Evidence Assessment and Analysis Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence

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1. Title of the project

The 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.

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3. Plain English Summary

Patients with certain clinical conditions such as those with atrial fibrillation, with mechanical or prosthetic heart valves or those with recurrent episodes of venous thromboembolism (VTE) are at high risk of thrombosis (blood clot) which may lead to the thromboembolism and consequently stroke if left untreated. These patients are required to take lifelong blood thinning drugs (called vitamin K antagonists) to avoid the associated risks. The treatment of patients with blood thinning drugs is termed anticoagulant therapy and it is estimated that 1.4% of the population in the UK require anticoagulant therapy.[1]

Warfarin is the most common vitamin K antagonist drugs given to prevent clot formation and causing strokes. However, there are serious side effects that can result from the patient being on the wrong dose of warfarin (over- or under- dosing) including bleeding or stroke. Therefore it is necessary to ensure that patients taking warfarin have ongoing monitoring of their blood coaguability.

The blood coaguability of patients taking warfarin is measured in terms of the international normalized ratio (INR) which is a standardised unit for measuring the time it takes for blood to clot. INR monitoring can be delivered using various options in the NHS. The options include INR monitoring managed by health care professionals in anticoagulant clinics based in hospitals using laboratory testing or managed in primary care (with or without the use of laboratory services). The use of a personal INR testing machine at home (known as a point-of-care test), allows patients to perform self-testing or self-management. Self-testing is when patients perform the test themselves and the results of the test are managed by healthcare professionals. Self-management is when patients perform the test and alter the dose of anticoagulation therapy themselves according to a personalised protocol. Self-testing and self-management are together referred as self-monitoring. Self-monitoring is considered as one of the options for INR monitoring in the NHS, but there is limited evidence on the effectiveness compared to other ways of delivering services. It is believed that the use of point-of-care tests, for self-monitoring, may avoid unnecessary visits to hospitals while allowing regular INR monitoring and timely adjustment of warfarin dosing to avoid adverse events. This may result in the improved outcomes that are important for patients including patient's quality of life.

This project will perform a literature search of a number of medical databases and will review relevant studies of the point-of-care devices. The results of the studies will be summarised in terms of the ability of the devices to improve clinical and patient-related factors. The costs of

the devices will be identified and an economic model will be constructed to estimate the benefits to the patient of the devices in relation to how much they cost. Where possible the patient's quality of life will be taken into account in judging how cost-effective the devices are. The results of the project will be used by the National Institute for Health and Care Excellence (NICE) to make guidance to the National Health Service in England on the use of the devices.

4. Decision problem

4.1 Purpose of the decision to be made

Point-of-care devices for measuring coagulation status in people receiving long-term vitamin K antagonist therapy allow both patient self-testing and self-management. Defined here as:

- Self-testing - when the patient performs the point-of-care test themselves and have their test result managed by their healthcare provider (e.g. general practitioner, nurse, specialised clinic)
- Self-management - when a trained patient performs the point-of-care test, interprets their test result and adjusts their dose of anticoagulant according to a pre-defined protocol.

Self-testing and self-management together are herein referred to as *self-monitoring* in this protocol.

The purpose of this appraisal is to assess the current evidence for the clinical effectiveness and cost-effectiveness of self-monitoring (self-testing and self-management) using CoaguChek system and alternative point-of-care testing devices compared to standard monitoring in people receiving long-term vitamin K antagonist therapy.

4.2 Clear definition of the intervention

The following point-of-care devices for monitoring anticoagulation status are CE marked and currently available for use in the NHS: CoaguChek S and XS devices (Roche Diagnostics, Basel, Switzerland), INRatio2 PT/INR monitor, (Alere Inc., San Diego CA, USA) and) ProTime Microcoagulation system - International Technidyne Corporation, ITC (Nexus Dx, Edison, NJ, USA). The following devices are proposed to be investigated within the scope of this appraisal.

4.2.1 CoaguChek S and XS devices

The CoaguChek system is a point-of-care testing device developed by the Roche Diagnostics, which measures prothrombin time and INR (the globally recommended unit for measuring thromboplastin time) in people on oral anticoagulation therapy. CoaguChek S and CoaguChek

XS devices are intended for patient self-monitoring. The most recent model (CoaguChek XS) comprises a meter and specifically designed test strips for blood sample analysis (fresh capillary or untreated whole venous blood). The CoaguChek XS system purports to have the following advantages over the CoaguChek S: i) 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; ii) test strips have onboard quality control that is automatically run with every test, rather than having to perform external quality control; iii) test strips do not have to be refrigerated; iv) a smaller blood sample can be used; v) the meter is smaller and lighter.

4.2.2 INRatio2 PT/INR monitor

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 and the results for prothrombin time and INR are reported.

4.2.3 ProTime Microcoagulation system

The ProTime Microcaogulation system is designed for measuring prothrombin time and INR. 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.

4.3 Populations and relevant subgroups

The population being considered for this appraisal consists of people for whom long-term vitamin K antagonists therapy in intended.

There are a number of clinical conditions which require long-term vitamin K antagonists therapy to reduce the risk of thrombosis. The most common of such clinical conditions are atrial fibrillation, heart valve disease, and venous thromboembolism.

4.3.1 Atrial fibrillation

Atrial fibrillation is caused by unorganised atrial contraction resulting in the disruption of blood movement which may lead to the thromboembolism and consequently stroke if left untreated. Atrial fibrillation is the most common heart arrhythmia and affects around 800,000 people in the UK, or 1.3% of the population.[2] Prevalence increases with age, affecting 0.5%

of people aged 50-59 years, and around 8% of people aged over 65 years.[3] Atrial fibrillation is more likely to affect men than women, and is more common in people with other conditions, such as high blood pressure, atherosclerosis or other heart conditions, such as a heart valve problem. An average proportion of 47% of patients with atrial fibrillation currently receive anticoagulation therapy, such as warfarin.[1] 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 the risk by 50–70%.[1,4,5]

4.3.2 Artificial heart valves

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, other diseases including rheumatic fever, lupus, cardiomyopathy or endocarditis. Aortic stenosis is the most common type of valve disease. It affects one in 20 adults over the age of 65.[6,7] 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.[8,9]

4.3.3 Deep vein thrombosis and pulmonary embolism

Venous thromboembolism is a condition in which a blood clot (a thrombus) forms in a vein and then dislodges to travel in the blood (an embolus). A venous thrombus most commonly occurs in the deep veins of the legs or pelvis; this is then called a deep vein thrombosis (DVT). If it dislodges and travels to the lungs, to the pulmonary arteries, it is called a pulmonary embolism (PE) which in some cases may be fatal. Major risk factors for VTE include a prior history of DVT, age over 60 years, surgery, obesity, prolonged travel, acute medical illness, cancer, immobility, thrombophilia (an abnormal tendency for the blood to clot) and pregnancy.

It has been estimated that every year 25,000 people in the UK die from preventable hospital acquired VTE and that it causes over 500,000 deaths in Europe. Non-fatal VTE is also important as it can cause serious longer-term conditions such as post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). PTS, which is characterised by minor skin changes, pain, swelling or leg ulceration, affects 20-40% of patients after DVT of the lower limb and have a significant impact on their quality of life.

CTEPH, which is caused by obstruction of the pulmonary arteries,- may lead to heart failure in some patients.

4.4 Place of the intervention in the treatment pathway(s)

The place of the point-of-care tests on the treatment pathway for this appraisal is informed by the following published guidelines:

- Guidelines on oral anticoagulation with warfarin, prepared by the British Committee for Standards in Haematology[10]
- The NICE anticoagulation commissioning guide[1]
- The NICE clinical guideline on atrial fibrillation CG36[11]
- The SIGN clinical guideline on antithrombotics: indication and management[12]
- The NICE clinical guideline on venous thromboembolic diseases CG144[13]
- The NICE clinical guideline on venous thromboembolism-reducing the risk CG92[14]
- Guidelines on the management of valvular heart disease produced by the European Society of Cardiology.[15]

According to the NICE clinical guideline on atrial fibrillation and the SIGN clinical guideline on antithrombotics,[11,12] the most effective treatment considered for the treatment of atrial fibrillation is dose-adjusted warfarin, the most common vitamin K antagonist drug. Lifelong anticoagulation therapy with warfarin is also recommended in all patients after artificial valve replacement.[15] Long-term vitamin K antagonists therapy is recommended in patients with confirmed DVT or PE taking into account the patient's risk of VTE recurrence and the risk of bleeding.[13,14] Warfarin, especially if taken incorrectly, can cause severe bleeding (haemorrhages). Therefore, it is necessary to ensure that people taking warfarin have ongoing monitoring of their blood coaguability. The anticoagulant effect of warfarin is measured in terms of the INR which is a standardised unit for measuring the time it takes for blood to clot.

The routine monitoring of blood coagulation can take several configurations. The NICE anticoagulation commissioning guide[1] states that UK 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.

In this assessment, we are investigating the role of point-of-care tests for the self-monitoring of INR by people at home. The point-of-care test is therefore being considered in this appraisal as an alternative for standard UK anticoagulation therapy services.

The NICE clinical guideline on atrial fibrillation[11] 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.

4.5 Relevant comparators

In UK clinical practice, INR monitoring is currently managed by a range of healthcare professionals including nurses, pharmacists and general practitioners. INR monitoring can be carried out in primary care and secondary care.

4.6 Key factors to be addressed

The specific objectives of this appraisal are to:

- Systematically review the evidences on clinical-effectiveness of self-monitoring (self-testing and self-management) using CoaguChek, INRatio2 PT/INR monitor and ProTime Microcoagulation system point-of-care devices, compared to the standard monitoring practice, in people receiving long-term vitamin K antagonist therapy;
- Systematically review existing economic evaluations on self-monitoring technologies for people receiving long-term vitamin K antagonist therapy;
- Develop a *de novo* economic model to assess the cost-effectiveness of both self-testing and self-management (using CoaguChek XS system, INRatio2 PT/INR monitor and ProTime Microcoagulation system as self-monitoring technologies) for people receiving long-term vitamin K antagonist therapy, versus standard monitoring practice.

4.7 Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment (e.g. key factors for which evidence is already accepted).

We will not carry out a formal appraisal of the precision and accuracy of CoaguChek S and CoaguChek XS in INR measuring, as this is outside the scope of the current appraisal. However, we will gather information of the precision and accuracy of the two models from the published literature and by contacting the manufacturer. Furthermore, we are planning to perform sensitivity analyses according to the different models of the CoaguChek system.

4.8 Existing reviews

Initial scoping searches for this appraisal identified a Cochrane review[16] and few technology assessment reports[17-19] assessing different models of managing oral anticoagulation therapy. These publications focused on several randomised controlled trials (RCTs), which reported relevant outcomes in terms of clinical effectiveness. In particular, the Cochrane review included both the CoaguChek S and the CoaguChek XS devices. The CoaguChek XS system is the simplified version of CoaguChek S and uses the same technology as its precursor. We consider both versions of CoaguChek suitable for inclusion in this assessment.

5. Report methods for assessing the outcomes arising from the use of the interventions

A systematic review of the evidence on the clinical effectiveness of self-monitoring in people receiving long-term vitamin K antagonist therapy using CoaguChek system and two - alternative technologies: INRatio2 PT/INR monitor and ProTime Microcoagulation system compared with the current standard monitoring practice will be undertaken following the general principles of the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care[20] and NICE Diagnostics Assessment Programme Manual.[21]

5.1 Population

People for whom long-term vitamin K antagonists therapy is intended.

5.2 Setting

Self INR monitoring supervised by primary or secondary care

5.3 Interventions

The interventions being considered in this appraisal are:

- CoaguChek system (S and XS models) ,

- INRatio2 PT/INR monitor,
- ProTime Microcoagulation system

5.4 Comparators

The comparator being considered is standard practice, which includes INR monitoring managed by healthcare professionals. INR monitoring can be carried out in primary care, in secondary care or in a "shared provision" setting:

- **Primary care** - INR monitoring can be carried out in primary care anticoagulant clinics using point-of-care tests or laboratory analysers. In the latter, blood samples are sent to a central laboratory based at a hospital (**shared provision**);
- **Secondary care -** INR monitoring can be carried out in hospital-based anticoagulant clinics using point-of-care tests or laboratory analysers.

5.5 Outcomes

Studies will be included if they provide data on any of the following outcomes:

Clinical outcomes:

- Number of bleeds or blood clots
- Morbidity (e.g. thromboembolic and cerebrovascular events) and mortality from INR testing and vitamin K antagonist therapy;
- Time in therapeutic range (TTR);
- 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.

Intermediate outcomes:

- 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.

5.6 Study design

We will prioritise RCTs for inclusion in the systematic review of clinical effectiveness (see Section 4.8 for rationale). However, where RCTs of CoaguChek XS system, INRatio2 PT/INR monitor and ProTime Microcoagulation system are not identified we will consider non-randomised evidence (including observational studies), providing they include relevant outcomes for this appraisal.

Exclusion criteria

We will exclude the following types of report:

- Biological studies;
- Reviews, editorials and opinions;
- Case reports;
- Non-English language reports;
- Conference abstracts published before 2012.

5.7 Search strategy

Extensive sensitive electronic searches will be conducted to identify reports of published and ongoing studies on the clinical effectiveness of CoaguChek, alternative point-of-care devices and comparator tests for the self-monitoring of patients on oral anticoagulant therapy. In particular, the search strategies will be designed to retrieve randomised clinical trials as well as non-randomised evidence (including observational studies) which assess CoaguChek XS system, INRatio2 PT/INR monitor, and ProTime Microcoagulation system. Systematic reviews will be also retrieved to check their reference lists for potentially relevant studies. To identify relevant RCTs we are proposing to focus initially on the Cochrane systematic review of oral anticoagulation published by Garcia-Alamino and colleagues in 2010,[16] which include a total of 18 RCTs.[16] The Cochrane review has similar inclusion criteria to this proposed assessment and was last updated in November 2007. Therefore, to ensure that the workload is manageable within the time scale for this appraisal, we intend to summarise the findings of the Cochrane review and supplement it by reviewing any relevant studies published since November 2007. Consequently, the search for RCTS will be restricted to reports published from 2007 onwards while the search for non-randomised evidence will be unrestricted by date of publication. Only reports published in English will be sought. In addition, conference abstracts published from 2012 onwards will be sought. Major electronic databases will be

searched including: MEDLINE, MEDLINE In-Process, Embase, Science Citation Index, Biosis and the Cochrane Controlled Trials Register. A preliminary MEDLINE search strategy is provided in Appendix A. The MEDLINE search will be adapted to search other relevant databases. The Cochrane Database of Systematic Reviews, the HTA Database and DARE will be searched for reports of systematic reviews as well as for background publications.

Current research registers, including Current Controlled Trials, Clinical Trials and WHO International Clinical Trials registry will be searched. Recent conference proceedings including those of the European Haematology Association and American Society of Hematology will also be screened.

In addition, relevant websites of key professional organisations and of testing device manufacturers will be checked for additional data and information.

5.8 Data extraction strategy

Two reviewers will independently screen the titles and abstracts of all reports identified by the search strategies. Full text copies of all studies deemed to be potentially relevant will be obtained, and assessed independently by two reviewers for inclusion. Any disagreements will be resolved by discussion or arbitration by a third party.

A data extraction form will be developed and piloted for the purpose of this assessment. One reviewer will extract information on study design, characteristics of participants, settings, characteristics of interventions, alternative interventions and comparators, and outcome measures as described above. A second reviewer will check the data extraction. Any disagreements will be resolved by discussion or arbitration by a third party.

Study data from the manufacturers that meet the inclusion criteria, and are received during the review process, will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

5.9 Quality assessment strategy

A single reviewer will assess the methodological quality of the included studies and findings checked by a second reviewer. Any disagreements will be resolved by consensus or arbitration by a third party. Studies will not be included or excluded on the basis of methodological quality.

The quality of all the included RCTs will be evaluated using Cochrane Risk of Bias tool.[22] Other study designs will be assessed using existing published tools or adapting criteria specific to a particular study design (e.g. non-randomised studies will be assessed against the Cochrane Collaboration Non-randomised Studies Group criteria).[22]

5.10 Methods of analysis/synthesis

If appropriate, meta-analysis will be performed to estimate a summary measure of effect of the relevant outcomes. Summary statistics of binary data will be calculated as relative risk (RR) using mantel-Haenszel method and for continuous data as weighted mean difference (WMD) using inverse-variance method. For the estimates of RR and WMD 95% confidence intervals (CIs) and p-values will be calculated. A fixed effects model will be used to calculate the pooled estimates. The statistical heterogeneity across studies will be explored by using Chi squared and I-squared statistics. Where significant heterogeneity is detected across the studies, random effects model will be used to calculate the pooled estimates. We are planning to perform subgroup analyses according to the type of anticoagulation therapy management (self-testing and self-management).

If data permit, we will perform sensitivity analyses based on:

- Low risk of bias studies only;
- According to various targeted conditions (e.g. atrial fibrillation, heart valve disease);
- According to service provision for anticoagulation management (i.e. primary care, secondary care);
- According to different models of CoaguChek.

6. Report methods for synthesising evidence of cost effectiveness

Relevant economic evidence on self-monitoring technologies for people receiving long-term vitamin K antagonist therapy will be systematically identified, appraised for quality, and properly summarised.

6.1 Identifying and systematically reviewing published cost-effectiveness studies

Scoping searches have identified a previous systematic review of economic studies evaluating point-of-care testing devices for people receiving long-term vitamin K antagonist therapy.[17] We aim to update this systematic review using a similar search strategy. We will search relevant bibliographic databases including MEDLINE, MEDLINE In-Process, Embase, Science Citation Index, Health Management Information Consortium (HMIC), NIHR Economic Evaluations Database (NEED) and the HTA Database. Any identified full

economic evaluations will be appraised against the NICE reference case.[21] The main findings of existing economic evaluations will be summarised in a narrative way and tabulated for comparison.

6.2 Evaluation of costs and cost effectiveness

Following the synthesis of cost effectiveness evidences, an economic model will be developed to assess the alternative self-monitoring strategies (CoaguChek XS system, INRatio2 PT/INR monitor and ProTime Microcoagulation system). The model will be populated using results from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g. utilities), routine sources of cost data, and if necessary some study specific cost estimates (based on expert opinion). This model will be used to estimate the effectiveness and cost-effectiveness of alternative self-monitoring strategies for people receiving long-term vitamin K antagonist therapy. The evidence on costs and cost-effectiveness will be evaluated according to the recommendations of the NICE Diagnostics Assessment Programme manual.[21]

6.3 Development of a health economic model

The proposed appraisal will evaluate, using Markov modelling methods, the clinical and cost-effectiveness of self-testing and self-management strategies for people receiving long-term vitamin K antagonist therapy. The economic model will incorporate the pathways of care that individuals currently follow under standard practice in the NHS, as well as proposed new pathways for self-testing and self-management (informed by a review of current guidelines and expert opinion). It will simulate thromboembolic and haemorrhagic events for people receiving long-term vitamin K antagonist therapy, based on the estimated risks of these events occurring under current standard models of care, and the application of relative reductions/increases in risk resulting from improved/reduced control of INR conferred by alternative monitoring strategies.

To help structure the event pathways, previous economic models in this area will be reviewed. The advice of clinical experts and the availability of evidence will also help guide decisions on the key morbidity/mortality events to include in the economic model. Risks for these events under standard practice will be informed by observed event rates in the control groups of applicable randomised controlled trials (identified by the systematic review of clinical effectiveness). Relative risks for the morbidity/mortality outcomes will be applied to baseline risks to estimate the absolute risks for events under self-testing and self-management strategies (using alternative technologies). If the data are not sufficient for modelling the

direct impact of the monitoring strategies on adverse morbidity/mortality outcomes, estimated effects on time in therapeutic range may be used in conjunction with further analyses demonstrating the link between this intermediate outcome and the final health outcomes.

If sufficient evidence can be identified, the economic model will compare the alternative monitoring strategies for hypothetical cohorts of people with atrial fibrillation, heart valve disease, and VTE. However, it may be the case that studies assessing the effects of self-monitoring (for all people receiving long-term vitamin K antagonist therapy) do not report the risks of haemorrhagic and thromboembolic events by underlying indication. Nevertheless, modelled events will be assigned the costs and consequences appropriate to the underlying condition being assessed (e.g. stroke for atrial fibrillation and artificial heart valves, or DVT and PE for VTE). People experiencing these events will be modelled to incur the expected treatment costs, and will transit to a post-treatment state defined by their health status and level of independence (e.g. independent, moderate disability, fully dependent). Proportions of people experiencing these outcomes will be informed by the clinical effectiveness review, and/or focussed reviews of studies reporting functional outcomes following morbidity events. Any on-going health and social care costs associated with time spent in these states will be applied, as will health related quality of life weights, allowing cumulative costs and QALYs to be tracked for each strategy over cycles of the model. The model will initially be run over a 10 year period, but the impact of adopting longer time horizons (including the patient's life time) will be explored in sensitivity analyses (longer time horizons will be also used to explore the impact of longer period of anticoagulation therapy in children). We anticipate that a 10-year time horizon will be sufficient to demonstrate the main health and cost impacts of any identified differences in adverse event rates (between the alternative monitoring approaches), while avoiding the uncertainty of making assumptions about event rates far into the future. In the event that one approach is found to be more effective but not cost-effective at 10 years, analyses based on longer time horizons will help to inform the decision on the cost-effectiveness of the alternatives.

Data on the resource use and costs associated with alternative monitoring strategies will be informed by existing clinical guidelines and published literature, expert opinion, manufacturers and suppliers prices, and other routine sources of unit cost data.[23,24] As noted above, study specific costs will be generated if suitable data from other sources are not available. For example, we will investigate the training and on-going support costs required to enable patients to self-monitor, and the anticipated running cost for such services which may not currently be well established in the NHS. This will be guided through discussions

with health professionals with experience delivering and managing such services. The costing perspective will be that of the NHS and Personal Social Services.

Data on the health state utilities associated with the underlying conditions requiring vitamin K antagonist therapy, prior to and following adverse morbidity events will be derived from the published literature, including the structured review of economic evaluations. Specific searches will be undertaken in clinical and economic databases, including a search of the CEA Registry.

The results of the model will be presented in terms of a cost-utility analysis (e.g. costs for and number of QALYs generated by each strategy). Each strategy will be compared incrementally to its next less effective non-dominated comparator, to estimate its incremental cost per quality adjusted life year gained (QALY). The modelling exercise will use the net benefit framework to identify the optimal monitoring strategy at different threshold ratios of willingness to pay per QALY. To characterise the joint uncertainty surrounding point estimates of incremental costs and effects, probabilistic sensitivity analysis will be undertaken.[25] The results of this analysis will be presented in the form of cost-effectiveness acceptability curves (CEACs) and frontiers (CEAFs). Further deterministic sensitivity analysis will be used to address other forms of uncertainty.

7. Handling information from the companies

Following a request for information, any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any academic-in-confidence data provided will be highlighted in yellow and underlined.

8. Competing interests of authors

None

9. Timetable/milestones

Milestone	Date to be completed
Draft protocol	13/05/13
Final protocol	05/06/13
Progress report	02/09/13
Draft version of report	28/10/13
Final version of report	25/11/13

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11. APPENDICES

MEDLINE Search Strategy - DRAFT

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1 exp 4-Hydroxycoumarins/
2 warfarin.tw.
3 vitamin k antagonist$.tw.
4 *anticoagulants/ad
5 international normali?ed ratio?.tw.
6 or/1-5
7 Self Administration/
8 Self Care/
9 point of care systems/
10 poc.tw.
11 ((patient$ or self) adj3 (monitor$ or manag$ or measur$)).tw.
12 or/7-11
13 6 and 12
14 coaguchek.tw.
15 inratio$.tw.
16 protime$.tw.
17 coagulometer$.tw
18 or/13-17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt
21 randomi?ed.ab.
22 placebo.ab.
23 drug therapy.fs.
24 randomly.ab.
25 trial.ab.
26 groups.ab.
27 or/19-26
28 exp animals/ not humans/
29 27 not 28
30 18 and 29
31 limit 30 to yr=2007-current
32 (coaguchek xs or inratio$ or protime$ or pro time$).tw.
33 31 or 32
34 limit 33 to english language

Additional information that is needed by NETSCC, HTA and NICE:

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