National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Self-monitoring coagulometers (CoaguChek XS system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for self-testing or self-managing coagulation status in people with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy is intended

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. It includes a brief description of the topic, a description of the analytical structure and model, a discussion of the analytical difficulties, and a brief summary of the results. It is not a complete summary of the diagnostics assessment report, and it is assumed that the reader is familiar with that document. This overview contains sections from the original scope and the diagnostics assessment report, as well as referring to specific sections of these documents.

1 Background

1.1 Introduction

The Coaguchek XS system (Roche Diagnostics) was selected by the Medical Technologies Advisory Committee (MTAC) for the Diagnostics Assessment Programme to develop recommendations on its use in the NHS. Two other point-of-care coagulometers, the INRatio2 PT/INR monitor (Alere) and ProTime Microcoagulation system (International Technidyne Corporation (ITC)), were identified during the scoping phase and included in the assessment as alternative technologies.

The purpose of this assessment is to evaluate the clinical and cost effectiveness of using CoaguChek XS system, INRatio2 PT/INR monitor and ProTime Microcoagulation system for self-monitoring (self-testing or self-managing) coagulation status in people with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy is intended. Provisional recommendations on the use of these technologies in the NHS will be formulated by the Diagnostics Advisory Committee at the Committee meeting on 8 January 2014.

1.2 The Conditions

There are a number of conditions which 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 the NICE clinical guideline on venous thromboembolic diseases (CG144) and therefore, this population is not included in the scope of this diagnostics assessment of self-monitoring coagulometers.

Atrial fibrillation

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; around 8% of people aged over 65 years. 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, or heart valve problems.

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 every year in the UK. Treatment with warfarin reduces this risk by 50–70%.

Heart valve disease

Valve disease can affect blood flow through the heart in two ways; valve stenosis, where the valve does not open fully, and valve regurgitation (or incompetence) where the valve does not close properly, allowing blood to leak backwards. Disease can occur in any of the four heart valves, although disorders of the aortic and mitral valves are more serious.

The main causes of heart valve disease are congenital heart disease and other diseases such as rheumatic fever, lupus, cardiomyopathy or endocarditis. Aortic stenosis is the most common type of valve disease and it affects one in 20 adults over the age of 65 years in the UK.

Data from the UK heart valve registry (UKHVR) indicate that approximately 0.2% of the UK population has prosthetic heart valves. Around 6,500 adult heart valve replacements (using mechanical or biological valves) are carried out each year, of which around 5,000 are aortic valve replacements.

Patients with mechanical heart valves (and some patients with prosthetic valves) are susceptible to thromboembolism and need lifelong anticoagulant therapy.

1.3 Patient issues and preferences

The time and cost of attending an anticoagulation clinic is a significant burden for people on long-term oral anticoagulation therapy. It impacts significantly on both their working life and family life. Patients reported that warfarin clearly interacted with variables such as their diet, medication and lifestyle, and self-monitoring allowed these variables to be incorporated into their treatment more effectively. Patients also reported that self-monitoring gave them greater

understanding and ownership of their condition, and that one significant benefit is that it allows them to travel (www.anticoagulationeurope.org).

There is also a significant amount of anxiety for patients associated with waiting for their results from a coagulation test and in continuing normal daily activities without knowing their risk of a bleed or clot.

1.4 Diagnostic and care pathways

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 guidelines state that INR can be measured effectively in venous or capillary blood samples, which are easier to obtain but slightly less accurate. People being tested should receive a written copy of their INR result including any necessary dose adjustments and a date for the next check.

The guidelines state 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 two 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).

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.

INR monitoring can be managed by local anticoagulant clinics in primary care, but often clinics are based in secondary care, requiring travel to hospital. The NICE anticoagulation commissioning guide (2007) states that anticoagulation therapy services can be delivered in a number of different ways, and that mixed models of provision may be required across a local health economy. This could include full service provision in secondary or primary care, shared provision, domiciliary provision or self-management. Services may be managed by a range of healthcare professionals including nurses, pharmacists and general practitioners.

The NICE clinical guideline on atrial fibrillation recommends that self-monitoring of INR should be considered for patients with atrial fibrillation receiving long-term anticoagulation, if they prefer this form of testing and if the following criteria are met:

- the patient (or a designated carer) is both physically and cognitively able to perform the self-monitoring test
- an adequate supportive educational programme is in place to train patients and/or carers
- the patient's ability to self-manage is regularly reviewed
- the equipment for self-monitoring is regularly checked via a quality control programme.

The guidelines on valve disease also state that appropriate education and training to allow patient self-management of anticoagulation should be provided, where possible.

1.5 The population

The population considered in this assessment is people with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy is intended. This scope excludes people who have had a venous thromboembolism and are receiving long-term vitamin K antagonist therapy.

2 The technologies

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 two 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 performing the INR test themselves and then contacting their health professional with the reading to receive advice on any change to the dosage of the anticoagulant that may be required. Self-managing refers to the user performing 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.

Using these coagulometers may enable patients to be monitored more regularly and reduce the frequency of visits to hospital. This may improve health outcomes for patients 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.

2.1 Coaguchek XS system

The Coaguchek XS system (Roche Diagnostics) comprises a meter and specifically designed test strips which can analyse a blood sample (fresh

capillary blood or fresh untreated whole venous blood) and calculate the prothrombin time (PT) 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 which 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.

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 application of the sample and the monitor automatically stores the result in memory. The user is guided through the process by on-screen graphical instructions.

The CoaguChek test strip contains a lyophilized reagent consisting of thromboplastin and a peptide substrate. When a blood sample is applied, thromboplastin activates coagulation, which leads to the formation of thrombin. At the same time the meter starts to measure the time. The enzyme thrombin cleaves the peptide substrate, generating an electrochemical signal. Depending on the time elapsed when 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.

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.

The CoaguChek meter is supplied with 4 x AAA batteries, a CoaguChek Softclix finger pricker and 20 Softclix 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 x 78 mm x 28 mm and weighs 127 g (without batteries).

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 ISI of 1.0 compared to 1.6; test strips have onboard quality control that is automatically run with every test, rather than having to perform external quality control; test strips do not have to be refrigerated; a smaller blood sample can be used; and the meter is smaller and lighter. The CoaguChek XS Plus is an upgraded XS model aimed primarily at healthcare professionals, which is suitable for home testing and possesses additional features to the XS system including increased storage and connectivity for data management.

2.2 INRatio2 PT/INR monitor

The INRatio2 PT/INR Monitor (Alere) performs a modified version of the one-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.

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 PT and INR results. Instructions and test results on displayed on an LCD. The monitor can store the results so that past test results can be reviewed.

The test strip comprises 2 layers of transparent plastic laminated to each other which 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 three pairs of silver electrodes, one 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 via a strip connector.

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 via the electrodes. Clot cells have reagents applied and the reagents are different for each channel. One channel contains the thromboplastin reagent for the PT test. The other two channels contain reagents that produce a low and high control time, regardless of the clotting time of the sample.

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 (T = 0). 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 T = 0 until the clotting endpoint is reached is the PT time. The monitor software calculates the INR of the sample using PT time and calibration coefficients.

The InRatio2 monitor performs a self-test when it is turned on and each test strip has a code which is accepted by the monitor if the strip code is in the correct format. The monitor uses four AA batteries or a Mains adapter as a power source, and can interface a printer or computer via the RS232 serial communication.

2.3 ProTime Microcoagulation system

The ProTime Microcoagulation System is designed for measuring prothrombin time and International Normalised Ratio. The test is performed in a cuvette which contains the reagents. Two different cuvettes are available depending on the amount of blood that needs to be collected and tested: the standard ProTime cuvette and the ProTime3 cuvette.

The standard ProTime cuvette has five micro-channels, which contain the dried reagents required to perform triplicate testing of the PT assay and two levels of controls. The ProTime3 cuvette has three functional micro-channels: two micro-channels perform the controls, and one micro-channel performs the PT test. The standard ProTime cuvette is designed to hold 65µL of blood (approximately 3 drops) to fill all five micro-channels. The ProTime3 cuvette collects 27 µL of blood (approximately 1 large drop of fresh capillary blood or venous whole blood) to fill the three micro-channels. The instrument draws the precise volume of blood into the micro-channels of each cuvette, which contain dried thromboplastin, stabilisers and buffers. An array of LEDs detects the motion of sample and reagent mixtures as they move through a precision restriction in each channel. The blood is pumped back and forth until a clot forms, obstructing the channel and slowing the flow of blood. The instrument detects the clot when the blood movement decreases below a predetermined rate.

The ProTime instrument and cuvettes are pre-calibrated so no calibration is necessary.

2.4 The comparator

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

3 The evidence

This section summarises data from the diagnostics assessment report compiled by the External Assessment Group (EAG).

3.1 Clinical effectiveness

The External Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of self-monitoring coagulation status in people with atrial fibrillation or heart valve disease for whom long-term vitamin K antagonist therapy is intended. Details of the systematic review can be found starting on page 13 of the diagnostics assessment report. Studies were included if they appeared relevant to the outcomes listed in the decision problem:

Intermediate outcomes:

- Time and values in therapeutic range;
- INR values;
- Test failure rate;
- Time to test result;
- Patient compliance with testing and treatment;
- Frequency of testing;
- Frequency of visits to primary or secondary care clinics.

Clinical outcomes:

- Frequency of bleeds or blood clots;
- Morbidity (e.g. 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:

- People anxiety associated with waiting time for results and not knowing their current coagulation status and risk;
- Acceptability of the tests;
- Health-related quality of life.

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 and it was unclear which model of the system was used in 6 of these 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). No trials that exclusively assessed the clinical effectiveness of INRatio were identified. The ProTime system was used in the other 2 trials. In all six trials based in the UK, the CoaguChek system (either CoaguChek or version 'S') was used for the INR measurement. A summary of the main characteristics of the included 26 trials is shown in table 1.

Table 1 Summary of the included RCTs

	CoaguChek XS	CoaguChek S/ CoaguChek	CoaguChek Plus	CoaguChek+INRatio	ProTime
Total no of studies	4	17	1	2	2
PSM	2	14	1	1	1
PST	2	2	0	1	1
PSM and PST	0	1	0	0	0
AC clinic-standard care	4	9	0	2	1
GP/Physician-standard care	0	4	1	0	1
AC clinic or GP/Physician-standard care	0	4	0	0	0
UK	0	6	0	0	0
Non-UK	4	12	1	2	2
AF only	0	2	0	0	0
AHV only	0	4	1	1	0
Mixed only (AF+AHV+others)	4	12	0	1	2
Total sample size	414	3910	1155	222	3062

Note: AC clinic-standard care: In two trials, reporting CoaguChek XS[54] and CoaguChek S[55] PST within AC clinic was the usual care.

AC: Anticoagulant; PSM; Patient self-management; PST:Patient self-testing; AHV: Artificial heart valves; AF:Atrial fibrillation.

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. The key findings are summarised below.

Evidence on intermediate outcomes

Time and values in therapeutic range

18 trials reported INR time in therapeutic range (TTR) although there was variation in the measures used for reporting TTR 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 TTR was higher in self-monitoring participants compared with those in standard care and, in five of these trials, the difference between intervention groups was statistically significant. Three of the UK-based trials reported no significant differences between self-monitoring and standard care. The detailed results from each trial can be found on page 50 of the diagnostics assessment report.

12 trials reported INR values in therapeutic range and again, 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% for standard care. In four trials that reported the proportion of participants in therapeutic range, the values ranged from 53% to 72.9% for self-monitoring and from 43.2% to 72% for standard care. Ten of the trials reported higher proportion of INR measurements or larger proportions of participants in therapeutic range for self-monitoring than for standard care.

Among participants with artificial heart valves, self-monitoring resulted in a significantly higher INR time in therapeutic range or INR values in therapeutic range compared with standard care (Tables 2 and 3). In two trials that

included participants with atrial fibrillation, no TTR differences were found between self-monitoring and standard care.

Type of test	Study ID	Measure	PSM/PST	Control	P value
CoaguChek S or CoaguChek	Sidhu 2001 UK	%	76.5	63.8	<0.0001
CoaguChek/ INRatio	Azarnoush 2011 France	Mean % (SD)	61.5 (19.3)	55.5 (19.9)	0.0343

Table 2: INR Results – INR time in therapeutic range

Type of test	Study ID	Measure	PSM/PST	Control	P value
Coaguchek S or Coaguchek	Horstkotte 1996 Germany	% of INR values	43.2	22.3	<0.001
CoaguChek Plus	Koertke 2001 Germany	% of INR values	79.2	64.9	<0.001
Coaguchek S or Coaguchek	Eitz 2008 Germany	% of INR values	79	65	<0.001
Coaguchek S or Coaguchek	Soliman Hamad 2009 Netherlands	Mean % per patient (SD)	72.9 (11)	53.9 (14)	0.01

Table 3: INR Results – INR value in target range

Time to test result

One trial reported the time for each INR monitoring (i.e. 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 monitoring by self-managed participants was 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-months follow up, the total time spent for anticoagulation monitoring by participants in standard care was 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 compliance with testing

One trial reported more than 98% compliance with self-testing and of those who did not comply with self-testing, two had difficulties performing the test or experienced disruption caused by hospitalisation, and one lost the CoaguChek meter. In another trial 75% (30/40) of participants did not report any problems with the use of the device and expressed willingness to continue with self-monitoring. The remaining participants who did not comply with 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

21 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 observed 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). Forest plots are shown on pages 31-35 of the diagnostics assessment report. The results were not affected by the removal of the UK-based trials or by the removal of the trials assessing ProTime and/or INRatio. Similarly, sensitivity analyses restricted to CoaguChek XS trials demonstrated 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 significantly impact on the findings (RR 0.59, 95% CI 0.27 to 1.30, p=0.19).

A subgroup analysis by type of anticoagulant management therapy was performed by the External Assessment Group. 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 a significantly higher risk in self-testing participants than in those receiving standard care was revealed (RR 1.15, 95% CI 1.03 to 1.28, p=0.02). No significant differences in the risk of major bleeding were observed between self-management (RR 1.09, 95% CI 0.81 to 1.46, p=0.58) and self-testing (RR 0.99, 95% CI 0.80 to 1.23) compared with standard care. When only minor bleeding events were assessed, a significant increased risk was observed 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-managed (RR 0.84, 95% CI 0.53 to 1.35, p=0.47).

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

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 (Forest plots can be found on pages 37-40 of the diagnostics assessment report). 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 significantly 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).

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 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 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). Among participants with mixed clinical indication (atrial fibrillation, artificial heart valves, or other conditions), the effect was larger but not statistically significant than that observed in participants receiving standard care (RR 0.57, 95% CI 0.30 to 1.09, p=0.09).

Mortality

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).

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) (Forest plot can be found on page 42). 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) (Forest plot can be found on page 43 of the diagnostics assessment report). 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. Significantly fewer deaths were recorded among participants who self-monitored their therapy compared with those who were routinely managed by their GP/ physician (RR 0.52, 95% CI 0.30 to 0.90, p=0.02) (Forest plot can be found on page 44 of the diagnostics assessment report).

The results of the sensitivity analyses according to the type of point-of-care monitor can be found on page 48 of the diagnostics assessment report.

Evidence on patient reported outcomes

People anxiety associated with waiting time for results and not knowing their current coagulation status and risk

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

Acceptability of the tests

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%). Details of these trials can be found on page 59 of the diagnostics assessment report.

One of these trials reported that 93% of participants rated their satisfaction with regard to self-monitoring (using either INRatio or CoaguChek S) as high or good. When asked about the overall relative satisfaction with the device, 43% of participants favoured INRatio, 36% CoaguChek S, and 21% both devices in equal way. One trial conducted in children, reported that the majority of participants (13 out of 14 participating families, 92%) opted for the use of CoaguChek XS device.

Health-related quality of life.

Health-related quality of life outcomes were reported in 9 trials using a variety of different measures (details can be found on page 61 of the diagnostics assessment report). Four trials used Sawicki's questionnaire to measure quality of life and significantly 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 hassles although one trial reported an increased level of distress in participants who received education but did not directly monitor their anticoagulation therapy.

Two UK-based trials reported no significant 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 which were adapted from the Lancaster tool, the SEIQol tool and a series of focus groups. Five common themes emerged from the interviews conducted on participants in self-management: knowledge and management of condition and self empowerment, increased anxiety and obsession with health, self efficacy, relationship with health professionals, and societal and economic cost. One trial, conducted in the Netherlands, measured quality of life in participants with artificial heart valves by using the SF-36v2. Significant improvements in quality of life scores in the physical component summary

were reported in participants who self-managed their therapy compared with those receiving standard care.

Another trial measured quality of life by means of the Health Utilities Index Mark 3. They reported significant gain in health utilities at the two-year follow up among self-testing participants that used ProTime 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 ($p=0.002$).

One trial compared self-management with self-testing in children and provided quality of life data using the KIDCLOT PAC QL© parent- proxy (parents QOL and their assessment of child's' QOL) and the child teen KIDCLOT PAC QL©. The five common themes identified were: awareness, communication, relationship between parent and child, flexibility, and anxiety.

3.2 Costs and cost effectiveness

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 within the de novo economic models 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, INRatio2 PT/INR monitor or the ProTime Microcoagulation system.

Systematic review of cost effectiveness evidence

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. Tabulated summaries of the economic evaluations and their assessment against the NICE reference case can be found on page 77 and page 82 of the diagnostics assessment report, respectively.

The results of the studies included in the systematic review varied widely and demonstrated that the cost-effectiveness of self-monitoring was dependent on a number of key factors.

The adopted perspective and the initial costs associated with self-monitoring appeared to significantly impact 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 effect estimates applied to self-monitoring in reducing thromboembolic and bleeding events compared with those applied to standard care also appeared to impact cost effectiveness. The two 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 which applied large effect estimates resulted in a high probability of self-monitoring being cost-effective.

The two UK based economic evaluations were based on data from the same trial and one evaluation adopted an NHS and wider societal perspective while 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 as these two evaluations applied small effect estimates, consistent with those observed 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 significant difference between standard INR monitoring and patient self-monitoring in terms of major thromboembolic or haemorrhagic events. Therefore, the External Assessment Group performed a meta-analysis of relevant trials including evidence from a number of European trials where standard care is similar to that provided in the UK in terms of approach, frequency and the level of INR control achieved.

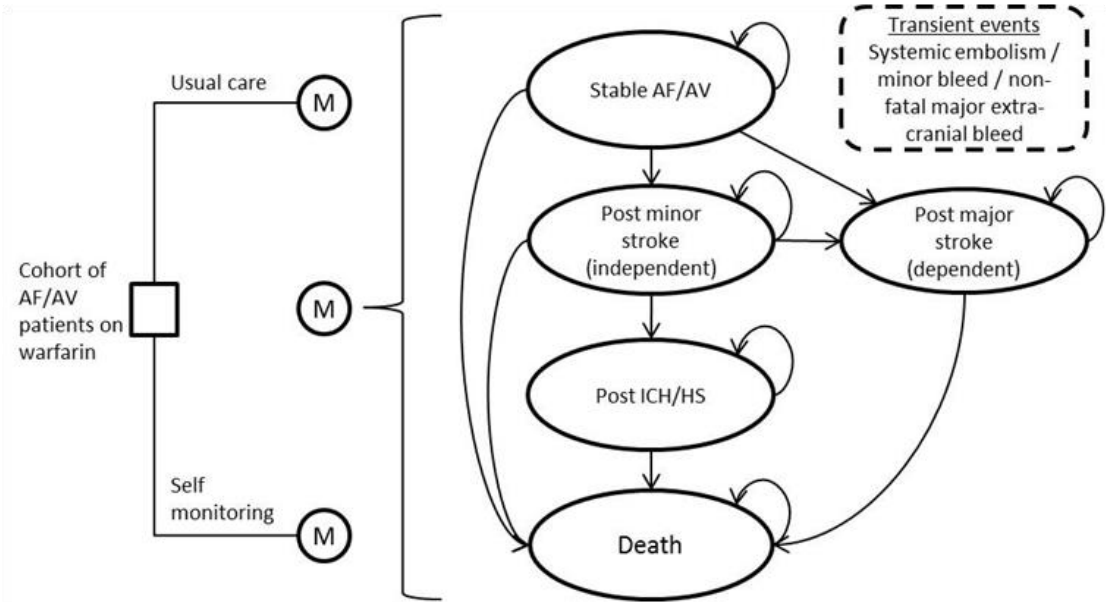
Economic analysis

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 three different point-of-care coagulometers: Coaguchek XS system, INRatio2 PT/INR monitor and the ProTime Microcoagulation system.

Model structure

The structure of the Markov model is 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 Roche (the manufacturer of CoaguChek XS), and this model was also used to inform the structure of the new economic model.

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 ten-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 on a quarterly (three 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 (SE), minor haemorrhage, and major haemorrhage (intra-cranial haemorrhage (ICH), including haemorrhagic stroke (HS), gastrointestinal (GI) bleed, and others). A constraint was applied whereby simulated people could only experience one event per cycle. A diagram of the model structure is in figure 1.



Notes: M, Markov process; AF, atrial fibrillation; AV, artificial heart valves; ICH, intracranial haemorrhage; HS, haemorrhagic stroke

Figure 1 Schematic of the model structure

Model inputs

The model was populated using data derived from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g. baseline risks), routine sources of cost data, and where necessary some study-specific cost estimates based on expert opinion. The input parameters for the model are described starting on page 88 of the diagnostics assessment report.

Costs

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. Details of the costs and resources used in the economic analysis can be found starting on page 95 of the diagnostics assessment report.

Health related quality of life and QALY decrements

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.

Utilities associated with acute events were applied for the three month period following the event. For post event states with associated on-going 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. Full details on utility values are presented starting on page 106 of the diagnostics assessment report.

Base-case results

For the purposes of decision making, the ICERs per QALY gained will be considered. The following assumptions were applied in the base case analysis:

- 66.45% of standard care monitoring occurs in primary care with practice nurses.
- 60% of the cohort have atrial fibrillation, 40% have an artificial heart valve.
- Average age of the cohort is 65 years, and 55% are male.
- 50% of self-monitoring people self-test, 50% self-manage.
- The increase in the number of tests performed per year with self-monitoring is 23.
- Relative treatment effects are estimated and applied separately for self-testing and self-management.
- 15% of participants do not commence self-monitoring following training (training failure).
- 10% of participants discontinue self-monitoring within a year of commencing.
- Self-monitoring device costs are annuitized over five years.
- 75% of devices are reused by another patient when a patient discontinues self-monitoring.

The results indicated that over a 10 year period, the introduction of self-monitoring would reduce the proportion of people suffering a thromboembolic event by 2.5%, whilst slightly increasing the proportion suffering a major haemorrhagic event by 1.4%.

The predicted monitoring costs are higher with self-monitoring compared with standard care, but the overall net health and social care costs are similar and in some cases lower, and the QALY gains are greater. Therefore, in the base case scenario, the self-monitoring strategies compare favourably with standard care, except for the ProTime Microcoagulation system where the

incremental cost per QALY gained is £47,640. Owing to the lower cost of the INRatio2 device and testing strips, coupled with the assumption of equivalent clinical effectiveness, INRatio2 dominates CoaguChek XS. However, it should be noted that no direct evidence of clinical effectiveness was identified exclusively for INRatio2 from the systematic review. The base case results are present in table 4.

Strategy	**Mean costs**	**Incremental costs**	**Mean QALYs**	**Incremental QALYs**	**ICER***	**ICER Vs. standard care**
Self-monitoring - INRatio2	£7,295	£0	5.507	0	-	Dominant
Standard monitoring	£7,324	£29	5.479	-0.027	Dominated	-
Self-monitoring -CoaguChek XS	£7,333	£37	5.507	0	Dominated	£319
Self-monitoring -ProTime	£8,609	£1,314	5.507	0	Dominated	£47,604

Table 4: Cost effectiveness of point-of-care coagulometers in the base-case analysis.

Notes: *ICER expressed relative to the next less costly non-dominated alternative, assuming equivalent effects for the alternative self-monitoring devices.

Analysis of alternative scenarios

Several scenario analyses were performed by the External Assessment Group:

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

Exclusive self-management with INRatio2 and CoaguChek XS was cost-saving under the base case assumptions, whereas self-testing was not cost-effective. The results also showed the mixed self-monitoring strategy (50% self-testing, 50% self-management) to be cost saving with CoaguChek XS and INRatio2 in comparison with exclusive secondary care testing. When

applying the pooled relative risk 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. The results of the different scenario analyses are shown in table 5.

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER*	ICER vs. standard care
1. Base case (100% self-management versus standard care)						
Self-monitoring - INRatio2	£6,370	-	5.534	-	-	Dominant
Self-monitoring -CoaguChek XS	£6,407	£37	5.534	0	Dominated	Dominant
Standard monitoring	£7,324	£954	5.479	-0.054	Dominated	-
Self-monitoring -ProTime	£7,691	£1,321	5.534	0	Dominated	£6,797
2. Base case (100% self-testing versus standard care)						
Standard monitoring	£7,324	-	5.479	-	-	-
Self-monitoring - INRatio2	£8,221	£897	5.479	0	£2,699,665	£2,699,665
Self-monitoring -CoaguChek XS	£8,258	£37	5.479	0	Dominated	£2,811,298
Self-monitoring -ProTime	£9,528	£1,306	5.479	0	Dominated	£6,631,414
3. Base case (100% primary care)						
Standard monitoring	£7,132	-	5.479	-	-	-
Self-monitoring - INRatio2	£7,208	£75	5.507	0.027	£2,749	£2,749
Self-monitoring -CoaguChek XS	£7,245	£37	5.507	0	Dominated	£4,108
Self-monitoring -ProTime	£8,522	£1,314	5.507	0	Dominated	£50,689
4. Base case (100% secondary care)						
Self-monitoring - INRatio2	£7,469	-	5.507	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,506	£37	5.507	0	Dominated	Dominant
Standard monitoring	£7,704	£235	5.479	-0.027	Dominated	-
Self-monitoring -ProTime	£8,783	£1,314	5.507	0	Dominated	£39,963

Strategy	Mean costs	Incremental costs	Mean QALYs	Incremental QALYs	ICER*	ICER vs. standard care
5. Self-monitoring (50-50 split between self-testing and self-management) versus standard care, but applying pooled relative risk estimates for all self-monitoring as a whole						
Self-monitoring - INRatio2	£6,753	-	5.53	-	-	Dominant
Self-monitoring -CoaguChek XS	£6,790	£37	5.53	0	Dominated	Dominant
Standard monitoring	£7,324	£571	5.479	-0.051	Dominated	-
Self-monitoring -ProTime	£8,073	£1,321	5.53	0	Dominated	£14,690
6. Self-monitoring (50-50 split between self-testing and self-management) versus secondary care anticoagulation clinic testing, applying pooled relative risk estimates from RCTs where this represented the comparator						
Self-monitoring - INRatio2	£7,064	-	5.532	-	-	Dominant
Self-monitoring -CoaguChek XS	£7,102	£37	5.532	0	Dominated	Dominant
Standard monitoring	£7,704	£639	5.479	-0.053	Dominated	-
Self-monitoring -ProTime	£8,386	£1,321	5.532	0	Dominated	£12,872
7. Self-monitoring with CoaguChek (50-50 split between self-testing and self-management) versus standard care, applying pooled relative risk estimates trials including only CoaguChek						
Self-monitoring -CoaguChek XS	£7,019	-	5.531	-	-	-
Standard monitoring	£7,324	£305	5.479	-0.052	Dominated	Dominated

Table 5: Cost-effectiveness by type of self-monitoring and standard care comparator (primary/secondary care)

Notes: *ICERs expressed relative to the next less costly non-dominated alternative, assuming equivalent effects for the alternative self-monitoring devices.

The External Assessment Group undertook alternative non-base case scenarios, to assess the impact of using self-monitoring to replace standard monitoring tests (i.e. no increase in the number of tests performed 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 INRatio2 and CoaguChek XS remained cost saving in comparison with exclusive secondary care anticoagulation clinic monitoring. Further details can be found starting on page 117 of the diagnostics assessment report.

Sub-group 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 year-old cohort with atrial fibrillation was estimated to cost £2,574 per QALY gained when using INRatio2 and £4,160 per QALY gained when using the CoaguChek XS system. Self-monitoring with ProTime was estimated to cost £58,584 per QALY gained. For a 65 year old artificial heart valve cohort, self-monitoring with INRatio2 and CoaguChek XS was found to be more effective and less costly (dominant) compared with standard monitoring.

A further analysis was carried out for the atrial fibrillation cohort using the baseline risks observed 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 CoaguChek XS and INRatio2 only rose above £20,000 per QALY when the baseline TTR was set at >72.6%.

Further details of the sub-group analyses can be found starting on page 120 of the diagnostics assessment report.

Sensitivity analyses

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 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.

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 risk of all cause mortality following a stroke was set at 14.5. Under this scenario, the ICERs for self-monitoring with CoaguChek XS and INRatio2 dominated standard monitoring. However, it should be noted that the standardised mortality ratio estimated for an 18-55 year old cohort of artificial heart valve participants 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.

Further details of these sensitivity analyses can be found starting on page 123 of the diagnostics assessment report.

Probabilistic sensitivity analyses of the base case were performed to examine the uncertainty in the cost-effectiveness of self-monitoring. Self-monitoring with the Coaguchek XS system and the INRatio2 monitor were estimated to have an 80% and 81% chance of being cost-effective at a threshold of £20,000 per QALY gained, respectively. However, it should be noted that there is no direct RCT evidence to demonstrate the clinical effectiveness of

the INRatio2 monitor. The ProTime Microcoagulation system had a lower chance of being cost effective compared with standard care, as a result of the higher cost of the monitor. Further details of the probabilistic sensitivity analyses can be found starting on page 129 of the diagnostics assessment report.

4 Issues for consideration

Clinical effectiveness

1. This assessment of 26 randomised controlled trials indicates that the use of point-of-care coagulometers for self-monitoring of anticoagulation therapy leads to significantly fewer thromboembolic events compared with standard anticoagulation control in primary care or specialised clinics.

2. Self-monitoring nearly halved the risk of thromboembolic events in people with artificial heart valves and there was a statistically significantly greater reduction in thromboembolic events among self-managed people compared with those in self-testing.

3. Self-monitoring did not result in a significant reduction in the number of major and minor bleeding events compared with standard care. No significant differences in the risk of major bleeding were observed between self-management or self-testing versus standard care. When only minor bleeding events were assessed, a significant increased risk was observed in self-testing participants compared with those in standard care. No significant increased risk was observed in self-managing participants.

4. Among people with artificial heart valves, self-monitoring significantly reduced the risk of mortality but among people with mixed clinical indication, the risk of mortality was not reduced. There was lower all-cause mortality through self-management but not through self-testing. In particular, significantly fewer deaths were observed among people

who self-managed their anticoagulant therapy compared with those who received standard anticoagulation control in primary care.

5. In 23 of the 26 trials, the INR time in therapeutic range was higher in self-monitoring people compared with those receiving standard care. In five of these trials the difference between intervention groups was statistically significant.

6. Patient compliance with testing was reported to be high (at least 80%) and trial participants expressed high satisfaction and willingness to continue with self-monitoring.

7. The included trials varied considerably in terms of clinical indications for anticoagulation therapy, type of control care, reporting structure for the time and/or values in therapeutic range, type and structure of the pre-intervention training and education programme, length of follow up, and methodological study quality, and therefore, although the meta-analysis results demonstrated low statistical heterogeneity there remains uncertainty that clinical heterogeneity may have over or underestimated the effects.

8. 22 of the 26 trials investigated the use of the CoaguChek system and therefore, the results are more robust for the CoaguChek system than for the ProTime and INRatio monitors. Given the broadly similar performance of all the monitors compared with the gold standard laboratory test, it was assumed appropriate to consider pooled estimates of effect across all studies and monitors. However, there is no direct comparative evidence between the monitors so the results should be interpreted with caution.

9. There is no direct RCT evidence to demonstrate the clinical effectiveness of the INRatio2 monitor.

10. Only limited data were available for people with atrial fibrillation and consequently no reliable conclusions could be drawn in relation to this patient population.

11. All included trials enrolled highly selected samples of people requiring anticoagulation therapy, and so there is uncertainty about the external validity of the results. There also remains some uncertainty on the applicability of pooled results to the UK population because of uncertainty relating to the applicability of the standard care comparators in the trials.

Cost effectiveness

12. In the base case analysis, self-monitoring with the Coaguchek XS system has an ICER of £319 per QALY gained compared with standard monitoring. Self-monitoring with the InRatio2 monitor dominates the Coaguchek XS system and standard monitoring although it should be noted that there is no direct RCT evidence for the clinical effectiveness of the InRatio2 monitor. Self-monitoring with the ProTime microcoagulation system has an ICER of £47,604 per QALY gained compared with standard monitoring.

13. The base case cost-effectiveness findings are most applicable to self-monitoring strategies using the Coaguchek XS system because the majority of the trials in the clinical effectiveness evidence used the Coaguchek system. There is variation in the version of the Coaguchek system used in the different trials but data suggest that the Coaguchek XS system is very similar in performance to previous versions of the monitor (see page 18 of the diagnostics assessment report). There are very few studies that compare the performance of the Coaguchek XS system with that of the INRatio2 monitor or the ProTime microcoagulation system.

14. Although self-monitoring (50% self-testing, 50% self-management) is likely to increase the cost of INR monitoring cost, it is likely to be cost-effective as a result of the significant reductions in thromboembolic events. This finding assumes that the pooled relative effects of self-testing and self-management, obtained from the meta-analysis of all RCTs, are applicable to the UK setting.

15. The base case cost effectiveness findings showed that self-management alone is highly cost effective (dominant) but that self-testing alone is not cost effective, compared with standard monitoring. These findings are based on the contrasting pooled effect estimates, obtained from the meta-analysis of RCTs, on thromboembolic events for self-testing and self-management. The pooled effect estimate for self-testing was small and non-significant (RR 0.99) compared with the large and significant pooled effect estimate for self-management (RR 0.51).

16. The model findings were robust to individual changes in the baseline risk of thromboembolic events and the relative effect of self-monitoring on these events, through feasible ranges. However, when the lower baseline risk of thromboembolic events was combined with the upper confidence limit for the relative risk associated with self-management (RR 0.69), the ICERs for self-monitoring rose above £30,000 per QALY gained compared with standard monitoring. 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.

17. Alternative scenarios assessed the potential for self-monitoring to be cost-effective if used to replace clinic based testing without increasing the frequency of testing. This showed that when holding all other base case parameters constant, self-monitoring (50% self-testing, 50% self-managing) was more costly than standard primary care monitoring, but less costly than standard secondary care monitoring. These findings were, however, sensitive to the unit costs applied to standard care monitoring visits.

18. Sensitivity analysis showed that self-monitoring with CoaguChek XS and INRatio2 dominated standard monitoring in a cohort of children with an artificial heart valve on long-term vitamin K antagonist therapy. However, it should be noted that the standardised mortality ratio

estimated for an 18-55 year old cohort of artificial heart valve participants 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 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Access to the device may be of particular benefit to groups receiving long-term vitamin K antagonist therapy, such as children and young adults in education or older people, who may find travel to clinics for INR testing difficult or demanding.

In addition, access to the device may benefit some people with disabilities who may find travel to clinics for INR testing difficult or demanding.

Users must be physically and cognitively able to perform the self-monitoring test correctly.

Atrial fibrillation and valve disease is more common in older people.

6 Implementation

Patients must be assessed to determine they are both physically and cognitively able to perform self-monitoring correctly. Training and educational tools are needed to teach patients about self-monitoring. A patient’s ability to self-monitor must be regularly reviewed.

A quality control programme is needed to ensure equipment is regularly checked.

Implementation of self-monitoring may require significant changes to be made to current anticoagulation clinic services. Some services may no longer be needed.

7 Authors

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December 2014

Appendix A: Sources of evidence considered in the preparation of the overview

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

Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, Croal B, Ramsay CR, Brazzelli M. 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. Aberdeen HTA Group, Institute of Applied Health Sciences, University of Aberdeen, 2013.

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

I Manufacturers/sponsors:

Technologies under consideration

- Roche Diagnostics
- Alere Ltd.

II Professional/specialist and patient/carer groups:

- AF Association
- Airedale, Wharfedale & Craven CCG
- AntiCoagulation Europe (ACE)
- Arrhythmia Alliance
- British Cardiac Patients

- British Society for Haemostasis and Thrombosis
- Department of Health
- Healthcare Improvement Scotland
- HeartLine
- Lifeblood: The Thrombosis Charity
- Medicines & 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

Appendix B Glossary of terms

International normalised ratio (INR): Globally recommended unit for measuring thromboplastin time, which renders different measurements comparable despite the different thromboplastins used. It is calculated as:

$$INR = (\text{Patient's PT} / \text{Normal mean PT})^{ISI}$$

For example: The PT of a patient receiving oral anticoagulant is 64 seconds (= 18% Quick). The prothrombin time of a normal plasma is 22 seconds (= 100% Quick). The ISI of the thromboplastin used is 0.93. Substituting this value in the formula above gives the following INR:
(64) / (22) 0.93 = 2.7 INR

This signifies a coagulation time that is 2.7 times longer than the standard. The longer the patient's coagulation time, the higher the INR.

Prothrombin time (PT): Time (in seconds) taken for a blood sample to clot in the presence of added thromboplastin.