therapy

The ERG is overall satisfied with the resource use and costs assumed for the administration of heparin. However, the ERG is unclear as to why a more accurate prescribing pattern for heparin wasn't reflected in the model given that the company resourced to clinical experts. Clinical opinion sought by the ERG advised that UFH would only be prescribed for a minority (around 5%) of patients with PE. Furthermore, the proportion of patients receiving different types of LMWH (25% dalteparin, 25% tinzaparin and 25% enoxaparin) was not considered reflective of current clinical practice as enoxaparin is the most commonly used drug, with dalteparin and tinzaparin use combined being similar (or slightly higher) to the use of enoxaparin.

The ERG requested clarification from the company with regards to the rationale for using an equal weight for each of the four heparin products. The company's response is presented in Box 32.

Box 32: Company's rationale for assuming an equal market share (25%) for the four heparin products (Company's response to clarification, B10).

Patients are likely to receive a LMWH for VTE treatment but there are quite marked regional

differences in the brand of LMWH used. For simplicity, we applied an equal share to the available brands. Unfractionated heparin tends to be used in more severe hospitalised patients and while the number of patients treated with UFH is smaller, the duration of treatment with UFH is longer. Therefore we felt that a 25% share for all four products was justifiable.
Abbreviations used in the box: LMWH, low molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism

Furthermore, the calculation of the dose and respective cost of enoxaparin, dalteparin and tinzaparin, should be dependent on patient weight. To consistently estimate an average dose and cost for each treatment within the model, the company needed to assume an average body weight. The ERG did not find this information anywhere in the submission or the economic model, hence requested clarification from the company. The company's response is presented in Box 33.

Box 33: Company's assumed average body weight provided at clarification, (Company's response to clarification, B7).

Heparin is dosed by weight, with additional consideration for patient factors such as renal function. The dose selected in our model (100mg/1ml) is appropriate for patients weighing 55-65kg, as per the dosage chart for 1.5mg/kg enoxaparin.

In light of the above, the ERG believes the company has only considered a patient's weight when calculating the dose of enoxaparin. Moreover, the ERG does not consider 55-65kg to be representative of the average weight of the VTE population. Clinical experts advised the ERG that patients with VTE are more likely to be overweight despite their age (patients enter the model aged 50.8 years).

As a result, the ERG has estimated the cost of LMWH based on a revised market share of: enoxaparin (45%), dalteparin (35%) and tinzaparin (20%) for the average patient weight of 80kg (Table 68). This produced an average cost of £9.03 for LMWH. Given the extremely small difference between the final cost of LMWH obtained by the ERG and the one used in the model, the ERG did not run any additional scenario analysis.

Table 68: ERG revised cost heparin cost

LMWH	Cost / market share	Reference
Cost of enoxaparin per day	£9.77	BNF[68]: 1.5 mg/kg (150 units/kg) every 24 hours, 80kg require 12,000 units.

		120-mg (0.8-mL, 12 000-units) syringe = £9.77
Proportion of patients receiving enoxaparin	45%	Assumption
Cost of dalteparin per day	£8.47	BNF[68]:15,000-unit (0.6-mL) syringe for 69 to 82kg bodyweight = £8.47
Proportion of patients receiving dalteparin	35%	Assumption
Cost of tinzaparin per day	£8.34	BNF[68]: 175 units/kg once daily, 80kg require 14,000 units. 0.7-mL (14 000-unit) syringe = £8.34
Proportion of patients receiving tinzaparin	20%	Assumption
Average cost of LMWH	£9.03	Weighted average of the three LMWHs
Abbreviations used in the table: BNF, British National Formulary; LMWH, low molecular weight heparin		

With regards to the duration of parenteral treatment, clinical opinion sought by the ERG explained that the blinding procedures in the Hokusai-VTE trial were likely to have led to an increase in the heparin treatment duration when compared with clinical practice. Also the company does not present any justification for the choice of different treatment durations for heparin in the warfarin and the edoxaban (and dabigatran) arms of the model.

As previously mentioned, the ERG believes that the company should have opted for either:

- Modelling the treatment duration of heparin to reflect the Hokusai-VTE trial (i.e. 7.5 days for edoxaban and 8.5 days for warfarin); or
- Modelling the treatment duration with heparin according to the NICE Clinical Guideline 144, which sets a minimum of 5 days of heparin together or before warfarin and the licensed 5 days of lead-in heparin for edoxaban.

The ERG modelled both options and estimated the respective costs. Results are presented in Section 6.2.

Warfarin and NOACs

The ERG is generally satisfied with the resource use and costs assumed for the administration of warfarin, dabigatran and rivaroxaban. However, the estimated cost of edoxaban warrants further discussion.

As previously mentioned, there were no assumptions made with regards to the dose of edoxaban administered to patients. The company mentions that the daily cost of edoxaban is assumed to be £2.10, based on [redacted]. The rivaroxaban packs

referred to in the CS are for 15 mg and 20 mg rivaroxaban tablets thus the daily cost of rivaroxaban of £2.10 is obtained by dividing £58.8 by 28 or by dividing £210 by 100.

Therefore the dose of edoxaban in the economic analysis is not explicitly stated or costed.

Finally the ERG notes that the NICE Guide to the 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)".[96]

The ERG notes that the company provided a revised cost for warfarin based on the costs reported in eMIT. However the company only considered a dose of 10mg daily based on a 28 tablet pack of 5 mg which led a daily warfarin cost of £0.0164. Clinical experts advised the ERG that the average dose of warfarin is 5mg per day hpwever this varies greatly from patient to patient, and in time; hence the need for regular INR monitoring. The experts also noted that the Hokusai-VTE trial had a slightly younger group of patients than the UK average which could explain their higher estimate of 10mg per day. Moreover many patients are on more complex regimes such as 3mg one day 4mg the next which is why patients can receive both 1mg and 3mg tablets.

To reflect the prescriptions of warfarin seen in clinical practice the ERG weighted the estimated cost per mg using the quantity of warfarin items prescribed as reported by Prescription Cost Analysis Data (PCA) 2014 for primary care in England.[97] The ERG reviewed data contained within eMIT (12 month period until the end of June 2014) and notes that the cost of warfarin for the 28 tablet pack at 0.5mg is £0.65 (based upon 25,577 data points); 1mg, £0.19 (based upon 405,275 data points); 3mg, £0.21 (based upon 276,240 data points) and at 5mg is £0.23 (based upon 91,218 data points). The ERG estimated the cost of warfarin per mg using all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg). The calculations for this analysis are presented Table 93 in the Appendix. Based on this cost the ERG considers the cost of £0.04 per day to be a closer estimate for the cost of warfarin; the results based on this analysis are presented in Section 6.2. The ERG notes costs for other therapies included within this STA were not found to be present within eMIT.

When eMIT data is not available, the NICE Guide to the Methods of Technology Appraisal 2013 recommend the NHS drug tariff as opposed to the BNF, "For medicines that are predominantly prescribed in primary care, prices should be based on the Drug Tariff".[96] Even though the NHS drug

tariff is updated more regularly than the BNF (every month vs every 6 months) the ERG considers the costs applied by the company to be appropriate for a 2014 cost year.

Monitoring costs

The company estimated INR monitoring costs for patients receiving warfarin treatment. The remaining anticoagulant regimens were assumed not to require any monitoring visits throughout the duration of treatment. The costs applied in the model for patients receiving warfarin are presented in Table 69.

Table 69: Warfarin INR monitoring visits

Warfarin monitoring	Resource use and cost	Reference
INR monitoring visit	**£27.00***	NHSRC 2013-2014[67] weighted average of: "WF10A service code 324 Non- consultant led, Non-Admitted Face to Face Attendance, Follow-up" £19 and "WF10A service code 324 Consultant led, Non-Admitted Face to Face Attendance, Follow-up" £32
Number of INR monitoring visits per cycle	**0.9***	Assumption based on rivaroxaban submission: 9 visits in first three months, then 5 visits per quarter (=24 per year). Given that 1 year is 26 cycles, then 24/26 = 0.9.
*Corrected values provided at clarification stage Abbreviations used in the table: INR, international normalised ratio; NHSRC, National Health Service Reference Costs		

ERG comment on monitoring

The ERG is unclear why the company decided to take the average of the number of INR monitoring visit per cycle, when it could have used the data presented in Table 69 to accurately reflect the costs of monitoring. This is particularly relevant as the distribution of monitoring visits across the year is skewed, with the majority of visits happening during the first 3 months. Hence, the impact of patients dropping out of the model (due to death or discontinuation of treatment) before or after 3 months is not the same. The company could have easily estimated a more realistic and accurate number of visits by assuming:

- 9 visits in the first 3 months, i.e. 9 visits in the first 12 weeks / 6 cycles = 1.5 per cycle for the first 6 cycles;
- then 5 visits per quarter, i.e. 5 visits per 16 weeks / 8 cycles = 0.625 per cycle for the subsequent cycles.

Clinical experts advising the ERG considered the modelled monitoring schedule for warfarin to be slightly overestimated (especially in the case of stable patients), but also explained that this varies across clinical practice. It was mentioned that for initial 3 months of treatment 9 visits is a reasonable assumption but that after this period, 3 visits per quarter seems more reasonable than 5 visits.

The clinical experts also considered that, if treatment was extended beyond 12 months, the schedule modelled by the company would significantly overestimate the number of monitoring appointments typically required in clinical practice in subsequent years, which would consist of approximately 10 visits per year.

In addition, clinical experts advised that the follow-up visits are often delivered by nurses.

In light of this, the ERG conducted a scenario analysis reducing the number of visits required in the first year (for the base case) to 3 visits per quarter after the initial 3 months and in the following years to 2 visits per quarter when lifelong treatment is assumed. This analysis also considered the cost of follow-up visits based on non-consultant-led anticoagulation clinic attendance rather than a weighted average of consultant and non-consultant led attendances. The results of this analysis are presented in Section 6.2.

NOAC monitoring

Clinical opinion sought by the ERG informed that there are some expected monitoring costs associated with edoxaban, dabigatran and rivaroxaban beyond what is considered standard monitoring for VTE patients. Patients on NOACs will visit their GP ideally to undergo an urea and electrolytes test. Therefore the monitoring costs associated with edoxana are underestimated in the economic model.

The ERG conducted a scenario analysis to reflect different options for NOAC monitoring. As clinical opinion advised that this likely varies across clinical practice, the ERG undertook three scenarios, in accordance to the clinical advice received:

a) Average scenario: patients on NOACs receive an annual visit where they receive U&E;
b) Most conservative scenario: patients on NOACs have an annual appointment with their GP where they receive no tests;
c) Less conservative scenario: patients receive biannual visits where they receive U&E.

The results of this analysis are presented in Section 6.2.

5.4.8.3 Costs of index VTE and initial treatment

As explained in Section 5.4.2 all patients enter the model with index VTE and in the on treatment health state. During their treatment period patients incur the costs of diagnosis and hospitalisation (first cycle only) and treatment of the index VTE event. These are now described.

Superseded see erratum

Hospitalisation and diagnosis

The company assumed that all patients would be hospitalised as a result of their index DVT or PE event. As described in Section 5.4.2, patients with index DVT or PE were not modelled separately, so the company weighted the total inpatient costs by the proportion of DVT and PE patients. The company used baseline data from the Hokusai-VTE trial, which showed that 59.3% of index VTE events presented as DVT.

The hospitalisation costs are applied to the first cycle in the model, hence all patients in the model are assumed to be hospitalised for their index VTE for 2 weeks.

In addition to hospitalisation costs the company assumes 50% of hospitalised patients will receive outpatient diagnostic tests for their index DVT or PE. The costs applied in the model for hospitalisation and diagnosis of index DVT and PE are presented in Table 70.

Table 70: Diagnosis and treatment of an index DVT or PE

Item	Cost	Reference
Inpatient costs		
Hospitalization – DVT patients	£711.53	NHSRC 2013-2014[67]: "YQ51A Deep Vein Thrombosis with CC Score 12+": 3,264 stays £949 "YQ51B Deep Vein Thrombosis with CC Score 9-11" 3,803 stays £874 "YQ51C Deep Vein Thrombosis with CC Score 6-8": 5,685 stays £1,015 "YQ51D Deep Vein Thrombosis with CC Score 3-5": 10,481 stays £785 "YQ51E Deep Vein Thrombosis with CC Score 0-2": 16,650 stays £478
Hospitalization – PE patients	£1,596	NHSRC 2013-2014[67]: "DZ09D Pulmonary Embolus with CC Score 12+": 1,623 stays £4,343 "DZ09E Pulmonary Embolus with CC Score 9-11": 3,656 stays £2,840 "DZ09F Pulmonary Embolus with CC Score 6-8": 8,482 stays £1,989 "DZ09G Pulmonary Embolus with CC Score 3-5" 15,647 stays £1,419 "DZ09H Pulmonary Embolus with CC Score 0-2" 15,676 stays £986
Total Inpatient costs	£1,071.00	Assuming 59.3% of patients presented with DVT alone.
Diagnosis costs		
Doppler Ultrasound	£49.00	NHSRC 2013-2014[67] "RA23Z Ultrasound Scan less than 20 minutes"
CT angiography	£91.00	NHSRC 2013-2014[67] "RA08Z Computerised Tomography Scan, one area, no contrast":
Electrocardiogram (ECG)	£118.00	NHSRC 2013-2014[67] “EA47Z, Electrocardiogram Monitoring and stress testing, service code 324, Anticoagulant Service”
Chest X-ray*	£106	PSSRU 2014 [69]13.5 Hospital radiographer - outpatient contact (p.239)
Echocardiogram*	£65	NHSRC 2013-2014[67] "RA60A Simple Echocardiogram, 19 years and over"
D-dimer	£13.06	NICE CG92[17] costing from 2008/2009: £12 inflated to 2013/2014 using HCHS index
Proportion of patients receiving	50%	Assumption from Rivaroxaban submission[95]

imaging and diagnosis		
Outpatient appointment or emergency admission*	£65	PSSRU 2014[69] 13.5 General practitioner - per patient contact (p.195): £46 (Per patient contact lasting 11.7 minutes) and £67 (Per patient contact lasting 17.2 minutes) NHSRC 2013-2014[67] "VB01Z Emergency Medicine, Any Investigation with Category 5 Treatment": 234,259 £81
Total outpatient cost	£221.03	Sum of outpatient costs, weighted by proportion of patients receiving imaging
*Costs included by the company during clarification Note the costs and references reported here relate to those provided at clarification Abbreviations used in the table: CC, complication and comorbidity; CT, computerised tomography; DVT, deep vein thrombosis; NHSRC, National Health Service Reference Costs; NICE, National Institute for Health and Care Excellence; PE, pulmonary embolism; PSSRU, Personal Social Services Research Unit		

Treatment of index VTE

Whilst hospitalised, patients receive anticoagulation treatment. Patients immediately start accruing drug treatment costs for the index VTE when they enter the model until they stop or discontinue treatment. These costs have been described in the previous subsection for the different treatment regimens.

ERG comment on costs of index VTE and initial treatment

Hospitalisation and diagnosis

The ERG has several concerns with the company's calculation of cost associated with index DVT and PE.

Firstly, the ERG notes that the company assumed 100% of patients would receive inpatient care for their index DVT or PE event. Clinical opinion sought by the ERG advised that approximately 30% of patients with proximal DVT and 50% of patients with PE are likely to be treated as inpatients in UK clinical practice. Therefore the ERG changed this assumption in the economic model and conducted a scenario analysis that considered 30% of DVT cases and 50% of PE cases require hospitalisation. The results of this analysis are presented in Section 6.2.

Secondly, the ERG consulted clinical experts about the proportion of people who would receive diagnostic tests and if these depend on the type of VTE event. Clinical experts advised that all patients would receive diagnostic tests (not just 50% of patients as assumed in the company's base case) and that the tests received would not be the same for DVT and PE events.

The ERG requested clarification from the company as to why only 50% of patients receive diagnostic tests in the model and why diagnostic costs do not depend upon the type of VTE event. The company's response is presented in Box 34.

Box 34: Company's response to outpatient costs applied in the model (Company's response to clarification, B9)

These tests are for the diagnosis of PE; 50% estimate was used in the submission for rivaroxaban…. Procedures and associated diagnosis costs were not assumed to be different between PE and DVT. We believe that this is a conservative assumption. The first effect of not distinguishing the higher costs of PE diagnosis from those of DVT is that there will be a systematic underestimate of the costs associated with index events accruing to patients treated with all of the comparators in the analysis; this will not affect the ICERs. Secondly, this will potentially underestimate the costs associated with recurrent events. Since edoxaban is associated with a very low comparative rate of recurrence, we believe that this assumption could underestimate the comparative cost savings with this agent.
Abbreviations used in the box: DVT, deep vein thrombosis; ICER, incremental cost-effectiveness ratio; PE, pulmonary embolism

The ERG reviewed the company's response but is unclear as to why the company stated, "These tests are for the diagnosis of PE" when 50% of patients regardless of their VTE (DVT or PE) are assumed to receive diagnostic tests in the model.

Furthermore, for the purpose of estimating the cost of recurrence, the ERG acknowledges the company's point as to why not differentiating the costs of PE and DVT might underestimate the total cost savings associated with edoxaban. Therefore, the ERG estimated the diagnostic costs in accordance to the clinical expert opinion received. A summary of the diagnostic tests which includes revised costs for an electrocardiogram and chest x-ray proposed by the clinical experts for DVT and PE event are presented in Table 71.

Table 71: Diagnostic costs according to the type of VTE estimated by the ERG

Outpatient cost	Reference	DVT	PE
Doppler Ultrasound	NHSRC 2013-14[67] "RA23Z Ultrasound Scan less than 20 minutes" £49	✔	X
CT angiography	NHSRC 2013-14[67] "RA08Z Computerised Tomography Scan, one area, no contrast" £91	X	✔
Electrocardiogram (ECG)	NHSRC 2013-14[67] "EA47Z Electrocardiogram Monitoring and stress testing, directly accessed diagnostic services " £57	X	✔
D-dimer	NICE CG92[17] costing from 2008/2009: £12 inflated to 2013/2014 using HCHS index £13.06	✔	✔
Chest x-ray	Assumption from TA287[95] (£15.72, cost year 2011) £16.17*	✔	✔
Echocardiogram	NHSRC 2013-14[67] "RA06A Simple Echocardiogram, 19 years and over" £65	X	✔
Outpatient	Average of outpatient appointment (PSSRU[69], £56.50)	✔	✔

appointment	and emergency admission (NHSRC 2013-14[67] VB01Z Emergency Medicine, Any Investigation with Category 5 Treatment £81) £65		
Cost per patient		**£143.23**	**£307.23**
Abbreviations used in the table: CT, computed tomography; CG, clinical guideline; DVT, deep vein thrombosis; NHSRC, Nation Health Service Reference Costs; TA, technology appraisal; PE, pulmonary embolism; *Inflated to 2014 prices using HCSC index			

The ERG ran a scenario analysis where the relevant diagnostic costs are applied according to the type of VTE event. Results of this analysis are presented in section x.

Treatment of index VTE

The ERG agrees that patients suffering from index VTE immediately start anticoagulation treatment.

5.4.8.4 Costs of recurrent VTE events

As previously discussed in Section 5.4.2, rVTE is a tunnel state. This means that patients are only allowed to stay in this state for one cycle (2 weeks). In the initial submission, the 2-week costs associated with recurrent VTEs consisted of hospitalisation costs alone; however, during clarification this was revised to include diagnostic and anticoagulation treatment costs. Hence, patients were assumed to accrue the initial costs of anticoagulation treatment (including the heparin lead-in) for the 2 weeks. After that period patients go back to the on treatment state where they will continue with their previous treatment regimen.

Similarly to index VTE, 100% of patients were assumed to be hospitalised for one cycle (2 weeks). The costs applied by the company for a recurrent VTE are presented in Table 72. The ERG notes that the inpatient and the diagnostic costs are the same as the ones estimated for the initial VTE event presented in Table 70 and described in the previous subsection.

Table 72: Cost of recurrent VTE

Item	Cost
Total Inpatient costs*	£1,071.00
Total diagnostic costs	£221.03
Total cost of recurrence	£1,292
*Assuming 59.8% DVT patients Note diagnostic costs were added for recurrent events by the company at clarification	

ERG comment on the cost of recurrent VTE events

With regards to the estimation of recurrent VTE costs, the following issues should be discussed:

- Hospitalisation and diagnosis of rVTE;

- Treatment received after the rVTE.

Hospitalisation and diagnosis of rVTE

As discussed in the previous subsection, clinical opinion sought by the ERG advised that only around 30% of patients with proximal DVT and 50% of patients with PE are likely to be treated as inpatients in UK clinical practice. During clarification the ERG asked the company why all patients were assumed to be hospitalised for a recurrence. The company's response is presented in Box 35.

Box 35: Company's rationale for assuming 100% of patients are hospitalised for a VTE event (Company's response to clarification, B1)

> We assumed that all patients are hospitalised when VTE recurrence is experienced. Although efforts are underway to increase the proportion of VTE that is treated in the ambulatory setting, the great majority of cases are hospitalised.

In light of the clinical opinion provided to us, the ERG changed this assumption in the economic model and considered that 30% of recurrent DVT cases and 50% of recurrent PE cases require hospitalisation; these proportions are consistent with those considered in Scenario 5.4.8.3 for the index event.. The results of this analysis are presented in Section 6.2.

After consulting clinical opinion, the ERG believes diagnostic tests are also necessary for patients presenting with a recurrent VTE; hence, the ERG has conducted a scenario analysis where 100% of patients will receive the outpatient costs associated with diagnostic tests; moreover these will be according to the type of VTE event (DVT or PE) based on those reported in Table 71 for the index event. The results of this analysis are presented in Section 6.2.

Treatment received after the recurrent VTE

As previously discussed in Section 5.4.2, the ERG believes that the assumption that patients return to their original anticoagulation therapy after recurrence lacks clinical plausibility.

The ERG consulted clinical experts around the appropriateness of assuming that patients receive the same anticoagulation treatment prescribed after their index event. Despite the noted variations in clinical practice, the experts stated that the resulting treatment for a recurrence would ultimately depend on the anticoagulant received at the time of recurrence. Overall, if the recurrence occurred whilst the patient was receiving warfarin, it is likely the patient would continue to receive warfarin, but with a higher INR target range. However, if the recurrence occurred whilst the patient was receiving a NOAC (edoxaban, dabigatran or rivaroxaban), the patient would initiate a treatment course of LMWH (5 days) followed by warfarin.

5.4.8.5 *Complications associated with VTE events*

A summary of the acute and long-term costs associated with PTS, CTEPH and LT CTEPH modelled by the company are presented in Table 73.

Table 73. Summary of the costs associated with severe PTS and CTEPH included within the company's model

Complication	Intervention	Cost	Proportion of patients incurring cost	Reference
PTS	Cost of vascular surgery outpatient appointment (first)*	£161.76 per patient	100%	Resource use: Goodacre *et al*. 2006[98] NHS Reference Costs 2013-2014[67]: "W701B service code 107 Non Consultant-led, Non-Admitted Face to Face Attendance, First"22,843 stays £111 "W701B service code 107 Consultant led,Non-Admitted Face to Face Attendance, First" 160,273 stays £169
	Cost of vascular surgery outpatient appointment (following)*	£135.50 per patient	100%	Resource use: Goodacre *et al*. 2006[98] NHS Reference Costs 2013-2014[67]: "W701A service code 107 Non Consultant-led, Non-Admitted Face to Face Attendance, Follow-up"24,516 stays £82 "W701A service code 107 Consultant led,Non-Admitted Face to Face Attendance, Follow-up" 201,718 stays £142
	2 GP visits per year*	£46 per patient	100%	Resource use: Goodacre *et al*. 2006[98] PSSRU 2014[69]: General practitioner unit cost: per patient contact lasting 11.7 minutes, including direct care staff costs, with qualification costs: £46
CTEPH	Pulmonary endarterectomy*	£7,412.09 per patient	56.8%	Proportion of patients requiring pulmonary endarterectomy: Pepke-Zaba *et al*. 2011[99] NHS Reference Costs 2013-2014[67], weighted average of: - DZ02H "Complex Thoracic Procedures, 19 years and over, with CC Score 6+" : 1,944 stays, £10,284 - DZ02J "Complex Thoracic Procedures, 19 years and over, with CC Score 3-5": 3,314 stays, £7,254 - DZ02K "Complex Thoracic Procedures, 19 years and over, with CC Score 0-2": 4,578 stays, £6,307 All pertaining to OPCS code L041 "Pulmonary thromboendodartectomy"
	Proportion of patients receiving drug therapy	NA	51.5%	Proportion of patients: Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013.[100]
	Sildenafil	£208 per cycle	69.4%	Proportion of patients: Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013. [100] Cost from: BNF[68] - Revatio (sildenafil) 20 mg, 90-tab pack = £446.33 indication 20 mg three times daily.

	Bosentan	£755 per cycle	28.3%	Proportion of patients: Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013. [100] Cost from: BNF[68] - Tracleer (bosentan) 62.5 mg, 56-tab pack = £1,510.21 indication 62.5 mg twice daily.
	Total*	£4,394per cycle	100%	Average total costs weighted by proportion of patients undergoing surgery, and distribution of market shares between sildenafil and bosentan.
LT CTEPH	Proportion of patients receiving drug therapy	NA	51.5%	Proportion of patients: Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013. [100]
	Sildenafil	£208 per cycle	69.4%	Proportion of patients: Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013. [100] Cost from: BNF[68] - Revatio (sildenafil) 20 mg, 90-tab pack = £446.33 indication 20 mg three times daily.
	Bosentan	£755 per cycle	28.3%	Proportion of patients: Fourth Annual report: Key findings from the National Audit of Pulmonary Hypertension for the United Kingdom, April 2012 to March 2013. [100] Cost from: BNF[68] - Tracleer (bosentan) 62.5 mg, 56-tab pack = £1,510.21 indication 62.5 mg twice daily.
	Total	£184 per cycle	100%	Average total costs weighted by distribution of market shares between sildenafil and bosentan.

*Updated costs provided by the company during clarification

Abbreviations used in table: BNF, British National Formulary; CC, complication and comorbidity; CTEPH, chronic thromboembolic pulmonary hypertension; HRG, Healthcare Resource Group; LT, long term; NA, not applicable; OPSC, classification of interventions and procedures; PEA, pulmonary endarterectomy; PTS, post-thrombotic syndrome

As previously discussed in Section 5.4.2, CTEPH is a tunnel state. All patients discontinue anticoagulation therapy after the event. Some patients will move to the LT-CTEPH where they receive CTEPH-related treatment until they die incurring a cost of £184 per cycle.

PTS was not considered as a health state in the model, instead the cost of PTS was applied to a proportion of patients in the on treatment and off treatment states.

ERG comment on complications associated with VTE events

PTS

The ERG considers the resource use estimates for PTS taken from Goodacre *et al.* [98] to be consistent with previous STAs, but the company did not describe how this paper was identified or selected.

Goodacre *et al*. [98] aimed to estimate the cost-effectiveness of testing strategies for DVT from a UK perspective. After reviewing this paper the ERG considers this study to be a relevant source to inform the resource use for PTS.

CTEPH

The ERG notes that the proportion of CTEPH and LT-CTEPH patients receiving sildenafil or bosentan in the model does not add up to 100% (but instead 97.7%). During clarification the company explained that the source used to estimate these percentages included bosentan and sildenafil as the 2 main drug categories, with the remaining of the drugs only adding up to 2.3%, hence the company decided to exclude these. Even though the proportion of patients left out is considerably small (2.3%), form a methodological point of view, the company should have re-weighted the percentage of patients on sildenafil and bosentan to add up to 100%.

In the model it was assumed that 50% of patients with LT-CTEPH receive drug therapy. Expert opinion sought by the ERG advised that 100% of patients with LT-CTEPH will receive drug therapy. Moreover, experts advised that the majority of patients (75%) undergoing a pulmonary endarterectomy would receive drug therapy prior to surgery and a minority of patients (10%) will also receive drug therapy after surgery. During clarification the ERG asked the company to justify the assumption that the proportion of patients receiving drug therapy (50%) is equal for a CTEPH and LT-CTEPH. The company's response is presented in Box 36.

Box 36: Company's rationale for assuming that the proportion of patients receiving drug therapy is equal for a CTEPH and LT-CTEPH (Company's response to clarification, B29)

Our understanding of clinical practice is that the treatment of CTEPH is not different after one cycle of our model (2 weeks), and that this is an acceptable assumption for that reason.
Abbreviations used in the box: CTEPH, chronic thromboembolic pulmonary hypertension

Overall, the ERG considers the cost of LT-CTEPH is underestimated in the model. The ERG reviewed previous STAs for the ongoing cost of managing a patient with CTEPH. Within TA261[57], TA287[58] and TA327[59] this was based on the estimate of £1,219 per month made for NICE CG92[17] (2010 prices) that included the average cost of bosentan, sitaxentan and sildenafil.

Furthermore, the ERG believes the dose of bosentan for LT-CTEPH has been underestimated based on the recommendation within the BNF[68]. After 4 weeks of bosentan the dose should be increased from 62.5mg twice daily to 125 mg twice daily, consequently there is an increase in cost from £755 per cycle to £1,510.

Finally, as previously discussed, clinical experts have advised the ERG that patients would continue to receive anticoagulant treatment following CTEPH to reduce the risk of further recurrence. These patients would be extremely vulnerable to recurrent VTEs and hence it would be inappropriate to withdraw them from anticoagulant treatment at a time they need it most.

Therefore the ERG conducted a scenario analysis in which the NICE CG92 estimate for LT-CTEPH was applied in the model (£1,280 2014 prices).[17] The results of this analysis are presented in Section 6.2.

The ERG also notes that the source used to inform the proportion of patients undergoing pulmonary endarterectomy for their CTEPH was taken from Pepke-Zaba *et al*. but the company failed to describe how this source was identified and selected.[99] Despite this, the ERG found similar proportions of patients undergoing surgery within TA327 (50.3%) and TA261 (68.4%) based on the studies by Condliffe *et al*. 2008[101] and Condliffe *et al*. 2009[101, 102].

5.4.8.6 Adverse effects of treatment

Table 74 presents a summary of the acute costs associated with HIT, CRNMB, MB and stroke and the ongoing post-stroke costs used in the economic model.

Table 74 Summary of adverse event costs included within the company's model

Adverse event	Cost per patient	Reference
HIT	£617.61	NHSRC 2013-14[67], weighted average of: - SA12G "Thrombocytopenia with CC score 8+" : 667 stays, £2,504 - SA12H "Thrombocytopenia with CC score 5-7" : 1,327 stays, £1,236 - SA12J "Thrombocytopenia with CC score 2-4" : 4,302 stays, £649 - SA12K "Thrombocytopenia with CC score 0-1" : 9,990 stays, £396 All pertaining to ICD10 code D69.5 "Secondary thrombocytopenia"
CRNMB	£149.00	NHSRC 2013-2014[67]: VB07Z "Emergency Medicine, Category 2 Investigation with Category 2 Treatment" Activity:20,55,465
MB	£1,136.00	NHSRC 2013-2014[67], weighted average of: - FZ38G Gastrointestinal Bleed, with Multiple Interventions, with CC Score 5+: 1,023 stays, £5,040 - FZ38H Gastrointestinal Bleed, with Multiple Interventions, with CC Score 0-4: 1,331 stays, £3,167 - FZ38J Gastrointestinal Bleed, with Single Intervention, with CC Score 8+: 1,031 stays, £3,048 - FZ38K Gastrointestinal Bleed, with Single Intervention, with CC Score 5-7: 1,957 stays, £2,763 - FZ38L Gastrointestinal Bleed, with Single Intervention, with CC Score 0-4: 7,285 stays, £1,996 - FZ38M Gastrointestinal Bleed, without Interventions, with CC Score 9+: 2,273 stays, £2,084 - FZ38N Gastrointestinal Bleed, without Interventions, with CC Score 5-8: 11,367 stays, £1,344 - FZ38P Gastrointestinal Bleed, without Interventions, with CC Score 0-

		4: 65,047 stays, £788 All HRGs related to bleeds
Stroke	£3,182.41	NHSRC 2013-2014[67], weighted average of: -AA35A "Stroke with CC Score 16+" :2,829 stays,£8,858 -AA35B "Stroke with CC Score 13-15":7,511 stays,£7,145 -AA35C "Stroke with CC Score 10-12":15,671 stays,£5,169 -AA35D "Stroke with CC Stroke 7-9":28,755 stays,£3,566 -AA35E "Stroke with CC Score 4-6":46,153 stays, £2,489 -AA35F "Stroke with CC Score 0-3":41,484,£1,833
Post-stroke	£7,485.54 per annum; £288 per cycle	Lunego-Fernandez *et al*. 2013[103] (2008/2009 costs inflated to 2013/2014 using HCHS index)
Note costs updated by the company at clarification are reported Abbreviations used in the table: CC, complication and comorbidity; CRNMB, clinically relevant non-major bleed; HCHS, Hospital and Community Health Services index; HIT, heparin-induced thrombocytopenia; MB, major bleed; NHSRC, National Health Service Reference Costs;		

As described in Section 5.4.2, HIT, CRNMB, MB and stoke are tunnel states; hence, their associated treatment costs are applied within the 2 week cycle the event occurred. Post-stroke is modelled as a separate health state where patients incur a cost of £288 per cycle over their lifetime. The long-term costs of stroke were taken from Lunego-Fernandez *et al.* who reported the acute and long-term costs of stroke in patients with prior arterial fibrillation.[103] The 153 patients included in the analysis had a total of 191 strokes during the study period. Of these, 162 (85%) were ischemic, 17 (9%) were haemorrhagic strokes, and 12 (6%) were of unknown type. After stroke, patients were newly admitted into long-term warden, nursing, or residential care; averaged across all stroke cases surviving the acute period (n = 136), new institutionalisation after stroke resulted in an average annual stay in long-term care of 56 days.

ERG comment on adverse effects of treatment

Overall the costs outlined in Table 74 appear reasonable. The ERG notes that the company did not describe how Lunego-Fernandez *et al.* study was identified or selected.[103] However, clinical opinion and consultation of previous STAs informed that the costs used by the company for post-stroke in their analysis is appropriate.

In conclusion, the ERG is concerned with the clinical plausibility of some of the assumptions underlying the cost estimation in the model. The ERG also disagrees with the monitoring resources assumed for warfarin and the NOACs. The issues identified by the ERG can be summarized as:

- The company assumed 100% of patients would receive inpatient care for their index DVT or PE event. Clinical opinion sought by the ERG advised that approximately 30% of patients with proximal DVT and 50% of patients with PE are likely to be treated as

inpatients in UK clinical practice. Clinical experts also advised that all patients would receive diagnostic tests (not just 50% of patients as assumed in the company's base case) and that the tests received would not be the same for DVT and PE events.

- The company assumed that patients experiencing a recurrent event go back to their original anticoagulation therapy after the event, even if the regimen hasn't been effective in preventing recurrence. The company also assumes that after 12 months, recurring patients only receive 2 weeks of anticoagulation therapy. Clinical opinion sought by the ERG indicates that both assumptions are highly implausible.
- It is likely that the company is overestimating the monitoring regimen required for warfarin patients and underestimating the monitoring regimen for edoxaban (and the other NOACs) patients.

5.4.9 Cost effectiveness results

The ERG finds the base case results presented in the CS (Table B89 and Table B90, pg 180) slightly confusing. Therefore the ERG presents the company's base case results in Table 75. The ERG notes that the results presented are the ones reported after the clarification stage, where the ICER comparing edoxaban with warfarin went from dominant to £2,451.

Edoxaban + initial heparin parental treatment presents a cost per QALY gained of £2,451 compared with warfarin + initial heparin parental treatment. Compared with dabigatran, edoxaban produces cost savings of £38 and results in more QALYs, thus is considered dominant. Rivaroxaban dominates edoxaban, being less expensive and producing more QALYs than edoxaban.

Table 76 reports the fully incremental cost-effectiveness analysis, which shows that rivaroxaban is the drug that yields the lower costs and produces more QALYs compared with the other 3 treatments, followed by warfarin, then edoxaban and finally dabigatran.

Table 75. Company's base case results

Results per patient	**Edoxaban + heparin (1)**	**Warfarin + heparin (2)**	**Dabigatran + heparin (3)**	**Rivaroxaban (4)**	**Incremental value**		
					(1-2)	**(1-3)**	**(1-4)**
Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.0185	0.0057	-0.0091
ICER					**£2,451**	**Dominant**	**Dominated**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year							

Table 76. Fully incremental cost-effectiveness results

Treatment	Cost	QALYs	Incremental cost	Incremental QALY	Incremental ICER
Rivaroxaban	£4,015.7	12.426	-	-	-
Warfarin	£4,032.6	12.398	£16.9	-0.028	Dominated
Edoxaban	£4,077.9	12.416	£45.4	0.019	Dominated
Dabigatran	£4,116.2	12.411	£38.3	-0.006	Dominated
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

The company presented model outcomes at the end of 12 months and compared these with the observed events in the Hokusai-VTE trial at 12 months. These are presented in Table 77.

The company states that, *"it is important to note that the incidence of these outcomes (Recurrent VTE, HIT, CRNMB, MB, Stroke, CTEPH and death) as captured in the Hokusai-VTE study represent the number of first events. However due to the structure of this cost-effectiveness model, it was not possible to estimate the number of first events; instead, the estimates in the model refer to the total number of events experienced"* (CS, page 175).

The ERG disagrees with this statement as some of the events estimated in the model (for example, recurrent VTE), were estimated with phase-specific data and not with time-to event data. As such, these represent more than just first events and include further events. Furthermore, and as previously discussed, other events could have been modelled with phase-specific model but instead were modelled with time-to-event data with no justification provided (for example MBs). The ERG updated the values provided by the company to reflect the number of events observed in the trial according to the phase-specific analysis, where phase specific analysis data were used to estimate the probability of events in the model. Results are presented in Table 77.

In Table 78 the ERG presents the model outcomes in the overall analysis (50 years).

Table 77. Summary of model results compared with clinical data at 12 months

Outcome	Hokusai-VTE events		Model events	
	Edoxaban N=4118	Warfarin N=4122	Edoxaban N=4118	Warfarin N=4122
Recurrent VTE			69	86
HIT	0	0	1	1
CRNMB	298	368	296	376
MB	56	66	61	65
Stroke	26	26	26	26

Outcome	Hokusai-VTE events		Model events	
	Edoxaban N=4118	Warfarin N=4122	Edoxaban N=4118	Warfarin N=4122
CTEPH	1	0	27	27
Death	35	33	40	42
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; HIT, heparin induced thrombocytopenia; MB, major bleed; VTE, venous thromboembolism				

Table 78. Summary of model results

Outcome	Model events	
	Edoxaban N=4118	Warfarin N=4122
Recurrent VTE	3567	3582
HIT	46	46
CRNMB	317	403
MB	66	70
Stroke	29	29
CTEPH	27	27
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; HIT, heparin induced thrombocytopenia; MB, major bleed; VTE, venous thromboembolism		

5.4.10 Sensitivity analyses

The company carried out a series of sensitivity analyses to test the robustness of model results to changes in model parameters. Specifically, the company presented result of deterministic (Section 5.4.10.1) and probabilistic (Section 5.4.10.2) sensitivity analyses. The results here presented correspond to those provided by the company upon the clarification stage.

5.4.10.1 Deterministic sensitivity analysis

Scenario analyses

The company carried out a single scenario analysis, where the OR for VTE recurrence for edoxaban vs warfarin was taken from the Hokusai-VTE trial, instead of the NMA (base-case analysis). Results are presented in Table 79.

Table 79: Scenario analysis OR estimations for edoxaban vs warfarin

OR for edoxaban vs. warfarin	Estimations from NMA	Estimations from Hokusai-VTE RCT
OR for VTE recurrence	[redacted]	[redacted]
OR for CRNMB	[redacted]	[redacted]
OR for MB	[redacted]	[redacted]
Abbreviations used in the table: CRNMB, clinically relevant non major bleed; MB, major bleed; NMA, network		

meta-analysis; OR, odds ratio; RCT, randomised controlled trial; VTE, venous thromboembolism

When the values from Hokusai-VTE RCT were applied in the model, the ICER for edoxaban compared to warfarin reduced from £2,452 in the base case to £1,948; the associated total costs and QALYs are presented in Table 80.

Table 80: Scenario analysis results

Intervention	Total cost	Total QALYs	Incremental cost	Incremental QALYs	ICER
Warfarin	£4,033	12.398	-	-	-
Edoxaban	£4,076	12.420	£43	0.0222	£1,958
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

ERG comment on scenario analysis

The ERG notes that the use of ORs from the Hokusai-VTE trial raises the same concerns as using the ORs obtained from the NMA. The reason for this is that the Hokusai-VTE analysis was based on the assumption of PH and this assumption is likely to be the basis for the PH assumption in the economic model as well as in the NMA. Furthermore, the ORs obtained in the trial are not statistically significant when comparing recurrent VTE for edoxaban and warfarin. The decrease in the final ICER for edoxaban vs warfarin from £2,452 in the base case to £1,948 is therefore not very informative. This decrease is explained by the lower ORs for recurrent VTE and MB for edoxaban compared to warfarin however these are still not statistically significant.

Alternatively, the company could have presented the final ICER obtained by using the trial data for recurrent VTE events for edoxaban (i.e, not using ORs). By doing so the company could have used individual patient-level data and no assumptions would have to be made on the relationship of the hazards between edoxaban and warfarin over time. In order to include the other NOACs in the analysis the company may still have had to assume PH between the NOACs, which is potentially a flawed assumption however, the analysis of edoxaban vs warfarin would be more robust.

Exploratory and sensitivity analyses undertaken by the ERG are presented in Section 6.

Subgroup analysis

The company selected subgroups in line with the NICE scope. Subgroup analyses were undertaken focusing on:

- patients with an index PE, with or without DVT;

- patients undergoing fixed durations of treatment of: 3 months, 6 months and lifelong treatment.

The company stated that evidence did not allow for subgroup analysis to be undertaken in the DVT population (with respect to the NMA); therefore no results for a DVT-only subgroup were presented (CS, pg 197).

Baseline data for warfarin were taken from the Hokusai-VTE trial for the PE subgroup and then transition probabilities were derived for the NOACs following the same method described in the base case model. ORs were obtained from the NMA and when there were no data available for an event, the OR was assumed the same as in the base case analysis.

The ERG identified 2 mistakes in the PE model. The company used the OR for recurrence of VTE obtained in the NMA estimated for the entire VTE population, and not for the PE subgroup. Therefore the ERG replaced the OR for VTE recurrence for edoxaban, dabigatran and rivaroxaban compared to warfarin, respectively, to reflect the correct estimates in the PE subgroup. The other mistake identified refers to the cost of hospitalisation associated with index VTE, where the company considered that a proportion of index events would be DVT episodes. The ERG has corrected this so it reflects only PE index events.

The results for the PE (with or without DVT) population based on 12-month treatment duration are presented in Table 81.

Table 81: Cost-effectiveness results: patients with an index PE, with or without DVT: treatment duration = 12 months (corrected by the ERG)

Results per patient	**Edoxaban + heparin (1)**	**Warfarin + heparin (2)**	**Dabigatran + heparin (3)**	**Rivaroxaban (4)**	**Incremental value**		
					(1-2)	**(1-3)**	**(1-4)**
Total costs (£)	£4,621	£5,021	£4,653	£4,562	-£400	-£33	£59
QALYs	12.12	12.09	12.11	12.11	0.03	0.00	0.01
ICER					**Dominant**	**Dominant**	**£6,507**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year							

The company also presented results from a PE (with or without DVT) population using lifelong treatment duration. These results are presented in Table 82.

Table 82: Cost-effectiveness results: patients with an index PE, with or without DVT: treatment duration = lifelong

Results per patient	Edoxaban + heparin (1)	Warfarin + heparin (2)	Dabigatran + heparin (3)	Rivaroxaban (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
Total costs (£)	£23,141	£25,460	£23,963	£23,240	-£2,319	-£822	-£100
QALYs	12.38	12.16	12.42	12.39	0.22	-0.04	-0.01
ICER					**Dominant**	**£23,101**	**£12,069**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year							

The results from varying the duration of treatment are presented in Table 83 alongside the base case (12 month duration) for ease of reference.

Table 83: Results for patients undergoing fixed durations of treatment of: 3 months, 6 months, Life-long

Results per patient	Edoxaban+ heparin (1)	Warfarin+ heparin (2)	Dabigatran + heparin (3)	Rivaroxaban (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
Treatment duration = 3 months							
Total costs (£)	£2,822	£2,854	£2,836	£2,761	-£32	-£14	£61
QALYs	12.38	12.37	12.37	12.39	0.01	0.01	0.00
ICER					**Dominant**	**Dominant**	**Dominated**
Treatment duration = 6 months							
Total costs (£)	£3,225	£3,233	£3,247	£3,164	-£7	-£21	£62
QALYs	12.39	12.38	12.39	12.40	0.01	0.01	-0.01
ICER					**Dominant**	**Dominant**	**Dominated**
Treatment duration = 12 months (base case)							
Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER					**£2,451**	**Dominant**	**Dominated**
Treatment duration = lifelong							
Total costs (£)	£22,720	£21,301	£23,513	£22,698	£1,419	-£793	£23
QALYs	12.55	12.36	12.55	12.62	0.19	-0.00	-0.07
ICER					**£7,608**	**£312,569**	**Dominated**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.							

Fully incremental cost-effectiveness results for each subgroup can be found in the CS (pgs 192 to 196).

ERG comment on subgroup analysis

The company's subgroup analysis is in line with the scope for this STA (CS, Table A7, pages 34-35). However the following additional subgroups were also outlined in the scope:

- The type of VTE (DVT and PE);
- Patients for whom the need for long-term anticoagulation is uncertain and aspirin or no preventative treatment might be considered;
- Patients with active cancer and include any effect on the patients' cancer or cancer treatment.

The ERG believes it would have been possible for the company to perform an analysis for DVT patients as the Hokusai-VTE trial presented DVT subgroup data. Therefore, there were DVT data available for warfarin, edoxaban and at least rivaroxaban (as the EINSTEIN-DVT trial only looked at DVT patients). During clarification the ERG asked the company to clarify why a DVT subgroup analysis was not possible given the available data. The company's response is presented in Box 37.

Box 37: Company's rationale for not undertaking a DVT subgroup analysis using available data (Company's response to clarification, B11)

The primary objective of the network meta-analysis was to derive estimates of the relative effect of edoxaban versus the other NOACs and warfarin on efficacy and safety outcomes in patients with VTE. As a secondary objective, we evaluated the subgroup of patients with PE, where a) the unmet clinical need remains high, and b) sufficient data to compare a number of agents are available. Thus, the DVT-only subgroup was outside the scope of the NMA and a full analysis across the class would not have been possible.
Abbreviations used in the box: DVT, deep vein thrombosis; NOAC, novel oral anticoagulant; NMA, network meta-analysis; PE, pulmonary embolism; VTE, venous thromboembolism

The ERG does not agree that DVT patients were outside the scope of the NMA, as they were part of the NICE original scope. Therefore the ERG conducted the NMA for DVT patients and obtained an ICER for this subgroup. Results are presented in Section 6.2.

As previously described in Section 5.4.4 the ERG accepts evidence did not allow the company to undertake any further subgroup analyses as the Hokusai-VTE trial did not include patients for whom warfarin wasn't considered an appropriate anticoagulation treatment and there was an extremely small

number of patients with cancer, which according to the definition of cancer in the UK, wouldn't be considered active cancer patients.

With regards to the results obtained in the PE subgroup, results are broadly similar to the base case analysis and the PE subgroup for 12 months of treatment received. Edoxaban dominates warfarin and dabigatran and the ICER comparing edoxaban with rivaroxaban is £6,507 (when before rivaroxaban dominated edoxaban).The total costs of each treatment regimen is higher in the PE subgroup. This is essentially due to higher CTEPH costs (as the entire population is at risk of CTEPH in this subgroup) and also due to treatment costs, as recurrence is assumed to be different for PE patients compared to the entire VTE population. The total QALYs are roughly the same as the ones obtained in the base case.

With regards to the treatment duration subgroup analysis, as described in Section 5.4.5, clinical experts advised the ERG that the duration of treatment depends on patients individual risk factors and ultimately if the event was provoked or unprovoked. The majority of patients with a provoked event are anticipated to receive 3 months of treatment; whereas patients with an unprovoked event or recurrent events are anticipated to receive lifelong treatment. Hence the consideration of different treatment durations added value to the company analysis.

However, the ERG does not believe the company accurately reflected the warfarin monitoring schedule seen in clinical practice for a 3 month treatment period. As discussed in Section 5.4.8.2 the company averaged the number of INR appointments across all cycles instead of applying a more intense schedule for the initial 3 months followed by less frequent visits once a patient's INR stabilises. As a result the company underestimates the cost of monitoring for a 3 month treatment period from 1.5 visits per cycle to 0.9 visits per cycle. For completeness the ERG re-ran this scenario using 1.5 visits per cycle, this resulted in an incremental cost of £148 as opposed to £32. The ICER for edoxaban compared with warfarin remained dominant.

The results seem fairly consistent across different treatment periods, with rivaroxaban always dominating edoxaban (i.e. less expensive and yielding more QALYs). The only exception is dabigatran, which goes from being dominated in 3 months, 6 months and 1 year treatment duration scenarios to presenting a lifetime treatment duration ICER of £312,569 per QALY. However, the reason for this is not only the increase in cost savings produced by edoxaban compared to dabigatran, but the extremely small loss of QALYs in edoxaban compared to dabigatran (0.003). Therefore, this ICER should be interpreted with caution, as it is extremely close to actually portraying a dominant ICER (if edoxaban results in the same QALY gain as dabigatran).

For shorter treatment durations (3 and 6 months), rivaroxaban was found to be the dominant strategy and edoxaban was always the second option. However for lifelong treatment, warfarin was less costly than the NOACs. In this scenario, rivaroxaban dominated edoxaban and dabigatran, and the ICER of rivaroxaban vs warfarin was £5,363.

One way sensitivity analysis (OWSA)

The company carried out OWSA by changing the following model inputs:

- transition probabilities for warfarin using 95% Confidence Interval bounds as low and high values;
- probabilities of complications while on warfarin or NOAC using 95% Confidence Interval bounds as low and high values;
- probability of death using 95% Confidence Interval bounds as low and high values;
- hazard ratio for VTE recurrence compared to warfarin using 95% Confidence Interval bounds as low and high values;
- utility values and utility decrement using 95% -Confidence Interval bounds as low and high values;
- costs with a variation of +/-20% (assumption).

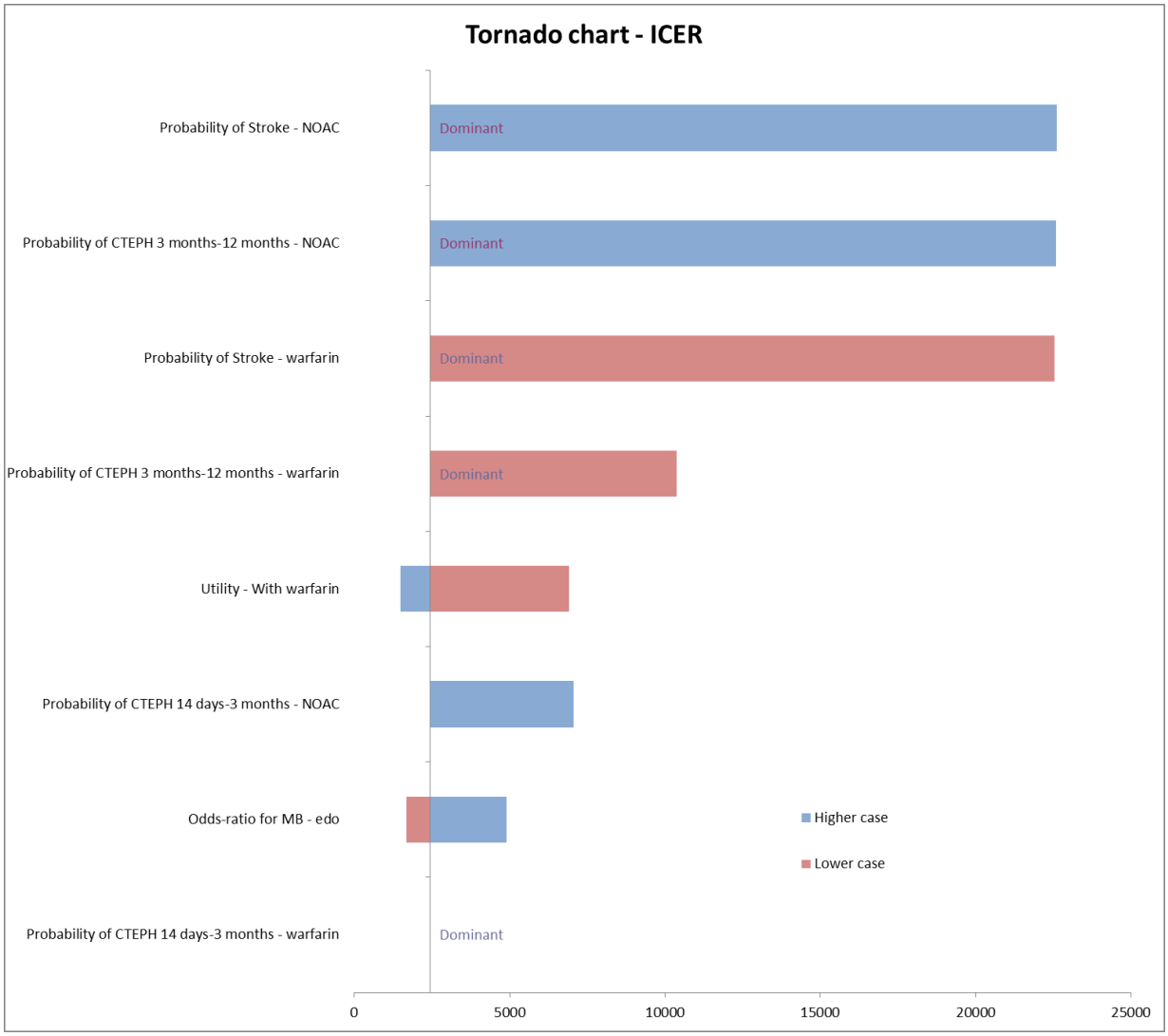
The variables included in the OWSA are presented in Table 93 in the Appendix.

In the response submitted at clarification, the company presented tornado charts for the eight most influential parameters in the population of VTE patients. Edoxaban was compared separately to each of the other comparators. Where edoxaban was dominant or dominated against other comparators in the base case (i.e. dabigatran and rivaroxaban), the tornado charts were presented in terms of Net Monetary Benefit (NMB) using a £20,000 willingness-to-pay threshold. A summary of the results for each comparison is presented in the subsections that follow.

Edoxaban vs warfarin

The tornado chart presenting the 8 most influential parameters for the comparison of edoxaban against warfarin is displayed in Figure 19. The vertical axis represents the base case ICER of £2,541.

Figure 19: Tornado chart for edoxaban vs warfarin, ICER perspective (reproduced from the company's updated results submitted at clarification [Figure B1, page 12])



The 3 parameters reported as most influential for the comparison of edoxaban with warfarin were the following:

- the probability of stroke with NOACs;
- the probability of CTEPH between 3 months and 12 months with NOACs;
- and the low value of probability of stroke with warfarin.

The other variables reported to have led to a noteworthy impact were (listed in order of decreasing ICER):

- probability of CTEPH between 3 months and 12 months with warfarin: Higher case ICER £10,377; lower case ICER, dominant;
- probability of CTEPH 14 days-3 months – NOAC: Higher case ICER, £7,052;

- utility decrement of warfarin: Lower case ICER, £6,902;
- OR edoxaban vs warfarin for MB: Higher case ICER, £4,908.

Edoxaban vs dabigatran

The tornado chart presenting the eight most influential parameters for the comparison of edoxaban against dabigatran is displayed in Figure 20. The vertical axis represents the incremental NMB of £152:

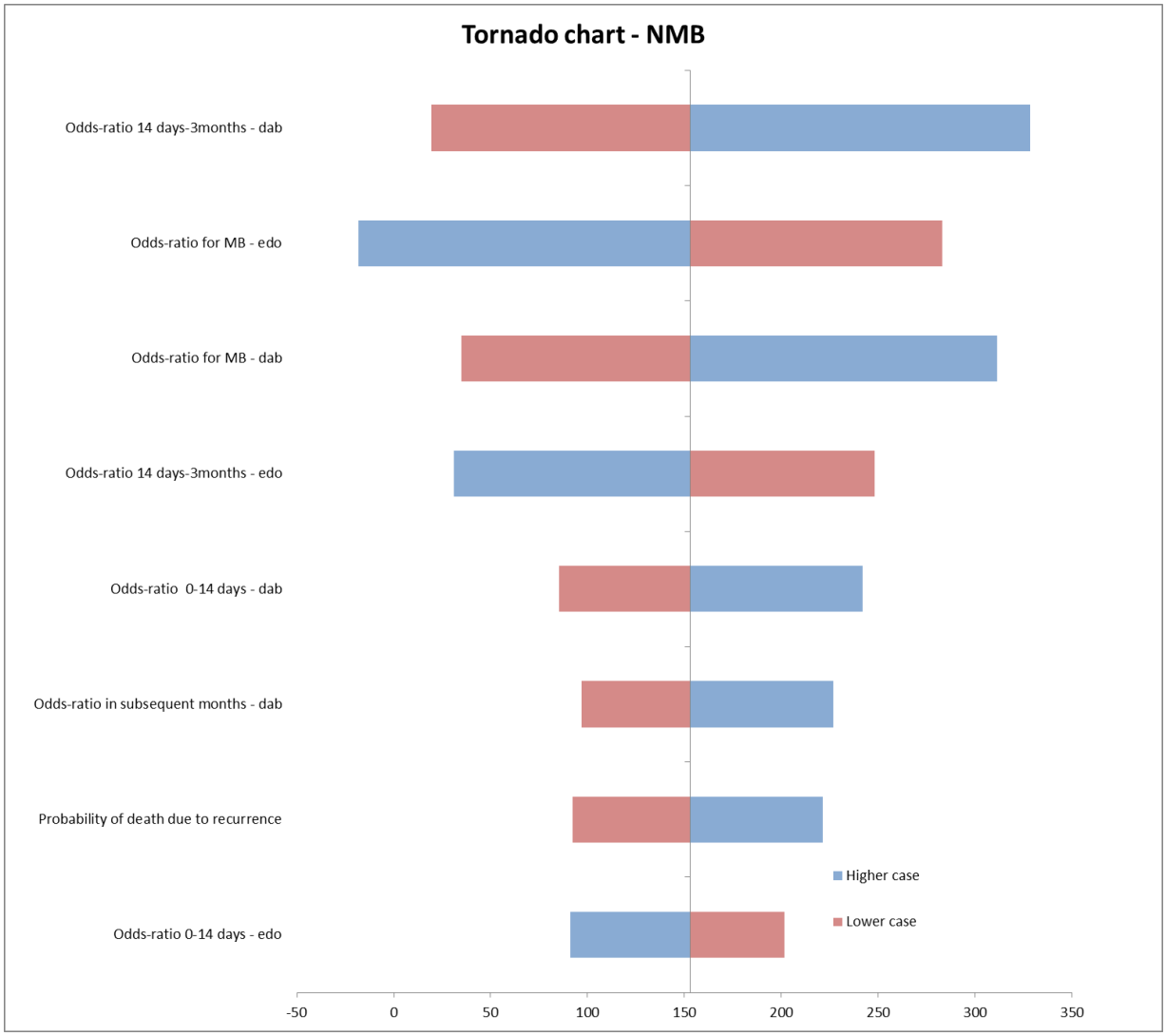
$$\lambda\Delta E - \Delta C = NMB$$

Where:

- λ = WTP threshold
- ΔE = incremental QALYs
- ΔC = incremental costs

Therefore, 20,000*0.0057 +38 = £152

Figure 20: Tornado chart for edoxaban vs dabigatran, NMB perspective (reproduced from the company's updated results submitted at clarification [Figure B2, page 14])



The 4 key identified parameters were:

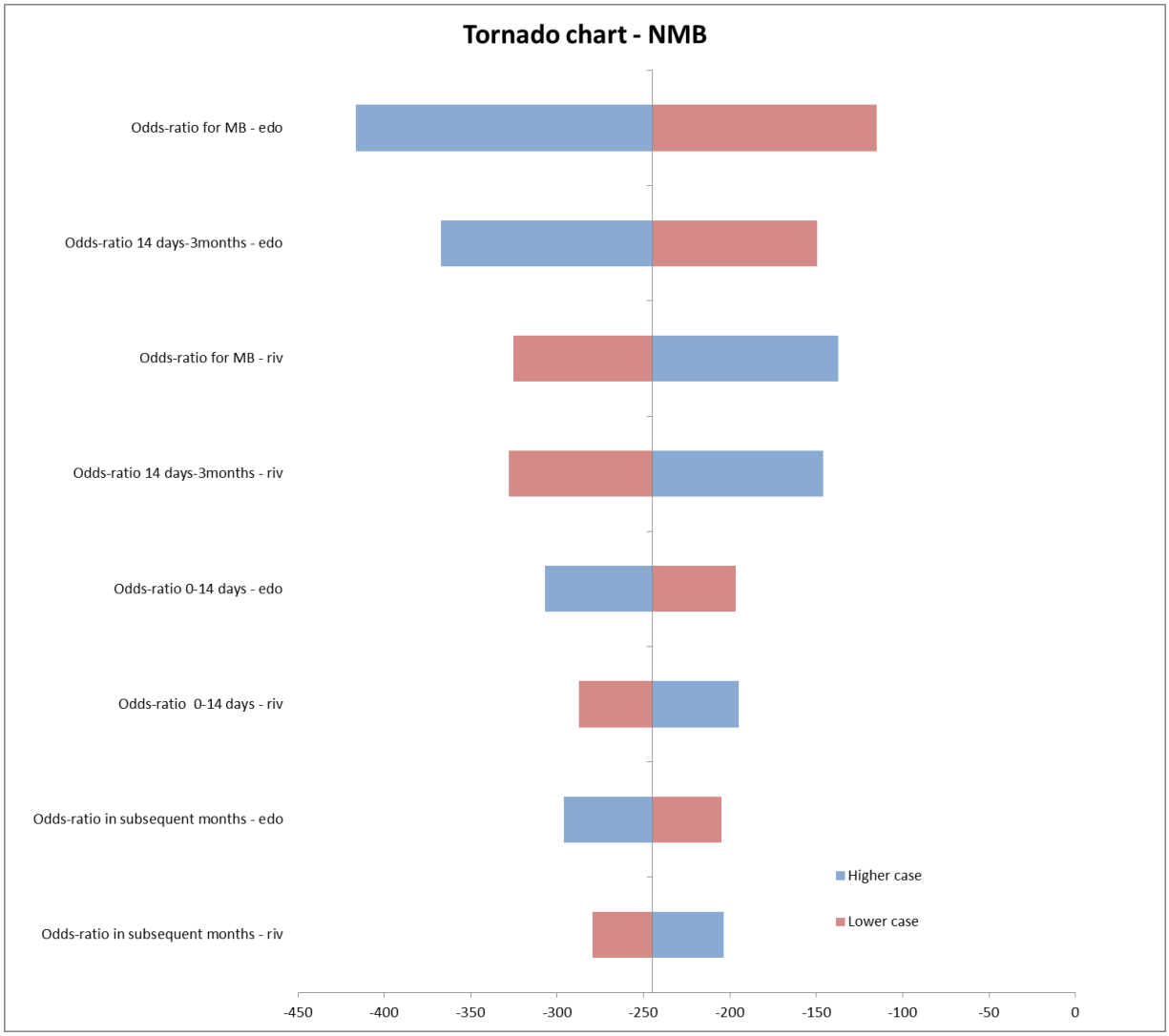
- OR dabigatran vs warfarin for MB: Lower case ICER: £5,094,386;
- OR edoxaban vs warfarin VTE recurrence 14 days-3months: Higher case: £180,870;
- OR dabigatran vs warfarin VTE recurrence 14 days-3months: Lower case: £45,755;
- OR edoxaban vs warfarin for MB: Higher case ICER: £12,974.

Edoxaban vs rivaroxaban

The tornado chart presenting the eight most influential parameters for the comparison of edoxaban against warfarin is displayed in Figure 21. The vertical axis represents the incremental NMB of -£244 (20,000*-0.0091 -62 = -£244).

All tested parameters had a negative NMB; hence none of the parameters had any impact on the conclusion (i.e. edoxaban is always dominated by rivaroxaban).

Figure 21: Tornado chart for edoxaban vs. rivaroxaban, NMB perspective (reproduced from the company's updated results submitted at clarification [Figure B2, page 14])



ERG comment on OWSA analysis

The ERG is concerned with the relevance and robustness of the OWSA. The choice of the input parameters to be varied wasn't justified by the company and, in some cases, reflects clinically implausible scenarios. The three inputs identified as being the key model drivers for edoxaban vs warfarin (probability of stroke and CTEPH with NOACs and probability of stroke with warfarin) are

based on the assumption that the probability of these events might be different depending on the treatment received. As would be expected, when the probability of CTEPH or stroke is varied just in one arm of the economic model, the ICER changes substantially as these are expensive and serious conditions. However, varying the probability of these events in only one arm of the model doesn't have face validity, as there is no clinical rationale for CTEPH or stroke to be linked to the type of treatment received. By including irrelevant parameters in the analysis (but with a substantial impact on the ICER), and by presenting only the eight most influential parameters in the model, the company rendered their OWSA largely irrelevant. During clarification the ERG also asked the company to present total costs, total QALYs, and ICERs for the upper and lower value for each input listed; however these were not provided.

Additionally, there is a lack of transparency in the OWSA reported. Not only have the tornado diagrams not been provided in the Excel model, but the macros running the OWSA in the model don't work. Furthermore, the ERG manually ran the scenario where the probability of VTE recurrence with edoxaban was changed to its upper limit on the 95% Confidence Interval range (1.174) and obtained an ICER of £7,181. This hasn't been reported in the list of inputs with "noteworthy" impact, which included ICERs from around £10,000 to around £5,000.

For utility values and utility decrements the company estimated 95% Confidence Intervals as low and high values, however the ERG is not clear how the standard deviations in the calculation presented were obtained. This was not reported by the company.

The ERG questions the appropriateness of varying the overall health state costs by +/-20%. The ERG believes this approach loses granularity because the specific costs or resource use within each health state that influence the results cannot be identified. The ERG notes that the resource use associated with warfarin monitoring should have been explicitly varied between plausible values, as this is expected to be a key model parameter.

Finally, it seems somewhat implausible that no parameter would influence the ICER of edoxaban vs rivaroxaban.

5.4.10.2 Probabilistic sensitivity analysis (PSA)

Parameter uncertainty was explored using PSA. Individual parameters within the model were assigned a distribution and the model was run for 2,000 simulations to generate total costs and QALYs. The inputs reportedly varied in the PSA and the assigned distributions are outlined in Table 94 the Appendix.

Probabilities, such as VTE-related death rate and event rates, were sampled from a beta distribution (bounded by 0 and 1). ORs were assumed to be distributed according to a lognormal distribution

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except for the ones estimated from the NMA (risk of recurrence, of MB and CRNMB were modelled with a non-parametric distribution for the ORs). In the initial submission by the company, costs and utilities were sampled from a normal distribution. During clarification these were revised to a gamma distribution (bounded from 0 to infinity) for costs and relative utility decrements (applied multiplicatively) and a beta distribution for utility decrements applied additively. For costs the standard deviation was assumed to equal 10% of the mean value, whereas for utilities the standard deviation was taken from the base case source.

To summarise the probability of cost-effectiveness at a willingness-to-pay (WTP) threshold of £20,000 the company presented the following for each comparison with edoxaban:

- the cost-effectiveness plane;
- percentages of simulations falling into each quadrant (presented in Table 95, Table 96 and Table 97 the Appendix);
- the cost-effectiveness acceptability curve (CEAC).

A summary of the PSA results provided by the company at clarification are presented in the sections that follow.

Edoxaban vs warfarin

Figure 22: Incremental cost-effectiveness plane edoxaban vs warfarin (reproduced from CS submitted at clarification, Figure B4, page 16)

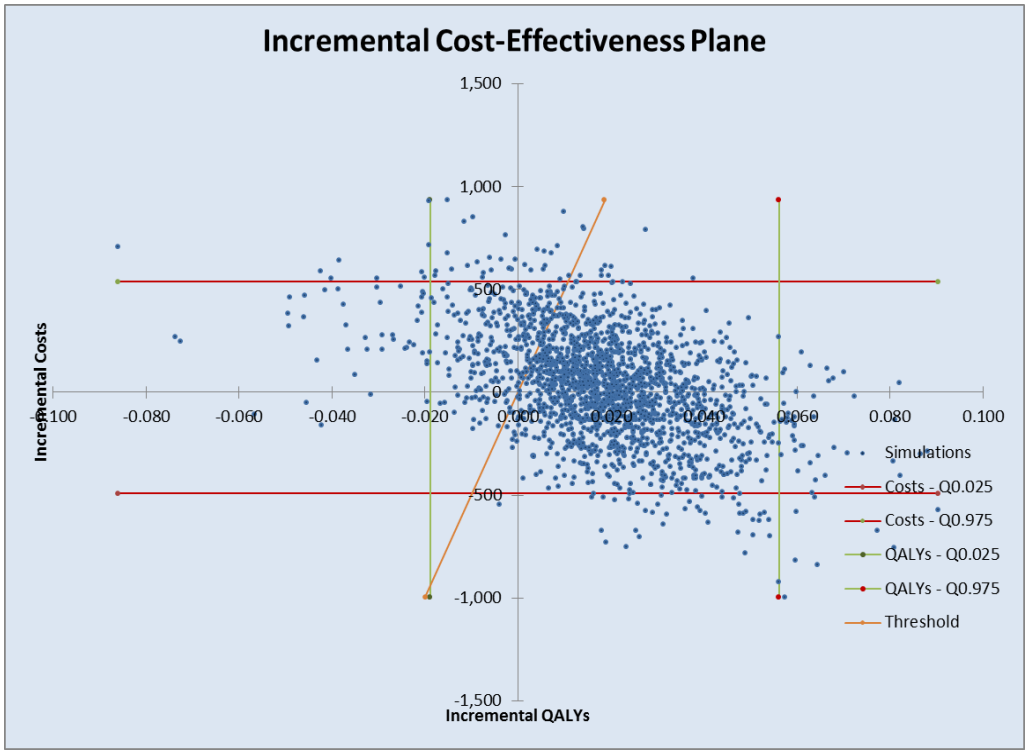
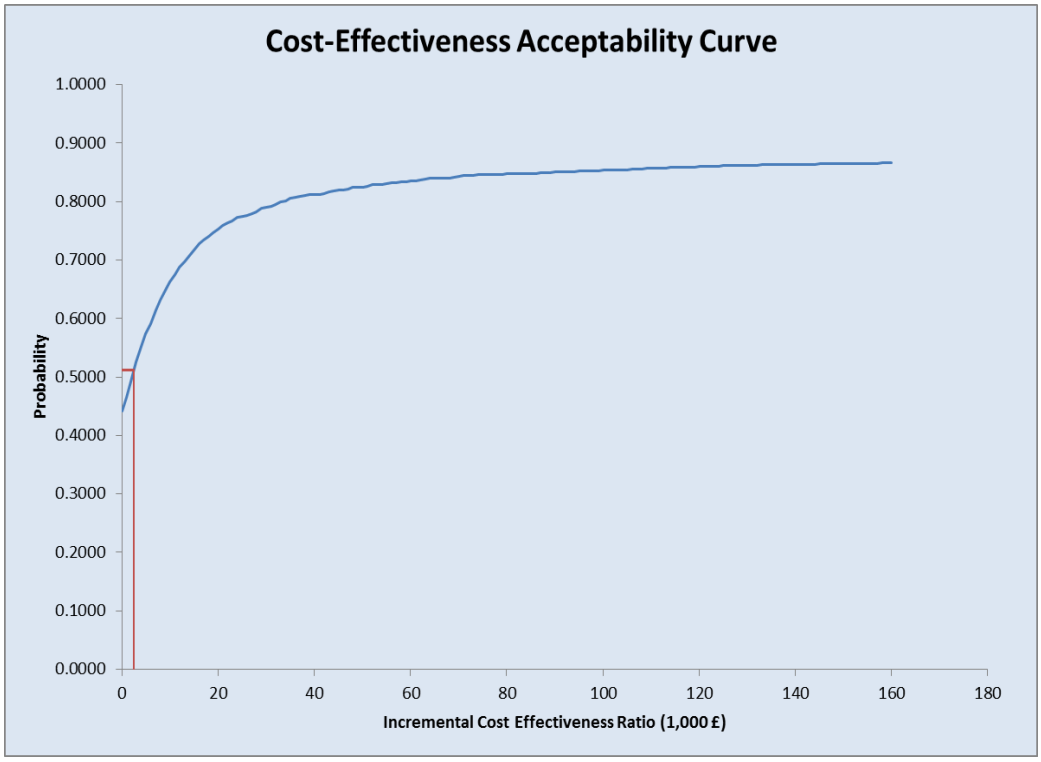


Figure 23: CEACs edoxaban vs warfarin (reproduced from CS submitted at clarification, Figure B5, page 17)



Edoxaban vs rivaroxaban

Figure 24: Incremental cost-effectiveness plane edoxaban vs rivaroxaban (reproduced from CS submitted at clarification, Figure B4, page 17)

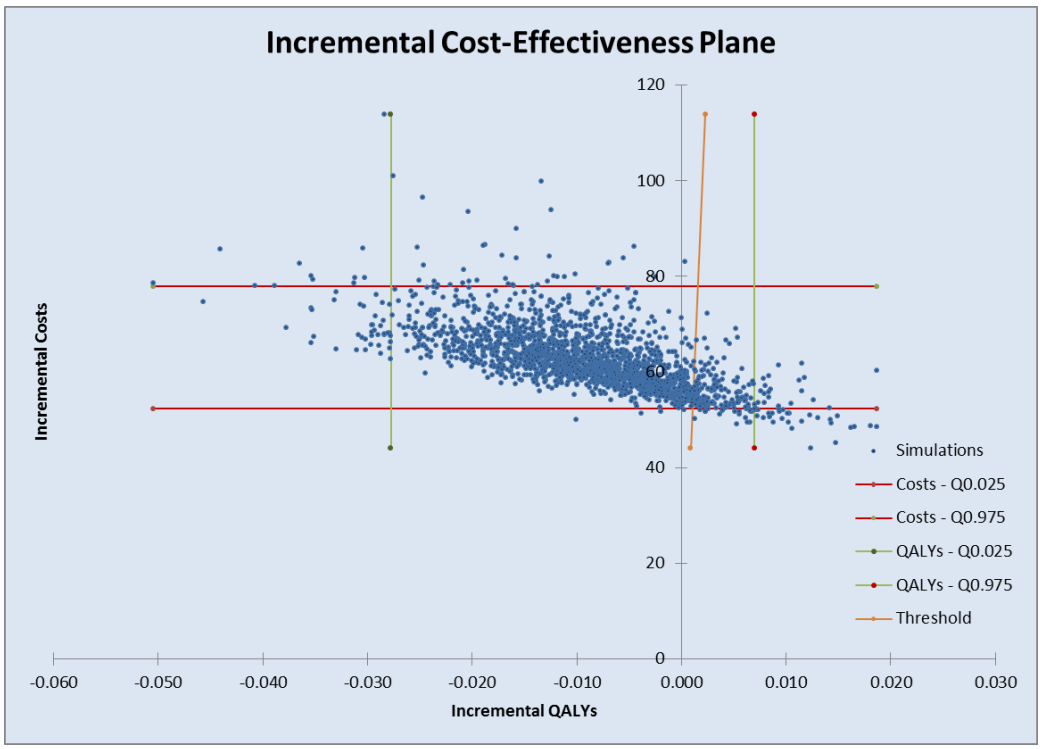
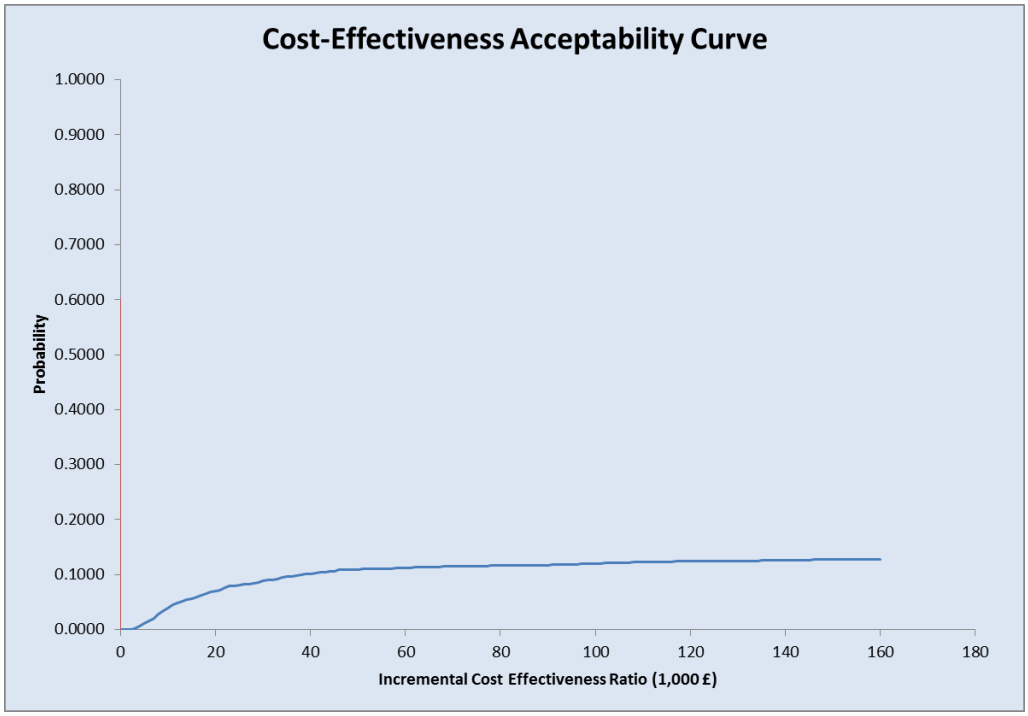


Figure 25: CEAC edoxaban vs rivaroxaban (reproduced from CS submitted at clarification, Figure B7, page 18)



Edoxaban vs dabigatran

Figure 26: Incremental cost-effectiveness plane edoxaban vs rivaroxaban (reproduced from CS submitted at clarification, Figure B8, page 19)

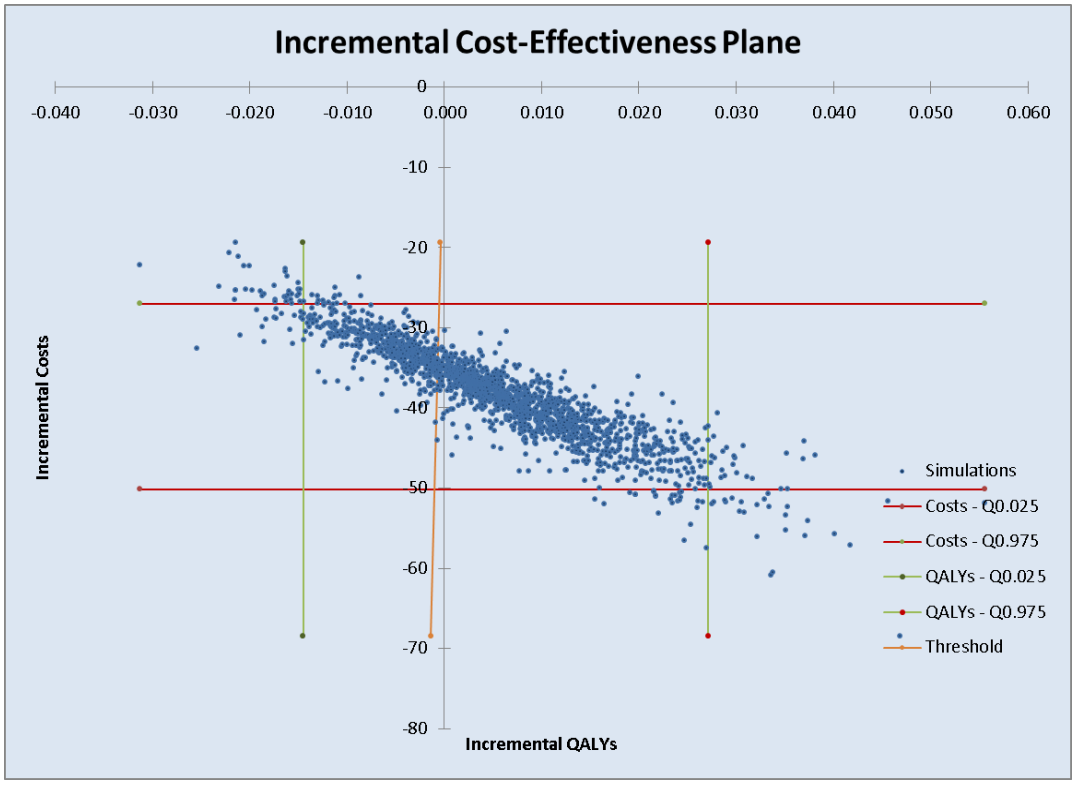
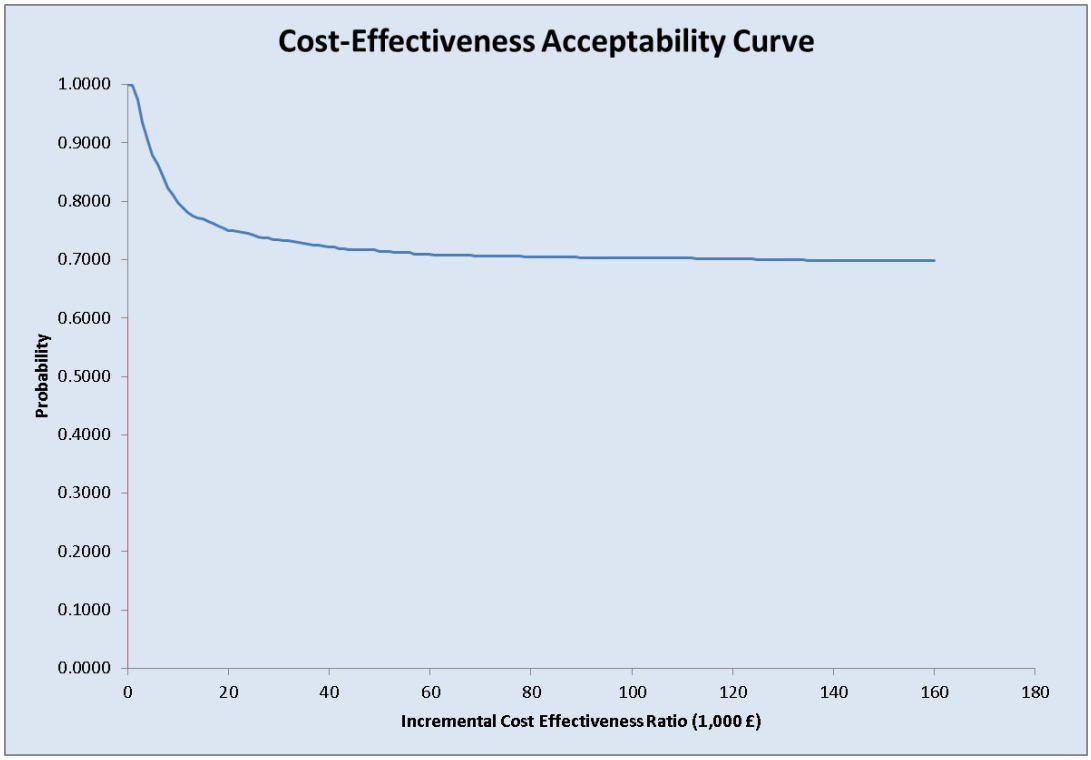


Figure 27: CEAC edoxaban vs dabigatran (reproduced from CS submitted at clarification, Figure B9, page 20)



ERG comment on PSA

The ERG notes that a non-parametric distribution was assigned to the ORs for the NOACs' treatment effectiveness (i.e. VTE recurrence and bleeding events) hence these parameters were not varied in the PSA. The ERG is unclear why the CODA output from WinBUGS for the NMA was not used as the basis for including the ORs estimates in the PSA. The CODA provides a list of all values generated from the full posterior distribution in a format suitable for export to Excel that can be used in PSA (Dias *et al.*[54]).

Also, as highlighted previously for the deterministic analysis, the company only considered the overall costs associated with a health state rather than the unit costs and resource use.

For completeness the ERG has generated these probabilities from the model in Table 84 for both the VTE population (base case) and the PE subgroup analysis.

Table 84: Probability of edoxaban being considered cost-effective at a WTP threshold of £20,000 and £30,000

Comparator	Probability of edoxaban being cost-effective at a WTP threshold of:	
	£20,000 per additional QALY	£30,000 per additional QALY
VTE population (base case)		
warfarin	73.65%	78.25%
rivaroxaban	7.40%	9.40%

dabigatran	74.80%	73.15%
PE subgroup		
warfarin	62.45%	64.85%
rivaroxaban	7.55%	9.30%
dabigatran	76.90%	75.25%
Abbreviations used in the table: PE, pulmonary embolism; QALY, quality-adjusted life year; VTE, venous thromboembolism; WTP, willingness-to-pay		

Analysis of Figure 22 and Figure 23 indicate that at a £20,000 WTP, edoxaban has approximately 70% probability of being cost-effective when compared to warfarin. Even with a £160,000 WTP, the probability of edoxaban being cost-effective compared to warfarin is never above 85%. Edoxaban is likely to generate more QALYs and be more expensive than warfarin (however by only a small increment).

Analysis of Figure 24 and Figure 25 indicate that at a £20,000 WTP, edoxaban compared with rivaroxaban has less than 10% probability of being cost-effective. Even with a £160,000 WTP, the probability of edoxaban being cost-effective compared to warfarin is never above 20%. Edoxaban is most likely to generate less QALYs and be more expensive than dabigatran.

Analysis of Figure 26 and Figure 27 indicate that at a £20,000 WTP, edoxaban has approximately 75% probability of being cost-effective when compared to dabigatran. As the WTP increases, the probability of edoxaban being cost-effective compared to dabigatran also decreases. This is because edoxaban is always cheaper than dabigatran (Figure 26) hence a higher WTP threshold offsets the higher cost of dabigatran.

The ERG is concerned with the validity of the PSA results. The company's decision not include key clinical parameter estimates calculated in the NMA considerably removes the usefulness of the PSA.

5.4.11 Model validation and face validity check

In their submission, the company reports that validation was assessed using two primary criteria, internal (verification) and external consistency (validation). Internal verification aimed to assess whether the model was implemented correctly, and examined the extent to which the mathematical calculations were performed correctly. Face validation aimed to evaluate if the model was constructed and used in accordance with clinical practice.

The company reports that internal validity was assessed by using the techniques of extreme value analysis, where minimum and maximum values for appropriate parameter values were substituted, using parallel inputs for all interventions for efficacy, costs and utilities, and running logical

consistency tests. Secondly, equations (i.e. those for converting rates to probabilities) were reported to have been validated against their source and coding accuracy checked.

The company stated that external consistency was assessed by checking the face validity of the model, and comparing the results of the analysis against published results (cross validation). It was also reported that it was checked whether the model included all aspects of the patient pathway considered important, and whether they are related in ways consistent with medical science. The company mentioned that it assessed whether the best available data sources were used, and whether the setting, population, interventions, outcomes, assumptions, and time horizons corresponded to those of decision problem.

Finally, the model was reported to have been delivered to an independent academic modeller who reviewed all assumptions and calculations of the model, and provided comments to enhance the transparency and robustness of the model.

Despite the validation procedures reported by the company, the ERG found several inconstancies in the model inputs (miss-reporting of the sources used and inconstancy in the selection of data sources used to model different estimates), a few problems with model formulae in the base case model and several issues in the calculations undertaken in the PE subgroup model. is the ERG notes that costs hadn’t been updated to reflect the current financial year in the original model, which should have been identified through a basic validation process.

The ERG also has several concerns with the clinical validity of some of the assumptions made in the model, mainly related with the cessation of anticoagulation therapy.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG carried out a series of model corrections (Section 6.1), and scenario analyses (Section 6.2) on the company's model. In addition, the ERG presents the most plausible base case ICER estimate, for each of the relevant comparisons in this STA (Section 6.2).

6.1 Model corrections

After identifying some technical errors, the ERG has decided to make the following adjustments to the company's base case model:

- The stroke utility value reported within Locadia *et al*.[82] (0.33) was adjusted to reflect the age of the modelled patients.

- The ERG corrected the utility decrement associated with HIT which was adjusted twice to reflect the cycle length in the base case model. Therefore the ERG has corrected this so the utility value is adjusted only once.

After these corrections were applied in the model, the base case ICERs remained the same for edoxaban vs warfarin, dabigatran and rivaroxaban respectively.

6.2 ERG scenario analyses

In this section of the report the ERG presents the additional scenario analysis undertaken and reports the impact on the final base-case ICERs.

The scenario analyses undertaken by the ERG were explained throughout Section 5 of the report. These are the following:

1. The ERG changed the OR comparing the probability of recurrence for edoxaban with the probability of recurrence for warfarin used in the economic analysis to one to reflect not only the lack of statistical significance in the difference of recurring VTE events in the NMA and the Hokusai-VTE trial but also to reflect clinical expert opinion.
2. The ERG used the company's phase-specific data to model the baseline probability of bleeding events with warfarin, instead of the time-to-event data used by the company in the base case analysis.
3. The ERG changed the OR comparing the probability of MB for edoxaban with the probability of MB for warfarin used in the economic analysis to 1 to reflect not only the lack of statistical significance in the difference of MB events in the NMA and the Hokusai-VTE trial but also to reflect clinical expert opinion.

4. The ERG conducted a scenario analysis using the phase-specific data for recurrent VTE-related mortality obtained in the Hokusai-VTE trial.
5. The ERG conducted a scenario analysis using the recurrent VTE-related mortality estimate used in TA 327, where the probability of dying of recurrence for dabigatran is 3%.[104]
6. The ERG increased the duration of the decrement in a patient's QoL after recurring VTE and MB in the model.
7. The ERG increased the duration of the decrement in a patient's QoL after recurring VTE and aMB in the model using the values reported in Cohen *et al*. to model recurrent VTE.[78]
8. The ERG considered a scenario where the disutility associated with CRNMBs was removed from the economic analysis.
9. The number of INR monitoring visits for warfarin patients was reduced from 24 visits in the first year to 18 visits, to reflect three visits per quarter after the first 9 visits over the initial three months, instead of five visits per quarter.
10. A revised 5mg/day warfarin cost using PCA 2014[97] for all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg) was used in the model.
11. The treatment duration of heparin was changed to reflect the Hokusai-VTE trial (i.e. 7.5 days for edoxaban and 8.5 days for warfarin)
12. The treatment duration of heparin was changed to reflect clinical experts' advice (i.e. 6.5 days for warfarin and 5 days for edoxaban)
13. The ERG assumed that 30% of recurrent DVT cases and 50% of recurrent PE cases require hospitalisation.
14. Index and recurrent VTE diagnostic costs were applied to 100% of patients and according to the type of VTE event: DVT, £143.23; PE, £307.23.
15. The ERG conducted a scenario analysis in which the NICE CG92[17] estimate for the LT-CTEPH cost was applied in the model (£1,280 at 2014 price-year), combined with anticoagulation treatment costs.
16. The ERG removed the utility decrement associated with warfarin from the economic analysis.
17. The ERG removed the stroke health state from the model.
18. The ERG conducted scenario analysis to reflect different options for NOAC monitoring. As clinical opinion advised that this likely varies across clinical practice, the ERG undertook three scenarios, in accordance to the clinical advice received:
    a) Most conservative scenario: patients on NOACs have an annual appointment with their GP where they receive no tests
    b) Average scenario: patients on NOACs receive an annual visit where they receive U&E
    c) Less conservative scenario: patients receive biannual visits where they receive U&E

19. The number of INR monitoring visits for warfarin patients was reduced from 24 visits in the subsequent years of treatment (for the company's scenario analysis of lifelong treatment) to 10 visits per year.

Table 85 presents the results of the different scenario analyses conducted by the ERG. As it can be observed, the number of INR monitoring visits required by patients on warfarin is one of the key drivers of the ICER comparing edoxaban with warfarin. The six main drivers of the economic analysis identified by the ERG are as follows:

- Number of INR monitoring visits assumed for warfarin. Note that assuming two less visits per quarter in the final three quarters of the year lead to an increase in the final ICER from £2,451 to £18,953 per QALY gained.
- The level of monitoring assumed for patients on NOACs. Even though the company assumed that no monitoring is required for patients on NOACs above the standard of care for VTE patients, clinical expert opinion advised the ERG that some monitoring takes place to assess a patient's kidney function. Depending on the level of monitoring assumed, the ICER comparing edoxaban to warfarin ranges from £4,780 to £7,315.
- The utility loss associated with warfarin treatment. When the ERG assumed that warfarin treatment does not have an impact in patients QoL the ICER for edoxaban compared with warfarin increased to £6,902 per QALY gained.
- The duration of the parental heparin treatment given before or simultaneously with edoxaban and warfarin respectively.
- The effectiveness of edoxaban compared with warfarin with regards to the probability of recurrence. In the model this is translated in the OR for recurrent VTE used in the analysis.
- The data used to model VTE-related mortality in the model.

The ERG notes that in all the scenario analyses, rivaroxaban dominates edoxaban. With regards to dabigatran, the two key model inputs impacting the final ICER for edoxaban vs dabigatran are the OR used to model the probability of recurrence for dabigatran compared with warfarin and the data used to estimate the VTE-related mortality in the model. When the data from TA327 are used for VTE-related mortality in the model, the ICER for edoxaban vs dabigatran goes from dominant to £28,116. The reason why the ICERs presented in Table 59 for dabigatran and rivaroxaban are not sensitive to the changes in the INR monotoring for warfarin is that these ICERs compare the two drugs against edoxaban.

Finally, when the warfarin INR monitoring changes for the lifelong treatment duration, the final ICER comparing edoxaban with warfarin goes from £7,608 (in the lifelong scenario) to £42,781, showing

again how the model results are extremely sensitive to varying the INR monitoring assumption for warfarin.

Table 85. Results of the ERG's scenario analysis

	Results per patient	Edoxaban+ heparin (1)	Warfarin+ heparin (2)	Dabigatran+ heparin (3)	Rivaroxaban (4)	Incremental value		
						(1-2)	(1-3)	(1-4)
0	**Base case**							
	Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER					£2,451	Dominant	Dominated
1	**OR comparing the probability of recurrence for edoxaban with the probability of recurrence for warfarin used = 1**							
	Total costs (£)	£4,081	£4,033	£4,114	£4,019	£48	-£34	£62
	QALYs	12.41	12.40	12.41	12.42	0.01	0.00	-0.01
	ICER (compared with base case)					£3,667	£9,678	Dominated
2	**Hokusai-VTE phase-specific data used to model the baseline probability of bleeding events with warfarin**							
	Total costs (£)	£4,063	£4,016	£4,105	£3,999	£48	-£42	£65
	QALYs	12.41	12.40	12.41	12.42	0.02	0.01	-0.01
	ICER (compared with base case)					£2,587	Dominant	Dominated
3	**OR comparing the probability of MB for edoxaban with the probability of MB for warfarin used =1**							
	Total costs (£)	£4,079	£4,033	£4,119	£4,020	£46	-£40	£58
	QALYs	12.42	12.40	12.41	12.42	0.02	0.01	0.00
	ICER (compared with base case)					£2,650	Dominant	Dominated
4	**Hokusai-VTE phase-specific data used to model recurrent VTE-related mortality**							
	Total costs (£)	£3,733	£3,696	£3,768	£3,674	£36	-£35	£58
	QALYs	11.56	11.55	11.57	11.57	0.01	0.00	-0.01
	ICER (compared with base case)					£2,975	£15,111	Dominated
5	**TA327[104] data used to model recurrent VTE-related mortality**							
	Total costs (£)	£4,033	£3,991	£4,072	£3,971	£43	-£39	£62
	QALYs	12.64	12.62	12.64	12.64	0.01	0.00	-0.01
	ICER (compared with base case)					£3,019	£28,116	Dominated

6	**Increase in the duration of the decrement on apatient's QoL for recurring VTE and MBs in the model using Sullivan *et al.*[79]**							
	Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
	QALYs	12.44	12.42	12.43	12.45	0.02	0.01	-0.01
	ICER (compared with base case)					£2,464	Dominant	Dominated
7	**Same utility for index VTE and recurrent VTE, increase in the duration of the decrement on a patient's QoL using Cohen *et al.*[78]**							
	Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
	QALYs	12.44	12.42	12.44	12.45	0.02	0.01	-0.01
	ICER (compared with base case)					£2,464	Dominant	Dominated
8	**Disutility associated with CRNMBs removed from the economic analysis**							
	Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£2,467	Dominant	Dominated
9	**Nine INR monitoring visits in the first 3 months (1.5 visits per cycle for the first 6 cycles); then 3 visits per quarter after the initial 3 months (0.5 visits per cycle for the remaining 20 cycles) using the cost of a non-consultant-led anticoagulation clinic attendance**							
	Total costs (£)	£4,078	£3,727	£4,116	£4,016	£351	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£18,953	Dominant	Dominated
10	**Revised 5mg/day warfarin cost using PCA 2014[97] for all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg)**							
	Total costs (£)	£4,078	£4,040	£4,116	£4,016	£38	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£2,060	Dominant	Dominated
11	**The treatment duration of heparin to reflect the Hokusai-VTE trial (i.e. 7.5 days for edoxaban and 8.5 days for warfarin)**							
	Total costs (£)	£4,113	£4,033	£4,116	£4,016	£80	-£4	£97
	QALYs	12.42	12.40	12.41	12.42	0.02	0.01	-0.01
	ICER (compared with base case)					£4,324	Dominant	Dominated
12	**Number of days of heparin co-administration with warfarin reduced to from 8.5 to 6.5 days**							

	Total costs (£)	£4,078	£3,998	£4,116	£4,016	£80	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£4,303	Dominant	Dominated
13	**Index and recurrent VTE: 30% of DVT cases and 50% of PE cases require hospitalisation**							
	Total costs (£)	£3,181	£3,135	£3,217	£3,119	£47	-£36	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£2,517	Dominant	Dominated
14	**Index and recurrent VTE diagnostic costs are applied to 100% of patients and according to the type of VTE event: DVT, £143.23; PE, £307.23**							
	Total costs (£)	£4,061	£4,015	£4,099	£3,998	£45	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£2,453	Dominant	Dominated
15	**NICE CG92[17] estimate for LT-CTEPH (£1,280 per month, 2014 prices)**							
	Total costs (£)	£4,530	£4,484	£4,569	£4,467	£46	-£39	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£2,486	Dominant	Dominated
16	**Utility decrement associated with warfarin treatment removed**							
	Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
	QALYs	12.42	12.41	12.41	12.43	0.01	0.01	-0.01
	ICER (compared with base case)					£6,902	Dominant	Dominated
17	**Stroke health state removed**							
	Total costs (£)	£3,284	£3,240	£3,321	£3,222	£44	-£37	£62
	QALYs	12.42	12.41	12.42	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£2,361	Dominant	Dominated
18a	**NOAC patients receive annual visit with no tests (most conservative approach)**							
	Total costs (£)	£4,121	£4,033	£4,159	£4,059	£88	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£4,780	Dominant	Dominated

18b	**NOAC patients receive an annual visit where they receive U&E**							
	Total costs (£)	£4,123	£4,033	£4,161	£4,061	£90	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£4,883	Dominant	Dominated
18c	**NOAC patients receive biannual visit where they receive U&E (less conservative approach)**							
	Total costs (£)	£4,168	£4,033	£4,206	£4,106	£135	-£38	£62
	QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
	ICER (compared with base case)					£7,315	Dominant	Dominated
19	**The number of INR monitoring visits for warfarin patients was reduced from 24 visits after 12 months to 10 visits per year (lifelong treatment scenario)**							
	Total costs (£)	£22,720	£14,740	£23,513	£22,698	£7,980	-£793	£23
	QALYs	12.54	12.36	12.55	12.62	0.19	0.00	-0.07
	ICER (compared with base case)					£42,781	£312,874	Dominated

Abbreviations used in the table: CG, clinical guideline; CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; ICER, incremental cost-effectiveness ratio; INR, international normalised ratio; NOAC, novel oral anticoagulant; OR, odds ratio; PE, pulmonary embolism; PTS, post thrombotic syndrome; QALYs, quality-adjusted life years; QoL, quality of life; U&E, urea and electrolytes; VTE, venous thromboembolism,

Superseded see erratum

The ERG also undertook the economic analysis for the DVT subgroup with the data provided by the company after clarification. The ERG used the ORs obtained through the analysis reported in Section x to estimate the relative effectiveness of edoxaban, dabigatran and rivaroxaban compared to warfarin in DVT only patients. The ERG took the baseline probability of recurrent VTE and bleeding for DVT patients on warfarin in the Hokusai-VTE trial. The probability of other events, for example HIT or stroke, wasn't changed in the model as this is the same across the different treatment arms. Results of the ERG analysis are presented in Table 86.

The results obtained in the DVT subgroup analysis are similar to the base case results. The ERG notes that as there are no data on the proportion of recurrent DVT and PE event separately, the baseline proportion of DVT and PE events was used in the DVT subgroup analysis to estimate the number of PE recurrent events, which was necessary to estimate the number of CTEPH cases in the model.

Table 86. ERG DVT subgroup analysis results

Results per patient	**Edoxaban + heparin (1)**	**Warfarin + heparin (2)**	**Dabigatran + heparin (3)**	**Rivaroxaban (4)**	**Incremental value**		
					(1-2)	**(1-3)**	**(1-4)**
Total costs (£)	£3,732	£3,685	£3,774	£3,669	£47	-£41	£63
QALYs	12.50	12.48	12.49	12.50	0.02	0.01	-0.01
ICER					£2,927	Dominant	Dominated
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year							

6.3 ERG base case ICER

In this section of the report the ERG presents their alternative base case ICER. In Table 87 the ERG presents an alternative base case ICER which reflects the Hokusai-VTE trial. Therefore the ICERs presented are for edoxaban compared with warfarin and dabigatran and rivaroxaban are not included in the analysis. Due to it being derived from a direct comparison in a randomised controlled trial (Hokusai-VTE), and given the uncertainty in the NMA results (discussed in Section 4.4), the ERG believes this ICER represents the most robust comparison of edoxaban with warfarin based on the available evidence. The key assumptions underlying the final ICER are:

- The ERG used the Hokusai-VTE OR comparing the probability of recurrence for edoxaban with the probability of recurrence for warfarin;

- The ERG used the company's phase-specific data to model the baseline probability of bleeding events with warfarin, instead of the time-to-event data used by the company in the base case analysis;
- The ERG used the Hokusai-VTE OR comparing the probability of bleeding for edoxaban with the probability of recurrence for warfarin;
- The ERG used the phase-specific data for recurrent VTE-related mortality obtained in the Hokusai-VTE trial;
- The ERG increased the duration of the decrement in a patient's QoL after recurring VTE and MB in the model;
- The ERG removed the disutility associated with CRNMBs.
- The number of INR monitoring visits for warfarin patients was reduced from 24 visits in the first year to 18 visits, to reflect three visits per quarter after the first nine visits over the initial three months, instead of five visits per quarter;
- A revised 5mg/day warfarin cost using PCA 2014[97] for all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg) was used in the model;
- The treatment duration of heparin was changed to reflect the Hokusai-VTE trial (i.e. 7.5 days for edoxaban and 8.5 days for warfarin);
- The ERG assumed that 30% of recurrent DVT cases and 50% of recurrent PE cases require hospitalisation;
- Index and recurrent VTE diagnostic costs were applied to 100% of patients and according to the type of VTE event: DVT, £143.23; PE, £307.23;
- The ERG used the NICE CG92[17] estimate for the LT-CTEPH cost in the model (£1,280 at 2014 price-year), combined with anticoagulation treatment costs;
- The ERG removed the stroke health state from the model;
- The ERG assumed that patients on NOACs have an annual appointment where they receive a U&E test.

The ERG believes that assuming one annual visit with a U&E test undertaken for NOAC patients reflects the average monitoring schedule expected for VTE patients. However additional analyses are presented to reflect potential alternative NOAC monitoring schedules.

Table 87. ERG base case ICER reflecting Hokusai-VTE trial

Results per patient	Edoxaban+ heparin	Warfarin+ heparin	Incremental value
Company's base case (with ORs from Hokusai-VTE)			
Total costs (£)	£4,076	£4,033	£43
QALYs	12.42	12.40	0.022
ICER			£1,958
Hokusai-VTE phase-specific data used to model the baseline probability of bleeding events with warfarin			
Total costs (£)	£4,062	£4,016	£46
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£2,063
ICER with all changes incorporated			£2,063
Hokusai-VTE phase-specific data used to model recurrent VTE-related mortality			
Total costs (£)	£3,731	£3,697	£34
QALYs	11.57	11.55	0.014
ICER (compared with base case)			£2,433
ICER with all changes incorporated			£2,551
Increase in the duration of the decrement on a patient's QoL for recurring VTE and MBs in the model using Sullivan *et al.* [79]			
Total costs (£)	£4,076	£4,033	£43
QALYs	12.44	12.42	0.022
ICER (compared with base case)			£1,972
ICER with all changes incorporated			£2,574
Disutility associated with CRNMBs removed from the economic analysis			
Total costs (£)	£4,076	£4,033	£43
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£1,968
ICER with all changes incorporated			£2,593
Nine INR monitoring visits in the first 3 months (1.5 visits per cycle for the first 6 cycles); then 3 visits per quarter after the initial 3 months (0.5 visits per cycle for the remaining 20 cycles) using the cost of a non-consultant-led anticoagulation clinic attendance			

Total costs (£)	£4,076	£3,727	£349
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£15,739
ICER with all changes incorporated			£21,505
Revised 5mg/day warfarin cost using PCA 2014[97] for all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg)			
Total costs (£)	£4,076	£4,040	£36
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£1,632
ICER with all changes incorporated			£21,057
The treatment duration of heparin to reflect the Hokusai-VTE trial (i.e. 7.5 days for edoxaban and 8.5 days for warfarin)			
Total costs (£)	£4,111	£4,033	£78
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£3,522
ICER with all changes incorporated			£23,324
Index and recurrent VTE: 30% of DVT cases and 50% of PE cases require hospitalisation			
Total costs (£)	£3,180	£3,135	£45
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£2,031
ICER with all changes incorporated			£23,352
Index and recurrent VTE diagnostic costs are applied to 100% of patients and according to the type of VTE event: DVT, £143.23; PE, £307.23			
Total costs (£)	£4,059	£4,015	£43
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£1,960
ICER with all changes incorporated			£23,352
NICE CG92[17] estimate for LT-CTEPH (£1,280 per month, 2014 prices)			
Total costs (£)	£4,528	£4,484	£44
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£1,997
ICER with all changes incorporated			£23,389
Stroke health state removed			

Total costs (£)	£3,282	£3,240	£42
QALYs	12.43	12.41	0.02
ICER (compared with base case)			£1,869
ICER with all changes incorporated			£23,251
NOAC patients receive an annual visit where they receive U&E			
Total costs (£)	£4,141	£4,033	£88
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£3,990
ERG's alternative base case ICER			
ICER with all changes incorporated			**£26,028**
Variations from the base case based on alternative assumption for NOAC monitoring			
NOAC patients receive annual visit with no tests (most conservative approach)			
Total costs (£)	£4,119	£4,033	£87
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£3,990
ICER with all changes incorporated			**£25,910**
NOAC patients receive biannual visit where they receive U&E (less conservative approach)			
Total costs (£)	£4,166	£4,033	£133
QALYs	12.42	12.40	0.022
ICER (compared with base case)			£6,022
ICER with all changes incorporated			**£28,805**

Abbreviation used in the table: CG, clinical guideline; CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; ICER, incremental cost-effectiveness ratio; INR, international normalised ratio; NOAC, novel oral anticoagulant; OR, odds ratio; PE, pulmonary embolism; PTS, post thrombotic syndrome; QALYs, quality-adjusted life years; QoL, quality of life; U&E, urea and electrolytes; VTE, venous thromboembolism

Table 87 shows the ERG's alternative base case ICER which incorporates all the Hokusai-VTE trial estimates available in the model. The final ERG alternative base case ICER is £26,028.

Table 87 also presents the different ICERs for when the NOAC moitoring regimen is varied in the model. If patients visit their GP once a year without receiving any tests, then the ICER is £25,910. If the NOAC monitoring schedule consists of biannual visits with U&E tests, the ICER increases to £28,805. Finally, if it is assumed that patients on NOACs do not need any extra monitoring beyond what would be expected for VTE patients, then the ICER is £23,251.

The ERG notes that the alternative base case ICER presented in Table 87 reflects a lead-in heparin regimen of 7.5 days for edoxaban. Changing this assumption in the model to reflect 5-days lead-in of heparin for edoxaban decreases the final ICER to £23,766. The ERG also notes that the alternative base case ICER presented incorporates the underlying PH assumption made in the Hokusai-VTE data analysis. However the ERG does not have access to the individual patient-level data necessary to model the trial without use of ORs.

In Table 88 we present the ICERs for edoxaban compared with warfarin, dabigatran and rivaroxaban respectively. These ICERs reflect the NMA but also incorporate clinical opinion provided to the ERG with respect to some assumptions in the model. The key assumptions underlying the alternative ICERs are:

- The ERG changed the OR comparing the probability of recurrence for edoxaban with the probability of recurrence for warfarin used in the economic analysis to one to reflect not only the lack of statistical significance in the difference of recurring VTE events in the NMA and the Hokusai-VTE trial but also to reflect clinical expert opinion;
- The ERG used the company's phase-specific data to model the baseline probability of bleeding events with warfarin, instead of the time-to-event data used by the company in the base case analysis;
- The ERG changed the OR comparing the probability of MB for edoxaban with the probability of MB for warfarin used in the economic analysis to one to reflect not only the lack of statistical significance in the difference of MB events in the NMA and the Hokusai-VTE trial but also to reflect clinical expert opinion; the ERG used the recurrent VTE-related mortality estimate from TA 327[104], where the probability of dying of recurrence for dabigatran was reported as 3%;
- The ERG increased the duration of the decrement on a patient's QoL after recurring VTE and MB in the model;
- The ERG removed the disutility associated with CRNMBs;

- The number of INR monitoring visits for warfarin patients was reduced from 24 visits in the first year to 18 visits, to reflect three visits per quarter after the first nine visits over the initial three months, instead of five visits per quarter;
- A revised 5mg/day warfarin cost using PCA 2014[97] for all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg) was used in the model;
- The treatment duration of heparin was changed to reflect clinical experts' advice (i.e. 6.5 days for warfarin and 5 days for edoxaban);
- The ERG assumed that 30% of recurrent DVT cases and 50% of recurrent PE cases require hospitalisation;
- Index and recurrent VTE diagnostic costs were applied to 100% of patients and according to the type of VTE event: DVT, £143.23; PE, £307.23;
- The ERG used the NICE CG92[17] estimate for the cost of LT-CTEPH (£1,280 at 2014 price-year), combined with anticoagulation treatment costs;
- The ERG removed the stroke health state from the model;
- The ERG assumed that patients on NOACs have an annual appointment where they receive a U&E test.

Finally in Table 89 the ERG presents the alternative base case ICER (reported in Table 87) for different treatment durations, three months, six months and lifetime treatment. The NOAC monitoring regimen assumed was one annual visit with U&E test done.

Table 88. ICERs reflecting NMA and clinical opinion

Results per patient	Edoxaban+ heparin (1)	Warfarin+ heparin (2)	Dabigatran+ heparin (3)	Rivaroxaban (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
Base case							
Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER					£2,451	Dominant	Dominated
OR comparing the probability of recurrence for edoxaban with the probability of recurrence for warfarin used = 1							
Total costs (£)	£4,081	£4,033	£4,114	£4,019	£48	-£34	£62
QALYs	12.41	12.40	12.41	12.42	0.01	0.00	-0.01
ICER (compared with base case)					£3,667	£9,678	Dominated
ICER with all changes incorporated					£3,667	£9,678	Dominated
Hokusai-VTE phase-specific data used to model the baseline probability of bleeding events with warfarin							
Total costs (£)	£4,063	£4,016	£4,105	£3,999	£48	-£42	£65
QALYs	12.41	12.40	12.41	12.42	0.02	0.01	-0.01
ICER (compared with base case)					£2,587	Dominant	Dominated
ICER with all changes incorporated					£3,849	£9,747	Dominated
OR comparing the probability of MB for edoxaban with the probability of MB for warfarin used =1							
Total costs (£)	£4,079	£4,033	£4,119	£4,020	£46	-£40	£58
QALYs	12.42	12.40	12.41	12.42	0.02	0.01	0.00
ICER (compared with base case)					£2,650	Dominant	Dominated
ICER with all changes incorporated					£4,293	£452,800	Dominated
TA327[104] data used to model recurrent VTE-related mortality							

Total costs (£)	£4,033	£3,991	£4,072	£3,971	£43	-£39	£62
QALYs	12.64	12.62	12.64	12.64	0.01	0.00	-0.01
ICER (compared with base case)					£3,019	£28,116	Dominated
ICER with all changes incorporated					£4,206	£998,339	Dominated
Increase in the duration of the decrement in patients' QoL for recurring VTE and MBs in the model using Sullivan *et al.*[79]							
Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
QALYs	12.45	12.42	12.43	12.45	0.02	0.01	-0.01
ICER (compared with base case)					£2,464	Dominant	Dominated
ICER with all changes incorporated					£4,199	£655,795	Dominated
Disutility associated with CRNMBs removed from the economic analysis							
Total costs (£)	£4,078	£4,033	£4,116	£4,016	£45	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER (compared with base case)					£2,467	Dominant	Dominated
ICER with all changes incorporated					£4,243	Dominant	Dominated
Nine INR monitoring visits in the first 3 months (1.5 visits per cycle for the first 6 cycles); then 3 visits per quarter after the initial 3 months (0.5 visits per cycle for the remaining 20 cycles) using the cost of a non-consultant-led anticoagulation clinic attendance							
Total costs (£)	£4,078	£3,727	£4,116	£4,016	£351	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER (compared with base case)					£18,953	Dominant	Dominated
ICER with all changes incorporated					£30,022	Dominant	Dominated
Revised 5mg/day warfarin cost using PCA 2014[97] for all formulations of warfarin (0.5mg, 1mg, 3mg, 5mg)							

Total costs (£)	£4,078	£4,040	£4,116	£4,016	£38	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER (compared with base case)					£2,060	Dominant	Dominated
ICER with all changes incorporated					£29,413	Dominant	Dominated
Number of days of heparin co-administration with warfarin reduced to from 8.5 to 6.5 days							
Total costs (£)	£4,708	£3,998	£4,116	£4,016	£80	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER (compared with base case)					£4,303	Dominant	Dominated
ICER with all changes incorporated					£32,356	Dominant	Dominated
Index and recurrent VTE: 30% of DVT cases and 50% of PE cases require hospitalisation							
Total costs (£)	£3,181	£3,135	£3,217	£3,119	£47	-£36	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER (compared with base case)					£2,517	Dominant	Dominated
ICER with all changes incorporated					£32,246	Dominant	Dominated
Index and recurrent VTE diagnostic costs are applied to 100% of patients and according to the type of VTE event: DVT, £143.23; PE, £307.23							
Total costs (£)	£4,061	£4,015	£4,099	£3,998	£45	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER (compared with base case)					£2,453	Dominant	Dominated
ICER with all changes incorporated					£32,243	Dominant	Dominated
NICE CG92[17] estimate for LT-CTEPH (£1,280 per month, 2014 prices)							
Total costs (£)	£4,530	£4,484	£4,569	£4,467	£46	-£39	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER (compared with base					£2,486	Dominant	Dominated

case)							
ICER with all changes incorporated					£32,260	Dominant	Dominated
Stroke health state removed from the model							
Total costs (£)	£3,284	£3,240	£3,321	£3,222	£44	-£37	£62
QALYs	12.42	12.41	12.42	12.43	0.02	0.01	-0.01
ICER (compared with base case)					£2,361	Dominant	Dominated
ICER with all changes incorporated					£32,119	Dominant	Dominated
NOAC patients receive an annual visit where they receive U&E							
Total costs (£)	£4,123	£4,033	£4,161	£4,061	£90	-£38	£62
QALYs	12.42	12.40	12.41	12.43	0.02	0.01	-0.01
ICER (compared with base case)					£4,883	Dominant	Dominated
ICER with all changes incorporated (all+16b)					**£35,899**	**Dominant**	**Dominated**

Abbreviation used in the table: CG, clinical guideline; CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; ICER, incremental cost-effectiveness ratio; INR, international normalised ratio; NOAC, novel oral anticoagulant; OR, odds ratio; PE, pulmonary embolism; PTS, post thrombotic syndrome; QALYs, quality-adjusted life years; QoL, quality of life; U&E, urea and electrolytes; VTE, venous thromboembolism

Table 89. Results for different treatment periods

Results per patient	Edoxaban+ heparin (1)	Warfarin+ heparin (2)	Dabigatran+ heparin (3)	Rivaroxaban (4)	Incremental value		
					(1-2)	(1-3)	(1-4)
12 months – ERG base case (NOAC patients receive an annual visit where they receive U&E)							
Total costs (£)	£2,632	£2,259	£2,635	£2,542	£373	-£3	£90
QALYs	11.60	11.58	11.60	11.60	0.01	0.00	-0.01
ICER with all ERG changed incorporated					**£26,028**	**£6,169**	**Dominated**
3 months							
Total costs (£)	£1,591	£1,579	£1,570	£1,500	£12	£21	£91
QALYs	11.61	11.60	11.61	11.61	0.01	0.00	0.00
ICER with all ERG changes Incorporated					**£2,221**	**Dominated**	**Dominated**
6 months							
Total costs (£)	£1,924	£1,797	£1,910	£1,833	£126	£14	£91
QALYs	11.61	11.60	11.61	11.61	0.01	0.00	-0.01
ICER with all ERG changes Incorporated					**£15,369**	**Dominated**	**Dominated**
Lifelong							
Total costs (£)	£20,162	£10,153	£20,787	£20,100	£10,009	-£626	£62
QALYs	11.41	11.24	11.42	11.45	0.18	-0.01	-0.04
ICER with all ERG changes incorporated					**£57,072**	**£102,014**	**Dominated**
Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.							

Table 88 presents an ICER of £35,899 for edoxaban vs warfarin. The ICER comparing edoxaban to dabigatran is similar to the base case ICER, where edoxaban dominated dabigatran. The same is true for edoxaban vs rivaroxaban which ICER remains dominated.

Finally in Table 89 the ICERs presented reflect the ERG alternative base case ICER for different treatment periods. The ICERs increase with treatment duration, with the lifelong treatment duration ICER being £57,072 for edoxaban compared to warfarin.

7 OVERALL CONCLUSIONS

7.1 Summary of clinical-effectiveness issues

The company presented data for the safety and efficacy of edoxaban 60mg OD (or 30mg OD for frail, elderly or patients with poor liver or kidney function) in the treatment and prevention of VTE based on one clinical trial. The ERG considers the Hokusai-VTE, presented in the CS for this STA, to be a well conducted, multi centre international, double-blind, RCT with a large sample of patients. The primary efficacy endpoint of Hokusai-VTE was recurrent symptomatic VTE for which edoxaban was proven to be non-inferior to warfarin.

The analysis of data for the trial safety endpoint, major bleeding, also showed edoxaban was also non inferior to warfarin. Tests of statistical significance proved superior for composite endpoint of major bleeding and CRNMB.

The Hokusai-VTE trial design was different from other trials evaluating NOACs in that patients could have their drug dose altered at the beginning and during the conduct of the study depending on the presence of characteristics of frailty and poor kidney or liver or liver function. It was also possible for physicians to alter the dose during the conduct of the trial and extend treatment right up until the trial end (12 months). The relevance of this design is that the Hokusai-VTE study patients took the study drugs for longer than they would in routine clinical practice.

The poor external validity of the patient population recruited on to the Hokusai-VTE trial to the UK VTE population is also a concern. However, trials of other NOACs have similarly included patients with demographic profiles which differ from those seen in UK clinical practice.

The degree of monitoring that is required to ensure patients do not require a dose reduction from 60mg to 30mg of edoxaban is unclear from the CS.

The limited data provided within the CS for those with a diagnosis of active cancer at trial entry was not subject to analysis, possibly because of the small number of patients with the diagnosis who experienced an event. The ERG is advised by the clinical experts that standard UK clinical practice for patients with a VTE who have active cancer is to be managed with long term LMWH.

There are currently no direct head-to-head data to compare edoxaban with other NOACs and so the ability to draw conclusions about their relative efficacy is limited by the uncertainty around the indirect effect estimates generated from the NMA.

When comparing each of the NOACs with warfarin, there are no large differences in treatment effects for the outcomes between the different NOACs in the PE and DVT populations.

7.2 Summary of cost-effectiveness issues

The company's analysis was based on Hokusai-VTE, a high quality randomised controlled trial. The formulae within the economic model are generally sound. The company conducted subgroup analyses for PE patients and for different treatment durations which was requested in the NICE final scope.

The ERG considers that more transparency should have been employed in the selection and presentation of data inputs. Important data such as CTEPH and PTS data collected in Hokusai-VTE trial were not reported (or acknowledged) in the CS. The ERG is also concerned with the lack of clinical validity of some of the assumptions made in the economic model. The ERG's main concerns are related to:

- The modelled effectiveness of edoxaban (and the other NOACs) in preventing recurrent VTE. Analysis of Hokusai-VTE data for the risk of recurrence with edoxaban does not seem to agree with the modelled risk of recurrence for edoxaban using the NMA ORs applied to baseline warfarin recurrence. Overall the risk of recurrence for edoxaban seems to be underestimated in the economic analysis.
- Given that the phase-specific analysis was used for the estimation of the recurring events, the same approach should have been taken for the estimation of bleeding events. Using these different analyses for the estimation of recurrent VTE events and treatment adverse events bias the analysis as second (and potentially third) recurrent events are being included in the analysis whilst only first bleeding events are being considered, resulting in an underestimation of bleeding events overall.
- When comparing the difference in the number of events occurring in the model and in the time-to-event analysis it seems that the difference in CRNMBs and MBs works in different directions, with the difference in CRNMBs favouring edoxaban and the difference in MBs favouring warfarin.
- The mortality associated with recurrent VTE in the model is overestimated. When the safety analysis set (on-treatment study period) is used to model the mortality associated with recurrent VTE, there seems to be an overestimation of death events compared to what would be expected in real-life clinical practice. This is likely to be related to the high number of "unexplained deaths where VTE cannot be ruled out" reported in Hokusai-VTE. These account for 91% of the VTE-related deaths reported in the trial.
- It is likely that the company's model is overestimating the monitoring regimen required for warfarin patients and underestimating the monitoring regimen for edoxaban (and the other NOACs) patients.

The ERG is concerned that uncertainty in the model and respective outputs hasn't been properly explored by the company. The relevance and robustness of the OWSA and PSA are flawed and these analyses are unlikely to have truly captured the uncertainty around the final ICER. The final ICER is sensitive to minor changes in the monitoring schedules of warfarin and edoxaban. The ERG alternative base case ICER for edoxaban vs warfarin (based on the Hokusai-VTE trial data) is £26,398, which compares to the company's base case ICER of £2,451. The ICER increases with treatment duration, with the lifelong treatment duration ICER being £57,072 for edoxaban compared to warfarin.

The ERG has estimated additional ICERs to assess the cost-effectiveness of edoxaban compared with dabigatran and rivaroxaban and to reflect the NMA but also incorporate clinical opinion provided to the ERG with respect to some assumptions in the model. The ICER comparing edoxaban to dabigatran is similar to the base case ICER, where edoxaban dominated dabigatran. The same is true for edoxaban vs rivaroxaban which ICER remains dominated.

7.3 Implications for research

The ERG considers there is a need for further research into:

- HRQoL data related to warfarin use;
- The efficacy and safety of edoxaban compared with dabigatran, rivaroxaban and apixaban in the treatment and secondary prevention of VTE.

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9 APPENDIX

Table 90 Demographic and clinical characteristics of Hokusai-VTE trial patients[40]

	Edoxaban (N = 4118)	**Warfarin (N = 4122)**
Age — mean ± SD	55.7±16.3	55.9±16.2
Male sex — no. (%)	2360 (57.3)	2356 (57.2)
Weight — mean ± SD		
≤60 kg	524 (12.7)	519 (12.6)
61-100 kg	2983 (72.5)	2949 (71.5)
>100 kg	611 (14.8)	654 (15.9)
BMI — mean ± SD	ND	ND
Creatinine clearance ≥30 to ≤50 ml/min — no. (%)	268 (6.5)	273 (6.6)
Cause of DVT or PE — no. (%)		
Unprovoked	2713 (65.9)	2697 (65.4)
Temporary risk factor	1132 (27.5)	1140 (27.7)
Cancer	378 (9.2)	393 (9.5)
Previous VTE — no. (%)	784 (19.0)	736 (17.9)
Type of index event — no. (%)		
Deep-vein thrombosis	2468 (59.9)	2453 (59.5)
Pulmonary embolism	1650 (40.1)	1669 (40.5)
Both deep-vein thrombosis and pulmonary embolism	-	-
Neither deep-vein thrombosis nor pulmonary embolism	-	-
Known thrombophilic condition — no. (%)	ND	ND
Cancer at baseline, no. (%)	ND	ND
Abbreviations in Table: BMI, body mass index; DVT, deep vein thrombosis; ND, no data; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism		

Table 91 Demographic and clinical characteristics of the RE-COVER[46] and RECOVER-II[47] trials patients

	RE-COVER		**RE-COVER II**	
	Dabigatran (N = 1273)	**Warfarin (N = 1266)**	**Dabigatran (n=1280)**	**Warfarin (n=1288)**
Age — mean ± SD	55.0±15.8	54.4±16.2	54.7±16.2	55.1±16.3
Male sex — no. (%)	738 (58.0)	746 (58.9)	781 (61)	776 (60.2)
Weight — mean ± SD	85.5±19.2	84.2±18.3	83.2±19.7	82.9±19.6
BMI — mean ± SD	28.9±5.7	28.4±5.5	28.4±5.8	28.4±5.8
Creatinine clearance ml/min	105.8±40.7	104.4±39.9	108.2±43.7	107.1±41.1
Cause of DVT or PE — no. (%)				
Unprovoked	ND	ND	ND	ND
Temporary risk factor	ND	ND	ND	ND
Cancer	ND	ND	ND	ND
Previous VTE — no. (%)	327 (25.7)	322 (25.4)	247 (19.3)	203 (15.8)
Type of index event — no. (%)				

Deep-vein thrombosis only	880 (69.1)	869 (68.6)	877 (68.5)	873 (67.8)
Pulmonary embolism only	270 (21.2)	271 (21.4)	298 (23.3)	297 (23.1)
Both deep-vein thrombosis and pulmonary embolism	121 (9.5)	124 (9.8)	104 (8.1)	117 (9.1)
Neither deep-vein thrombosis nor pulmonary embolism	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)
Known thrombophilic condition — no. (%)	ND	ND	ND	ND
Cancer at baseline, no. (%)	64 (5.0)	57 (4.5)	50 (3.9)	50 (3.9)
Abbreviations in Table: BMI, body mass index; DVT, deep vein thrombosis; ND, no data; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism				

Table 92 Demographic and clinical characteristics of the EINSTEIN-DVT[48] AND EINSTEIN-PE[49] trials patients

	EINSTEIN-DVT				**EINSTEIN-PE**	
	Acute DVT Study		**Continued Treatment Study**			
	Rivaroxaban (N = 1731)	**Standard Therapy (N = 1718)**	**Rivaroxaban (N = 602)**	**Placebo (N = 594)**	**Rivaroxaban (N = 2419)**	**Standard Therapy (N = 2413)**
Age — mean ± SD	55.8±16.4	56.4±16.3	58.2±15.6	58.4±16	57.9±7.3	57.5±7.2
Male sex — no. (%)	993 (57.4)	967 (56.3)	354 (58.8)	339 (57.1)	1309 (54.1)	1247 (51.7)
Weight						
≤50 kg	37 (2.1)	49 (2.9)	10 (1.7)	5 (0.8)	38 (1.6)	43 (1.8)
>50 –100 kg	1443 (83.4)	1422 (82.8)	491 (81.6)	488 (82.2)	2034 (84.1)	2010 (83.3)
>100 kg	245 (14.2)	246 (14.3)	85 (14.1)	87 (14.6)	345 (14.3)	359 (14.9)
BMI	ND	ND	ND	ND	ND	ND
Creatinine clearance — no. (%)						
<30 ml/min	6 (0.3)	9 (0.5)	0	5 (0.8)	4 (0.2)	2 (<0.1)
30–49 ml/min	115 (6.6)	120 (7.0)	37 (6.1)	44 (7.4)	207 (8.6)	191 (7.9)
50–79 ml/min	393 (22.7)	399 (23.2)	134 (22.3)	122 (20.5)	637 (26.3)	593 (24.6)
≥80 ml/min	1193 (68.9)	1170 (68.1)	373 (62.0)	373 (62.8)	1555 (64.3)	1617 (67.0)
Cause of DVT or PE — no. (%)						
Unprovoked	1055 (60.9)	1083 (63.0)	440 (73.1)	441(74.2)	1566 (64.7)	1551 (64.3)
Recent surgery or trauma	338 (19.5)	335 (19.5)	21 (3.5)	28 (4.7)	415 (17.2)	398 (16.5)
Immobilization	265 (15.3)	260 (15.1)	89 (14.8)	77 (13.0)	384 (15.9)	380 (15.7)
Estrogen therapy	140 (8.1)	115 (6.7)	23 (3.8)	22 (3.7)	207 (8.6)	223 (9.2)
Active cancer	118 (6.8)	89 (5.2)	28 (4.7)	26 (4.4)	114 (4.7)	109 (4.5)
Puerperium	6 (0.3)	11 (0.6)	1 (0.2)	0	-	-
Previous VTE — no. (%)	336 (19.4)	330 (19.2)	108 (17.9)	84 (14.1)	455 (18.8)	489 (20.3)
Type of index event — no. (%)						
Deep-vein thrombosis	1708/1731 (98.7)	1697 (only 1 distal)	386/602 (64.1)	356/594 (59.9)	ND	ND

		/1718 (98.8)				
Pulmonary embolism	12/1731 (0.6)	11/1718 (0.6)	216/602 (35.9)	238/594 (40.1)	ND	ND
Both deep-vein thrombosis and pulmonary embolism	-	-	-	-	-	-
Neither deep-vein thrombosis nor pulmonary embolism	-	-	-	-	-	-
Known thrombophilic condition — no. (%)	107 (6.2)	116 (6.8)	49 (8.1)	48 (8.1)	138 (5.7)	121 (5.0)
Cancer at baseline, no. (%)	ND	ND	ND	ND	ND	ND
Abbreviations in Table: BMI, body mass index; DVT, deep vein thrombosis; ND, no data; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism						

Table 93. Cost of warfarin per mg weighted using the quantity of warfarin items prescribed as reported by PCA

Strength (mg)	Tablets per pack	Cost per pack	Cost per mg	Prescribing (quantity '000s)	Market share	Weighted cost per mg	Mgs/day	ERG estimate average daily cost
1	28	£0.19	£0.01	305,621.69	51%	£0.01	5	£0.04
3	28	£0.21	£0.00	191,781.74	32%			
0.5	28	£0.65	£0.05	35,659.80	6%			
5	28	£0.23	£0.00	66,759.72	11%			

Table 94: One-way sensitivity analysis variables

Parameter	Base case	Lower limit	Upper limit
Clinical			
Transition probabilities while on warfarin			
VTE Recurrence 0-14 days	0.006	0.003	0.008
VTE Recurrence 14 days-3months	0.011	0.008	0.014
VTE Recurrence 3 months-12 months	0.005	0.002	0.007
VTE Recurrence after 12 months	0.005	0.002	0.007
Probabilities of adverse events while on treatment			
HIT - warfarin	0.000	0.000	0.001
HIT – NOAC	0.000	0.000	0.001
CRNMB – warfarin	0.089	0.081	0.098
MB – warfarin	0.016	0.012	0.020
Probabilities of complications while on warfarin			
CTEPH 0-14 days*	0.000	0.000	0.000
CTEPH 14 days-3 months*	0.000	0.000	0.000
CTEPH 3 months-12 months	0.020	0.009	0.039
Stroke	0.006	0.004	0.009
Probabilities of complications while on NOAC			

Parameter	Base case	Lower limit	Upper limit
CTEPH 0-14 days*	0.000	0.000	0.000
CTEPH 14 days-3 months*	0.000	0.000	0.000
CTEPH 3 months-12 months	0.020	0.009	0.039
Stroke	0.006	0.004	0.009
Probabilities of death while on warfarin			
Death due to VTE	0.006	0.000	0.008
Death due to recurrence	0.113	0.103	0.123
Transition probabilities after discontinuing treatment			
VTE Recurrence 14 days -3 months	0.056	0.049	0.063
VTE Recurrence 3 months-12 months	0.056	0.049	0.063
VTE Recurrence after 12 months	0.035	0.029	0.041
Going off treatment	0.400	0.300	0.500
Transition probabilities after HIT - warfarin			
Death	0.004	0.002	0.006
Transition probabilities after HIT - NOAC			
Going off treatment	0.400	0.300	0.500
Transition probabilities after CRNMB - warfarin			
Going off treatment	0.052	0.045	0.058
Transition Probabilities after CRNMB - NOAC			
Going off treatment	0.084	0.075	0.092
Transition Probabilities after MB - warfarin			
Going off treatment	0.388	0.373	0.403
Death	0.097	0.088	0.106
Transition probabilities after MB - NOAC			
Going off treatment	0.298	0.284	0.312
Transition Probabilities after CTEPH - warfarin			
LT CTEPH 0-14 days	0.000	0.000	0.010
LT CTEPH 14 days-3 months	0.000	0.000	0.010
LT CTEPH 3 months-12 months	0.330	0.316	0.344
Death after CTEPH	0.000	0.000	0.010
Transition Probabilities after CTEPH - NOAC			
LT CTEPH 0-14 days	0.000	0.000	0.010
LT CTEPH 14 days-3 months	0.000	0.000	0.010
LT CTEPH 3 months-12 months	0.330	0.316	0.344
Death	0.000	0.000	0.010
Transition probabilities while on LT- CTEPH - warfarin			
Death	0.000	0.000	0.010
Death after stroke	0.039	0.000	0.100
Treatment efficacy			
Transition probabilities after stroke while on warfarin			
Edoxaban			
0-14 days	[redacted]	[redacted]	[redacted]
14 days-3months	[redacted]	[redacted]	[redacted]
Subsequent months	[redacted]	[redacted]	[redacted]
Edoxaban - alternative from Hokusai-VTE			

Parameter	Base case	Lower limit	Upper limit
0-14 days	[redacted]	[redacted]	[redacted]
14 days-3months	[redacted]	[redacted]	[redacted]
Subsequent months	[redacted]	[redacted]	[redacted]
Dabigatran			
0-14 days	[redacted]	[redacted]	[redacted]
14 days-3months	[redacted]	[redacted]	[redacted]
Subsequent months	[redacted]	[redacted]	[redacted]
Rivaroxaban			
0-14 days	[redacted]	[redacted]	[redacted]
14 days-3months	[redacted]	[redacted]	[redacted]
Subsequent months	[redacted]	[redacted]	[redacted]
Odds-ratios for other events compared to warfarin			
Edoxaban			
MB	[redacted]	[redacted]	[redacted]
CRNMB	[redacted]	[redacted]	[redacted]
Edoxaban - Alternative from Hokusai-VTE			
MB	[redacted]	[redacted]	[redacted]
CRNMB	[redacted]	[redacted]	[redacted]
Dabigatran			
MB	[redacted]	[redacted]	[redacted]
CRNMB	[redacted]	[redacted]	[redacted]
Rivaroxaban			
MB	[redacted]	[redacted]	[redacted]
CRNMB	[redacted]	[redacted]	[redacted]
Utility decrement			
On treatment			
With warfarin	0.012	0.000	0.024
Recurrent VTE	0.125	-0.029	0.279
HIT	0.071	0.000	0.142
Other health states			
CRNMB	0.187	0.066	0.309
MB	0.305	0.087	0.523
CTEPH	0.298	-0.004	0.600
LT CTEPH	0.298	-0.004	0.600
Stroke	0.586	-0.395	1.567
Post stroke	0.122	0.033	0.211
Post-thrombotic syndrome	0.123	0.053	0.193
Costs per health state			
Costs per cycle			
Long-term CTEPH	£184.29	£147.43	£221.15
Post stroke	£287.91	£230.32	£345.49
Costs of events			
Recurrence	£1,292.21	£1,033.77	£1,550.66
HIT	£617.61	£494.09	£741.13
CRNMB	£149.00	£119.20	£178.80

Parameter	Base case	Lower limit	Upper limit
MB	£1,136.00	£908.80	£1,363.20
Stroke	£3,182.41	£2,545.92	£3,818.89
CTEPH	£4,394.35	£3,515.48	£5,273.22

*[redacted]
Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; NOAC, noval oral anticoagulant; PE, pulmonary embolism; PTS, post thrombotic syndrome; VTE, venous thromboembolism.

Table 95: Parameters used in PSA

Parameter	Base case	Distribution	Parameter 1	Parameter 2
Clinical				
Transition probabilities while on warfarin				
VTE Recurrence 0-14 days	0.0056	Beta (α,β)	23	4099
VTE Recurrence 14 days-3months	0.0108	Beta (α,β)	43	3929
VTE Recurrence 3 months-12 months	0.0045	Beta (α,β)	16	3562
VTE Recurrence after 12 months	0.0045	Beta (α,β)	16	3562
Probabilities of adverse events while on treatment				
HIT - warfarin	0.0002	Beta (α,β)	1	4121
HIT - NOAC	0.0002	Beta (α,β)	1	4118
CRNMB - warfarin	0.0893	Beta (α,β)	368	3754
MB - warfarin	0.016	Beta (α,β)	66	4056
Probabilities of complications while on warfarin				
CTEPH 0-14 days	0	LogNormalY (μ,σ)	-20	2
CTEPH 14 days-3 months	0	LogNormalY (μ,σ)	-20	2
CTEPH 3 months-12 months	0.01951	Beta (μ,σ)	0.020	0.012
Stroke	0.00631	Beta (α,β)	26	4096
Probabilities of complications while on NOAC				
CTEPH 0-14 days	0	LogNormalY (μ,σ)	-20	2
CTEPH 14 days-3 months	0	LogNormalY (μ,σ)	-20	2
CTEPH 3 months-12 months	0.01951	Beta (μ,σ)	0.020	0.012
Stroke	0.00631	Beta (α,β)	26	4096
Probabilities of death while on warfarin				
Death due to VTE	0.0058	Beta (α,β)	24	4098
Death due to recurrence	0.113	Beta (μ,σ)	0.113	0.021
Transition probabilities after discontinuing treatment				
VTE Recurrence 14 days -3 months	0.056	Beta (μ,σ)	0.056	0.059
VTE Recurrence 3 months-12 months	0.056	Beta (μ,σ)	0.056	0.059
VTE Recurrence after 12 months	0.035	Beta (μ,σ)	0.035	0.059
Transition probabilities after HIT - warfarin				
Going off treatment	0.4	Normal+ (μ,σ)	0.400	0.050
Death	16.6	LogNormalY (μ,σ)	2.808	0.612
Transition probabilities after HIT - NOAC				
Going off treatment	0.4	Normal+ (μ,σ)	0.400	0.050

Parameter	Base case	Distribution	Parameter 1	Parameter 2
Transition probabilities after CRNMB - warfarin				
Going off treatment	0.0516	Beta (α,β)	19	349
Death	0	LogNormalY (μ,σ)	-20	2
Transition Probabilities after CRNMB - NOAC				
Going off treatment	0.0839	Beta (α,β)	25	273
Transition Probabilities after MB - warfarin				
Going off treatment	0.3881	Beta (α,β)	26	41
Death	0.0968	Beta (α,β)	12	112
Transition probabilities after MB - NOAC				
Going off treatment	0.2982	Beta (α,β)	17	40
Transition Probabilities after CTEPH - warfarin				
LT CTEPH 0-14 days	0	Beta (α,β)	1	350
LT CTEPH 14 days-3 months	0	Beta (α,β)	1	350
LT CTEPH 3 months-12 months	0.33	Normal+ (μ,σ)	0.330	0.050
Death after CTEPH	0	Beta (α,β)	1	350
Transition Probabilities after CTEPH - NOAC				
LT CTEPH 0-14 days	0	Beta (α,β)	1	350
LT CTEPH 14 days-3 months	0	Beta (α,β)	1	350
LT CTEPH 3 months-12 months	0.33	Normal (μ,σ)	0.330	0.050
Death	0	Beta (α,β)	1	350
Transition probabilities while on LT- CTEPH - warfarin				
Death	0	Beta (α,β)	1	350
Transition probabilities after stroke while on warfarin				
Death after stroke	0.0385	Beta (α,β)	2.000	50.000
Treatment efficacy				
Hazard ratios for VTE recurrence compared to warfarin				
Edoxaban				
0-14 days	[redacted]	[redacted]		
14 days-3months	[redacted]	[redacted]		
Subsequent months	[redacted]	[redacted]		
Edoxaban - alternative from Hokusai-VTE				
0-14 days	[redacted]	[redacted]	[redacted]	[redacted]
14 days-3months	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent months	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran				
0-14 days	[redacted]	[redacted]		
14 days-3months	[redacted]	[redacted]		
Subsequent months	[redacted]	[redacted]		
Rivaroxaban				
0-14 days	[redacted]	[redacted]		
14 days-3months	[redacted]	[redacted]		
Subsequent months	[redacted]	[redacted]		
Odds-ratios for other events compared to warfarin				
Edoxaban				

Parameter	Base case	Distribution	Parameter 1	Parameter 2
MB	[redacted]	[redacted]		
CRNMB	[redacted]	[redacted]		
Edoxaban - alternative from Hokusai-VTE				
MB	[redacted]	[redacted]	[redacted]	[redacted]
CRNMB	[redacted]	[redacted]	[redacted]	[redacted]
Dabigatran				
MB	[redacted]	[redacted]		
CRNMB	[redacted]	[redacted]		
Rivaroxaban				
MB	[redacted]	[redacted]		
CRNMB	[redacted]	[redacted]		
Utility decrement				
On treatment				
With warfarin	-0.012	Beta (α,β)	0.012	0.006
Recurrent VTE	-0.125	Beta (α,β)	0.125	0.066
HIT	-0.071	Beta (α,β)	0.071	0.036
Other health states				
CRNMB	-0.187	Gamma (μ,σ)	0.187	0.062
MB	-0.305	Gamma (μ,σ)	0.305	0.111
CTEPH	-0.298	Gamma (μ,σ)	0.298	0.154
LT CTEPH	-0.298	Gamma (μ,σ)	0.298	0.154
Stroke	-0.586	Gamma (μ,σ)	0.586	0.500
Post stroke	-0.122	Gamma (μ,σ)	0.122	0.045
Post-thrombotic syndrome	-0.123	Gamma (μ,σ)	0.123	0.036
Costs per health state				
Costs per cycle				
Long-term CTEPH	£184.29	Gamma (μ,σ)	£184.29	£18.43
Post stroke	£287.91	Gamma (μ,σ)	£287.91	£26.46
Costs of events				
Recurrence	£1,292.21	Gamma (μ,σ)	£1,292.21	£129.22
HIT	£617.61	Gamma (μ,σ)	£617.61	£61.76
CRNMB	£149.00	Gamma (μ,σ)	£149.00	£14.90
MB	£1,136.00	Gamma (μ,σ)	£1,136.00	£113.60
Stroke	£3,182.41	Gamma (μ,σ)	£3,182.41	£318.24
CTEPH	£4,394.35	Gamma (μ,σ)	£4,394.35	£439.44

Abbreviations used in the table: CRNMB, clinically relevant non-major bleed; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; NOAC, noval oral anticoagulant; PE, pulmonary embolism; PTS, post thrombotic syndrome; VTE, venous thromboembolism.

Table 96: Percentages of simulations falling into each quadrant edoxaban vs. warfarin (reproduced from CS submitted at clarification, Table B8, page 16)

Quadrant	Proportion

North-East	46%
South-East (dominant i.e. edoxaban is less costly and more effective)	42%
South-West	2%
North-West (dominated i.e. edoxaban is more costly and less effective)	10%

Table 97: Percentages of simulations falling into each quadrant edoxaban vs. rivaroxaban (reproduced from CS submitted at clarification, Table B9, page 18)

Quadrant	Proportion
North-East	14%
South-East (dominant i.e. edoxaban is less costly and more effective)	0%
South-West	0%
North-West (dominated i.e. edoxaban is more costly and less effective)	86%

Table 98: Percentages of simulations falling into each quadrant edoxaban vs. dabigatran (reproduced from CS submitted at clarification, Table B10, page 19)

Quadrant	Proportion
North-East	0%
South-East (dominant i.e. edoxaban is less costly and more effective)	69%
South-West	31%
North-West (dominated i.e. edoxaban is more costly and less effective)	0%

Initial and updated search strategy provided at clarification for the cost-effectiveness search (CS, Appendix 10)

Medline

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	24,608	26,108
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	46,810	52,866
#3			(dvt or vte or dvts or vtes).mp.	9,743	11,671
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	39,136	42,880
#5	**Hits of P**		**or/1-4**		90,508
#6	I	Interventions	(edoxaban or lixiana or DU-176b).mp.	162	293
#7			(warfarin$ or coumadin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA).mp	20,958	24,081
#8			(dabigatran or bibr 1048 or pradax*).mp.	1,428	2,173
#9			(apixaban or bms 562247 or bms562247).mp.	624	1,041
#10			(rivaroxaban or bay 597939 or xarelto).mp.	1,048	1,707
#11	**Hits of I**		**or/6-10**		22,004
#12	S	Economic	Economics/	26,863	27,421

ID	PICOS	Category	Search terms	Initial	Update
#13			"costs and cost analysis"/	41,559	43,095
#14			Cost allocation/	1,939	1,976
#15			Cost-benefit analysis/	59,566	63,206
#16			Cost control/	20,134	20,813
#17			Cost savings/	8,634	9,189
#18			Cost of illness/	17,406	19,026
#19			Cost sharing/	1,917	2,065
#20			"deductibles and coinsurance"/	1,417	1,482
#21			Medical savings accounts/	481	487
#22			Health care costs/	26,800	29,059
#23			Direct service costs/	1,022	1,058
#24			Drug costs/	12,063	12,751
#25			Employer health costs/	1,063	1,080
#26			Hospital costs/	7,677	8,169
#27			Health expenditures/	13,573	14,390
#28			Capital expenditures/	1,942	1,968
#29			Value of life/	5,894	6,025
#30			exp economics, hospital/	19,348	20,195
#31			exp economics, medical/	13,541	13,982
#32			Economics, nursing/	3,899	4,025
#33			Economics, pharmaceutical/	2,528	2,601
#34			exp "fees and charges"/	26,928	27,925
#35			exp budgets/	12,028	12,343
#36			(low adj cost).mp.	19,931	27,629
#37			(high adj cost).mp.	7,355	8,727
#38			(health?care adj cost$).mp.	3,860	5,105
#39			(fiscal or funding or financial or finance).tw.	75,595	90,229
#40			(cost adj estimate$).mp.	1,334	1,551
#41			(cost adj variable).mp.	31	35
#42			(unit adj cost$).mp.	1,440	1,698
#43			(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	159,051	189,309
#44	**Hits of S**		**or/12-43**	42,898	42,898
#45	**Hits of P and I and S**		**5 and 11 and 44**	240	240
#46	**Limits**	**Humans**	**limit 45 to humans**	239	264
#47		**Update**	**limit 46 to updaterange="prmz[20140428-20141201235959]"**		
#48			**remove duplicates from 47**		

Cochrane

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	MeSH descriptor: [Venous Thromboembolism] this term only	400	420

ID	PICOS	Category	Search terms	Initial	Update
#2			MeSH descriptor: [Venous Thrombosis] explode all trees	2,283	2,298
#3			MeSH descriptor: [Pulmonary Embolism] explode all trees	909	921
#4			((venous or vein) near/2 (thrombosis or thromboses or thrombus or thromboembolism)):ti,ab,kw	4,908	5,154
#5			(dvt or vte or dvts or vtes):ti,ab,kw	1,233	1,310
#6			((pulmonary or lung) near/2 (embolism* or emboli)):ti,ab,kw	1,969	2,120
#7	**Hits of P**		**(#1 or #2 or #3 or #4 or #5 or #6)**	6,257	6588
#8	I and C	Interventions and Comparators	(edoxaban or lixiana or DU-176b):ti,ab,kw	44	58
#9			(warfarin$ or coumandin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA):ti,ab,kw	2,330	2,502
#10			(dabigatran or bibr 1048 or pradax*):ti,ab,kw	220	256
#11			(apixaban or bms 562247 or bms562247):ti,ab,kw	122	161
#12			(rivaroxaban or bay 597939 or xarelto):ti,ab,kw	215	274
#13	**Hits of I and C**		**(#8 or #9 or #10 or #11 or #12)**	2,641	2865
#14	**Hits and P and I and C**		**(#7 and #13)**	609	654
#15	**Limit**	**Cochrane Database (CDSR)**	**#14 in Economic Evaluations**	34	34
#16		**Update**	**#14 Online Publication Date from May 2014 to Dec 2014, in Economic Evaluations**	-	0

Embase

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	exp venous thromboembolism/ or thromboembolism/ or exp vein thrombosis/ or vein embolism/	188,020	180,233
#2			((venous or vein) adj (thrombosis or thromboses or thrombus or thromboembolism)).mp.	103,716	99,009
#3			(dvt or vte or dvts or vtes).mp.	19,214	17,728
#4			((pulmonary or lung) adj3 (embolism$ or emboli)).mp.	70,835	67,648
#5	**Hits of P**		or/1-4	204,252	195,817
#6	I	Interventions	(edoxaban or lixiana or DU-176b).mp.	993	788
#7			(warfarin$ or coumandin$ or jantoven or marevan or lawarin or waran or warfant or vitamin K antagonist$ or VKA).mp	70,982	67,466
#8			(dabigatran or bibr 1048 or pradax*).mp.	6,269	5,313
#9			(apixaban or bms 562247 or bms562247).mp.	3,322	2,766
#10			(rivaroxaban or bay 597939 or xarelto).mp.	5,271	4,405
#11	**Hits of I**		or/6-10	74,441	70,422
#12	S	Economic	Socioeconomics/	110,974	108,304
#13			Cost benefit analysis/	65,668	63,974

ID	PICOS	Category	Search terms	Initial	Update
#14			Cost effectiveness analysis/	101,453	96,535
#15			Cost of illness/	14,534	13,959
#16			Cost control/	50,100	47,939
#17			Economic aspect/	103,913	102,820
#18			Financial management/	101,610	99,969
#19			Health care cost/	132,781	127,514
#20			Health care financing/	11,532	11,387
#21			Health economics/	33,957	33,415
#22			Hospital cost/	14,270	13,630
#23			(fiscal or financial or finance or funding).tw.	109,623	103,662
#24			Cost minimization analysis/	2,562	2,445
#25			(cost adj estimate$).mp.	2,094	1,963
#26			(cost adj variable$).mp.	170	155
#27			(unit adj cost$).mp.	2,622	2,404
#28	**Hits of S**		or/12-27	680,327	658,273
#29	**Hits of P and I and S**		5 and 11 and 28	1,365	1,287

EconLit

ID	PICOS	Category	Search terms	Initial	Update
#1	P	Indication	TX ((venous or vein) AND (thrombosis or thromboses or thrombus or thromboembolism))	2	2
#2			TX (dvt or vte or dvts or vtes)	2	2
#3			TX ((pulmonary or lung) AND (embolism* or emboli))	5	6
#4	**Hits of P**		**or/1-3**	**8**	**9**