National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Rivaroxaban for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Bayer	Venous thromboembolism (VTE), which encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant healthcare problem, producing considerable morbidity, mortality, and resource utilisation (1). VTE has been at the forefront of government policy in recent years and is a clinical priority for the NHS in 2010/11 (2). Following the publication in July 2005 of the Government's response(3) to the Health Committee's report on the Prevention of Venous Thromboembolism (VTE) in Hospitalised Patients(4), the DH set up an independent expert working group to develop a national strategy on the prevention and treatment of VTE (5). This group have subsequently made recommendations concerning a systematic and integrated approach to VTE (6). This comes alongside NICE guidelines including the recent publication of Clinical Guideline 92 Venous Thromboembolism: reducing the risk of venous thromboembolism in patients admitted to hospital in 2010 (7), and a guideline on the management of venous thromboembolic disease which is currently in development and is due to be issued in 2012 (8).	Comments noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.

Section	Consultees	Comments	Action
	Bayer	DVT has an annual incidence of between 48 and 182 per 100,000. The figure often quoted is 1 per 1000 (9). Assuming a UK population of 61 million (10), the annual incidence of DVT could fall between approximately 29,000 and 111,000. Alternatively, using the figure of 1 per 1000 and a population of 61 million, gives an annual incidence of 61,000. The clinical course of DVT might be complicated by PE, recurrent episodes of DVT and the development of post-thrombotic syndrome (PTS) as well as Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Initial management of DVT is with SC LMWH or IV or SC heparin. Warfarin is started at the same time and heparin continued for at least 5 days and until the INR has been in range for 2 consecutive days. Course length depends on clinical aspects of the case. As many patients are managed as outpatients, administration of LMWH may require district nurse support and/or time to train the patient or carer to self-inject. Warfarin has a number of limitations including a narrow therapeutic index, response influenced by diet and drug interactions and the requirement for dose adjustment and frequent INR monitoring. There is no need for routine monitoring of coagulation parameters with rivaroxaban. Introduction of rivaroxaban is therefore likely to result in a reduced demand on costly anticoagulant services. Rivaroxaban also offers a single drug approach which will simplify management of DVT. There are no additional monitoring costs associated with rivaroxaban.	Comments noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.

Section	Consultees	Comments	Action
	Clinical Leaders of Thrombosis	Yes	Comment noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.
	CSAS	This topic is appropriate	Comment noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.
	Medicines and Healthcare products Regulatory Agency	It is important to establish the role of rivaroxaban for the treatment and prevention of thromboembolism, especially in view of its relatively high cost. Warfarin is used very widely, but its value is limited by the need for monitoring and dose adjustment and by its potential for interactions. Low molecular weight heparins are alternatives to oral vitamin K antagonists and clarity would be welcome on when rivaroxaban can be chosen instead.	Comments noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.

Section	Consultees	Comments	Action
	Pfizer	Pfizer would like to clarify that the remit of the appraisal is to appraise rivaroxaban for the treatment and secondary prevention of VTE in the general medical patient and not in cancer patients. We believe that given the difference in needs and the best standard of care between the general population and cancer that the treatment and secondary prevention of VTE in the cancer population warrants a separate health technology appraisal. The draft scope is not specific to cancer patients. In particular: • Current best practise, demonstrated by the CLOT study1, for VTE treatment and secondary prevention in the solid tumour population is dalteparin1,2,3. • Dalteparin is the only LMWH indicated for the treatment of VTE and prevention of its reoccurrence in patients with solid tumours. • Cancer patients are more prone to suffer form VTE than the general population which may occur as a result of their cancer as well as form their therapeutic interventions. • Drug interactions in terms of anticoagulants used are a key issue in cancer patients. • LMWHs cannot be considered interchangeable in terms of efficacy or safety due to their differing molecular weights and structures. This is especially important in cancer patients where drug interaction need to be considered2,3.	Following the consultation on the draft scope and the scoping workshop, subgroups according to underlying risk of recurrent thromoboembolism including the presence of active cancer are included in the other considerations section of the scope.
	Royal College of Nursing	Currently, rivaroxaban has only received marketing authorisation for the prevention of VTE in patients undergoing hip and knee replacement surgery. Four clinical RECORDS trials of rivaroxaban have yielded promising results and have the potential to advance the treatment and prevention of secondary VTE in general. In this context, it is therefore fitting that this single technology is duly referred to NICE for appraisal.	Comments noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.

Section	Consultees	Comments	Action
	Royal College of Pathologists and BSH	If introduced, this technology might significantly change treatment of thromboembolism. Referral to NICE is appropriate	Comment noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.
	Sanofi-aventis	It is appropriate.	Comment noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.
	Vascular Society of Great Britain & Ireland	Yes	Comment noted. Following the scoping workshop an appraisal of rivaroxaban was considered appropriate.
Wording	Bayer	Please could the remit/ appraisal objective be reworded to reflect our proposed licence: "To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment of patients with symptomatic DVT and the prevention of recurrent DVT and PE."	Comment noted. Following the scoping workshop, it was agreed that the remit will remain as 'To appraise the clinical and cost effectiveness of rivaroxaban within its licensed indication for the treatment and secondary prevention of venous thromboembolism'. However using the single remit NICE will schedule two technology appraisals, one for the DVT indication (which is the subject of this appraisal) and one for the PE indication.

Section	Consultees	Comments	Action
	Boehringer Ingelheim	Unclear whether one or two appraisals are being undertaken as treatment of VTE and secondary prevention of VTE are two separate indications	Consultees present at the scoping workshop advised that treatment and secondary prevention are a continuum. There are no clinical criteria to document when the treatment of the initial venous thromboembolism stops and secondary prevention begins. Therefore a single appraisal including both treatment and secondary prevention was considered appropriate.
	Clinical Leaders of Thrombosis	Yes	Comment noted. No actions required.
	CSAS	The wording is fair	Comment noted. No actions required.
	Medicines and Healthcare products Regulatory Agency	It would be of value to publish recommendations at around the time rivaroxaban is licensed for the treatment and prevention of thromboembolism	Following referral of an appraisal, NICE seeks to issue guidance as close as possible to the time of marketing authorisation.
	Royal College of Nursing	The wording of the draft remit succinctly outlines the Population, Intervention, Comparators and Outcomes (PICO) required for this single technology appraisal (STA).	Comment noted. No actions required.
	Royal College of Pathologists and BSH	Licensed indication is not yet known.	NICE liaises with the manufacturer regarding the details of the expected licensed indication.

Section	Consultees	Comments	Action
	Sanofi-aventis	Sanofi-aventis believe that further clarification is required to the wording to ensure it is clear whether the indication will be for the treatment and secondary prevention of VTE or more specifically proposed for the EXTENDED (beyond that in current practice) treatment of symptomatic VTE and prevention of recurrence. The latter of which has an implication on the overall current management of VTE within the UK	Comment noted. Rivaroxaban will be appraised within its marketing authorisation, evidence for duration of use may be considered as part of the appraisal.
	Vascular Society of Great Britain & Ireland	Satisfactory	Comment noted. No actions required.
Timing Issues	Bayer	The suggested timing is appropriate. Rivaroxaban will be the first direct factor Xa inhibitor to be licensed for this indication it is therefore appropriate that advice is issued to the NHS as soon as possible.	Comment noted. No actions required.
	Clinical Leaders of Thrombosis	Yes	Comment noted. No actions required.
	CSAS	The intervention is an oral anticoagulant which may be preferred by patients to low –molecular-weight heparin (such as enoxaparin) because it is an oral medication compared to alternatives delivered via subcutaneous injection	Comment noted. No actions required.
	Royal College of Nursing	Suggested timing is appropriate and while the STA will expedite the appraisal process, the time horizon should be sufficiently long to enable measurement of the proposed outcomes and in particular for the clinical efficacy and cost effectiveness of secondary VTE prevention.	Comment noted. No actions required.
	Royal College of Pathologists and BSH	As we are awaiting license submission, it does not need to be any quicker.	Comment noted. No actions required.
	Vascular Society of Great Britain & Ireland	Well timed and very topical	Comment noted. No actions required.

Section	Consultees	Comments	Action
Additional comments on the draft remit			

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Bayer	The background lists a number of risk factors for VTE – we have a number of suggestions to add to this list: • Recent surgery • Trauma • Immobilisation The annual incidence reported in the background relates to VTE and not specifically DVT. The annual incidence of DVT is between 48-182 per 100,000. The figure often quoted is 1 per 1,000 (1). The risk of subsequent episodes of VTE varies depending on treatment. It has been suggested that within 3 months of an untreated proximal DVT, around 50% of patients will develop symptomatic PE (2), and it has been seen that patients who are inadequately anticoagulated have a 47% frequency of recurrent VTE over 3 months (3). In contrast, clinically significant recurrence in the first 3 months occurs in less than 5% of patients if an adequate anticoagulant response is achieved (3,4).	The background section of the scope has been amended to take into account these comments.
	Bayer (cont)	Long-term complications of DVT include PTS, a chronic disorder which has been reported to occur in anything from 20% to 78% of patients (5-8). Post-thrombotic sequelae range from minor signs (i.e. stasis pigmentation, venous ectasia, slight pain and swelling) to severe manifestations such as chronic pain, intractable oedema and leg ulcers (8). Severe PTS occurs in approximately 25-30% of cases (5,6), and can require ongoing care with considerable socio-economic consequences (8). Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a rare and late possible sequela (9).	The background section in the scope has been updated to include details of post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension.

Section	Consultees	Comments	Action
	Medicines and Healthcare products Regulatory Agency	The third paragraph states: Continued treatment with an oral vitamin K antagonist, most commonly warfarin is usually given but other vitamin K antagonists such as acenocoumarol or phenindione may be considered for the treatment of people with an allergy or resistance to warfarin. It is not correct to say that acenocoumarol is appropriate for 'people with an allergy … to warfarin'. In fact, it is contraindicated in 'hypersensitivity to … related coumarin derivatives'. Also, it might be helpful to reflect that warfarin accounts for around 99.5% of the prescriptions for vitamin K antagonists. The following alternative wording is suggested: Treatment is continued orally with the vitamin K antagonist warfarin or, rarely, with either acenocoumerol or phenindione. It would also be more helpful to list 'family history of thromboembolic disease' as a risk factor for VTE, rather than just 'family history'.	The background section of the scope has been amended to take into account these comments.
	Pfizer	In the treatment and secondary prevention of VTE, cancer patients present a significantly different population to the general medical population in terms of their needs and best practice. As such we would recommend that the cancer population is reviewed in a separate HTA.	Following the consultation on the draft scope and the scoping workshop, subgroups according to underlying risk of recurrent thromoboembolism including the presence of active cancer are included in the other considerations section of the scope.
	Royal College of Nursing	The coverage of the draft scope and the evidence from previously undertaken RECORDS clinical trials suggest that the background information is complete and accurate	Comment noted. No actions required.
	Royal College of Pathologists and BSH	Continued therapy with heparin or low molecular weight heparin is not given simply because patients are at high risk of thromboembolism. There may be a problem in assessing high risk groups as they are excluded from the relevant trial.	The background section of the scope has been amended.

Section	Consultees	Comments	Action
The technology/ intervention	Bayer	Please could you add in this section that rivaroxaban holds a UK marketing authorisation for prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.	The technology section has been amended.
	Boehringer Ingelheim	Duration of treatment in each indication (treatment of VTE and secondary prevention of VTE) should be specified. These durations should be in-line with current clinical guidelines.	It is not standard practice for the duration of treatment to be included in the scope. The duration of treatment may be considered as evidence submitted to the appraisal.
	Clinical Leaders of Thrombosis	Yes	Comment noted. No actions required.
	Royal College of Nursing	This is complete and accurate as the background information	Comment noted. No actions required.
	Royal College of Pathologists and BSH	Yes	Comment noted. No actions required.
	Vascular Society of Great Britain & Ireland	Accurate	Comment noted. No actions required.
Population	Bayer	Please could the population be reworded to reflect our proposed licence: "confirmed symptomatic DVT"	The population in the scope has been amended accordingly.
	Boehringer Ingelheim	Duration of treatment for each indication should be specified.	It is not standard practice for the duration of treatment to be included in the scope. The duration of treatment may be considered as evidence submitted to the appraisal.

Section	Consultees	Comments	Action
	Clinical Leaders of Thrombosis	Subjects with unprovoked VTE and ongoing risk factors could be separated from those with provoked VTE.	Consultees at the scoping workshop considered that it was not necessary to differentiate between provoked and unprovoked venous thromboembolism.
	Medicines and Healthcare products Regulatory Agency	The need to include the word 'symptomatic' should be considered.	The population in the scope has been amended accordingly.
	Pfizer	We would recommend that cancer patients be excluded from this appraisal. If cancer patients are to be assessed, we would recommend a separate appraisal to review VTE treatment and secondary prophylaxis in this population.	Following the consultation on the draft scope and the scoping workshop, subgroups according to underlying risk of recurrent thromoboembolism including the presence of active cancer are included in the other considerations section of the scope.
	Royal College of Nursing	Population is appropriately defined. Should some inherited thrombophilic conditions warranting special management of VTE be considered separately or exclusively?	Consultees at the scoping workshop considered that this was not necessary to specify in the scope of the appraisal.

Section	Consultees	Comments	Action
	Royal College of Pathologists and BSH	If the application is to cover 'secondary prevention' as indicated in the title, then the population should include ' patients who have been treated for acute VTE for 6-12 months'	Consultees at the scoping workshop considered that it was not necessary to include this in the population. Aspects of the duration of treatment may be considered as evidence submitted to the appraisal.
	Sanofi-aventis	The population does not seem to be defined appropriately, specifically, which patient populations will be eligible for this drug? Are high-risk e.g. cancer patients included?	Following the consultation on the draft scope and the scoping workshop, subgroups according to underlying risk of recurrent thromoboembolism including the presence of active cancer are included in the other considerations section of the scope.
	Vascular Society of Great Britain & Ireland	Some reference should be made to the appropriateness of the use in management in post-operative thrombo-embolism.	Consultees at the scoping workshop considered that it was not necessary to include this in the scope.
Comparators	Bayer	We agree that these are the standard treatments currently used in the NHS with which rivaroxaban should be compared.	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Boehringer Ingelheim	Specify/define those at high risk of VTE	Following the consultation on the draft scope and the scoping workshop, the comparator has been amended to include "Continued therapy with unfractionated heparin or a low molecular weight heparin for people for whom a vitamin K antagonist is not considered an appropriate treatment".
	Clinical Leaders of Thrombosis	Yes	Comment noted. No actions required.
	Medicines and Healthcare products Regulatory Agency	Is it necessary to restrict the second comparator to 'people at high risk of venous thromboembolism or for whom a vitamin K antagonist is unsuitable'?	Following the consultation on the draft scope and the scoping workshop, the comparator has been amended to include "Continued therapy with unfractionated heparin or a low molecular weight heparin for people for whom a vitamin K antagonist is not considered an appropriate treatment".

Section	Consultees	Comments	Action
	Pfizer	We consider the comparators as described in the scope and in the EINSTEIN-DVT and EINSTEIN- PE trials to be appropriate for the general medical population. That is LMWH for at least 5 days plus VKA for 3,6 or 12 months4. However the comparators listed in the scope and those reported in the EINTSTEIN trials do not reflect best care for cancer patients. As demonstrated by the CLOT study dalteprin should be considered best care for solid tumour patients. The CLOT study has demonstrated that dalteparin alone for 6 months is superior to dalteparin for 5-7 days plus warfarin for 6 months in reducing the risk of recurrent VTE in patients with active cancer (solid tumours), with no significant difference in the rate of bleeding between the two groups1. Enoxaparin alone has not demonstrated superiority to enoxaparin plus warfarin (enoxaparin for at least 4 days; warfarin for 3 months in the secondary prevention of VTE in cancer patients5. Dalteparin is the only LMWH with a licensed indication for extended treatment of VTE and prevention of its occurrence in patients with solid tumours.	Consultees at the scoping workshop considered that the comparators listed were appropriate for people with cancer.
	Royal College of Nursing	The listed comparators in the draft scope are those currently used in clinical practice. However, initial treatment with UFH or LMWH and continued therapy with vitamin K antagonist (warfarin) appear to be the preferred efficacious choice	Comment noted. No actions required.
	Royal College of Pathologists and BSH	For most patients with acute VTE the LMWH-VKA combination is the appropriate comparator. The comparator for secondary prevention in the trial is placebo. (not VKA and not LMWH) High risk patients meriting long term anticoagulation on clinical grounds are excluded.	Comments noted. No actions required.

Section	Consultees	Comments	Action
	Sanofi-aventis	Regarding the comparators it would be helpful to describe the doses being compared especially with respect to the initial LMWH. This is important in order to determine whether the comparator doses used are consistent with standard practice in the NHS and that this is within licensed use in the UK. If the comparator dose studied is not the UK licensed dose, there will be implications as to the interpretation of the safety data. There is also an implication for duration of therapy. As the usual practice is to treat VTE for 3-6 months, when comparing the rivaroxaban study with other trials in VTE treatment it is important to take this into consideration. Sanofi-aventis believe that oral direct factor Xa inhibitors should be included as comparators.	It is not standard practice for dosage or duration of treatment to be included in the scope. Dosage and duration may be considered as part of the evidence submitted to an appraisal. Consultees at the scoping workshop advised that no other oral direct factor Xa inhibitors are currently used for this indication.
	Vascular Society of Great Britain & Ireland	Appropriate	Comment noted. No actions required.
Outcomes	Bayer	The elements which need to be taken into account in the decision to prolong VKA therapy are the risk of bleeding, the risk of recurrence and the patient's preference (10, 11).	Bleeding events and recurrent venous thromboembolism are included as outcomes in the scope. Patient preference was not considered an appropriate outcome following the consultation on the draft scope and the scoping workshop. The 'other considerations' section of the scope has been amended to state that if evidence allows that appraisal will consider subgroups based on risk of bleeding and risk of recurrence.

Section	Consultees	Comments	Action
		Net clinical benefit analysis is pre-specified within the statistical analysis plan of the pivotal Phase III study. We consider that this should be added as an outcome to those already listed.	It was agreed at the scoping workshop that net clinical benefit was covered by the outcomes already listed in the scope, since this is a composite measure of the cumulative incidence of symptomatic recurrent deep vein thrombosis and non fatal or fatal pulmonary embolism and clinically significant bleeding events.
	Boehringer Ingelheim	Include complications following PE, e.g. pulmonary hypertension.	Consultees at the scoping workshop agreed that chronic thromboembolic pulmonary hypertension should be included under the "complications following deep vein thrombosis" outcome measure already in the scope. It has also been added to the background information in the scope.
	Boehringer Ingelheim	Define bleeding events to ensure consistent with costs and quality of life. Include variation in outcomes based on INR control of patients taking warfarin.	Consultees at the scoping workshop agreed that clinical trials do not use a standardised definition of bleeding events.
	Clinical Leaders of Thrombosis	Yes	Comment noted. No actions required.

Section	Consultees	Comments	Action
	CSAS	These seem appropriate	Comment noted. No actions required.
	Medicines and Healthcare products Regulatory Agency	Consider amending the fourth bullet point to read: • Adverse effects of treatment including bleeding events and heparin-induced thrombocytopenia	Consultees at the scoping workshop agreed that heparin-induced thrombocytopenia would be covered under adverse effects of treatment.
	Royal College of Nursing	The listed outcome measures should provide a good basis for evaluating the clinical efficacy and cost effectiveness of rivaroxaban vis a vis its comparators. In one previous non inferiority RECORD trial, marginally higher bleeding outcome was reported for rivaroxaban over its comparator enoxaparin	Comment noted. No actions required.
	Royal College of Pathologists and BSH	Yes. However the study data available may not be of sufficient duration to capture long term effects such as post thrombotic syndrome.	Comment noted. No actions required.
	Sanofi-aventis	Yes. However, the definitions of major bleeding and clinically relevant bleeding used within clinical trials may differ between trials. It would be important to ensure that this problem is taken into consideration by the ERG and Appraisal committee of when making comparisons.	Comment noted. No changes required to the scope.
Economic analysis	Bayer	A lifetime horizon is appropriate to ensure all costs and benefits are captured.	Comment noted. No actions required.
	Royal College of Nursing	As previously stated, time horizon should be sufficiently long to allow for monitoring the outcomes measures listed.	Comment noted. No actions required.
	Royal College of Pathologists and BSH	Any reduction in costs of monitoring compared to warfarin may be difficult to assess.	Comment noted. No actions required.
	Sanofi-aventis	Sanofi-aventis agrees that the reference case applies and suggest that a lifetime analysis for the economic evaluation would be appropriate.	Comment noted. No actions required.

Section	Consultees	Comments	Action
	Vascular Society of Great Britain & Ireland	More reference should be made to duration of treatment	It is not standard practice to include duration of treatment in the scope. The duration of treatment may be considered as evidence submitted to the appraisal.
Equality and Diversity	Bayer	We do not consider there to be any relevant issues.	Comment noted. No actions required.
	Royal College of Nursing	Due consideration and patient education should be given to those patients recruited for VTE treatment, who on religious or cultural values, object to receiving porcine derived heparin	Comment noted. No changes to the scope required.
	Royal College of Pathologists and BSH	The lack of need for monitoring may benefit patients with limited mobility who no longer have to attend hospital/GP.	Comment noted. No actions required.
Other considerations	Bayer	Please could the following be added: "Consideration should be given to the potential advantage of rivaroxaban in terms of its lower requirement for therapeutic monitoring". "Consideration should be given to the potential advantage of rivaroxaban in terms of it offering a single drug approach to the management of DVT	Comments noted. However, this level of detail is not required in the scope.
	Sanofi-aventis	A higher dose than is licensed in the UK for enoxaparin has been used within the rivaroxaban EINSTEIN-DVT trial, and an overall longer duration of treatment compared to standard practice has been applied. The impact to the benefit/risk profile of rivaroxaban compared to the enoxaparin/VKA arm needs to be considered in light of these differences for the UK patient population.	Comment noted. The dosage of treatment and comparators may be considered as evidence submitted to the appraisal. No changes to the scope required.

Section	Consultees	Comments	Action
	Vascular Society of Great Britain & Ireland	Post-operative	Consultees at the scoping workshop considered that it was not necessary to include this in the scope.
Questions for consultation	Bayer	**What do you consider to be the relevant clinical outcomes and other potential health related benefits of rivaroxaban in the treatment and secondary prevention of venous thromboembolism particularly when compared with currently used treatment options?** The elements which need to be taken into account in the decision to prolong VKA therapy are the risk of bleeding, the risk of recurrence and the patient's preference (10) Net clinical benefit analysis is pre-specified within the statistical analysis plan of the pivotal Phase III. We consider that this should be added as an outcome to those already listed. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits** The submission will be based on the results of the pivotal Phase III study NCT00440193 and the extension study NCT00439725 Details of these studies can be found at: www.clinicaltrials.gov/	Comments noted. The 'other considerations' section of the scope has been amended to state that if evidence allows that appraisal will consider subgroups based on risk of bleeding and risk of recurrence. It was agreed at the scoping workshop that net clinical benefit was covered by the outcomes already listed in the scope, since this is a composite measure of the cumulative incidence of symptomatic recurrent deep vein thrombosis and non fatal or fatal pulmonary embolism and clinically significant bleeding events.

Section	Consultees	Comments	Action
	Bayer	**How are treatment and secondary prevention defined and differentiated in clinical practice? Should treatment and secondary prevention be considered separately in an appraisal?** It is difficult to differentiate as treatment length represents a continuum of treatment and secondary prevention. Treatment length is individualised due to patient risk-benefit profiles, e.g. cancer or previous DVT. **Is rivaroxaban intended to replace treatment with both heparin/low molecular weight heparin and a vitamin K antagonist?** Yes – rivaroxaban offers a single drug approach to the treatment of DVT and the prevention of recurrent DVT and PE. **Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?** For patients with differential risk levels, we may expect to find different levels of clinical and cost effectiveness based on outcomes achieved e.g. patients with cancer. **Should deep vein thrombosis and pulmonary embolism be considered separately?** Yes, for the treatment of the initial event but they cannot be separated as regards secondary prevention.	Comments noted. Consultees agreed that a single appraisal including both treatment and secondary prevention was considered appropriate. Comments noted. No actions required. The other considerations section of the scope has been amended to include subgroups based on risk of bleeding and risk of recurrence. Two appraisals one for DVT and one for PE have been scheduled in separately.

Section	Consultees	Comments	Action
	Bayer	**Should the appraisal differentiate between people with reversible risk factors who do not need long term treatment and people with a continuing risk factor?** It would be reasonable for the appraisal to consider appropriate treatment length according to existing guidelines and the clinical data presented. **Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes, as rivaroxaban offers the benefit of a single drug approach to DVT management with an oral, fixed dose medication that does not require routine monitoring of coagulation parameters. **Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Some potential benefits to the patient, e.g. in not having to attend a warfarin clinic, will not be captured in the QALY calculation.	Comments noted. Aspects of the duration and administration of treatment may be considered as evidence submitted to the appraisal.

Section	Consultees	Comments	Action
	Bayer	**NICE intends to appraise rivaroxaban for the treatment and secondary prevention of venous thromboembolism through its Single Technology Appraisal (STA) Process.** **Should treatment and secondary prevention of venous thromboembolism be considered together as a single STA, separately as two STAs, or as a Multiple Technology Appraisal (MTA)?** □ Treatment of patients with acute symptomatic DVT and the prevention of recurrent venous thromboembolic events should be considered as an STA. □ Treatment of patients with PE and the prevention of recurrent venous thromboembolic events should be considered as a separate STA at a later date. While it is appropriate that NICE evaluates both initial and longer treatment in comparison with rivaroxaban we would suggest that the overall evidence for each treatment strategy is evaluated in the same appraisal. Both the ACCP and draft SIGN guidelines support this view for the following reasons; 1.There is no clear division between treatment and prevention Treatment of DVT and secondary prevention is a continuum, there are no clinical criteria to document when the treatment of the initial VTE stops and secondary prevention begins. The ACCP guidelines discuss this to the extent that in the first three months treatment of the initial thrombosis predominates, after 3 months secondary prevention predominates.[11]	Comments noted. Two appraisals one for DVT and one for PE have been scheduled in separately. Consultees present at the scoping workshop advised that treatment and secondary prevention are a continuum. There are no clinical criteria to document when the treatment of the initial venous thromboembolism stops and secondary prevention begins. Therefore a single appraisal including both treatment and secondary prevention was considered appropriate.

Section	Consultees	Comments	Action
	Bayer	2. Efficacy of acute treatment needs to be assessed over the longer term The efficacy of initial anti-coagulation may only become apparent over a longer period. Trials evaluating acute treatment (LMWH, Fondapariux) have been required to have at least a 3-month follow-period. Indeed, ultrasound-identified residual thrombosis has been identified as a risk factor for recurrence.[12,13]. 3. Current drugs for the acute and longer period are administered concomitantly in the acute phase, effectiveness and costs are inter-dependent The cost and effectiveness of initial treatment is very much linked to the performance of concomitant warfarin and the quality of the transition to longer term warfarin in the individual patient. The duration of acute or initial treatment varies considerably; as this depends on the time it takes for warfarin to reach a therapeutic level at a stable dose for the individual patient. This is defined in the guidelines as two consecutive measurements days of INR measurements greater than 2.0. The mean duration of acute treatment in the Matisse DVT trial around 7 with a standard deviation of 2.2 days, in the RECOVER trial of dabigatran the median duration of post-randomization treatment was 6.0 (inter quartile range of 4.0 – 8.0, following a median pre-randomization treatment of 3.0 days). [14,15]	Comments noted. No changes required to the scope.
	Boehringer Ingelheim	In 'Questions for Consultations': Whilst treatment and secondary prevention should be should be considered in separate economic analyses as they are separate indications, they need not be considered in separate appraisals as they are proposed as a continuation of treatment. All potential significant and substantial health-related benefits resulting from the technology should be included in the QALY. Any additional benefits that are not health-related, and therefore not included in the QALY, should be excluded. Two other oral anticoagulants are expected to launch in these indications in the next couple of years. This means a Multiple Technology Assessment is more appropriate than potentially having three separate Single Technology Assessments occurring concurrently or in close succession.	Comments noted. In order to provide timely guidance to the NHS. Rivaroxaban has been referred as a single technology appraisal.
	Clinical Leaders	This treatment may have benefits for patients who are poorly controlled on	Comments noted. No changes

Section	Consultees	Comments	Action
	of Thrombosis	vitamin K antagonists or are intolerant to them. It will benefit those patients who cannot/will not attend for regular testing such as IV drug abusers. The reduction in the need for routine testing for patients anticoagulated with rivaroxaban will have benefits in reducing clinic and laboratory workload.	to the scope required.
	Medicines and Healthcare products Regulatory Agency	**Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately? Should deep vein thrombosis and pulmonary embolism be considered separately? Should the appraisal differentiate between people with reversible risk factors who do not need long term treatment and people with a continuing risk factor?** Comment: It may need to be borne in mind that some adverse effects with anticoagulants might only arise after long-term use. **Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Comment: Blocking the coagulation cascade at a different point may change outcomes. Otherwise, advantages of rivaroxaban include that it isn't warfarin, and does not present with the challenge of dose titration, genetic differences in elimination etc. Also it does not need to be injected. However, the long-term effects are unknown. **Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**	Comments noted. No changes to the scope required.

Section	Consultees	Comments	Action
		Comment: No need for monitoring or for injection. Fewer interactions than warfarin.	
	Royal College of Nursing	The relevant outcome measures are robust criteria for establishing the clinical efficacy and cost effectiveness of this STA. Potential health related benefits of rivaroxaban over its comparators include one daily fixed oral dose warranting no coagulation monitoring and no regular drug dose adjustment as required of Vitamin K antagonist. It also eliminates the needs for extra resources for the administration of heparin injection in those patients who are unable or reluctant to self administer the injection. Overall, the related benefits make rivaroxaban intuitively attractive for both patients and clinicians alike to make informed decision on choice of treatment appropriate to their needs.	Comment noted. No changes to the scope required.
	Royal College of Pathologists and BSH	The clinical outcomes of relevance are efficacy (recurrent thrombosis) and safety (bleeding), including deaths from either cause. Effects on long term sequelae are relevant but are not likely to be available. Recurrent thrombosis is also a major determinant of long term sequelae. Lack of monitoring, drug interactions and lifestyle effects could also be considered. Lack of monitoring may reduce total cost of care but this could easily be overestimated because the savings will be marginal. Data will come from the relevant trials: NCT00439725 NCT00440193 NCT00439777 Treatment applies to the first 3-6 months after a venous thrombotic event. Secondary prevention refers to (usually indefinite) treatment beyond that. There may be a problem with comparators for the secondary prevention because of the way the trial is designed. Patients who had an indication for long term anticoagulation were excluded and these would have been an appropriate population to study.	Comments noted. . Aspects of the duration and administration of treatment may be considered as evidence submitted to the appraisal. Following the consultation on the draft scope and the scoping workshop, subgroups according to underlying risk of recurrent thromoboembolism including the presence of active cancer are included in the other considerations section of the scope. Consultees present at the scoping workshop advised that treatment and secondary prevention are a continuum.

Section	Consultees	Comments	Action
		Not clear how patients with cancer are treated. Rivaroxaban would replace both VKA and LMWH in treatment of VTE. We should consider treating acute and secondary prevention as two STAs because the data available is quite different and the groups studied divergent.	There are no clinical criteria to document when the treatment of the initial venous thromboembolism stops and secondary prevention begins. Therefore a single appraisal including both treatment and secondary prevention was considered appropriate.
	Sanofi-aventis	In order to give a considered opinion, the following information would be useful: • The study design and results of EINSTEIN-EXTENSION, EINSTEINT-DVT, EINSTEIN-PE, would offer further information on the efficacy and safety of the technology within this scope • The patient inclusion criteria • The patient exclusion criteria	Comments noted. No changes to the scope required.
Additional comments on the draft scope.			

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Bristol Myers Squibb
Department of Health
NHS Quality Improvement Scotland
Public Health Wales NHS Trust
RICE – Research Institute for the Care of Older People