Appendix D – Clinical specialist statement template

Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation

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: Prof Michael Laffan

Name of your organisation: British Society for Haematology & Royal College of Pathologists

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓
- 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 standard therapy for patients at risk of stroke or systemic embolism from atrial fibrillation (AF) is anticoagulation using a vitamin K antagonist (VKA); usually warfarin. This is recommended in NICE guidance CG36 (2006) which also suggests aspirin may be suitable for low- and some moderate-risk patients. High risk patients should receive VKA. There is broad consensus on the indication and dosing and no other alternatives exist.

The principal drawback of using VKA is their extremely variable dose response, interactions with other drugs, interference by diet and the consequent need for repeated blood tests for monitoring and dose adjustment. Monitoring therapy is relatively complicated and requires specialised staff and equipment.

Patients with AF represent a wide range of risk. Assessment of risk is well developed and in CG36 a system similar to the well established CHADS2 scoring system is used. This can be used to guide treatment.

Dabigatran has been licensed for use as prophylaxis following hip or knee surgery for some time and now has a licence for this indication and is about to be launched in the UK. . There is no substantial experience with use in either AF or any current guidelines relating to its use.
We expect that dabigatran would be administered largely in primary care although it may also be initiated by hospital specialists. Additional specialist staff should not be required and overall administration should be easier than for warfarin (see below).

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?

The application is based almost entirely on the results of the RE-LY trial (NEJM 2009, 361:1139-51). This trial has been criticised on the grounds that the unblinded comparison between dabigatran and warfarin may have introduced bias and that the reported benefit of dabigatran derived largely from the unusually high rate of intracranial haemorrhage in the warfarin arm (http://www.ti.ubc.ca/sites/ti.ubc.ca/files/80.pdf and http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM247244.pdf)

The recent EMA positive opinion approved both the doses of dabigatran used in the RE-LY trial (110 and 150 mg bd) whereas we note that the FDA licensed only the 150mg dose. The reasons for the FDA decision are given in a well argued letter (NEJM 2011, 364:1788-90) in which they explain that they were unable to identify any subgroup of patients for whom the 110mg dose was more beneficial than the 150mg dose).

The entry criteria for the RE-LY trial represent a group of patients most of whom would receive VKA in the UK under current guidelines. The primary endpoints used in the trial were the clinically relevant events of stroke or systemic embolism compared with bleeding. Efficacy of INR control was comparable to current UK practice but is an important determinant of benefit. Overall, there is no significant extrapolation required in applying these results to UK practice.

UK guidelines for VKA use contain well developed and effective procedures for reversal of VKA therapy in the event of emergency or haemorrhage but at present there are no similar data on how to reverse Dabigatran.

The current NICE guideline contains a risk stratification system for anticoagulation therapy in patients with atrial fibrillation. Although the same risk assessment might be used in guidance for dabigatran, its reported greater efficacy (at the 150mg bd dose) with similar bleeding risk may warrant adjustment of recommendations to include a broader group than that for which VKA is recommended.

Dabigatran lacks many of the disadvantages associated with VKA: it does not need monitoring and has few interactions with diet or other drugs. Twice daily administration is a possible disadvantage and might affect compliance. Finally, the significantly higher drop-out rate for dabigatran in the RE-LY trial indicates that some patients may not tolerate dabigatran, primarily as a result of gastrointestinal symptoms.

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.

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)?

Overall, the delivery of this technology should be more straightforward and require fewer resources than the existing standard treatment using VKA. However achieving savings from the lack of monitoring may be restricted by the significant number of patients who will continue using VKA Transition might be complicated in the short term with the need for re-education of staff.