

Diagnosics consultation document

Self-monitoring coagulation status in people on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease: point-of-care coagulometers (the CoaguChek XS system and the INRatio2 PT/INR monitor)

The National Institute for Health and Care Excellence (NICE) is producing guidance on using the CoaguChek XS system and the INRatio2 PT/INR monitor in the NHS in England. The Diagnostics Advisory Committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report), which is available from <http://guidance.nice.org.uk/DT/InDevelopment>.

The Advisory Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality

legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology

- could have any adverse impact on people with a particular disability or disabilities.

Note that this document is not NICE's final guidance on the CoaguChek XS system and the INRatio2 PT/INR monitor. The recommendations in section 1 may change after consultation.

After consultation, the Committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the Committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the 'Diagnostics Assessment Programme process guide' (available at www.nice.org.uk/aboutnice/howwework/developingnicediagnostictechnologiesguidance).

Key dates:

Closing date for comments: 7 May 2014

Second Diagnostics Advisory Committee meeting: 13 May 2014

1 Provisional recommendations

1.1 The CoaguChek XS system is recommended for self-monitoring coagulation status in adults and children on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease if:

- the person prefers this form of testing **and**
- the person or their carer is both physically and cognitively able to self-monitor effectively.

1.2 The InRatio2 PT/INR monitor is recommended for self-monitoring coagulation status in adults and children on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease if:

- the person prefers this form of testing **and**
- the person or their carer is both physically and cognitively able to self-monitor effectively.

Although there is greater uncertainty of clinical benefit for the InRatio2 PT/INR monitor than for the CoaguChek XS system, the evidence indicates that the precision and accuracy of both monitors are comparable to laboratory-based INR testing.

- 1.3 Patients and carers should be trained in the effective use of the CoaguChek XS system or the InRatio2 PT/INR monitor and clinicians involved in their care should regularly review their ability to self-monitor.
- 1.4 Equipment for self-monitoring should be regularly checked using reliable quality control procedures. Ensure accurate patient records are kept and shared appropriately.
- 1.5 For people who may have difficulty with or who are unable to self-monitor, such as children or people with disabilities, their carers should be considered to help with self-monitoring.

2 The technologies

- 2.1 Three CE-marked point-of-care coagulometers for self-monitoring coagulation status were identified during scoping as being relevant to this assessment. One of these coagulometers, the ProTime microcoagulation system, was included in the assessment but has been removed from this guidance because it is no longer available to the NHS and its successor model is not intended for patient self-monitoring. Additional details of the coagulometers included in the guidance are provided in section 4.

3 Clinical need and practice

The problem addressed

- 3.1 The point-of-care coagulometers are designed to monitor the clotting tendency of blood in people on long-term vitamin K antagonist therapy, such as those with atrial fibrillation or artificial heart valves who are at risk of thrombosis. The tests allow monitoring by 2 different methods of care: self-testing and self-managing. Both methods are based on the international normalised ratio (INR), which is a standardised unit for measuring the time it takes for blood to clot. Self-testing refers to the user doing the INR test themselves and then contacting their healthcare professional with the reading for advice on any change to the dosage of the anticoagulant that may be needed. Self-managing refers to the user doing the INR test themselves and then self-adjusting the dosage of their anticoagulant medication by following an agreed care protocol. Together, these methods of care are referred to as self-monitoring.
- 3.2 The use of these coagulometers may reduce the frequency of visits to hospital or clinics for patients and enable them to be monitored more regularly. This may improve health outcomes by enabling the dose of therapy to be adjusted more accurately, thereby avoiding adverse events that can result from an over- or under-dose of long-term vitamin K antagonist therapy, such as stroke and major haemorrhage.
- 3.3 The purpose of this assessment is to evaluate the clinical and cost effectiveness of using the CoaguChek XS system and the INRatio2 PT/INR monitor for self-monitoring (self-testing or self-managing) coagulation status in people on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease.

The condition

- 3.4 There are a number of conditions that can result in people having an increased risk of thrombosis and consequently, receiving long-term vitamin K antagonist therapy. These conditions include atrial fibrillation and heart valve disease. Guidance on self-monitoring the coagulation status of people who have had a venous thromboembolism and are receiving long-term vitamin K antagonist therapy is included in [Venous thromboembolic diseases](#) (NICE clinical guideline 144) and so this population is not included in the scope of this diagnostics assessment of self-monitoring coagulometers.

Atrial fibrillation

- 3.5 Atrial fibrillation is the most common heart arrhythmia and affects around 800,000 people in the UK. It can affect adults of any age but it is more common in older people; 0.5% of people aged 50–59 years and around 8% of people aged over 65 years are estimated to be affected. Atrial fibrillation is also more common in men than women, and is more common in people with other conditions, such as high blood pressure, atherosclerosis and heart valve problems.
- 3.6 Approximately 47% of people with atrial fibrillation currently receive vitamin K antagonist therapy. It is estimated that a further 30% of people with atrial fibrillation could receive this therapy but currently do not. People with atrial fibrillation are at a 5–6 times greater risk of stroke, with 12,500 strokes directly attributable to atrial fibrillation occurring every year in the UK. Treatment with warfarin reduces this risk by 50–70%.

Heart valve disease

- 3.7 Valve disease can affect blood flow through the heart in 2 ways: valve stenosis, in which the valve does not open fully, and valve regurgitation (or incompetence) in which the valve does not close

properly, allowing blood to leak backwards. Disease can occur in any of the 4 heart valves, although disorders of the aortic and mitral valves are more serious.

- 3.8 The main causes of heart valve disease are congenital heart disease and other diseases such as rheumatic fever, lupus, cardiomyopathy and endocarditis. Aortic stenosis is the most common type of valve disease and it affects around 1 in 20 adults over the age of 65 years in the UK.
- 3.9 Data from the UK heart valve registry indicate that approximately 0.2% of the UK population has prosthetic heart valves. Around 6500 adult heart valve replacements (using mechanical or biological valves) are carried out each year, of which around 5000 are aortic valve replacements.
- 3.10 Patients with mechanical heart valves (and some patients with bioprosthetic valves) are susceptible to thromboembolism and need lifelong anticoagulant therapy.

The diagnostic and care pathways

- 3.11 New oral anticoagulants are an alternative to vitamin K antagonists and can be administered to reduce the risk of thrombosis or stroke. The new oral anticoagulants have fewer food and drug interactions than vitamin K antagonists and they do not need therapeutic monitoring. However, they may be unsuitable for some people such as people with mechanical heart valves, certain people with renal or liver dysfunction and those taking concurrent drugs that cannot be taken with the new oral anticoagulants. The individual summary of product characteristics should be consulted for specific details when prescribing a new oral anticoagulant. NICE technology appraisal guidance recommends the use of 3 new oral anticoagulants: [apixaban](#), [rivaroxaban](#) and [dabigatran etexilate](#), for

preventing stroke and systemic embolism in people with non-valvular atrial fibrillation.

3.12 [Guidelines on oral anticoagulation with warfarin](#), published by the British Committee for Standards in Haematology (Keeling et al. 2011), outline the process for INR monitoring for those receiving warfarin. The [NICE clinical knowledge summary](#) for oral anticoagulation states that INR can be most accurately measured in venous blood samples, but that capillary blood samples are also used because they are more convenient. People being tested should receive a written copy of their INR result including any necessary dose adjustments and a date for the next check.

3.13 The summary states that the INR should be measured:

- daily, or on alternate days, until it is within the therapeutic range (usually between 2.0 and 3.0, ideally 2.5) on 2 consecutive occasions
- then twice weekly for 1–2 weeks, followed by weekly measurements until the INR is stable within the therapeutic range
- thereafter, depending on the stability of the INR, at longer intervals (for example, up to every 12 weeks, if agreed locally).

3.14 More frequent monitoring of the INR is recommended for patients at risk of overcoagulation or bleeding, or those having problems adhering to treatment. Intravenous drug users, and people with hepatitis B, hepatitis C, or HIV, may be referred to a specialist clinic according to local arrangements.

3.15 INR monitoring can be managed by local anticoagulant clinics in primary care, but sometimes clinics are based in secondary care, involving travel to hospital. [The NICE anticoagulation commissioning guide](#) (2013) states that anticoagulation therapy

services can be delivered in a number of different ways, and that mixed models of provision may be needed across a local health region. This could include full service provision in secondary or primary care, shared provision, domiciliary provision and self-management. Services may be managed by a range of healthcare professionals including nurses, pharmacists and general practitioners.

4 The diagnostic tests

The interventions

The CoaguChek XS system

- 4.1 The CoaguChek XS system (Roche Diagnostics) comprises a meter and specifically designed test strips that can analyse a blood sample (fresh capillary blood or fresh untreated whole venous blood) and calculate the prothrombin time and the international normalised ratio (INR). These measures indicate the rate at which the blood clots. If the INR is too low, there is a higher risk of blood clots that can lead to a heart attack or a stroke. If the INR is too high, there is a higher risk of bleeding, which in severe cases can be gastrointestinal or intracerebral bleeding.
- 4.2 A code chip, which contains calibration data and the expiry date of the test strips, is inserted into the meter before it is switched on. Once the device is switched on, a test strip is inserted and the blood sample is applied. The test result is displayed approximately 1 minute after applying the sample and the monitor automatically stores the result in its memory. The user is guided through the process by on-screen graphical instructions.
- 4.3 The CoaguChek XS test strip contains a lyophilised reagent consisting of thromboplastin and a peptide substrate. When a blood

sample is applied, thromboplastin activates coagulation, which leads to the formation of thrombin. The enzyme thrombin cleaves the peptide substrate, generating an electrochemical signal. Depending on the time elapsed before it first appears, this signal is then converted by means of an algorithm into customary coagulation units and the result is displayed on the screen. This can be displayed as prothrombin time in seconds, quick value, or INR.

- 4.4 The CoaguChek XS system has a number of in-built quality control functions including checks of the electric components when switched on, the test strip temperature during testing, and checks on the test strip batch such as the expiry date and quality of each strip.
- 4.5 The CoaguChek XS meter is supplied with 4 × AAA batteries, a CoaguChek Softclicx finger pricker and 20 Softclicx XL lancets, 6 test strips, a user manual and carry case. The system can carry out about 60 tests per set of batteries. The meter is 138 mm × 78 mm × 28 mm and weighs 127 g (without batteries).
- 4.6 An earlier model of the CoaguChek XS system is the CoaguChek S system. The CoaguChek XS system is reported to have the following advantages over the CoaguChek S system: the thromboplastin used in the prothrombin time test strips is a human recombinant thromboplastin, which is more sensitive and has a lower international sensitivity index of 1.0 compared with 1.6; test strips have inbuilt quality control that is automatically run with every test; test strips do not have to be refrigerated; a smaller blood sample can be used; and the meter is smaller and lighter. Another model of the CoaguChek XS system is the CoaguChek XS Plus system. The XS Plus model is intended for use by healthcare

professionals only and is not indicated for individual INR self-monitoring.

The INRatio2 PT/INR monitor

- 4.7 The INRatio2 PT/INR monitor (Alere) does a modified version of the 1-stage prothrombin time test using a recombinant human thromboplastin reagent. The clot formed in the reaction is detected by the change in the electrical impedance of the sample during the coagulation process. The system consists of a monitor and disposable test strips.
- 4.8 The monitor provides a user interface, heats the test strip to the appropriate reaction temperature, measures the impedance of blood samples, and calculates and reports prothrombin time and INR results. Instructions and test results are displayed on an LCD. The monitor can store the results so that past test results can be reviewed.
- 4.9 The test strip comprises 2 layers of transparent plastic laminated to each other that contain 1 sample well, 3 clot cells, and narrow channels connecting the sample well and the clot cells. The top side of the bottom layer is printed with 3 pairs of silver electrodes (1 pair per cell) that start from inside the clot cells to the end of the strip where they are connected to the monitor main circuitry.
- 4.10 The INRatio2 PT/INR monitor analyses fresh capillary blood and when the blood sample is applied to the sample well, it is drawn through the narrow channels by capillary action to the clot cells, where the impedance of the sample is measured by the monitor through the electrodes. Clot cells have reagents applied and the reagents are different for each channel. One channel contains the thromboplastin reagent for the prothrombin time test. The other 2

channels contain reagents that produce a low and high control time, regardless of the clotting time of the sample.

- 4.11 Initially, the electrode impedance is infinite but drops to a minimum value when the blood sample fills the clot cells. The time when this initial minimum impedance is achieved is registered by the monitor as the start of the coagulation. As the reaction progresses, the sample impedance increases to a maximum and then gradually drops as the clotting proceeds. The elapsed time, in seconds, from the start until the clotting end point is reached is the prothrombin time. The monitor software calculates the INR of the sample using prothrombin time and calibration coefficients.
- 4.12 The INRatio2 PT/INR monitor does a self-test when it is turned on and each test strip has a code that is accepted by the monitor if the strip code is in the correct format. The monitor uses 4 × AA batteries or a mains adapter as a power source, and can connect to a printer or computer through the RS232 serial communication.

The comparator: INR testing

- 4.13 The comparator used in this assessment is INR testing in primary or secondary care using laboratory analysers or point-of-care tests.

5 Outcomes

The Diagnostics Advisory Committee (section 11) considered evidence from a number of sources (section 12).

How outcomes were assessed

- 5.1 The assessment consisted of a systematic review of the evidence on test performance and clinical-effectiveness data for the CoaguChek XS system, the INRatio2 PT/INR monitor, the ProTime microcoagulation system and comparator tests. The ProTime

microcoagulation system was in the assessment but has been removed from this guidance because it is no longer available to the NHS and its successor model is not intended for patient self-monitoring.

Clinical effectiveness

5.2 The External Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of self-monitoring coagulation status in people on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease.

5.3 Studies were included if they appeared relevant to the outcomes listed in the decision problem:

- Intermediate outcomes:
 - time and values in therapeutic range
 - international normalised ratio (INR) values
 - test failure rate
 - time to test result.
- Patient adherence to testing and treatment:
 - frequency of testing
 - frequency of visits to primary or secondary care clinics.
- Clinical outcomes:
 - frequency of bleeds or blood clots
 - morbidity (for example, thromboembolic and cerebrovascular events) and mortality from INR testing and vitamin K antagonist therapy
 - adverse events from INR testing, false test results, vitamin K antagonist therapy and sequelae.
- Patient-reported outcomes:
 - anxiety associated with waiting time for results and not knowing current coagulation status and risk

- acceptability of the tests
- health-related quality of life.

5.4 In total, 26 randomised controlled trials met the inclusion criteria and were included in this assessment. The CoaguChek system was used in 22 of the 26 trials: 9 trials used the CoaguChek S model, 4 trials used the CoaguChek XS model, 1 trial used the CoaguChek Plus model, and 2 trials used the CoaguChek model. It was unclear which model of the CoaguChek system was used in 6 of the 22 trials. In 2 of the remaining 4 trials either the CoaguChek S system or the INRatio monitor were used for INR measurement (results were not reported according to the type of point-of-care monitor, and the model of the INRatio monitor used in the trials was not reported). No trials that exclusively assessed the clinical effectiveness of INRatio were identified. The ProTime microcoagulation system was used in the other 2 trials. In all 6 trials based in the UK, the CoaguChek system (either CoaguChek or version 'S') was used for the INR measurement.

5.5 The evidence on the clinical effectiveness of the coagulometers for monitoring coagulation status was summarised by the External Assessment Group in 3 categories: intermediate outcomes, clinical outcomes, and patient-reported outcomes.

Performance of point-of-care coagulometers

5.6 The External Assessment Group did not carry out a formal evaluation of the performance of the CoaguChek system or the INRatio2 PT/INR monitor with regard to INR measurement because it was outside the scope of this assessment. However, an objective 'true' INR remains to be defined and INR determined in the laboratory is regarded as the gold standard to which all other measurement methods should be compared. Information on the

precision and accuracy of these point-of-care coagulometers was therefore gathered from the available literature.

- 5.7 A systematic review by Christensen and Larsen published in 2012 assessed the precision and accuracy of currently available point-of-care coagulometers including CoaguChek XS, INRatio and ProTime. The authors found that the precision of CoaguChek XS varied from a coefficient of variation of 1.4% to 5.9% based on data from 14 studies. The precision of INRatio and ProTime varied from 5.4% to 8.4% based on data from 6 studies. The coefficient of correlation for CoaguChek XS varied from 0.81 to 0.98, and that for INRatio varied from 0.73 to 0.95. The review concluded that the precision and accuracy of point-of-care coagulometers were generally acceptable compared with laboratory-based INR testing. The same conclusions were drawn by the Canadian Agency for Drugs and Technologies in Health report published in 2012 on point-of-care testing. Similarly, the international guidelines prepared in 2005 by the International Self-Monitoring Association for Oral Anticoagulation stated that 'Point-of-care instruments have been tested in a number of different clinical settings and their accuracy and precision are considered to be more than adequate for the monitoring of oral anticoagulation therapy in both adults and children'.
- 5.8 Six studies compared the performance of CoaguChek S with that of CoaguChek XS in relation to conventional INR measurement. The studies showed a good agreement between the 2 CoaguChek models and conventional laboratory-based testing results. However, the CoaguChek XS showed more accurate and precise results than CoaguChek S in both adults and children, especially for higher INR values (>3.5).

Evidence on intermediate outcomes

Time and values in therapeutic range

- 5.9 Eighteen trials (including 4 trials that used the CoaguChek XS system) reported INR time in therapeutic range although there was variation in the measures used for reporting time in therapeutic range so pooling the data was not appropriate. Time in therapeutic range ranged from 52% to 80% for self-monitoring and from 55% to 77% for standard care. In 15 of the 18 trials, time in therapeutic range was higher in self-monitoring participants compared with those in standard care and, in 5 of these trials (including 2 trials using the CoaguChek XS system), the difference between intervention groups was statistically significant. Three of the UK-based trials reported no statistically significant differences between self-monitoring and standard care.
- 5.10 Twelve trials reported INR values in therapeutic range and there was variation in the measures used so pooling the data was not appropriate. In 8 of these trials, the proportion of INR values in therapeutic range ranged from 43.2% to 80.8% for self-monitoring and from 22.3% to 72.0% for standard care. In 4 trials that reported the proportion of participants in therapeutic range, the values ranged from 53.0% to 72.9% for self-monitoring and from 43.2% to 72.0% for standard care. Ten of the trials reported higher proportions of INR values in therapeutic range or larger proportions of participants in therapeutic range for self-monitoring than for standard care.
- 5.11 Among participants with artificial heart valves, self-monitoring resulted in a statistically significant higher INR time in therapeutic range compared with standard care. In 2 trials that included participants with atrial fibrillation, no time in therapeutic range differences were found between self-monitoring and standard care.

Time to test result

- 5.12 One trial reported the time for each INR monitoring (that is, time from INR measurement to test results) and the total time spent for anticoagulant management during the 4-month follow-up period. The time spent for each INR measurement by self-managed participants was statistically significantly lower (mean 5.3 minutes, standard deviation [SD] 2.6 minutes) compared with the time spent by participants receiving standard care (mean 158 minutes, SD 67.8 minutes, $p < 0.001$). During the 4-month follow-up, the total time spent for anticoagulation monitoring by participants in standard care was statistically significantly higher (mean 614.9 minutes, SD 308.8 minutes) than the total time spent by participants who self-managed their therapy (mean 99.6 minutes, SD 46.1 minutes, $p < 0.0001$).

Patient adherence with testing

- 5.13 One trial reported more than 98% adherence with self-testing and of those who did not adhere, 2 had difficulties doing the test or experienced disruption caused by hospitalisation, and 1 lost the CoaguChek meter. In another trial 75% (30/40) of participants did not report any problems with using the device and expressed willingness to continue with self-monitoring. The remaining participants who did not adhere to the testing procedure (25%) reported difficulties with the technique or problems placing the fingertip blood drop on the right position on the test strip. This resulted in the need to use multiple strips to achieve a single reading.

Evidence on clinical outcomes

Bleeding

- 5.14 Twenty one trials reported a total of 1472 major and minor bleeding events involving 8394 participants. 476 major bleeding events were

reported in a total of 8202 participants and 13 of these 21 trials reported 994 minor bleeding events in a total of 5425 participants. No statistically significant differences were seen between self-monitoring participants (self-testing and self-management) and those in standard care for any bleeding events (relative risk [RR] 0.95, 95% confidence interval [CI] 0.74 to 1.21, $p=0.66$), major bleeding events (RR 1.02, 95% CI 0.86 to 1.22, $p=0.80$) and minor bleeding events (RR 0.94, 95% CI 0.65 to 1.34, $p=0.73$). The results were not affected by removing the UK-based trials or by restricting the included trials to those assessing the CoaguChek system. Similarly, sensitivity analyses restricted to trials using the CoaguChek XS system showed no differences from the all-trials results. A sensitivity analysis restricted to trials at low risk of bias slightly changed the estimate of effect but did not substantially impact on the findings (RR 0.59, 95% CI 0.27 to 1.30, $p=0.19$).

- 5.15 The External Assessment Group did a subgroup analysis by type of anticoagulant management therapy. No difference between self-management and standard care for any bleeding events (RR 0.94, 95% CI 0.68 to 1.30, $p=0.69$) was found but there was a statistically significant higher risk in self-testing participants than in those receiving standard care (RR 1.15, 95% CI 1.03 to 1.28, $p=0.02$). No statistically significant differences in the risk of major bleeding were seen between self-management (RR 1.09, 95% CI 0.81 to 1.46, $p=0.58$) or self-testing (RR 0.99, 95% CI 0.80 to 1.23) compared with standard care. When only minor bleeding events were assessed, there was a statistically significant increased risk in self-testing participants (23%) compared with those in standard care (RR 1.23, 95% CI 1.06 to 1.42, $p=0.005$) but not in those who were self-managing (RR 0.84, 95% CI 0.53 to 1.35, $p=0.47$).

- 5.16 Of the 21 trials, 2 trials enrolled participants with atrial fibrillation, 6 trials enrolled participants with artificial heart valves and 13 trials

enrolled participants with mixed indication. No statistically significant subgroup differences were found for bleeding events according to the type of clinical indication or the type of control standard care.

Thromboembolic events

- 5.17 Twenty one trials reported 351 major and minor thromboembolic events in a total of 8394 participants. Self-monitoring (self-testing and self-management) showed a statistically significant reduction in the risk of thromboembolic events by 42% (RR 0.58, 95% CI 0.40 to 0.84, $p=0.004$) compared with standard care. The risk reduction further increased to 48% when only major thromboembolic events were considered (RR 0.52, 95% CI 0.34 to 0.80, $p=0.003$). The risk of thromboembolic events substantially decreased when the analyses were restricted to non-UK trials (RR 0.50, 95% CI 0.32, 0.76, $p=0.001$); to CoaguChek trials (RR 0.52, 95% CI 0.38, 0.71, $p<0.0001$); and to trials at low risk of bias (RR 0.38, 95% CI 0.16 to 0.92, $p=0.03$).
- 5.18 Self-management halved the risk of thromboembolic events compared with standard care (RR 0.51, 95% CI 0.37 to 0.69, $p<0.0001$). In contrast, there was no statistically significant risk reduction for self-testing compared with standard care (RR 0.99, 95% CI 0.75 to 1.31, $p=0.56$). The subgroup difference between self-management and self-testing was statistically significant ($p=0.002$). Self-monitoring participants with artificial heart valves showed a statistically significant reduction in the number of thromboembolic events compared with those in standard care (RR 0.56, 95% CI 0.38 to 0.82, $p=0.003$). No statistically significant effect was shown among self-monitoring participants with mixed clinical indication (atrial fibrillation, artificial heart valves, or other conditions) compared with participants receiving standard care.

Mortality

- 5.19 Thirteen trials reported 422 deaths due to all-cause mortality in a total of 6537 participants. The risk reduction for all-cause mortality was not statistically significant between self-monitoring (self-testing and self-management) and standard care (RR 0.83, 95% CI 0.63 to 1.10, $p=0.20$).
- 5.20 Risk of death reduced by 32% through self-management (RR 0.68, 95% CI 0.46 to 1.01, $p=0.06$) but not through self-testing (RR 0.97, 95% CI 0.78 to 1.19, $p=0.74$) even though the test for subgroup differences was not statistically significant ($p=0.13$). Self-monitoring halved the risk of mortality in participants with artificial heart valves (RR 0.54, 95% CI 0.32 to 0.92, $p=0.02$) but not in those with mixed clinical indication for anticoagulant therapy (RR 0.95, 95% CI 0.78 to 1.16, $p=0.61$). The subgroup difference between participants with artificial heart valves and those with mixed indication with regard to the number of deaths was statistically significant ($p=0.05$). No data were available from trials that enrolled participants with atrial fibrillation. Statistically significantly fewer deaths were recorded among participants who self-monitored their therapy compared with those who were routinely managed by their GP/doctor (RR 0.52, 95% CI 0.30 to 0.90, $p=0.02$).

Evidence on patient-reported outcomes

Anxiety associated with waiting time for results and not knowing current coagulation status and risk

- 5.21 One trial ($n=28$) compared self-management with self-testing in children and reported that 1 parent did not favour self-management because of the increased anxiety about INR measurements.

Acceptability of the tests

- 5.22 Four trials conducted a questionnaire survey to assess acceptability to participants of self-testing and self-management using point-of-care devices. These trials reported high rates of acceptance for both self-management and self-testing (77% to 98%).
- 5.23 One of these trials reported that 93% of participants rated their satisfaction with regard to self-monitoring (using either the INRatio monitor or the CoaguChek S system) as high or good. When asked about the overall relative satisfaction with the device, 43% of participants favoured the INRatio monitor, 36% the CoaguChek S system, and 21% both devices in equal way. One trial conducted in children reported that most participants (13 out of 14 participating families, 92%) opted for the CoaguChek XS device.
- 5.24 An unpublished review from the National Thrombosis Service in the Netherlands reported the INR values from over 5000 patients on vitamin K antagonist therapy using either the CoaguChek XS system or the INRatio2 PT/INR monitor for self-monitoring. The review reported that the INR values within therapeutic range were comparable between the monitors. The other results in the review were considered academic in confidence by the manufacturer and therefore cannot be reported here.

Health-related quality of life

- 5.25 Health-related quality-of-life outcomes were reported in 9 trials using a variety of different measures. Four trials used Sawicki's questionnaire to measure quality of life, and substantially greater improvements in treatment satisfaction and self-efficacy were reported in the self-management arm compared with the standard care arm of the trials. All 4 trials reported a reduced level of distress

and daily inconvenience although 1 trial reported an increased level of distress in participants who received education but did not directly monitor their anticoagulation therapy.

- 5.26 Two UK-based trials reported no substantial differences in quality-of-life outcomes between self-monitoring participants and those receiving standard care. One trial reported quality-of-life data using the UK SF-36, the EuroQol scores and Lancaster's instrument. The other trial assessed themes that were adapted from the Lancaster tool, the SEIQol tool and a series of focus groups. Five common themes emerged from the interviews on self-management: knowledge and management of condition and self-empowerment, increased anxiety and obsession with health, self-efficacy, relationship with healthcare professionals, and societal and economic cost. One trial, conducted in the Netherlands, measured quality of life in people with artificial heart valves by using the SF-36v2. Substantial improvements in quality-of-life scores in the physical component summary were reported in people who self-managed their therapy compared with those receiving standard care.
- 5.27 Another trial measured quality of life by means of the Health Utilities Index Mark 3. It reported a statistically significant gain in health utilities at the 2-year follow-up among self-testing participants compared with those managed in high quality anticoagulant clinics ($p < 0.001$). The same investigators also measured anticoagulant satisfaction using Duke Anticoagulation Satisfaction Scale. They found that the degree of satisfaction was higher in self-testing participants compared with those in standard care ($p = 0.002$).
- 5.28 One trial compared self-management with self-testing in children and provided quality-of-life data using the KIDCLOT PAC QL

parent-proxy (parents' quality of life and their assessment of child's quality of life) and the child teen KIDCLOT PAC QL. The 5 common themes identified were: awareness, communication, relationship between parent and child, flexibility and anxiety.

Costs and cost effectiveness

5.29 The External Assessment Group conducted a systematic review to identify existing economic analyses for self-monitoring coagulation status. The review also sought to identify potentially relevant evidence sources to inform parameter values for the de novo economic model developed by the External Assessment Group. The de novo economic model constructed aimed to assess the cost effectiveness of self-monitoring coagulation status using the CoaguChek XS system, the INRatio2 PT/INR monitor or the ProTime microcoagulation system. The ProTime microcoagulation system was included in the assessment but has been removed from this guidance because it is no longer available to the NHS and its successor model is not intended for patient self-monitoring.

Systematic review of cost-effectiveness evidence

5.30 The systematic review identified 12 relevant economic evaluations. All of these evaluations compared INR self-monitoring strategies with standard care and were assessed against the NICE reference case by the External Assessment Group. The results of the studies included in the systematic review varied widely and showed that the cost effectiveness of self-monitoring was dependent on a number of key factors.

5.31 The adopted perspective and the initial costs associated with self-monitoring appeared to substantially affect the cost effectiveness. Self-monitoring strategies appeared more favourable than standard care when a wider societal perspective was adopted, as a result of lower time costs associated with fewer health service contacts. The

size of the estimates of effect applied to self-monitoring in reducing thromboembolic and bleeding events compared with those applied to standard care also appeared to affect cost effectiveness. The 2 UK-based evaluations applied effect estimates consistent with small or negligible differences between self-management and usual care with respect to time in therapeutic range and adverse thromboembolic and haemorrhagic events. This resulted in a low probability of self-monitoring being cost effective. Several studies that applied large effect estimates resulted in a high probability of self-monitoring being cost effective.

- 5.32 The 2 UK-based economic evaluations were based on data from the same trial. One evaluation adopted an NHS and wider societal perspective, and the other adopted an NHS and personal social services perspective. Self-monitoring strategies appeared to increase the costs of INR monitoring in the short term and because these 2 evaluations applied small effect estimates, consistent with those seen in the largest UK-based trial of patient self-management, self-monitoring of INR appeared unlikely to be cost effective. However, no UK-based trials have been sufficiently powered to detect a statistically significant difference between standard INR monitoring and patient self-monitoring in terms of major thromboembolic or haemorrhagic events. Therefore, the External Assessment Group carried out a meta-analysis of relevant trials including evidence from a number of European trials in which standard care is similar to that provided in the UK in terms of approach, frequency of testing and the level of INR control achieved.

Economic analysis

- 5.33 The External Assessment Group developed a de novo economic model designed to assess the cost effectiveness of self-monitoring

(self-managing and self-testing) coagulation status using 2 different point-of-care coagulometers: the CoaguChek XS system and the INRatio2 PT/INR monitor.

Model structure

- 5.34 The structure of the Markov model was based on the review of published models of INR self-monitoring and previous models evaluating the cost effectiveness of new anticoagulant drugs compared with warfarin therapy in people with atrial fibrillation. A further unpublished economic model of INR self-monitoring was provided by the manufacturer of CoaguChek XS, and this model was also used to inform the structure of the new economic model.
- 5.35 The Markov model compared the alternative monitoring strategies for a hypothetical cohort of people with atrial fibrillation or an artificial heart valve, and was used to simulate the occurrence of thromboembolic and bleeding events over a 10-year period. People with atrial fibrillation or an artificial heart valve represent the majority of people on long-term vitamin K antagonist therapy. The model simulated transitions between the discrete health states, and accumulated costs and quality-adjusted life years (QALYs) on a quarterly (3 month) cycle. Within each cycle, the simulated cohort was exposed to a risk of the adverse events as well as death from other causes. The adverse events included in the model were ischaemic stroke (minor, non-disabling, and major, disabling or fatal), systemic embolism, minor haemorrhage, and major haemorrhage (intra-cranial haemorrhage, including haemorrhagic stroke, gastrointestinal bleed, and others). A constraint was applied whereby the simulated cohort in the model could only experience 1 event per cycle.

Model inputs

- 5.36 The model was populated using data derived from the systematic clinical effectiveness review, other additional focused reviews to inform key parameters (for instance baseline risks), routine sources of cost data, and where necessary some study-specific cost estimates based on expert opinion.

Costs

- 5.37 Data on the resource use and costs associated with the alternative monitoring strategies were informed by published literature, existing guidance, expert opinion, manufacturers' and suppliers' prices, and other routine sources of unit cost data. Some costs were informed by expert opinion where suitable data from other sources were not available.

Health-related quality of life

- 5.38 The baseline utility value for people with atrial fibrillation or mechanical heart valve who were stable was taken as the baseline EQ-5D value from trial data, 0.738. This value was applied to 65–70 year old people and adjusted by the External Assessment Group to estimate age-specific baseline utilities in the model.
- 5.39 Utilities associated with acute events were applied for the 3-month period after the event. For post-event states with associated ongoing morbidity, the appropriate health state utilities were applied for all subsequent cycles spent in these states. Half cycle corrections were applied, by assuming that people experienced events on average at the mid-point of the cycle. Thus a patient starting off in the well state and experiencing a major stroke in a given cycle of the model, would accrue 6 weeks at the utility value for well and 6 weeks at the utility value for major stroke.

Base-case analysis

- 5.40 For the purposes of decision-making, the incremental cost-effectiveness ratios (ICERs) per QALY gained were considered. The following assumptions were applied in the base-case analysis:
- 66.45% of standard care monitoring was done in primary care by practice nurses.
 - 60% of the cohort had atrial fibrillation and 40% had an artificial heart valve.
 - Average age of the cohort was 65 years, and 55% were male.
 - 50% of people who self-monitor did self-testing and 50% self-managed.
 - The increase in the number of tests done per year with self-monitoring was 23 (that is, 35 tests compared with 12 tests in standard care).
 - Relative treatment effects were estimated and applied separately for self-testing and self-management.
 - 15% of participants did not start self-monitoring after training (training failure).
 - 10% of participants stopped self-monitoring within a year of starting.
 - Self-monitoring device costs were annuitized over 5 years.
 - 75% of devices were reused by another patient when a patient stopped self-monitoring.
- 5.41 The results indicated that over a 10-year period, introducing self-monitoring would reduce the proportion of people experiencing a thromboembolic event by 2.5%, while slightly increasing the proportion having a major haemorrhagic event by 1.4%.
- 5.42 The predicted monitoring costs were higher with self-monitoring compared with standard monitoring, but the total health and social

care costs were similar and in some cases lower. The QALY gains were greater for self-monitoring than standard monitoring. For all of the self-monitoring coagulometers there was a QALY gain of 0.027 compared with standard monitoring. Self-monitoring with the INRatio2 PT/INR monitor was £29 cheaper than standard monitoring. Self-monitoring with the CoaguChek XS system was £37 more expensive than standard monitoring. Therefore, in the base-case scenario, the self-monitoring strategies compared favourably with standard care. The INRatio2 PT/INR monitor dominated standard monitoring in the analysis because it was less costly and more effective. The ICER for the CoaguChek XS system was £319 per QALY gained compared with standard monitoring. The lower cost of the INRatio2 PT/INR monitor and testing strips, coupled with the assumption of equivalent clinical effectiveness, meant that the INRatio2 PT/INR monitor also dominated the CoaguChek XS system. However, it should be noted that no direct evidence of clinical effectiveness was identified exclusively for the INRatio2 PT/INR monitor from the systematic review.

Analysis of alternative scenarios

5.43 Several scenario analyses were done by the External Assessment Group:

- exclusive self-testing or self-management compared with standard monitoring in primary and secondary care
- exclusive primary or secondary care clinic testing compared with self-monitoring in primary and secondary care
- different pooled risk estimates applied.

5.44 For the exclusive self-management strategy, the INRatio2 PT/INR monitor and the CoaguChek XS system dominated standard monitoring under the base-case assumptions, whereas for the exclusive self-testing strategy, the ICERs were above £2 million per

QALY gained compared with standard monitoring. The results also showed that for a mixed self-monitoring strategy (50% self-testing, 50% self-management), the CoaguChek XS system and the INRatio2 PT/INR monitor dominated standard monitoring when exclusively carried out in secondary care. When applying the pooled relative risk estimates for adverse events (derived from all self-monitoring studies) to both self-testing and self-managing participants, the cost savings and QALY gains associated with self-monitoring increased.

- 5.45 The External Assessment Group carried out alternative non-base-case scenarios, to assess the impact of using self-monitoring to replace standard monitoring tests (that is, no increase in the number of tests done annually). It was assumed that there was no difference in clinical effectiveness between self-management, self-testing and standard care. Under most of these scenarios, standard monitoring was found to be less costly than self-monitoring. However, self-testing and self-management with the INRatio2 PT/INR monitor and the CoaguChek XS system dominated standard monitoring when carried out exclusively in secondary care.
- 5.46 Subgroup analyses showed the cost effectiveness of self-monitoring compared with standard care, stratified by indication (atrial fibrillation and artificial heart valves) and cohort age. Self-monitoring in a '65 years old with atrial fibrillation' cohort was estimated to cost £2574 per QALY gained when using the INRatio2 PT/INR monitor and £4160 per QALY gained when using the CoaguChek XS system, compared with standard monitoring. For a '65 years old with artificial heart valve' cohort, self-monitoring with the INRatio2 PT/INR monitor and the CoaguChek XS system was found to be more effective and less costly (dominant) compared with standard monitoring.

5.47 A further analysis was carried out for the atrial fibrillation cohort using the baseline risks seen for participants with better INR control in standard care, assuming a constant relative risk reduction for thromboembolic events associated with self-monitoring. As the INR time in therapeutic range increased in the control group, and the baseline risk of thromboembolic events consequently dropped, the cost effectiveness of self-monitoring also decreased. However, the ICERs for the CoaguChek XS system and the INRatio2 PT/INR monitor only rose above £20,000 per QALY gained when the baseline time in therapeutic range was set at greater than 72.6%.

Sensitivity analyses

5.48 Deterministic sensitivity analysis showed that the model-based findings were most sensitive to the baseline risk of thromboembolic events and the effectiveness of self-monitoring for preventing these events. The ICERs for the self-monitoring strategies rose above £30,000 per QALY gained when the baseline risk was set to 1.15% and the upper confidence limit for the relative risk of thromboembolic events associated with self-management (RR 0.69) was applied. The same was found when the lower baseline risk of thromboembolic events was coupled with the upper confidence limit of the pooled relative risk for self-monitoring (RR 0.89). It should be noted however that self-management on its own remained cost saving under the former combined scenario.

5.49 A sensitivity analysis was also conducted to approximate the cost effectiveness of self-monitoring for a cohort of children with an artificial heart valve on long-term vitamin K antagonist therapy. For this analysis, the cohort age was set to 10, the baseline risk of thromboembolic events was reduced to 1.4%, and the standardised mortality ratio for all-cause mortality following a stroke was set at 14.5. Under this scenario, self-monitoring with the CoaguChek XS

system and the INRatio2 PT/INR monitor dominated standard monitoring. However, it should be noted that the standardised mortality ratio estimated for an 18–55 year old cohort of people with artificial heart valves was applied because no robust data were identified to appropriately adjust the risk of death from all causes in children with an artificial heart valve.

- 5.50 Probabilistic sensitivity analyses of the base case were done to examine the uncertainty in the cost effectiveness of self-monitoring. Self-monitoring with the CoaguChek XS system and the INRatio2 PT/INR monitor were estimated to have an 80% and 81% probability of being cost effective if the maximum acceptable ICER was £20,000 per QALY gained, respectively. However, it should be noted that there is no direct randomised controlled trial evidence to show the clinical effectiveness of the INRatio2 PT/INR monitor.

6 Considerations

- 6.1 The Diagnostics Advisory Committee reviewed the evidence available on the clinical and cost effectiveness of self-monitoring coagulometers for self-testing or self-managing coagulation status in people on long-term vitamin K antagonist therapy who have atrial fibrillation or heart valve disease.
- 6.2 The Committee considered the clinical evidence on the use of point-of-care coagulometers in people with atrial fibrillation or artificial heart valves. The Committee noted that 26 randomised controlled trials compared the use of point-of-care coagulometers for self-monitoring with standard anticoagulation control. The Committee noted that self-monitoring nearly halved the risk of thromboembolic events and substantially reduced the risk of mortality in people with artificial heart valves compared with standard monitoring. However, the Committee also noted that self-

monitoring did not result in a statistically significant reduction in the number of major and minor bleeding events compared with standard monitoring. The Committee discussed the heterogeneity in the trials and the applicability of the pooled results from the meta-analysis of the trial data to the UK population. It noted that the meta-analysis results showed low statistical heterogeneity and concluded that self-monitoring offered clinical benefit because it was likely to result in a significant reduction in thromboembolic events. The Committee concluded that the pooled effect estimates from the meta-analysis were likely to be applicable to the UK because there are no confounding biological differences between people receiving vitamin K antagonist therapy in the UK and those in other countries.

- 6.3 The Committee discussed that 22 of the 26 trials included in the assessment investigated the use of the CoaguChek system and considered the different versions of the CoaguChek systems used in these trials. The Committee noted that there are substantial technical differences between the CoaguChek S system and the CoaguChek XS system and heard from clinical specialists and the manufacturer that changes had been made to the different versions to improve reliability and accuracy. The Committee considered the performance of the CoaguChek S and XS systems compared to the gold standard of laboratory-based INR testing and noted that the precision and accuracy of the 2 CoaguChek versions correlated with that of laboratory-based measurements. The Committee concluded that results from the CoaguChek XS system were likely to be at least as good as those obtained from trials in which previous versions of the system were used. The Committee also noted that 4 of the 22 trials investigated the use of the CoaguChek XS system and that 2 of these trials demonstrated a significant improvement in time in therapeutic range. The

Committee concluded that it was appropriate to pool the results of trials using different versions of the CoaguChek system and that these pooled results could demonstrate the clinical effectiveness of self-monitoring using the CoaguChek XS version of the system.

6.4 The Committee considered the evidence for the 2 different self-monitoring coagulometers; the CoaguChek XS system and the INRatio2 PT/INR monitor. The Committee noted that 22 of the 26 trials included in the assessment investigated the use of the CoaguChek system and noted that there was no direct randomised controlled trial evidence to show the clinical effectiveness of the INRatio2 PT/INR monitor. The Committee considered the evidence that showed the 2 coagulometers had a broadly similar performance in precision and accuracy with regard to time in therapeutic range measurement when compared with the gold standard of laboratory-based INR testing and therefore concluded that it was appropriate to extrapolate the clinical-effectiveness data from the CoaguChek system to the INRatio2 PT/INR monitor.

6.5 The Committee discussed the usability of the coagulometers and noted that small differences in devices can sometimes result in large differences in behaviour. The Committee considered the results of the systematic review by Christensen and Larsen (2012) and the unpublished review of over 5000 patients from the National Thrombosis Service in the Netherlands. It noted that although the unpublished review could not be considered methodologically robust, the results supported the findings of the systematic review that suggested that the INR values within therapeutic range were comparable between the CoaguChek XS system and the INRatio2 PT/INR monitor. The other results in the unpublished review were considered academic in confidence by the manufacturer and therefore cannot be reported here. The Committee concluded that any potential differences in the usability of the coagulometers did

not appear to affect their ability to measure INR. The Committee encouraged the publication of the review from the National Thrombosis Service in the Netherlands.

6.6 The Committee considered the differences in clinical outcomes between people who were self-managing their anticoagulation control and those who were self-testing. The Committee noted that there was a statistically significantly greater reduction in thromboembolic events among people who self-managed compared with those who self-tested. The Committee also noted that when only minor bleeding events were assessed, a statistically significantly increased risk was seen in self-testing participants compared with those in standard care. All-cause mortality was lower through self-management but not through self-testing. The Committee discussed possible reasons for the differences in results between self-managing and self-testing, and it heard from clinical specialists that people who self-manage their coagulation control may behave differently to those who self-test because they have greater responsibility for managing their coagulation control. The Committee noted that the largest trial in the assessment of self-testing did not show a reduction in clinical adverse events but did show an increase in the time in therapeutic range (Matchar et al. 2010). The Committee also noted that this trial had a high standard of coagulation control in the control arm, which could explain why no statistically significant difference in clinical adverse events was detected between the self-testing group and the standard care group. The Committee concluded that the high standard of coagulation control in the control arm of the trial may not reflect general UK clinical practice and so it was plausible that the increase in time in therapeutic range would lead to a statistically significant reduction in clinical adverse events if compared with UK standard coagulation control practice. The Committee concluded

that self-testing and self-managing were likely to be clinically effective and that self-testing was often a step towards self-management in clinical practice.

- 6.7 The Committee considered the clinical evidence for using self-monitoring in the population group with atrial fibrillation. The Committee noted that only 2 trials investigated self-monitoring in people with atrial fibrillation and 19 trials investigated self-monitoring in a mixed population that included people with atrial fibrillation. The Committee heard from clinical specialists that the clinical outcomes for people with atrial fibrillation are similar to those for people with artificial heart valves. The Committee also heard that people with artificial heart valves may be a younger population than people with atrial fibrillation. The Committee noted that it was not possible to isolate the data for people with atrial fibrillation from the mixed populations investigated in the 19 trials but concluded that it was likely that self-monitoring would result in similar clinical benefits in people with atrial fibrillation to those achieved in people with artificial heart valves.
- 6.8 The Committee considered the cost-effectiveness analysis carried out by the External Assessment Group on self-monitoring. In the base-case analysis, self-monitoring with the CoaguChek XS system resulted in an incremental cost-effectiveness ratio (ICER) of around £300 per quality-adjusted life year (QALY) gained (based on the pooled effect estimates from the meta-analysis) compared with standard monitoring. Self-monitoring with the INRatio2 PT/INR monitor dominated (that is, was less expensive and more effective than) the CoaguChek XS system and standard care, although the Committee noted that there was no direct randomised controlled trial evidence for the clinical effectiveness of the INRatio2 PT/INR monitor so clinical effectiveness equivalent to the CoaguChek XS system was assumed in the base case. The Committee concluded

that self-monitoring with the CoaguChek XS system is cost effective in light of the reduction in thromboembolic events seen in the pooled results of the trial data. However, although the INRatio2 PT/INR monitor dominated standard monitoring in the base-case analysis, the Committee did not consider this result to be as robust as that for the CoaguChek XS system because there was no direct evidence of clinical effectiveness for the INRatio2 PT/INR monitor that showed a reduction in thromboembolic events. The Committee noted the similar performance of the CoaguChek XS system and the InRatio2 PT/INR monitor compared with the gold standard of laboratory-based INR testing and concluded therefore that self-monitoring with the INRatio2 PT/INR monitor was likely to represent a cost-effective use of NHS resources.

- 6.9 The Committee considered the cost effectiveness of self-testing and self-managing individually. The findings showed that self-management alone is highly cost effective (dominant) but that self-testing alone is not cost effective, compared with standard monitoring. The Committee noted that these findings were based on the contrasting pooled-effect estimates obtained from the meta-analysis of randomised controlled trials, based on thromboembolic events while self-testing and self-managing. The Committee discussed the impact of 1 large trial by Matchar et al. (2010) (see section 6.5) on the cost effectiveness of self-testing and noted that although this trial did not show a reduction in clinical adverse events, it did show an increase in the time in therapeutic range. The Committee discussed the impact on the ICERs for self-testing if the economic model was driven by time in therapeutic range rather than adverse events. The Committee concluded that self-testing may be more cost effective if the model had been based on time in therapeutic range. The Committee also considered the costs of self-managing and self-testing and noted that self-testing

was more expensive because of higher administration costs. The Committee heard from the External Assessment Group that if the pooled-effect estimates from self-monitoring were applied to self-testing, self-testing would become cost effective even with the higher administration costs this incurred. The Committee concluded that it was likely that the increase in time in therapeutic range shown for self-testing in the trial would lead to a reduction in adverse events compared with standard clinical practice in the UK. The Committee therefore concluded that it was likely that the clinical benefits of self-testing had been underestimated in the economic analyses and that both self-testing and self-managing were cost effective.

6.10 The Committee considered the impact on people whose anticoagulation therapy is monitored by standard clinical practice. The Committee acknowledged the additional costs and inconvenience for patients of travelling to specialist clinics or hospital to be monitored. The Committee also noted the loss in productivity through absence from work or school to attend clinic appointments. The Committee acknowledged these costs were incurred outside the healthcare system and therefore not included in the reference case; however, it considered that self-monitoring may reduce the costs and inconvenience incurred by the patient. The Committee also noted that monitoring anticoagulation therapy can have a substantial impact on the quality of life of patients and their families because of the anxiety associated with the risks of bleeding and the consequent behavioural changes such as the length of time they are willing to spend away from home or the distances they are willing to travel. The Committee concluded that the main benefits of self-monitoring involve reducing the substantial burden associated with monitoring anticoagulation therapy for the patient and their families.

- 6.11 The Committee considered the different methods of self-monitoring for people having long-term vitamin K antagonist therapy. The Committee heard from a clinical specialist that computer algorithms may be used by some services to determine dose adjustments. The Committee noted that the cost of software licensing had not been included in the cost-effectiveness analyses and it discussed the implications of computer-based dosing for people who would self-manage their coagulation status. The Committee heard that there were alternative methods to determine dose adjustments and that a lack of internet access should not restrict a person's access to self-monitoring. The Committee considered an additional analysis by the External Assessment Group that investigated the impact of an additional cost for dose adjustment software on the base-case ICERs for self-managing. The Committee noted that the additional cost of software would need to be greater than £190 per patient per year to substantially affect the cost-effectiveness of self-managing with the coagulometers. The Committee concluded that the additional cost of software was unlikely to exceed this value and therefore, even with this potential additional cost, self-managing with the point-of-care coagulometers would still represent a cost-effective use of resources in the NHS.
- 6.12 The Committee considered the benefits for patients receiving vitamin K antagonist therapy of using point-of-care coagulometers. It heard from a patient expert on the Committee that self-monitoring is important to psychological wellbeing because it provides a sense of control for the patient and removes the need to frequently attend clinics or hospitals, which serve as a constant reminder of their condition. The Committee also heard that self-monitoring allows people to travel to visit, or act as a carer for, other family members, without having to worry about attending testing appointments or if testing facilities are available in other countries. The Committee

also heard that the current variation in access to self-testing strips on prescription for self-monitoring was of concern to patients because it restricted their freedom to move GP practice or move house to a different area in case the testing strips would no longer be prescribed. The Committee concluded that the benefits of self-monitoring for patients were not fully captured in the cost-effectiveness analyses.

- 6.13 The Committee considered the similarities between self-monitoring coagulation status and self-managing diabetes. The Committee heard from a patient expert that some patients are used to self-testing for conditions such as diabetes, hypertension and heart conditions. The Committee also heard from a clinical specialist that although there were similarities between self-testing for different conditions, there were intrinsic differences between self-testing for diabetes and coagulation. Vitamin K antagonists are more sensitive to diet and exercise, and act over a longer period of time than insulin. Therefore, the dose response for vitamin K antagonists is less predictable than for insulin and the risk of adverse events is perceived to be higher. The clinical specialist also reported that some patients were successfully self-monitoring their coagulation status but not all people receiving vitamin K antagonist therapy will be able to self-monitor and some may not wish to. The Committee noted that some groups of patients who may have difficulty with self-monitoring, such as children or those with a disability, may be able to self-test or self-manage with the help of a carer. The Committee concluded that there are different considerations for self-monitoring of coagulation status to those made for self-testing for diabetes, and that the decision for a patient to self-monitor should be made after a thorough discussion and subsequent agreement between the patient and the healthcare professional.

6.14 The Committee considered the impact of the increasing use of new oral anticoagulant drugs, which do not involve monitoring because of their predictable dose response. It heard from clinical specialists that there are factors that may influence clinical decisions and affect the number of people receiving warfarin: people receiving warfarin who have stable INRs are unlikely to switch to new oral anticoagulants because of the risk of destabilising their INR when switching between different anticoagulant therapies, and the new oral anticoagulants may be unsuitable for some, such as people with mechanical heart valves, certain people with renal or liver dysfunction or those taking drugs that cannot be taken at the same time as the new oral anticoagulants. The Committee also heard from clinical specialists that clinical concerns remain about the use of the new oral anticoagulants because there is currently no reliable way to reverse bleeding should it occur, and there is currently no test that can reliably monitor the level of the drugs or assess patient adherence to treatment because of the shorter half-life of the drugs. The Committee concluded that, because the new oral anticoagulants would not be suitable for all people who need anticoagulant therapy, and there are many people who will receive warfarin therapy rather than new oral anticoagulant therapy, self-monitoring coagulometers are still of clinical importance to the NHS and patients.

6.15 The Committee considered the need for quality control of individual patient coagulometers. The Committee heard from a clinical specialist that the National External Quality Assessment Service runs a scheme to ensure the accuracy of coagulometers used by healthcare professionals, and coagulometers used by patients could be checked against a professional coagulometer to ensure accuracy. The Committee concluded that this was a reliable method of ensuring accuracy of individual coagulometers.

7 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

8 Related NICE guidance

- [Apixaban for preventing stroke and systemic embolism in people with nonvalvular atrial fibrillation](#). NICE technology appraisal guidance 275 (2013).
- [Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation](#). NICE technology appraisal guidance 256 (2012).
- [Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation](#). NICE technology appraisal guidance 249 (2012).
- [Venous thromboembolic diseases](#). NICE clinical guideline 144 (2012).
- [Stroke](#). NICE clinical guideline 68 (2008).
- [Anticoagulation therapy service commissioning guide](#) NICE commissioning guide (2013).
- [Atrial fibrillation](#). NICE clinical guideline 36 (2006).

9 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Adrian Newland

Chair, Diagnostics Advisory Committee

April 2014

10 Diagnostics Advisory Committee members and NICE project team

Diagnostics Advisory Committee

The Diagnostics Advisory Committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this assessment appears below.

Standing Committee members

Professor Ron Akehurst

Professor in Health Economics, School of Health and Related Research (ScHARR), University of Sheffield

Dr Trevor Cole

Consultant Clinical and Cancer Geneticist, Birmingham Women's Hospital

Dr Paul Collinson

Consultant Chemical Pathologist and Professor of Cardiovascular Biomarkers, St George's Hospital

Dr Sue Crawford

General Practitioner (GP) Principal, Chillington Health Centre

Professor Ian A Cree

Senior Clinical Advisor, NIHR Evaluation Trials and Studies Coordinating Centre, University of Southampton

Professor Erika Denton

National Clinical Director for Imaging, NHS England, Honorary Professor of Radiology, University of East Anglia and Norfolk and Norwich University Hospital

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

David Evans

Lay member

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Professor Noor Kalsheker

Professor of Clinical Chemistry, University of Nottingham

Dr Mark Kroese

Vice Chair, Diagnostics Advisory Committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Dr Peter Naylor

General Practitioner (GP), Chair Wirral Health Commissioning Consortia

Professor Adrian Newland

Chair, Diagnostics Advisory Committee

Dr Richard Nicholas

Consultant Neurologist; Honorary Senior Lecturer, Heatherwood and Wexham Park Hospitals

Dr Gail Norbury

Consultant Clinical Scientist, Guys Hospital

Dr Diego Ossa

Director of Market Access Europe, Novartis Molecular Diagnostics

Mr Stuart Saw

Director of Finance, North East London and the City PCTs

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist at Sheffield Teaching Hospitals
Foundation Trust

Mr Paul Weinberger

CEO, DiaSolve Ltd, London

Mr Christopher Wiltsher

Lay member

Specialist Committee members

Mr Peter Birtles

Lay member

Mrs Diane Kitchen

Specialist Scientific Lead for Point-of-Care Programmes

Dr Niall O'Keefe

Clinical Lead Cardiothoracic Anaesthesia and Intensive Care

Dr Peter MacCallum

Senior Lecturer in Haematology

Ms Dianna Oxley

Lay member

Dr Rishabh Prasad

End of Life Clinical Lead, Leicester City Clinical Commissioning Group

Ms Sue Rhodes

Anticoagulant and VTE lead

NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Dr Sarah Byron

Topic Lead and Technical Adviser

Robert Fernley

Project Manager

11 Sources of evidence considered by the Committee

The diagnostics assessment report for this assessment was prepared by the Aberdeen HTA group:

Sharma P, Scotland G, Cruickshank M et al. Clinical and cost-effectiveness of point-of-care tests (CoaguChek system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for the self-monitoring of the coagulation status of people receiving long-term vitamin K antagonist therapy compared with standard UK practice: systematic review and economic evaluation.

November 2013.

Registered stakeholders

The following organisations accepted the invitation to participate in this assessment as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers/sponsors:

- Roche Diagnostics
- Alere Ltd.

Professional/specialist and patient/carer groups:

- Atrial Fibrillation Association
- Airedale, Wharfedale and Craven Clinical Commissioning Group
- AntiCoagulation Europe (ACE)
- Arrhythmia Alliance
- British Cardiac Patients
- British Society for Haemostasis and Thrombosis
- Children's Heart Federation
- Department of Health
- Healthcare Improvement Scotland

- HeartLine
- Lifeblood: The Thrombosis Charity
- Medicines and Healthcare products Regulatory Agency
- National Clinical Guidelines Centre
- NHS England
- NHS Improving Quality
- Pfizer
- Royal College of Nursing
- Royal College of Pathologists
- Visea Consultancy Ltd
- Welsh Government.