

Diagnostics Assessment Programme

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

Final scope

August 2013

1 Introduction

The CoaguChek XS system is manufactured by Roche Diagnostics. The Medical Technologies Advisory Committee identified the CoaguChek XS system as potentially suitable for evaluation by the Diagnostics Assessment Programme on the basis of a briefing note. The final scope was informed by the scoping workshop held on 30th April 2013 and by the assessment subgroup meeting held on 21st May 2013.

A glossary of terms is provided in appendix A.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE from the manufacturers and on information

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available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical 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.

The use of these coagulometers may reduce the frequency of visits to hospital for patients and enable them to be monitored more regularly. 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.

2.2 Product properties

2.2.1 CoaguChek XS system (Roche Diagnostics)

The CoaguChek XS system 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

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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).

2.2.2 InRatio2 PT/INR Monitor (Alere)

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The INRatio2 PT/INR Monitor 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 are 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

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is the PT time. The monitor software calculates the INR of the sample using PT time and calibration coefficients.

The Alere InRatio 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.

2.2.3 ProTime Microcoagulation System (International Technidyne Corporation (ITC))

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 65 μ L of blood (approximately 3 drops) to fill all five micro-channels. The ProTime3 cuvette collects 27 μ L 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.

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

3 Target conditions

There are a number of conditions which can result in people having a higher 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 group is not included in the scope of this diagnostics assessment of self-monitoring coagulometers.

3.1 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 anticoagulation therapy, such as warfarin. 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%.

3.2 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

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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.

3.3 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.

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3.4 Diagnostic pathway

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

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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.

4 Scope of the evaluation

Table 1: Scope of the evaluation

Decision question	Are self-monitoring coagulometers cost effective if used 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, in the NHS?
Populations	People with atrial fibrillation or heart valve disease for whom long term vitamin K antagonist therapy is intended

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Intervention	For self testing or self management: <ul style="list-style-type: none"> • CoaguChek XS system (Roche Diagnostics)
Alternative interventions	For self testing or self management: <ul style="list-style-type: none"> • INRatio2 RT/INR monitor (Alere) • ProTime Microcoagulation system (International Technidyne Corporation (ITC))
Comparator	<ul style="list-style-type: none"> • INR testing in primary care using laboratory analysers • INR testing in primary care using point of care tests • INR testing in secondary care using laboratory analysers • INR testing in secondary care using point of care tests
Healthcare setting	Self-use (self testing or self management) supervised by primary or secondary care
Outcomes	Intermediate measures for consideration may include: <ul style="list-style-type: none"> • INR values • Test failure rate • Time to test result • Patient adherence to testing schedule • Patient compliance with treatment • Frequency of testing • Frequency of visits to primary or secondary care clinics • Time in therapeutic range (TTR)
	Clinical outcomes for consideration may include: <ul style="list-style-type: none"> • Patient anxiety associated with waiting time for

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	<p>results and not knowing their current coagulation status and risk</p> <ul style="list-style-type: none"> • Number of bleeds or blood clots • Morbidity and mortality from testing, an under- or over-dose of vitamin K antagonist therapy, and treatment of bleeding or clots and associated sequelae • Adverse events from testing, false test results and vitamin K antagonist therapy • Health related quality of life <p>Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:</p> <ul style="list-style-type: none"> • Costs of equipment, reagents and consumables • Costs of staff and training of staff • Costs of training users or carers • Maintenance of equipment • Consumption of vitamin K antagonist therapy • Medical costs arising from on-going monitoring and treatment with vitamin K antagonist therapy • Medical costs arising from adverse events associated with testing and treatment <p>The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.</p>
Time horizon	Life time

5 Modelling approach

The aim and structure of the economic model will depend upon the final scope.

5.1 Existing models

One published Health Technology (HTA) report considered the clinical effectiveness and cost effectiveness of different models of managing long-term oral anticoagulation therapy (Connock et al., 2007). It reported that self-monitoring was clinically effective and safe in patients receiving long-term oral anticoagulation therapy. However, the economic evaluation showed that self-management was more expensive than routine care in a specialised UK anti-coagulation clinic and suggested that self-monitoring was unlikely to be cost-effective. Two HTA reports, one based in Ontario (2009) and one based in Belgium (Gailly et al., 2009), both reported that self-management was more cost effective than routine care.

5.2 Modelling possibilities

The issues that will need to be addressed, through modelling if necessary, include the short term outcomes from unstable INR values, side-effects of INR testing and the long-term outcomes associated with receiving long-term vitamin K antagonist therapy. The effect of Coagucheck XS testing on increased or reduced time in therapeutic range compared with current standard practice should be assessed. The potential variations in test accuracy and frequency of testing will need to be determined and modelled to identify resulting changes in final health outcomes. Assumptions about the size of the population eligible for self-monitoring will also have to be made with regard to the type of anticoagulation therapy being received and the ability of patients to self-monitor (both physically and cognitively).

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6 *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.

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.

7 *Implementation issues*

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 services. Some services may no longer be needed.

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Appendix A 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:

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

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:

$$(64) / (22) 0.93 = 2.7 \text{ INR}$$

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.

Appendix B Related NICE guidance and pathways

Related guidance

- Anticoagulation therapy service commissioning guide: NICE commissioning guide (2007). Available from: <http://www.nice.org.uk/usingguidance/commissioningguides/anticoagulationtherapyservice/anticoagulationtherapyservice.jsp>
- Stroke: NICE clinical guideline CG68 (2008). Available from: <http://guidance.nice.org.uk/CG68>. Date for review: April 2012 (Decision: the guideline should not be updated)
- Atrial fibrillation: NICE clinical guideline CG36 (2006). Available from: <http://guidance.nice.org.uk/CG36>. Date for review: August 2011 (Decision: the guideline is currently being updated)

Pathways

The self-monitoring coagulometers guidance will be included in several NICE pathways, for example: Chronic heart failure (published), Stroke pathway (published), Atrial fibrillation pathway (draft), Familial hypercholesterolaemia pathway (draft), Myocardial infarction secondary prevention (draft).

In some of these pathways, it may be appropriate to include the full recommendations of the guidance, in others it will only be necessary to give a link to the guidance.

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Appendix C References

Connock et al. (2007) Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling NIHR Health Technology Assessment Programme 11:38

Gailly, J, Gerkens, S, Van Den Bruel, A, Devriese, S, Obyn, C, and Cleemput, I. Use of point-of care devices in patients with oral anticoagulation: a Health Technology Assessment. KCE reports 117C. 2009. Belgian Health Care Knowledge Centre.

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