Appendix D – Clinical specialist statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Caroline Lovelock

Name of your organisation St George's University of London, St George's Healthcare NHS Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **X**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

Current Practice:
Persistent, permanent or paroxysmal atrial fibrillation is a risk factor for systemic or cerebral thromboembolism. Warfarin reduces this risk by 64% and aspirin by 27% compared to control. Current practice in the UK is to recommend either warfarin, aspirin or combination antiplatelet therapy, or no treatment, based on an individual's perceived level of risk. A number of methods for stratifying risk exist, including the algorithm used in the NICE guidelines, which categorises patients as being at high, moderate or low risk of thromboembolism. All guidelines recommend that patients at high risk of thromboembolism take oral anticoagulation, unless they have contraindications to treatment. The NICE guidelines recommend that patients at moderate risk can take either oral anticoagulation or aspirin, and that patients at low risk can take aspirin. However there is some debate as to whether aspirin has any role as a first line therapy for patients with AF. For those at moderate risk of thromboembolism and not at high risk of bleeding complications, oral anticoagulation is likely to be more beneficial than aspirin. For those at genuinely very low risk of thromboembolic events, no thromboprophylaxis may be needed. The recently published updated European Society of Cardiology guidelines on thromboprophylaxis in AF reflect this viewpoint.

Variation in current practice:
In general, thromboprophylaxis with oral anticoagulation is underused in patients with AF who are at high risk of thromboembolism. Some estimates suggest that an additional 20- 51% of patients with AF should be using oral anticoagulation. Clinicians are often reluctant to prescribe the only currently available treatment - warfarin, because of concerns that certain groups of patients may be at higher than average risk of warfarin related complications. Furthermore patients may be unwilling to take treatment that carries a risk of serious bleeding complications and/or requires regular monitoring with blood tests and dose adjustments.

Even among patients taking warfarin, there is variation in the proportion of time in which a satisfactory therapeutic response to the drug is achieved. This can vary

between centres supervising treatment as well as between individuals. Lower proportions of time spent in therapeutic range are associated with reduced warfarin efficacy.

Evidence for dabigatran as an alternative to warfarin in the prevention of stroke in patients with persistent, permanent or paroxysmal AF
Dabigitran is a direct competitive inhibitor of thrombin. The evidence for dabigatran as an alternative to warfarin in the prevention of stroke and systemic thromboembolism in patients with AF is based on the recently published RELY study, which randomised 18,113 patients to dabigatran 150mg bd, dabigatran 110mg bd, or dose adjusted warfarin. Median follow up was 2 years. The results demonstrated that dabigatran 110mg bd was associated with similar rates of stroke compared to warfarin, and lower rates of major haemorrhage. Dabigatran 150mg bd was associated with lower rates of stroke compared to warfarin, and similar rates of major haemorrhage. Both doses of dabigatran were associated with lower rates of intracranial haemorrhage.

Mention of dabigatran in current guidelines in the international community:
The European Society of Cardiology guidelines published in 2010 suggest how dabigatran might be introduced into the guidelines pending approval of both doses used in the RELY study. When patients are eligible for oral anticoagulation, the ESC guidelines suggest that dabigatran 150mg bd could be used when the bleeding risk is deemed to be low (as indicated by a low score on the HAS-BLED scale), and dabigatran 110mg bd could be used if the risk of bleeding is greater. For patients at moderate risk of thromboembolism - ie those with a moderate risk factor but no high risk factors for thromboembolism, dabigatran 110mg bd could be started in view of the lower extra- and intracranial bleeding complications compared to warfarin but similar levels of efficacy in ischaemic stroke prevention.

Dabigatran has recently been licensed for use as a thromboembolic prophylactic agent in patients with AF in the USA and Canada. In the USA, only a dose regimen of 150mg bd has been approved for this indication. The updated US ACCF/AHA/HRS guidelines published in 2011 advise that dabigatran can be considered as an alternative to warfarin in the prevention of systemic thromboembolism in patients with AF and risk factors for stroke, who do not have a prosthetic heart valve, severe renal failure or advanced liver disease. The exceptions are derived from the exclusion criteria used by the RELY study.

The Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010 recommend "when an oral anticoagulant is indicated for stroke prevention, most patients should receive dabigatran in preference to warfarin. Possible exceptions would include patients with a propensity to dyspepsia, gastrointestinal bleeding, or both and those at substantial risk of coronary events." They also recommend "the dose of 150mg bd is preferable to 110mg bd except in patients of low body weight, decreased renal function or at increased risk of major bleeding."

Setting for use of dabigatran
With the aid of clear guidelines dabigatran could be used in the same clinical settings as warfarin - ie in both primary and secondary care. At present there is no indication that any additional monitoring is required for patients on dabigatran. However it is advisable that primary care givers review all patients on dabigatran at regular intervals, as it may be necessary to consider changing patients to an alternative dosing schedule, if both are licensed, based on changing risk factor profiles.

The advantages and disadvantages of the technology
NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Advantages of dabigatran over conventional oral anticoagulation therapy with warfarin
Warfarin is a difficult drug to use - the dose required to achieve adequate levels of prophylaxis varies with time, and patients are required to having regular ongoing blood tests. Under-dosage undermines warfarin's efficacy at stroke prevention, and over-dosage increases the risk of serious bleeding complications. Intracranial haemorrhage is one of the most feared complications of warfarin therapy, and is associated with particularly high morbidity and mortality. Warfarin has a number of interactions with other drugs and foods, which can alter its efficacy.

Dabigatran has a number of advantages over warfarin therapy. Based on the results of the RELY study, both fixed doses of 110mg bd and 150mg bd are associated with a lower frequency of intracranial haemorrhage compared with warfarin, and the dose of 110mg bd is associated with a lower frequency of all major haemorrhages. Dabigatran at a dose of 110mg bd is non-inferior to warfarin for the prevention of ischaemic stroke and the dose of 150mg bd is superior to warfarin for the prevention of ischaemic stroke. Unlike warfarin, dabigatran can be given as a fixed dose, does not require monitoring, and has relatively few known drug interactions. These advantages may help to extend the use of oral anticoagulation to a greater number of potentially eligible patients with AF.

Disadvantages of dabigatran over warfarin
The main disadvantage of dabigatran over warfarin is the cost of the new medication, even taking into account the costs of ongoing monitoring required with warfarin use. There have been a number of publications using Markov decision models to examine the cost-effectiveness of dabigatran compared to warfarin, one of which was funded by dabigatran's manufacturer. Common to all analyses was the finding that dabigatran became more cost-effective in comparison to warfarin in patients with a high risk of both ischaemic stroke and intracranial haemorrhage. It may not be cost-

effective in patients with a moderate risk of ischaemic stroke and a low risk of intracerebral haemorrhage, although this will also depend on the actual cost of the drug. A limitation of all such analyses is that they depend on estimates of event rates on dabigatran from a single study, and they extrapolate event-rates derived from a study with a median of 2 years of follow up to much longer periods of time.

Other disadvantages of dabigatran relate to our lack of knowledge about dabigatran's role in special situations, such as patients with mechanical heart valves, coronary artery disease, or use alongside medications that either interact with dabigatran or have the potential to increase the risk for side effects such as major gastro-intestinal bleeding as detailed below.

Patient subgroups who may be at increased risk of adverse events on dabigatran.
Certain patient subgroups may not benefit from dabigatran, or may be at increased risk of adverse effects from dabigatran. In the RELY study patients with renal impairment (Cr clearance<30ml/min), liver disease, severe heart valve disorders, stroke within the last 14 days or severe stroke within the last 6 months, and the presence of a condition that increased the risk of haemorrhage were not enrolled and so the results of the study cannot be generalised to these groups.

Dabigatran interacts with P-glycoprotein inhibitors including several antiarrhythmic drugs such as amiodarone, quinidine, and verapamil, which increase the serum concentration of dabigatran. Some guidelines regarding the use of dabigatran for VTE prophylaxis post surgery recommend reducing the dose to 150mg od in patients taking amiodarone or verapamil, but the relative efficacy of this dose of dabigatran versus warfarin when used in conjunction with these drugs over long periods of time is not known.

Dabigatran may not be a suitable medication for patients who have difficulties with compliance as the elimination half life is relatively short (12-17 hours) and so missed doses will potentially leave patients unprotected. Furthermore there is no reliable laboratory method of checking compliance. This will make it difficult to objectively assess whether an ischaemic stroke occurring in a patient taking dabigatran was a treatment failure requiring a switch to a higher dose or to warfarin, or if it was due to treatment non-compliance.

There are concerns that the frequency of myocardial infarction was higher in the patients taking dabigatran versus warfarin in the Rely study, although this only reached borderline significance in the group taking dabigitran 150mg bd. There is some evidence that the renal excretion of thromboxane may be increased in patients on dabigatran who are not also taking aspirin, leading to a possible platelet activating effect. A trial is ongoing which is assessing the frequency of side-effects in patients with acute coronary syndromes (REDEEM study).

Cautions regarding the use of dabigatran.
The frequency of withdrawal from anticoagulation therapy was significantly higher in the treatment arm taking dabigatran at either dose compared with the treatment arm on warfarin in the RELY study. This appears to have been due to a higher incidence of adverse events in the dabigatran treatment arms. In particular the incidence of dyspepsia was twice as frequent in the dabigatran treatment arms.

There are still insufficient long term data regarding the use of dabigatran. The median follow up in the RELY study was 2 years, and additional adverse effects or drug interactions may become evident over time.

There are some data from a pre-specified subgroup analysis that patients aged >=75 years may be at higher risk of major extra-cranial bleeding events on dabigatran 150mg bd vs warfarin. However the reduced risk of intracranial haemorrhage on dabigatran 150mg bd vs warfarin was still present regardless of age.

If major bleeding events do occur on dabigatran, there is no specific antidote available.

Proposed rules on starting dabigatran

The AHA guidelines advise that patients already established on warfarin therapy with excellent control may have "little to gain" from switching to dabigatran. Re-analysis of the RELY study results stratified by different levels of warfarin control, showed that dabigatran 150mg bd was not more effective than warfarin in the prevention of ischaemic strokes when the mean time warfarin-users at any single centre spent in therapeutic range was >72.6%. However the beneficial effects of dabigatran in reducing the incidence of intracranial haemorrhage did not change with increasing warfarin control. These findings imply that if patients have excellent warfarin control and are at low risk of intracranial haemorrhage, they may not benefit from a switch to dabigatran, particularly because there is an increased risk of non-haemorrhagic side effects on dabigatran.

Application of the results of the RELY study to real life clinical practice

Aspects of the RELY study which may affect its generalisability include:

1. Exclusion of certain patient groups - including those with valvular heart disease, a condition that increased the risk of bleeding events, renal impairment, hepatic impairment and stroke within the last 2 weeks or a severe stroke within the last 6 months.
2. Half the patients recruited were on long term warfarin therapy at the time of randomisation, and therefore might be expected to have a lower rate of bleeding events compared to warfarin naive patients.
3. The use of open-label warfarin could have resulted in biased reporting of adverse events or outcome events.
4. The time spent in therapeutic range (TTR) in the warfarin arm averaged 64%. This was substantially lower than the average TTR reported from UK centres in the study which was 72%. The difference in efficacy of dabigatran compared to warfarin is likely to be less than that reported in RELY when warfarin control is very good.
5. With respect to decision making over the treatment of patients who present with AF and a recent stroke or TIA - only 20% of patients enrolled in RELY had a previous ischaemic stroke or TIA. These patients tended to be younger and were more likely to be taking warfarin than the remaining cohort. This again will have potentially reduced their likelihood of experiencing bleeding complications during the study - although this reduced risk should have been the same across all treatment groups. In a pre-specified subgroup analysis of these patients, neither dose of dabigatran was associated with a statistically significant reduction in the rate of stroke or systemic embolisation, but the lower dose of dabigatran was associated with a significantly reduced risk of all major bleeds and all-cause mortality, and a lower rate of intracranial haemorrhage compared with the higher dose of dabigatran.

Personal view of how dabigatran could be introduced for patients with AF to prevent thromboembolic events:
Pending an assessment of the cost effectiveness of dabigatran at different doses versus warfarin using UK data, the following are suggested recommendations for the introduction of dabigatran based on the above review of the literature.

Warfarin naive patients with no contraindications to oral anticoagulation and no history of renal impairment (CrCl < 30ml/min), liver disease, a mechanical heart valve, coronary artery disease, and who are likely to have good medication compliance:

1. For patients with a history of TIA or stroke:
Recommend dabigatran 110mg bd

2. For patients with no history of TIA or stroke, a high risk of stroke, and high risk of bleeding events or age >= 75 years
Recommend dabigatran 110mg bd

3. For patients with no history of TIA or stroke, a high risk of stroke and low risk of bleeding events or age <75 years
Recommend dabigatran 150mg bd

4. For patients with no history of TIA or stroke, a moderate risk of stroke and low risk of bleeding events or age <75 years
Recommend dose adjusted warfarin

5. For patients with no history of TIA or stroke, and a very low risk of stroke
Recommend no thromboprophylaxis or aspirin

Patients with any contraindication to using dabigatran as listed above and patients with a history of coronary artery disease:
Recommend dose adjusted warfarin

Patients already on warfarin:
1. If well controlled on warfarin:
Recommend: no switch to dabigatran

2. If poor control on warfarin (TTR < 70%) or thromboembolic event on warfarin:
Switch to dabigatran 110mg bd or 150mg bd depending on risk of major bleeds

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NO

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Additional resources needed for implementation:
NHS staff in both primary and secondary care would need extra education and training regarding the evidence for using dabigatran in patients with AF at risk of thromboembolic complications.

It would also be necessary to establish guidelines on the management of patients with major bleeding complications on dabigatran.