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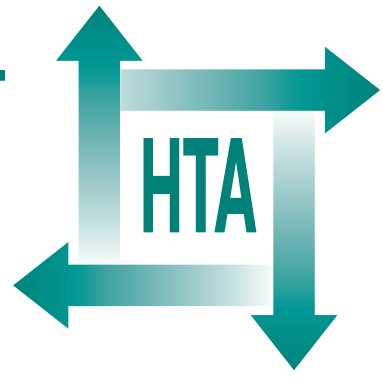

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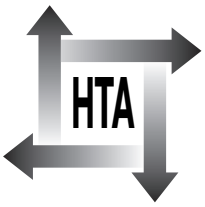

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The research reported in this monograph was commissioned by the HTA Programme as project number 05/33/01. The contractual start date was in September 2005. The draft report began editorial review in May 2006 and was accepted for publication in April 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling

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Objectives: To examine the clinical effectiveness and cost-effectiveness of self-testing and self-management of oral anticoagulation treatment compared with clinic-based monitoring.
Data sources: Major electronic databases were searched up to September 2005.
Review methods: A systematic review was undertaken of relevant data from selected studies. Results about complication events and deaths were pooled in meta-analyses using risk difference (RD) as the outcome statistic. Heterogeneity across trials and possible publication bias were statistically measured. Subgroup analyses (*post hoc*) were conducted to compare results of self-testing versus self-management, low versus high trial quality, trials conducted in the UK versus trials in other countries and industry versus other sponsors. A Markov-type, state-transition model was developed. Stochastic simulations using the model were conducted to investigate uncertainty in estimated model parameters.
Results: In the 16 randomised and eight non-randomised trials selected, patient self-monitoring of oral anticoagulation therapy was found to be more effective than poor-quality usual care provided by family doctors and as effective as good-quality specialised anticoagulation clinics in maintaining the quality of anticoagulation therapy. There was no significant RD of major bleeding events between patient self-monitoring and usual care controls and pooled analyses found that compared with primary care or anticoagulation control (AC) clinics, self-monitoring was statistically significantly associated with fewer thromboembolic events. However, the reduction in complication events and deaths was not consistently associated with the improvement of AC; in some trials this may be due to alternative explanations, including patient education and patient empowerment. Also, the improved AC and the reduction of major complications and deaths by patient self-monitoring were mainly observed in trials conducted outside the UK. According to UK-specific data, for every 100 eligible patients, 24% would agree to conduct self-monitoring, 17 of the 24 patients (70%) could be successfully trained and able to carry out self-monitoring and only 14 of these (80%) would conduct long-term self-monitoring. Seven cost-effectiveness studies were identified and the study that provided the most relevant UK data found that patient self-management was more expensive than current routine care (£417 versus £122 per patient-year) and concluded that using a cost-effectiveness threshold of £30,000 per quality-adjusted life-year (QALY) gained, patient self-management does not appear to be cost-effective. *De novo* modelling for this report found that the incremental cost per QALY gained by patient self-monitoring is £122,365 over 5 years and £63,655 over 10 years. The estimated probability that patient self-monitoring is cost-effective (up to £30,000/QALY) is 44% over a 10-year period. Wide adoption of patient self-monitoring of anticoagulation therapy would cost the NHS an estimated additional £8–14 million per year.
Conclusions: For selected and successfully trained patients, self-monitoring is effective and safe for long-term oral anticoagulation therapy. In general, patient

self-management (PSM) is unlikely to be more cost-effective than the current specialised anticoagulation clinics in the UK; self-monitoring may enhance the quality of life for some patients who are frequently away from home, who are in employment or education, or those who find it difficult to travel to clinics. Further research is needed into alternative dosing regimes, the clinical effectiveness and cost-effectiveness of patient education and training in long-term oral anticoagulation therapy, UK-relevant cost-effectiveness, the effectiveness of PSM in children, and the potential future developments of near-patient testing devices.

Contents

List of abbreviations

AC	anticoagulation control
ACC	anticoagulation clinic care
AF	atrial fibrillation
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
ESCAT	Early Self-Controlled Anticoagulation Trial
HCP	healthcare professional
ICER	incremental cost-effectiveness ratio
INR	International Normalised Ratio
ISI	International Sensitivity Index
ITT	intention-to-treat
MHRA	Medicines and Healthcare Products Regulatory Agency
MHV	mechanical heart valve
NEQAS	National External Quality Assessment Service
NPT	near-patient testing
POC	point of care
PSM	patient self-management
PST	patient self-testing
PT	prothrombin time
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RD	risk difference
SEIQoL	Schedule for the Evaluation of Individual Quality of Life
SF-36	Short Form with 36 Items
TP	thromboplastin
UK OAC model	UK oral anticoagulation model

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Many disorders, including common cardiac conditions, are linked to increased risk from thrombosis and require anticoagulant therapy. Oral anticoagulation control (AC) is used to reduce the chance of unwanted thrombosis. AC therapy lengthens the time it takes for a sample of a patient's blood to clot. Such therapy, usually with warfarin, requires frequent monitoring to maintain a beneficial balance between decreased clotting and the tendency for increased bleeding that results from therapy. Conventional monitoring has involved patients attending clinic for measurement of clotting speed. A physician then adjusts the patient's anticoagulant dose to achieve the desired balance between reduced clotting and tendency to bleed. Two other anticoagulation management strategies have been developed that employ near-patient testing (NPT) devices. With these devices, patients can measure clotting speed themselves ('patient self-testing'); a physician uses the result to adjust the patient's anticoagulant dose or the patients adjust the dose of anticoagulant themselves in the light of their own measurements with the NPT device ['patient self-management' (PSM)]. These two strategies are collectively referred to as patient self-monitoring.

It is estimated that approximately 950,000 people (2% of the general practice population) in the UK are currently taking warfarin and the numbers continue to increase by about 10% each year, primarily driven by its use for patients with atrial fibrillation. The future impact of this expansion is indicated by estimates that currently more than half of those with atrial fibrillation may remain unidentified and less than half of those identified may be receiving treatment. These estimates considered together with an ageing population mean that future service load could increase substantially.

Objectives and methods

This report aims to examine the clinical effectiveness and cost-effectiveness of self-testing and self-management of oral anticoagulation treatment compared with clinic-based monitoring.

Methods

Comprehensive bibliographic searches were undertaken up to September 2005 to identify randomised and non-randomised controlled studies of patient self-monitoring for long-term oral anticoagulation therapy. Data about AC, adverse events, mortality, attrition and patient acceptability were extracted from the retrieved studies. Results about complication events and deaths were pooled in meta-analyses using risk difference (RD) as the outcome statistic (in order to include many studies that reported zero events). Heterogeneity across trials and possible publication bias were statistically measured. Subgroup analyses (*post hoc*) were conducted to compare results of self-testing versus self-management, low versus high trial quality, trials conducted in the UK versus trials in other countries and industry versus other sponsors.

Comprehensive bibliographic searches of major electronic databases were undertaken up to September 2005 to identify cost-effectiveness studies that evaluated the cost-effectiveness of patient self-monitoring of anticoagulation. We also developed a Markov-type, state-transition model for the evaluation of cost-effectiveness of patient self-monitoring of oral anticoagulation compared with the usual care currently provided in the UK. Input values for the model were mainly based on a review of relevant literature. Stochastic simulations using the model were conducted to investigate uncertainty in estimated model parameters.

Results

Evidence about effectiveness

Sixteen randomised trials were included. Patient self-monitoring of oral anticoagulation therapy is more effective than poor-quality usual care provided by family doctors. Poor quality of AC managed by family doctors is particularly associated with a greater proportion of time spent below the target therapeutic clotting range. This could be much reduced by patient self-monitoring. Patient self-monitoring is as effective as good-quality specialised anticoagulation clinics in maintaining the quality of anticoagulation therapy.

There was no significant RD of major bleeding events between patient self-monitoring and usual care controls [RD –0.0039, 95% confidence interval (CI) –0.0154 to 0.0077]. Pooled analyses found that compared with primary care or AC clinics, self-monitoring was statistically significantly associated with fewer thromboembolic events (RD –0.0224, 95% CI –0.0334 to –0.0115) and deaths (RD –0.017, 95% CI –0.0287 to –0.0053). However, the reduction in complication events and deaths was not consistently associated with the improvement of AC. The observed reduction in complications and deaths in some trials may be due to alternative explanations, including patient education and patient empowerment. In addition, random or systematic errors could not be ruled out from the included trials. More importantly, findings of meta-analyses by pooling results from all trials may not be applicable to the UK setting. The improved AC and the reduction of major complications and deaths by patient self-monitoring were mainly observed in trials conducted outside the UK.

Eight non-randomised controlled studies were included. The sample sizes of these studies were generally small, and the period of follow-up was similar to that in the randomised trials. The results from non-randomised studies were similar to those from the randomised trials. The impact of including data from the non-randomised studies in meta-analyses of major complications and death outcomes was negligible.

Patient selection and acceptability

Not all patients are capable of performing self-monitoring and some patients find it unnecessary because of high-quality care provided by existing anticoagulation clinics. Selected patients may consider self-monitoring of oral anticoagulation as an invaluable option. For example, self-monitoring may enhance the quality of life for some patients who are frequently away from home, who are in employment or education or who find it difficult to travel to clinics.

Pooling of available data from all trials suggested that, on average, 33% of eligible patients agreed to participate in the trials; 80% of patients randomised to patient self-monitoring were successfully trained and/or able to conduct self-monitoring, and 87% of those who started self-monitoring continued monitoring to the end of study. According to UK-specific data, for every 100 eligible patients, 24% would agree to conduct self-monitoring, 17 of the 24 patients (70%) could be successfully trained and able to carry out self-monitoring and only 14 of these (80%) would conduct long-term self-monitoring.

Economic evaluation

Seven studies of evaluating the cost-effectiveness of patient self-monitoring of anticoagulation were identified. The applicability of six of these to the UK setting was limited. One UK study provided the most relevant data. This study found that patient self-management was more expensive than current routine care in the UK (£417 versus £122 per patient-year) and concluded that using a cost-effectiveness threshold of £30,000 per quality-adjusted life-year (QALY) gained, patient self-management does not appear to be cost-effective.

It was estimated that wide adoption of patient self-monitoring of anticoagulation therapy would cost the NHS an additional £8–14 million per year. The results of *de novo* modelling for this report found that the incremental cost per QALY gained by patient self-monitoring is £122,365 over 5 years and £63,655 over 10 years. The estimated probability that patient self-monitoring is cost-effective (up to £30,000/QALY) is 44% over a 10-year period. Therefore, self-monitoring by general patients of oral anticoagulation therapy is unlikely to be more cost-effective than current usual care in the UK.

Conclusions

For selected and successfully trained patients, self-monitoring is effective and safe for long-term oral anticoagulation therapy. Self-monitoring may enhance the quality of life for some patients who are frequently away from home, who are in employment or education, or those who find it difficult to travel to clinics. In general, patient self-monitoring is unlikely to be more cost-effective than the current high-quality care provided by specialised anticoagulation clinics in the UK.

Recommendations for further research

Published values of percentage of time or percentage of tests within the target range indicate that there is scope for further improvement of PSM beyond the performance currently achieved. Different dose algorithms and other procedures that could lead to alternative dosing regimes represent an element of PSM that might be profitably researched with the aim of improving performance.

Limited evidence indicated that patient education and training may improve clinical outcomes of anticoagulation therapy, even without performing PSM of AC. There is a lack of evidence about whether patient education alone is sufficient to reduce the risk of bleeding, thromboembolic complications and deaths in patients who receive long-term anticoagulation therapy. The clinical effectiveness and cost-effectiveness of patient education and training in long-term oral anticoagulation therapy need to be investigated.

Only one economic analysis of PSM of long-term anticoagulation therapy was identified that was directly relevant to the UK. Therefore, further cost-effectiveness research is required to build on the findings of this study, particularly taking into account the costs of PSM outside trial conditions. In addition, further consideration should be given to the measurement of the less tangible benefits of self-management, which the broad health measures used to calculate QALYs may not be able to capture.

Warfarin allows many children with heart disease to survive into healthy adulthood, but this brings families another set of problems. In addition to missing time off school to attend clinics, it makes timing of holidays difficult. For parents this may involve time away from work, with long clinic waits, often with other siblings. The PSM model, where children or carers have knowledge of changes in lifestyle and concurrent medication, may also be effective in reducing risks of adverse events. Although a few studies have been conducted on PSM of anticoagulation therapy in children, there is a lack of RCTs and, as far as we are aware, no clinical trials are being undertaken in this area. Future research needs to evaluate the effectiveness of PSM in children.

PSM of anticoagulation therapy arose from development of NPT devices sufficiently user-friendly and compact that some patients satisfactorily control their anticoagulation. Further progress in the design, conception and ease of use of NPT devices may broaden the spectrum of patients able to undertake PSM and provide alternatives for this model of management. It is important that potential future developments are subjected to appropriate quality control and that effectiveness is investigated with well-designed RCTs with sufficient follow-up to capture key outcomes of complication events (thromboembolism, bleeds) and mortality.

Chapter 1
Introduction

Many disorders, including common cardiac conditions, are linked to increased risk from thrombosis (formation of blood clots) and require anticoagulant therapy.[1] Such therapy, usually with warfarin, requires frequent monitoring to maintain a beneficial balance between decreased clotting and the tendency for increased bleeding that results from therapy and that can have serious adverse consequences.

Conventional monitoring has involved patients attending a clinic where a venous blood sample is analysed for clotting speed. The result is interpreted by a physician, who adjusts the patient's anticoagulant dose to achieve the desired balance between reduced clotting and tendency to bleed. The aim is to keep the patient's clotting speed within what is judged to be the therapeutic range for his or her condition.

Two alternative monitoring schemes have been developed that employ near-patient testing (NPT) devices. These devices allow measurement of clotting speed using a small whole blood sample from a finger prick. The patient can use the device at home. In 'patient self-testing' (PST), the clotting speed result is relayed to a physician, who then adjusts the patient's anticoagulant dose. In 'patient self-management' (PSM), patients adjust the dose of anticoagulant themselves in the light of the results from the NPT device.

This report aims to examine the clinical effectiveness and cost-effectiveness of PST and PSM of anticoagulation treatment compared with clinic-based monitoring.

Chapter 2
Background

Description of underlying health problem

Anticoagulation therapy and the need for monitoring

Oral anticoagulation control (AC) is used to reduce the chance of unwanted thromboembolism (clotting).[1] To do this, AC therapy lengthens the time it takes for a sample of a patient's blood to clot, a phenomenon called prolonged prothrombin time (PT). Warfarin treatment does this by reducing the active levels of certain proteins in the blood whose function is to bring about clotting. In particular, the proteins affected by warfarin are Factors II, VII and X.

The mechanism by which warfarin alters functional levels of these factors is as follows: after Factor II, VII and X protein molecules have been made, they undergo 'activation' in which some of the glutamic acid residues in their structures are modified by carboxylation. They are then able to bind calcium ions effectively and function in the clotting cascade. The enzyme that carboxylates Factors II, VII and X depends on a supply of vitamin K, which acts as a 'coenzyme'. Vitamin K is in limited supply and is consumed during the carboxylation reaction and so needs to be replaced or regenerated if activation of clotting factors is to continue. Replacement is slow and depends on vitamin K supply in the diet, but regeneration is fast and is achieved by specialised reductase enzymes that regenerate the active form of vitamin K. Warfarin displaces vitamin K from the reductases and they cannot function properly. Hence treatment with warfarin influences the activation of Factors II, VII and X and thereby prolongs PT and alters the risk of thrombosis and the tendency to bleed.

Warfarin dosage needs to be controlled carefully in the face of vitamin K delivery in the diet, the medically required prolongation of clotting time, the rate of synthesis of clotting factors (especially Factor VII), patient age, other medications, the levels of various dietary factors other than vitamin K and the presence of concurrent illness. This is why the patient's PT needs to be monitored frequently and regularly and, according to the result, the dose of warfarin correspondingly adjusted. The efficacy and safety of warfarin depend on maintaining the anticoagulant effect close to a defined therapeutic target.

At the start of warfarin treatment, 'normal' levels of active factors are already present; these cannot be deactivated and only become depleted due to natural turnover. Warfarin merely reduces the rate of their replacement by new activated factors; hence warfarin therapy takes several days to start working after the initiation of treatment.

New antithrombotic drugs, ximelagatran and dabigatran, have been developed that may replace warfarin so that regular monitoring of AC may no longer be needed.[2] However, ximelagatran was withdrawn from the market in February 2006 because of liver-related adverse effects.[3] Therefore, warfarin is unlikely to be replaced by new direct antithrombotic drugs in the near future.

Epidemiology

Long-term oral anticoagulation (predominantly warfarin) has been increasingly prescribed to patients with diverse indications such as non-rheumatic atrial fibrillation (AF), mechanical heart valves and the treatment and prophylaxis of venous thromboembolism in high-risk patients.[1]

It is estimated that approximately 950,000 people (about 2% of the general practice population) in the UK are currently taking warfarin and the numbers continue to increase by about 10% each year, primarily driven by its utilisation as thromboprophylaxis for patients with AF.[4] AF is the most common sustained cardiac rhythm disorder. It is a major risk factor for thromboembolism (decreased blood flow in the heart can promote the formation of clots) and the single most important independent risk factor for stroke. AF is usually associated with additional underlying disorders that 'stress' the atrial myocardium; more than two-thirds of patients have other cardiovascular disease, including valvular disease, coronary heart disease, hypertension, cardiomyopathy, congenital heart disease and constrictive pericarditis.[5] The likely future impact of increased use of AC is informed

by data showing that only one-quarter to one-third of patients with identified AF may currently be receiving treatment[6,7] and that, in the absence of screening programmes, about 60% of patients with AF remain unidentified.[4] These estimates considered together with an ageing population mean that the future service load could increase substantially.

Current service provision

Prothrombin time and the International Normalised Ratio (INR)

Oral anticoagulation has a narrow therapeutic index in order to balance the need of prevention of thromboembolic diseases and the avoidance of haemorrhagic side-effects. Under-anticoagulation (when the dose of warfarin is too low) increases the risk of thromboembolism (principally stroke in AF), whereas over-anticoagulation (where the dose of warfarin is too high) increases the risk of haemorrhagic side-effects. Responses to warfarin vary greatly among individuals and within the same patients, depending on age, diet, diseases and the use of other medications. Therefore, repeated measures of PT are necessary so that dose size and/or frequency can be adjusted.

When the PT of a blood sample is estimated, the sequence of reactions leading to clot formation is triggered by introduction of thromboplastin (TP) reagent. Different TPs are available and these have different sensitivities in detecting the prolonged clotting time characteristic of patients receiving AC. Due to this variation in TP performance, it has become necessary to standardise TPs according to an International Sensitivity Index (ISI).

The procedure for determining the ISI of a new TP reagent is as follows: PTs of normal plasmas and plasmas from patients in receipt of AC therapy are measured with the new TP and also with an international reference TP. A graph of PT with the new TP is plotted against PTs with the international standard TP (x-axis); both axes are logarithmic. The slope of the resulting relationship is designated the ISI. An ISI >1 signifies a TP that is more sensitive than the reference TP at detecting the prolonged clotting time of AC patients' blood.

The TP reagent of known ISI is then used to determine patients' PT and that of a batch of normal plasmas. The ratio (R) of a patient's PT to normal plasma PT is thereby obtained. The patient's INR value is then given by the ratio raised to the power of ISI:

$$\text{INR} = R^{\text{ISI}}$$

If the ISI of the TP is 1, then R = INR.

The introduction of ISI and INR procedures has improved AC. Problems may arise due to lack of linearity in the relationship between a new TP and reference TP, or because the ISI for a TP may vary depending on the coagulometer instrument used.

Clinic monitoring of patient INR

In the UK, the conventional model of management of patients receiving oral anticoagulant therapy is based on hospital clinics [anticoagulation clinic care (ACC)]. Patients visit a hospital-based clinic approximately every 4–6 weeks to have a blood sample taken. Blood is tested in the laboratory for the INR and the dose of warfarin is then recommended.

Current guidelines specify a target degree of anticoagulation for different indications.[8] The target INR is 2.5 for most indications, including AF, but is higher (3.5) for some indications, such as mechanical prosthetic heart valve or recurrence of venous thromboembolism while on warfarin therapy. Management of a patient taking warfarin needs to include awareness of factors that may affect the patient's response to warfarin and also knowledge of the patient's history of warfarin dosing relative to the measured INR values over time. Poor control of anticoagulation (too high or too low INR) increases the risk of serious complications such as stroke and gastrointestinal bleeding.

The performance of anticoagulation clinics has not always been ideal, in terms of either INR control, adverse events or patient satisfaction.[4] Figures for clinics using manual systems (clinician judgement, dosing algorithms) for dosing show a point prevalence of patients achieving therapeutic INR levels of between 43 and 55%, improving to 65% in other clinic models.[9] This compares with 54% achieved in general practice clinics using similar methods and treating a similar population.[10] These data for routine performance within UK anticoagulation clinics compare very favourably with routine data from other countries, particularly the USA[11] and Germany,[12] where rates of 40% are found.

Recently, the costs of long-term oral anticoagulation have been evaluated in several

trials in the UK. A randomised trial in Birmingham found that the costs (to the NHS) of conventional anticoagulation management in hospital clinics were £69 per patient per year [95% confidence interval (CI) £57–81].[13] When patient costs were included (based on a survey of patients attending anticoagulation clinics), the total cost of anticoagulation management in hospital clinics was £171.[14] A further trial in Birmingham estimated the cost of routine care either in secondary or primary care to be about £90 per patient per year.[15]

If we assume that approximately 1 million patients currently require anticoagulation therapy in the UK, then the total annual cost of conventional management for the NHS in England and Wales is in the order of £90 million.

Description of new intervention

The emergence of point-of-care (POC) testing devices has allowed the development of new models of anticoagulation care, including PST and PSM.

NPT devices enable the INR to be estimated in primary care and therefore reduce the need for patients to visit the hospital clinic and reduce laboratory time. In the PST model, patients are trained to test their own INR, but clinicians decide the dose of warfarin. PSM enables patients not only to test their own INR but also to manage adjustments to warfarin dose. Greater autonomy and potential self-control over their disease may be attractive aspects for patients. Operation of NPT devices requires skill and understanding and it is likely only a minority of long-term anticoagulation patients are suited to these models of management.

Currently, there are three portable, battery-driven, PT coagulometers with satisfactory evaluations performed by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) that have shown acceptable and comparable INR values across the therapeutic range. These are the ProTime 3 Microcoagulation System, Roche CoaguChek S and the Hemosense INRatio instruments (*Table 1*). Good performance has been demonstrated with commercially available NPT coagulometers, in terms of accuracy, reproducibility and long-term reliability, when used by selected patients.[16,17]

Patients require an educational programme of theory and practice delivered by a trained healthcare professional (HCP) in order to use NPT devices safely and effectively and to learn how to interpret INR results appropriately for self-management. Competence is assessed by an

TABLE 1 *Near-patient testing PT time measuring devices*

Cost and operational details	CoaguChek S® (Roche)	ProTime 3® (ITC)	INRatio® (Hemosense)
Machine cost (£)	399.00	840	399.00
Test strips (×12) cost (£)	30.53		45.21
Test strips (×48) cost (£)	119.35		174.10
Cuvettes (×6) cost (£)		25.00	
Cuvettes (×25) cost (£)		113.60	
Specimen collection	Test strip/iron oxide particles/ thromboplastin	Test cuvette/Tenderlett device/ cuvette containing thromboplastin	Test strip/ thromboplastin
Quantity of blood (μl)	10	27	15
Detection principle	Iron oxide particles/ photoreflection	Photoptic detection of decreased blood flow	Change in electrical impedance as blood clots
Type of blood	Whole blood – venous or capillary	Whole blood – venous or capillary	Whole blood – capillary
Thromboplastin (ISI)	Rabbit brain	Recombinant	Recombinant
Memory store	30 test results	39 test results	60 test results
Internal quality control	Supplied by manufacturer	Integral to test cuvette	Integral to test strip
Calibration	Lot-specific code chip new test strips	Instrument and cuvettes precalibrated	Test-strip specific code

experienced HCP before patients proceed with PST or PSM. Recent UK guidelines[18] recommend:

- training for HCP patient-trainers
- 6-monthly assessment of patient's NPT competence by a responsible clinician
- routine internal quality control of NPT performance at regular intervals and also when a new batch of disposables (e.g. strips) is to be used
- regular external quality control [e.g. using the UK National External Quality Assessment Service (NEQAS) system, or by duplicate measures at a reliable anticoagulation clinic]
- retesting of unexpectedly high or low results.

There have been few economic evaluations of PST or PSM of anticoagulation therapy. The existing cost-effectiveness analyses in other countries[19,20] are based on estimates of cost-effectiveness and clinical effectiveness which may not be relevant to the circumstances in the UK, and/or may be challenged by research evidence that is more recently available. Recently, a randomised trial in Birmingham[21] found that a primary care model utilising NPT and computerised dosing cost £169 (95% CI £149 to £190) per patient per year.[13] A further trial in Birmingham found that PSM cost £417 (95% CI £394 to £442) per patient per year.[15]

Some international research implies that PST and PSM of coagulation control are at least as good as (or possibly better than) that achieved within routine care by clinics. These findings from outside the UK need to be viewed with some caution because routine care by anticoagulation clinics in other countries may not be as well established as in the UK[22] and therefore performance of PSM and PST in these studies may have been judged against comparators inappropriate to the UK context.

The diffusion into the NHS of the new models of monitoring AC therapy is difficult to gauge but currently is probably minimal. In contrast, PSM has been widely adopted in several other European countries, most notably in Germany. These healthcare systems are underpinned by fiscal arrangements different from those in the UK NHS. It can be presumed that these countries have decided that PSM is cost-effective for selected patients (i.e. those able and compliant). It should be recognised that such decisions may have been made against a background of relatively poor-performing conventional management of AC therapy.

A large future increase in UK patients requiring AC therapy monitoring is likely. The consequential pressure on clinic-based monitoring means that PSM or PST models of management might offer a way of relieving such pressure or of providing a cost-effective alternative to conventional monitoring for at least a proportion of patients.

Chapter 3
Methods

Search strategy

The following databases were searched for any primary studies of patient self-testing and self-management of oral anticoagulation control:

- MEDLINE (Ovid) 1966 to September week 1 2005
- EMBASE (Ovid) 1980 to 2005 week 38
- CINAHL (Ovid) 1982 to September week 2 2005
- Cochrane Library (CENTRAL) (Wiley Internet version) 2005 Issue 3.

Searches included text words and index terms, which encompassed: anticoagulant, anticoagulation; warfarin, coumadin, coumarin; near patient tests; patient self-testing, patient self-management; international normalised ratio. The MEDLINE, Cochrane Library and CINAHL searches were not restricted by methodological filters in order to identify any studies [randomised controlled trials (RCTs) and non-RCTs] relevant to PST or PSM of oral anticoagulation therapy An RCT methodological 'filter' was incorporated in the search of EMBASE. References from the searching of all electronic databases (MEDLINE, EMBASE, CINAHL and Cochrane Library) were pooled into a single database using Reference Manager, and duplicates were excluded. No language or date restrictions were applied. Full search strategies are shown in Appendix 1.

The references of retrieved articles (including published relevant guidelines and systematic reviews) were scanned for any relevant studies. Ongoing and completed but unpublished studies were sought in the National Research Register.

A comprehensive search for literature on cost and cost-effectiveness of PST and PSM of oral AC was conducted. Studies on costs, quality of life (QoL), cost-effectiveness, and modelling were identified from the following bibliographic databases:

- MEDLINE (Ovid) 1966 to week 1 2005
- Cochrane Library (NHS EED, DARE and HTA database) (Wiley Internet version) 2005 Issue 3
- HEED September 2005.

Search strategies are shown in Appendix 1.

Inclusion and exclusion criteria

Clinical effectiveness review

Two reviewers (FS and CS) independently screened all titles and abstracts for RCTs and non-RCTs using the following inclusion criteria:

- intervention: NPT in primary care, PST and PSM of oral anticoagulant therapy
- comparator: routine anticoagulation clinics (in secondary or primary care)
- outcomes: anticoagulation control, adverse events including bleeding events and thromboembolism, patient satisfaction and QoL.

Searches for primary studies were not restricted by study design. The relevance of non-RCTs was assessed by one reviewer (FS) according to the same criteria as above.

Cost-effectiveness review

- Study design: economic evaluation studies: cost-analysis, cost-effectiveness, cost–utility and cost–benefit studies; existing health economic reviews were also assessed.
- Outcomes: QoL, costs and incremental cost-effectiveness ratios (ICERs) were assessed.

Studies were excluded if they did not evaluate NPT or PST, or did not use coumarins as anticoagulant treatment.

Data extraction

The following data were independently extracted by two reviewers (FS and CS): AC models compared; country of origin; study design; sample size; patient inclusion and exclusion criteria; characteristics of patients such as age, indications for anticoagulation therapy and target INR range; comparability of patients between different arms; outcome measures (including length of time in target range, percentage of patients in target range, the risk of thromboembolic and haemorrhagic events and other side-effects); costs; length of follow-up; results; patient acceptability; and QoL measures. Disagreements were resolved by consensus.

Relevant non-RCTs and economic evaluation studies were reviewed and data were extracted by one reviewer and checked by another.

Quality assessment strategy

The quality of RCTs was assessed in terms of the method of patient allocation, concealment of randomisation, blinding of patients, care providers and outcome assessors, whether or not an intention-to-treat (ITT) analysis was performed and drop-outs or withdrawals.[23] The quality of non-randomised studies was assessed according to criteria set out by Khan and colleagues 2001.[23]

Evidence synthesis methods

Quality of AC is usually measured in clinical trials (RCTs and non-RCTs) by percentage of time INR spent in the therapeutic range or percentage of INR values in range. The results of individual trials could be weighted by the number of patient-years or the number of INR tests to provide a pooled estimate. However, the data from trials were usually insufficient or unreliable to estimate 95% confidence intervals (CIs) for pooled estimates.

Risk difference (RD) was used as the outcome statistic in meta-analysis for major complications and deaths reported in RCTs and non-RCTs. The use of RD has two advantages in this meta-analysis. First, trials that reported zero events or deaths in both arms can be included in the meta-analysis. This is important because the number of trials involved was small and many trials reported zero complication events or deaths in one or two comparison groups. Second, trials that used poor-quality controls (which also tended to have a great number of events) may be less over-weighted by the use of RD than other methods. However, Peto's odds ratio method was used (as recommended for meta-analyses of rare events by Bradburn and colleagues[24]) so as to compare the results of different methods for meta-analysis.

Heterogeneity across trials was measured statistically. Possible publication bias was examined by funnel plot-related statistical analyses. Subgroup analyses (*post hoc*) were conducted to compare results of PST versus PSM, low versus high trial quality, trials conducted in the UK versus trials in other countries and industry versus other sponsors. Statistical analyses were conducted using STATA 8 software (STATA Corp.). QUORUM guidelines[25] were followed for review of RCT studies.

Findings from included economic evaluation studies were summarised by narrative review.

Chapter 4

Results: evidence from controlled studies

Quantity of research available

A total of 2953 titles and abstracts were screened for inclusion in the review of clinical effectiveness, and 78 relevant studies were assessed in more detail. Sixteen RCTs and seven non-RCTs that evaluated the effectiveness of PST or PSM of oral anticoagulation therapy compared with routine care in an anticoagulation clinic met the inclusion criteria (*Figure 1*).

Clinical effectiveness results

Clinical effectiveness: randomised trials

Sixteen randomised trials were included (*Table 2*).[12,16,26–39] An ongoing trial without results was not included.[40] Six trials were conducted in the UK, four in Germany, two in The Netherlands, two in the USA, one in Canada and one in Spain. Ten of the 16 trials were at least partially sponsored by industry.

Three trials included patients with mechanical heart valve (MHV) replacement only, and two trials included patients with AF only. Eleven trials included patients with mixed indications, although MHV replacement and AF were the two most common reasons for the long-term anticoagulant therapy. Three trials included new patients starting long-term anticoagulant therapy.[26,33,38] One UK trial selected patients whose control of anticoagulant therapy was unstable during the previous 6 months.[32] Patients included in most trials had been undergoing anticoagulant therapy for 1–12 months. The mean age of patients ranged from 42 to 75 years across all trials.

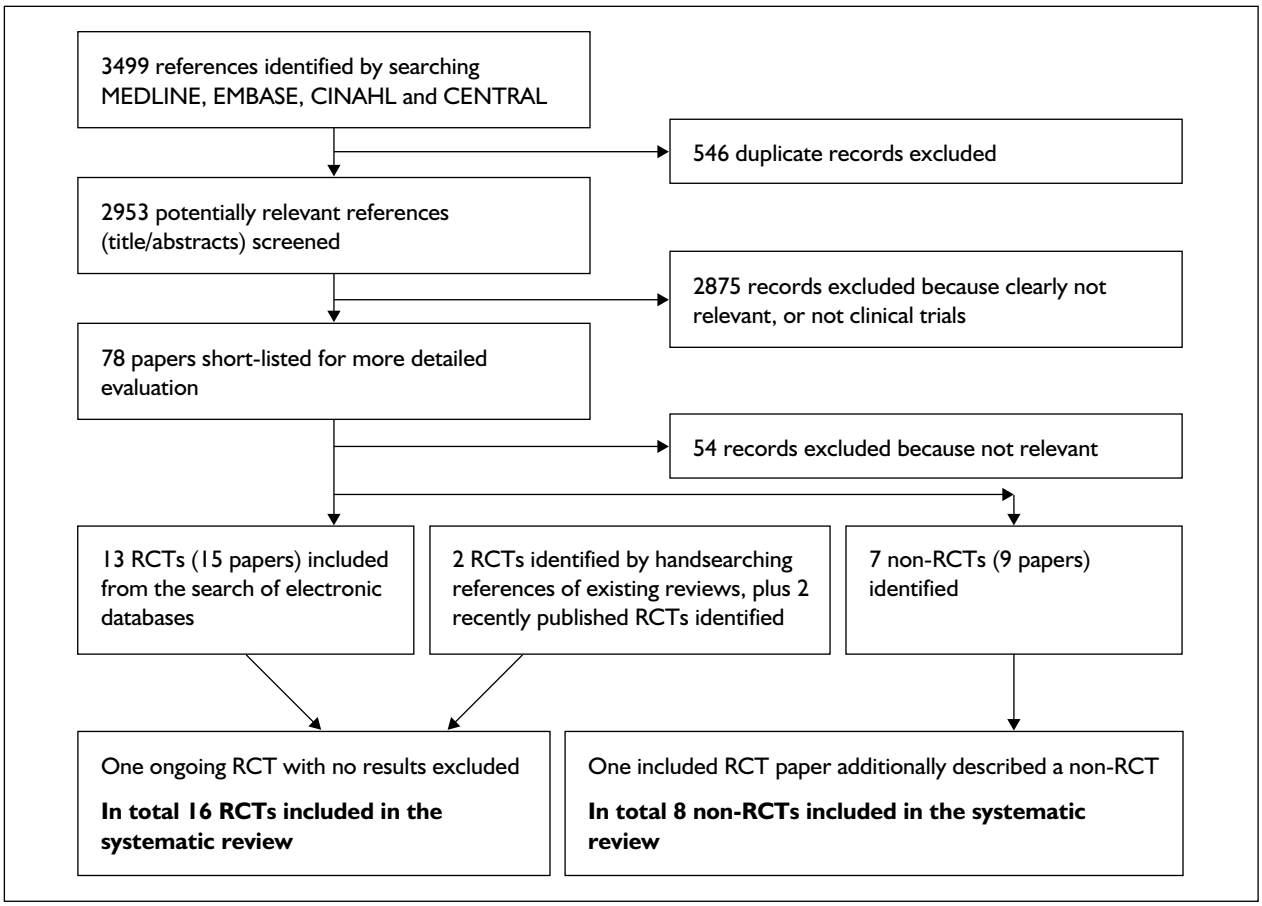

FIGURE 1 *Flow chart of identification of relevant controlled trials*

TABLE 2 *Main study characteristics – randomised controlled trials*

Study	Country	Duration (months)	Sample size		Indications	Use of AC (baseline control)	Mean age (years)	Male (%)	Funding source
			PST/PSM	Control					
Beyth, 2000[26]	USA	6	163	162	Mixed	New (unstable)	75/75	43	Public
Cromheecke, 2000[27]	The Netherlands	3	50	50	Mixed	4 (±2.2) years (NR)	42/42	59	Not stated
Fitzmaurice, 2002[28]	UK	6	30	26	Mixed	⩾6 months (≥ 60%)	63/69	76	Industry
Fitzmaurice, 2005[29]	UK	12	337	280	Mixed	⩾6 months (68%)	64/66	65	Public
Gadisseur, 2003[30]	The Netherlands	6	52 + 47	60 (161)	Mixed	⩾3 months (64%)	54/62	71	Industry
Gardiner, 2005[16]	UK	6	44	40	Mixed	⩾8 months (NR)	58/58	63	Industry
Gardiner, 2006[39]	UK	6	PSM/PST 55/49	–	Mixed	⩾8 months (NR)	59.9	60.6	Partially industry
Horstkotte, 1998[31]	Germany	~18	75	75	MHV	NR	NR	NR	Not stated
Khan, 2004[32]	UK	6	44	41 + 40	AF	⩾12 months (unstable, 60%)	71/75	60	BUPA
Kortke, 2001[33]	Germany	>24	579	576	MHV	New (unstable)	63	66	Not stated
Menendez-Jandula, 2005[34]	Spain	~12	368	369	Mixed	⩾3 months (NR)	65/65	53	Industry
Sawicki, 1999[12]	Germany	6	90	89	MHV/AF	2 (±5) years (29–36%)	55/55	70	Industry
Sidhu, 2001[35]	UK (Northern Ireland)	24	51	49	MHV	Not new (NR)	61/68	46	Industry
Sunderji, 2004[36]	Canada	8	70	70	Mixed	⩾1 month (NR)	58/62	71	Industry
Voller, 2005[37]	Germany	~5	101	101	AF	Not new (NR)	65/64	66	Industry
White, 1989[38]	USA	2	26	24	Mixed	New (unstable)	50/49	56	Industry

NR, not reported.

Table 3 shows the interventions investigated in the included RCTs. The trials compared anticoagulation self-testing (n = 5) or self-management (n = 9) or both (n = 1), with primary care or family doctor-managed anticoagulation (n = 6) or specialised anticoagulation clinics (n = 7) or both (n = 2). One trial compared PSM and PST without the inclusion of a usual care control.[39] The duration of intervention follow-up was from 2 months to more than 2 years. In most trials, patients were trained in two sessions lasting 1–2 hours for self-testing with or without self-dosing. CoaguCheck® (Roche) was used in 12 of the 16 trials, ProTime® (ITC) in three trials and the device used for PSM was not reported in one trial[37] (*Table 3*).

Quality of RCTs included

Results of quality assessment of included RCTs are shown in *Table 4*. One of the included studies was a cross-over trial.[27] One trial was terminated prematurely because of difficulty in patient recruitment.[37] The trial by Horstkotte and colleagues was published only in an abstract[31] and the quality of this trial could not be properly assessed because the methods of patient selection, patient allocation, outcome measures and any withdrawals from the trial were not reported.

Randomisation procedures were not clear in five trials[16,26,31,37,39] but appeared adequate in nine. It is judged that in five of the 16 trials patient allocation had been properly concealed.[12,29,34,36,41] In other trials, the patient allocation was not concealed or details reported in the publication were not sufficient to decide whether it was concealed. It may be impossible to mask patients and investigators in these trials, although a few trials had masked data collectors or physicians who decided whether dosages of warfarin should be modified.

Data on patient withdrawal were available in 12 trials (*Table 4*). More patients dropped out in the PSM group (2–42%) than in the control group (0–10%) in 10 of the 11 trials that compared PSM/PST and usual care control. Patients who withdrew during or after training for self-testing tended to be older and female. The authors of these trials may have a different understanding about ITT analysis. In the trial by Sawicki,[12] for example, ITT analysis was to analyse patients according to their original assigned group but patients who dropped out were excluded. ITT analysis is defined as that data from patients who changed allocated treatment or dropped out were included in data analysis according to the original allocated group.

The number of patients included in each trial ranged from 50 to 1200. The sample size was greater than 500 in three trials.[29,33,34] More than 600 patients were included in the Birmingham trial (SMART trial) by Fitzmaurice and colleagues.[29,33,34] Patient allocation was appropriately concealed and ITT analysis was conducted. However, outcomes were not blindly measured, and the drop-out rate was high (41.5% in the PSM group and 10.0% in the usual care control group). The Spanish trial by Menendez-Jandula and colleagues[34] included 737 patients, which was seemingly well designed, with adequate allocation concealment, ITT analysis and blind assessment of complication outcomes. In Menendez-Jandula and colleagues' trial, acenocoumarol or phenoprocoumon was used for oral anticoagulation therapy, whereas warfarin is most commonly used in the UK. Since the half-lives of acenocoumarol or phenoprocoumon are different from that of warfarin, the results of the trial by Menendez-Jandula and colleagues may not be applicable to the UK.

The Early Self-Controlled Anticoagulation Trial (ESCAT) in Germany is the largest among the RCTs identified, which included 1200 patients with heart valve replacement.[33,42] Data from the first 600 patients were published in English;[42] the results showed fewer bleeding and thromboembolic events in the PSM group. The partial data presented in English have been widely cited and included in reviews. In this review, we used a paper published in German that reported data from all patients in the ESCAT trial.[33] Results for all patients suggested that there were significantly fewer thromboembolic events but similar bleeding events in the PSM group compared with the control group. The number of patients included in ESCAT is relatively large and the period of follow-up is long. The quality of the trial is not high because of lack of detail about patient allocation concealment, lack of ITT analysis and lack of data on patient withdrawals. The number of deaths was not reported. The authors were contacted and they submitted data on the number of deaths for each of the two groups.

Anticoagulation control results from RCTs

Table 5 shows the results for AC, as measured by time within the therapeutic range or INR tests in the therapeutic range. The time in the therapeutic range ranged from 55 to 93.0% in self-testing or self-management patients and from 34.2 to 77.0% in the control patients. Weighted by the number of patient-years, the pooled estimate of INR time in

TABLE 3 *Interventions investigated by the included studies*

Study	Intervention (device used)	Intervention testing frequency (weeks)		Control	Control group testing frequency (weeks)		Training sessions × hours
		Planned	Actual		Planned	Actual	
Beyth, 2000[26]	PST + Consultant (ProTime)	1–4	NR	Physician	NR	NR	2 × 1
Cromheecke, 2000[27]	PSM (CoaguChek)	1–2	1.2	AC clinic	1–2	1.3	2 × 2
Fitzmaurice, 2002[28]	PSM (CoaguChek)	2	1.6	PC clinic	NR	5	2 × 1–2
Fitzmaurice, 2005[29]	PSM (CoaguChek)	2	1.8	AC/PC clinic	NR	5.4	2 × 1–2
Gadisseur, 2003[30]	PST/PSM (CoaguChek)	1	1	PEd/AC clinic	NR	3.26/3.03	3 × 1.5–2
Gardiner, 2005[16]	PST + clinic (CoaguChek)	1	NR	AC clinic	4	NR	2 × NR
Gardiner, 2006[39]	PSM vs PST (CoaguChek)	2	1.8	–	–	–	NR
Horstkotte, 1998[31]	PST (CoaguChek)	0.5	0.6	Physician	NR	2.7	NR
Khan, 2004[32]	PST (CoaguChek)	1	NR	PEd/AC clinic	NR	NR	2 × 2
Kortke, 2001[33]	PSM (CoaguChek)	1	NR	Physician	NR	NR	NR
Menendez-Jandula, 2005[34]	PSM (CoaguChek)	1	NR	AC clinic	4	NR	2 × 2
Sawicki, 1999[12]	PSM (CoaguChek)	0.5–1	NR	Physician/AC clinic	2	NR	3 × 1–1.5
Sidhu, 2001[35]	PSM (CoaguChek)	1	0.9/1.35	Physician/AC clinic	NR	4	2 × 3
Sunderji, 2004[36]	PSM (ProTime)	1	1.3	Physician	NR	2.5	2 × 2–3
Voller, 2005[37]	PSM (unknown)	NR	0.93	Physician	NR	2.6	NR
White, 1989[38]	PST (ProTime)	NR	NR	AC clinic	NR	NR	NR

NR, not reported; PC, primary care; PEd, patient education.

TABLE 4 *Quality of included trials*

Study	Randomisation	Allocation concealment	Blinding	ITT analysis	Power calculation	Difference at baseline	Total drop-outs (%)		Other notes
							Intervention	Control	
Beyth, 2000[26]	NC	No/NC	Data abstractor	Yes	Yes	Similar	41.1	0.0	Multicomponent trial
Cromheecke, 2000[27]	Sealed envelopes	No/NC	No	No	Yes	Similar	2.0	0.0	Cross-over trial
Fitzmaurice, 2002[28]	Computer coding	No/NC	No	No	No	M/F ratio	23.3	0.0	
Fitzmaurice, 2005[29]	Central telephone	Yes	No	Yes	Yes	Age	41.5	10.0	
Gadisseur, 2003[30]	Random numbers	Yes	Dosing physician	No	Yes	Age and M/F ratio	NR	NR	
Gardiner, 2005[16]	NC	No/NC	No	No	No	MHV patients	31.8	2.5	
Gardiner, 2006[39]	NC	NC	No	No	No	Similar	PSM 25.5 vs PST 26.5	–	PSM vs PST, no usual care control
Horstkotte, 1998[31]	NC	No/NC	No	No	No	Not clear	NR	NR	Abstract only
Khan, 2004[32]	Random numbers	No/NC	No	No	Yes	Similar	9.1	4.9	Third arm not randomised
Kortke, 2001[33]	Masters random list	No/NC	No	No	No	Similar	NR	NR	Preliminary report in English. All patients' report in German
Menendez-Jandula, 2005[34]	Central telephone	Yes	Complication assessor	Yes	Yes	Previous thromboembolic events	21.5	2.4	Follow-up period not clear
Sawicki, 1999[12]	Coordinating centre	Yes	Laboratory and documentation assistant	No?	Yes	Similar	10.0	15.7	
Sidhu, 2001[35]	Random numbers	No/NC	No	No	No	Not clear	31.4	0.0	
Sunderji, 2004[36]	Computer coding	Yes	No	Yes	Yes	Age	24.6	4.3	
Voller, 2005[37]	NC	No/NC	No	No	Yes	Not clear	NR	NR	Trial terminated early
White, 1989[38]	Shuffled envelopes	No/NC	No	Yes	No	Similar	11.5	4.2	

NC, not clear; NR, not reported.

range was 71.8% in the PSM/PST group and 61.8% in the control group. These pooled estimates included three trials that reported INR values in range but not INR time in range.[12,31,33] Excluding these three trials and using 12 trials that provided data on time in range, the pooled estimate of INR time in range was 67.4 and 63.4, respectively.

For the comparison of PST/PSM and usual care control, the quality of AC (INR % time in range) is summarised in *Table 6*, according to types of usual care control used in the trials. PSM was as effective as specialised anticoagulation clinics (67.1 versus 66.3%). The quality of AC was improved by PSM as compared with poor-quality usual care by family doctors (mostly in Germany and North America) (74.8 versus 59.8%). The difference in INR % time in range between the PSM and usual care was greater in trials of patients with MHV replacement than in trials of patients with no MHV or mixed indications (14.8 versus 6.2 and 3.4%, respectively).

PST and PSM were directly compared in two trials.[30,39] There was no significant difference between the two groups. In pooled analysis, trials were further grouped by PST or PSM and no clear pattern could be seen (*Table 6*).

Data on time (or tests) below, in and above the therapeutic range was available from eight trials (*Figure 2*).[12,26,29,35–38,42] Pooled estimates according to types of usual care control used in trials are shown in *Table 7*. It can be seen that anticoagulation was overall more likely to be below the therapeutic range rather than above the range in these trials (18.8 versus 6.2% in the PST/PSM group and 29.6 versus 6.8% in the control group, respectively). The overall difference in time below the range between PST/PSM and the control group was greater (18.8 versus 29.6%) than the difference in time above the range (6.2 versus 6.8%, PST/PSM versus control). However, studies with a higher proportion of time below the therapeutic range were mainly those in which the usual care was

TABLE 5 *RCT results: anticoagulation control*

Study	Intervention	Control	INR time in range (%)		INR values in range (%)	
			Control	Intervention	Control	Intervention
Beyth, 2000[26]	PST + Consultant	Physician	34.2	58.5	–	–
Cromheecke, 2000[27]	PSM	AC clinic	49.0	55.0	–	–
Fitzmaurice, 2002[28]	PSM	PC clinic	77.0	74.0	72.0	66.0
Fitzmaurice, 2005[29]	PSM	AC/PC clinic	68.0	70.0	60.0	62.0
Gadisseur, 2003[30]	PST/PSM	PEd/AC clinic	67.9 (PEd) 63.5 (UC)	66.9 (PST) 68.6 (PSM)	61.3 (PEd) 58.7 (UC)	63.9 (PST) 66.3 (PSM)
Gardiner, 2005[16]	PST	AC clinic	64.0	61.0	–	–
Gardiner, 2006[39]	PSM vs PST	–	–	PSM: 69.9 PST: 71.8	–	–
Horstkotte, 1998[31]	PST	Physician	–	–	22.3	43.2
Khan, 2004[32]	PST	PEd/AC clinic	70.4	71.1	–	–
Kortke, 2001[33]	PSM	Physician	–	–	64.9	79.2
Menendez-Jandula, 2005[34]	PSM	AC clinic	64.9	64.3	55.6	58.6
Sawicki, 1999[12]	PSM	Physician/AC clinic	–	–	43.2	53.0
Sidhu, 2001[35]	PSM	Physician/AC clinic	63.8	76.5	58.0	67.6
Sunderji, 2004[36]	PSM	Physician	63.2	71.8	58.7	64.8
Voller, 2005[37]	PSM	Physician	46.7	72.4	58.5	67.8
White, 1989[38]	PST	AC clinic	75.0	93.0	68.0	87.0

PC, primary care; PEd, patient education; UC, usual care.

TABLE 6 *Pooled estimates[a] of INR % time in range, weighted by the number of patient-years*

Type of control care	No. of trials	No. of person-years	INR time in range (%)		Difference between groups (%)
			Control group	PSM/PST group	
According to control and intervention care provided					
AC clinic	8	1534.0	66.3	67.1	0.6
Clinic/PST	4	141.8	67.8	67.7	–0.1
Clinic/PSM	5[b]	1422.1	66.2	67.0	0.6
Doctor	5	2801.2	59.8	74.8	15.0
Doctor/PST	2	372.6	27.2	49.3	22.3
Doctor/PSM	3	2428.6	64.8	78.7	13.9
Clinic/doctor	2	242.0	57.5	67.6	11.7
According to MHV %					
MHV 0%	2	114.2	65.7	72.0	6.2
MHV mixed	10	1823.1	62.2	65.9	3.4
MHV 100%	3	2639.9	61.3	76.0	14.8
All trials	15	4577.2	61.8	71.8	10.0

[a] For pooled estimates, results of individual trials were weighted by the number of person-years.
[b] One trial included both PSM and PST.

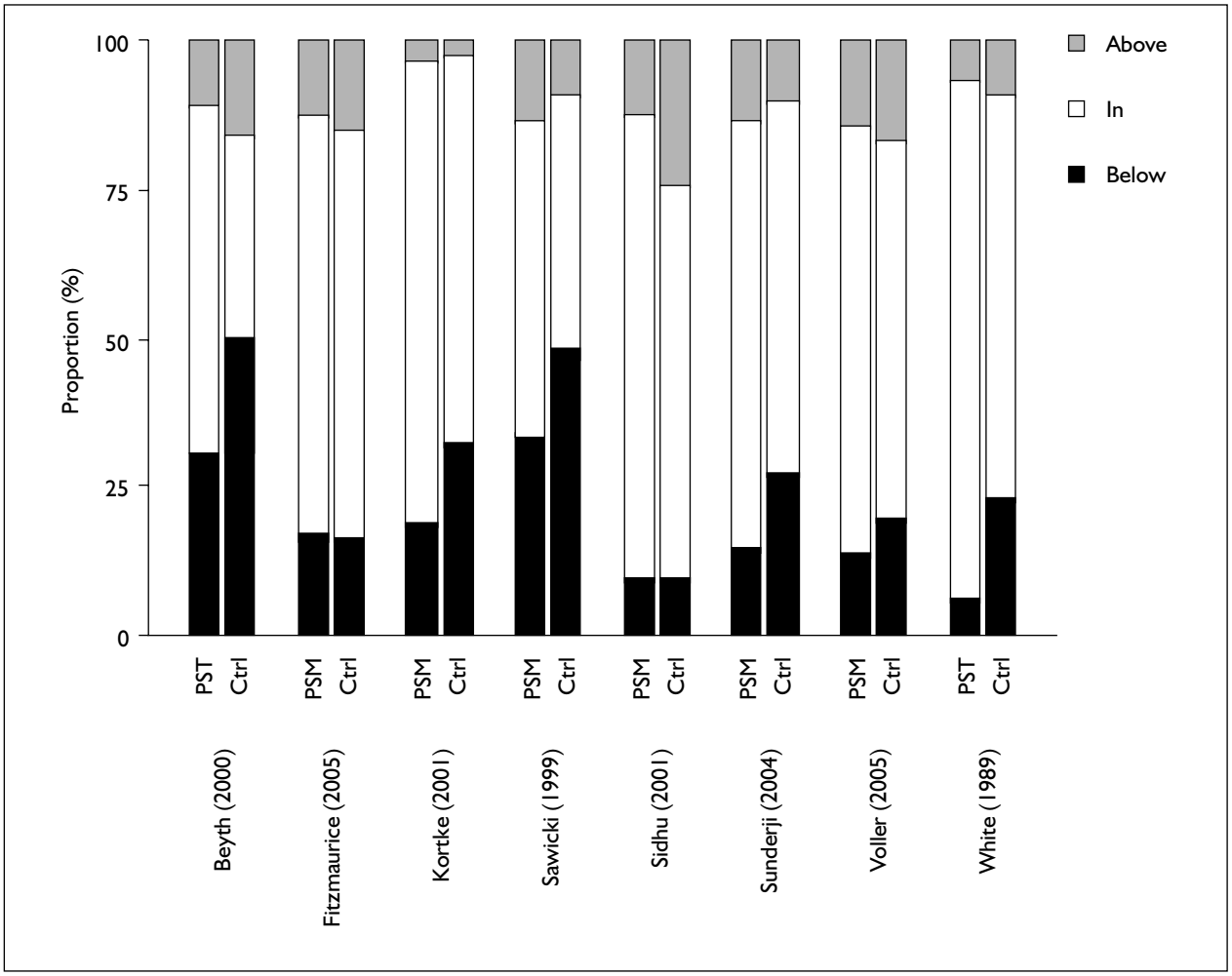

FIGURE 2 *INR time or tests below, in and above the therapeutic range: PST/PSM versus conventional care*

TABLE 7 *Pooled estimates of INR % time below, in and above the therapeutic range, weighted by the number of patient-years and according to types of usual care control used in trials*

Type of usual care control	No. of trials (patient)	Control group (%)			PST/PSM group (%)		
		Below	In	Above	Below	In	Above
AC clinic	2 (667)	16.8	68.9	14.4	17.2	70.6	12.2
Doctor	4 (1822)	33.1	63.0	3.8	19.2	76.7	4.0
Doctor/clinic	2 (279)	22.1	57.5	20.5	19.4	67.6	12.9
All trials	8 (2768)	29.6	63.5	6.8	18.8	75.0	6.2

provided by doctors. The proportion of time spent below the therapeutic range was much lower in the PSM group than that in the control care provided by doctors (19.2 versus 33.1%), whereas there was little difference between the PSM group and specialised AC clinics (17.2 versus 16.8%) (*Table 7*).

Major complications and death results from RCTs

The analysis of major complications and deaths focused on the comparison of PST/PSM and usual care control. AC was the most commonly reported outcome, but bleeding and thromboembolic complications are of primary importance and, considering their rarity, require longer follow-up. Two trials differed from the others with regard to these outcomes: in the trial by Beyth and colleagues,[26] which included 325 patients newly started on AC therapy, the primary outcome measure was the first major bleeding event during a 6-month period; in the trial of Voller and colleagues, which aimed to evaluate thromboembolic or haemorrhagic complications in patients taking long-term AC for permanent non-valvular AF, the study was terminated prematurely because of difficulty in patient recruitment.[37]

Table 8 shows results on major bleeding events, thromboembolic events and deaths from individual trials. Death outcome was not reported in five trials.[27,30–33] The authors of the five trials were contacted by email, and further information was received from all authors.

RD was used as the outcome statistic in meta-analysis for major complications and deaths. The use of RD has two advantages in this meta-analysis. First, trials that reported zero events or deaths in both arms can be included in meta-analysis. This is important because of the small number of trials involved. Second, trials that used poor-quality controls (which also tended to have a great number of events) are not over-weighted. However, the Peto's odds ratio method (as recommended for meta-analyses of rare events[24]) was also used. The results of meta-analyses by the two methods did not differ in most cases. The results are summarised in *Table 9*.

The difference in major haemorrhagic events between the PST/PSM and usual care group was not statistically significant (–0.0039, 95% CI –0.0154 to 0.0077; *Table 9* and *Figure 3*). Self-monitoring was on average associated with significantly fewer thromboembolic events than management by family doctors, primary care or anticoagulation clinics (*Table 9* and *Figure 4*). The pooled RD was –0.0224 (95% CI –0.0334 to –0.0115. There was no statistically significant heterogeneity across trials in both meta-analyses (I^2 = 0%, p = 0.80; and I^2 = 26%, p = 0.17 respectively).

There was no statistically significant heterogeneity across trials for death outcome (I^2 = 13%, p = 0.31). Pooled estimates indicated that the risk of death was statistically significantly reduced in PST/PSM groups as compared with that in control groups; RD –0.0170 (95% CI –0.0287 to –0.0053) (*Table 9* and *Figure 5*).

Funnel plots were not statistically asymmetric for major bleeding events (p = 0.20 and 0.52 by Begg's and Egger's test, respectively), for thromboembolic events (p = 0.77 and 0.18, respectively) and for death outcome (p = 0.14 and 0.96, respectively). The basic assumption underlying Begg's and Egger's tests is that small studies may report larger treatment effect as compared with larger studies. In the above meta-analyses, larger trials are actually associated with greater treatment effect for thromboembolic events and deaths (*Figures 4* and *5*).

Subgroup analyses

Although results of individual trials in meta-analyses are not statistically significantly heterogeneous, differences in the results across

TABLE 8 *Major complications reported in randomised trials of patient self-monitoring of oral anticoagulation*

Study	Sample size		Major bleeding events		Thromboembolic events		Deaths	
	Control	PST/PSM	Control	PST/PSM	Control	PST/PSM	Control	PST/PSM
Beyth, 2000[26]	162	163	17	8	21	14	26	21
Cromheecke, 2000[27]	50	50	0	0	1	0	0[a]	0[a]
Fitzmaurice, 2002[28]	26	30	1	0	0	0	1	0
Fitzmaurice, 2005[29]	280	337	4	5	3	4	11	12
Gadisseur, 2003[30]	60 (PEd) 161 (UC)	52 (PST) 47 (PSM)	2 1	0 2	0 0	0 0	0[a] 0[a]	0[a] 0[a]
Gardiner, 2005[16]	40	44	0	0	0	0	0	1
Horstkotte, 1998[31]	75	75	9	5	3	1	0[a]	0[a]
Khan, 2004[32]	41	44	0	1	0	0	0[a]	0[a]
Kortke, 2001[33]	576	579	34	42	32	16	34[a]	18[a]
Menendez-Jandula, 2005,[34]	369	368	7	4	20	4	15	6
Sawicki, 1999[12]	89	90	1	1	2	1	1	1
Sidhu, 2001[35]	49	51	0	1	0	1	4	0
Sunderji, 2004[36]	70	70	1	0	2	0	0	0
Voller, 2005[37]	101	101	0	1	1	0	0	0
White, 1989[38]	24	26	0	0	1	0	0	0

PEd, patient education; UC, usual care.
[a] Data received from authors of the study by personal communication.

TABLE 9 *Results of meta-analyses of major complications and deaths: patient self-monitoring versus usual care for oral anticoagulation therapy*

Outcome statistic and method	No. of trials (patients)	Estimate (95% CI)	Heterogeneity: I^2 (%)
Bleeding events			
Risk difference			
Fixed effect (M–H)	15 (4091)	–0.0039 (–0.0154 to 0.0077)	0 ($p = 0.80$)
Random effects (D–L)	15 (4091)	–0.0019 (–0.0108 to 0.0069)	0 ($p = 0.80$)
Peto's odds ratio	12 (3859)	0.892 (0.638 to 1.245)	5 ($p = 0.40$)
Thromboembolic events			
Risk difference			
Fixed effect (M–H)	15 (4091)	–0.0224 (–0.0334 to –0.0115)	26 ($p = 0.17$)
Random effects (D–L)	15 (4091)	–0.0144 (–0.256 to –0.0032)	26 ($p = 0.17$)
Peto's odds ratio	11 (3720)	0.468 (0.327 to 0.668)	0 ($p = 0.56$)
Deaths			
Risk difference			
Fixed effect (M–H)	15 (4091)	–0.0170 (–0.0287 to –0.0053)	13 ($p = 0.31$)
Random effects (D–L)	15 (4091)	–0.0076 (–0.0169 to 0.0017)	13 ($p = 0.31$)
Peto's odds ratio	8 (3214)	0.610 (0.438 to 0.849)	0 ($p = 0.54$)

D–L, DerSimonian–Laird method; M–H, Mantel–Haenszel method.

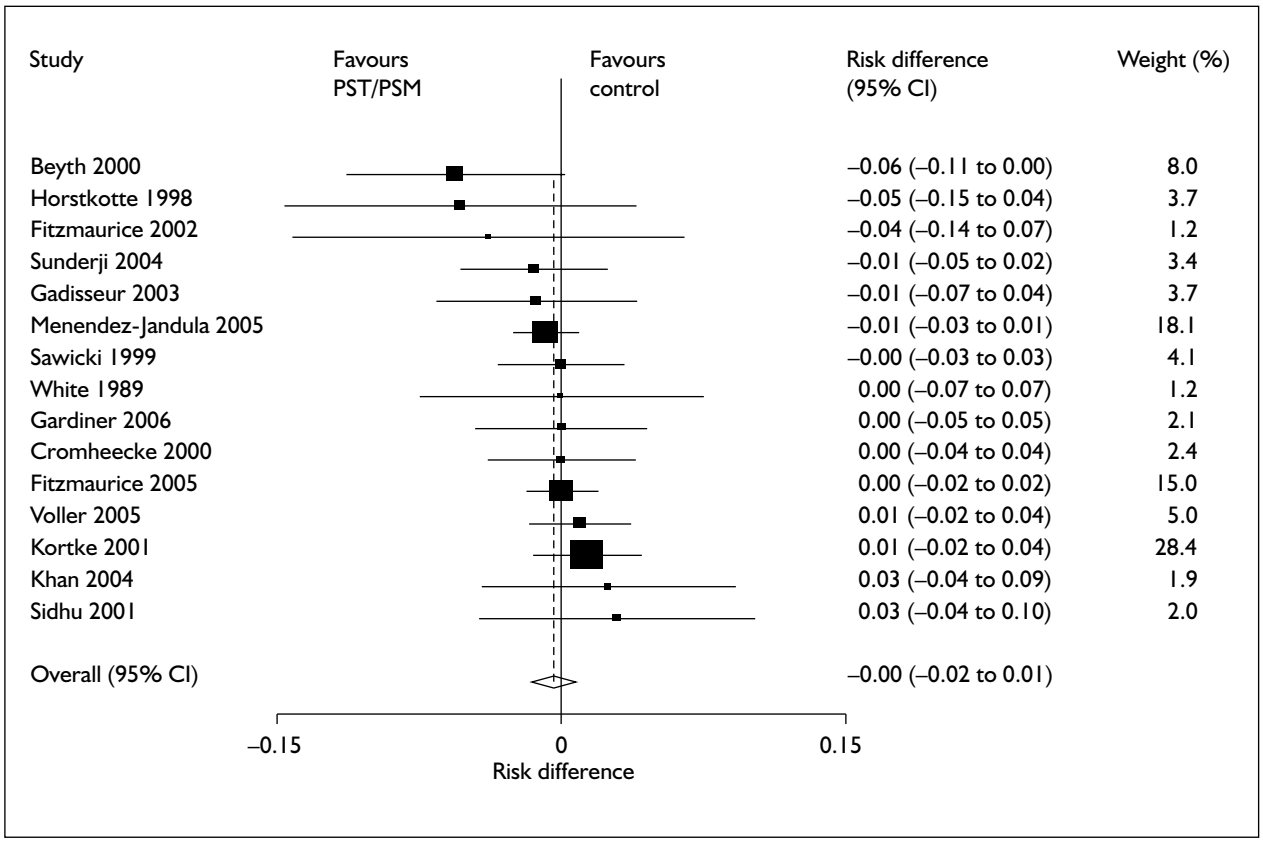

FIGURE 3 *Haemorrhagic events: self-testing or self-management versus usual anticoagulation care*

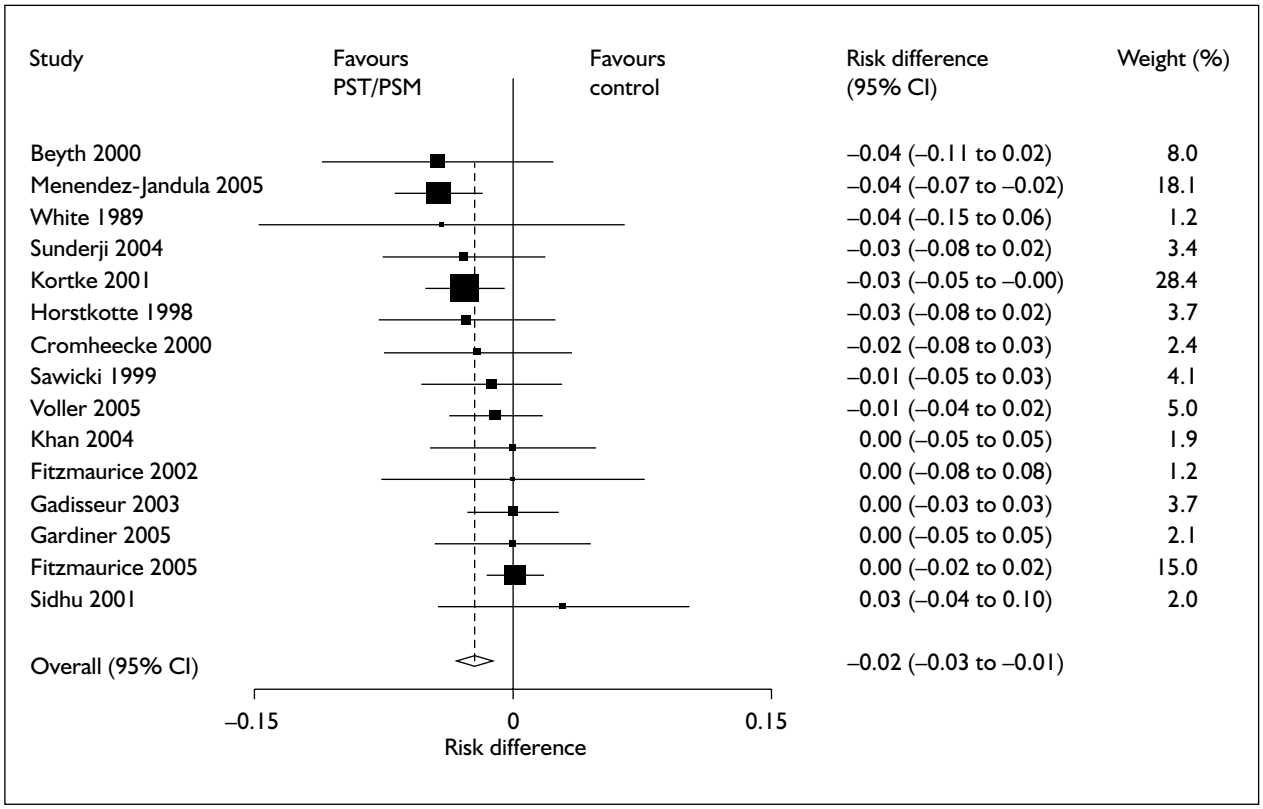

FIGURE 4 *Thromboembolic events: self-testing or self-management versus usual anticoagulation care*

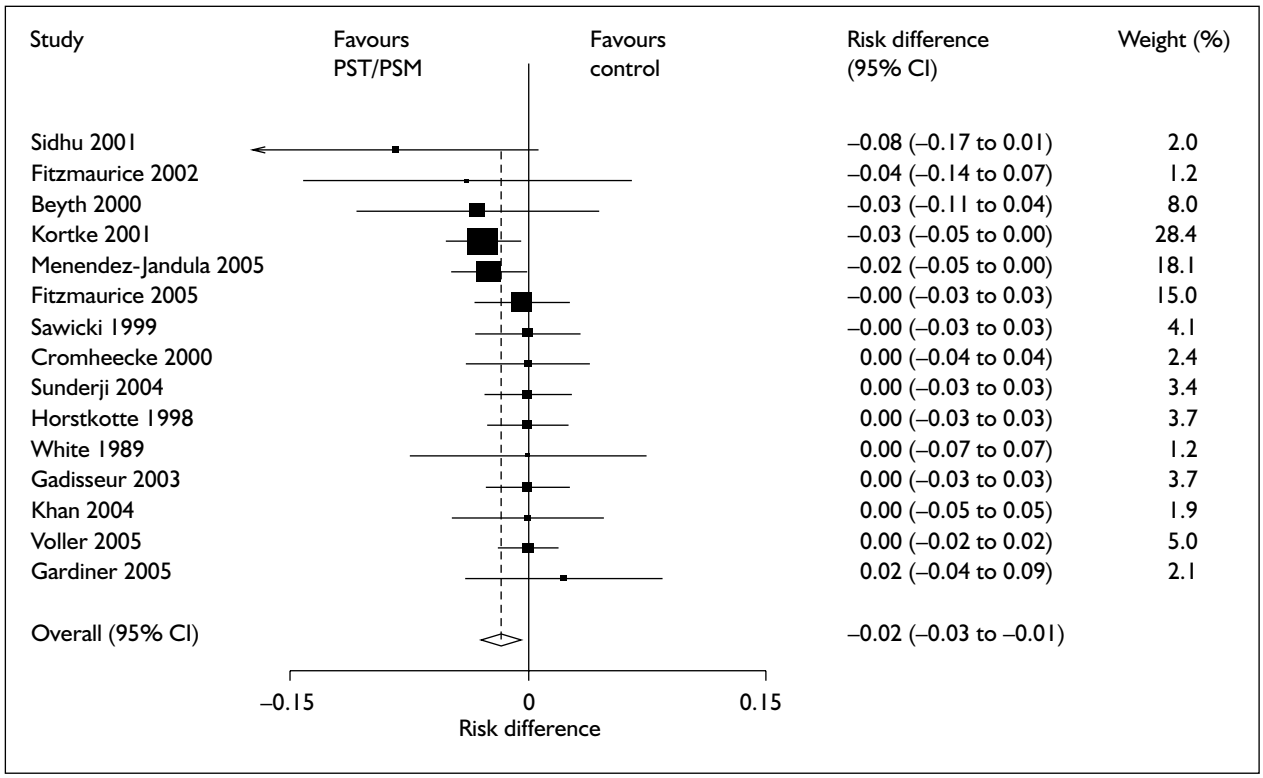

FIGURE 5 *Deaths: self-testing or self-management versus control care of anticoagulation therapy*

trials were visually obvious (*Figures 3–5*). Trials included in the meta-analyses were conducted in different countries, and there are differences in methods of PSM, the quality of usual care, trial design and conduct. In addition, the pooled estimates are dominated by two large trials. The trials by Kortke and colleagues[33] and Menendez-Jandula and colleagues[34] contributed to 46.5% of the total weight in meta-analyses (28.4 and 18.1%, respectively; *Figures 3–5*). Subgroup analyses were conducted to explore possible clinically or methodologically important differences and the impact of dominant trials.

Figure 6 shows results of sensitivity or subgroup analyses (detailed data are given in Appendix 2). The results of subgroup analyses should be interpreted with great caution and considered useful mainly for exploratory purposes for three reasons. First, these subgroup analyses were *post hoc* and not pre-specified in the review protocol. Second, the number of trials included was small and the different subgroups analysed were unlikely to be independent, particularly because the results were dominated by a few large trials. More importantly, it was very likely that a few statistically significant interactions could be observed purely by chance because of the large number of subgroup analyses conducted.

There were no statistically significant subgroup interactions when trials were separated according to types of control interventions, differences in percentage of time in the therapeutic range between PST/PSM and control groups, percentage of patients with MHV indications, whether patient allocation was adequately concealed, whether ITT analysis was used, level of drop-outs, length of follow-up and whether the trial was sponsored by industry.

The estimated effect of PST/PSM versus usual care for thromboembolic events and deaths was greater in the two largest trials[33,34] than the other 13 trials, although the interaction between the subgroups was not statistically significant ($p = 0.06$ for thromboembolic events and $p = 0.14$ for deaths). Trials with blinded outcome assessors tended to report greater RDs for bleeding and thromboembolic events (interaction $p = 0.06$ and 0.08, respectively) compared with trials with non-blinded assessors.

For bleeding complications, the difference in the results was statistically significant when trials of PST were compared with trials of PSM (subgroup interaction $p = 0.03$), and when trials using the CoaguChek device were compared with trials using the ProTime device for PSM (interaction $p = 0.05$).

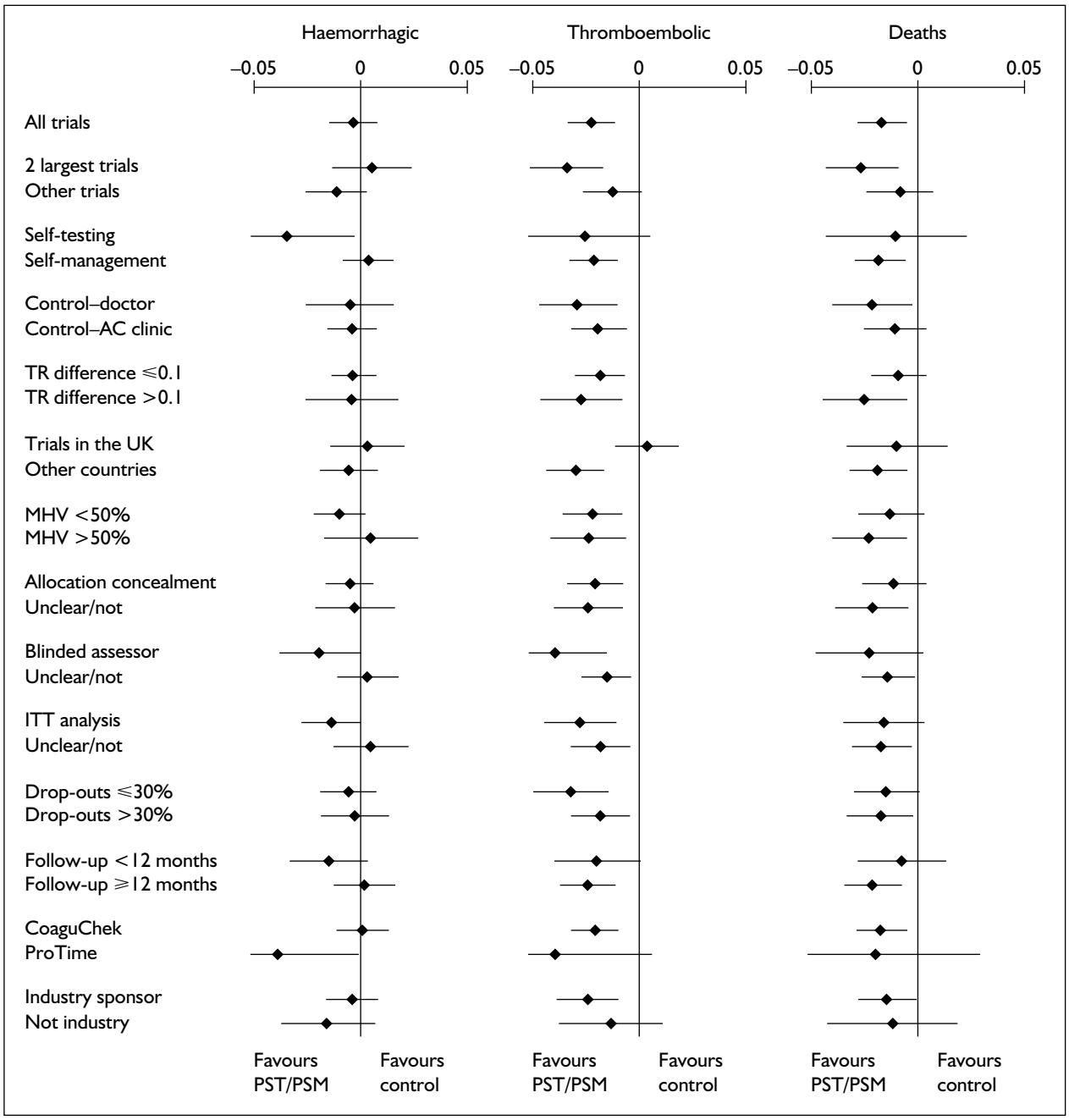

FIGURE 6 *Results of sensitivity/subgroup analyses (risk difference). TR, proportion of tests in therapeutic range.*

The RD in thromboembolic events was statistically significant in trials outside the UK (–0.030, 95% CI –0.043 to –0.016) but not in the UK trials (0.003, 95% CI –0.012 to 0.018). The interaction between the trials conducted outside the UK and trials in the UK was statistically significant ($p = 0.0012$). The RD in deaths between the PST/PSM and the control group was statistically significant according to trials conducted in other countries (–0.0191, 95% CI –0.0325 to –0.0057). However, trials conducted in the UK found a smaller and statistically non-significant RD in deaths between the PSM and the control group (–0.0098, 95% CI –0.0337 to 0.0141).

Meta-regression analyses were also conducted to explore the RD in major complications or death and lengths of follow-up, difference in percentage of time in range and percentage of drop-outs in the PST/PSM group. The only statistically significant result was that the RD in deaths was associated with length of follow-up ($\beta = -0.0013$, $p = 0.04$), that is, the longer the follow-up, the greater is the reduction in the risk of death by self-

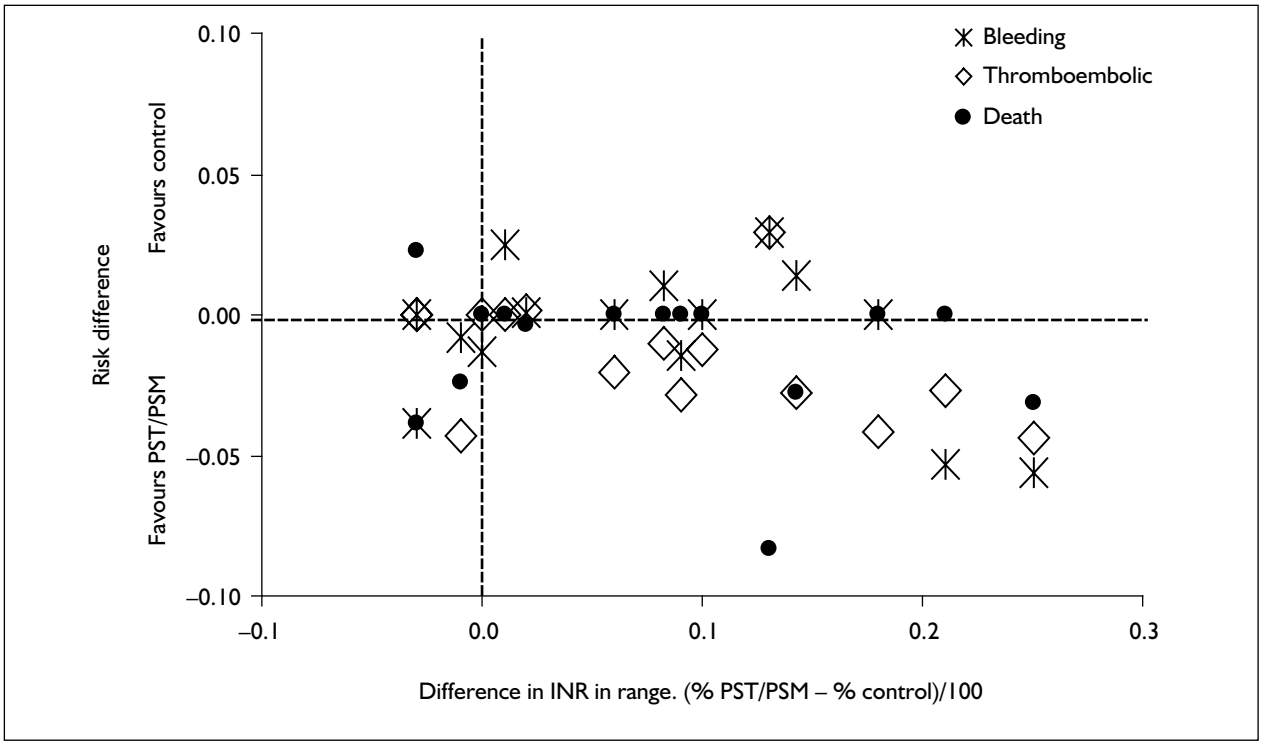

FIGURE 7 *Difference in anticoagulation control against risk difference of complications and deaths*

monitoring. One possible explanation for this observation is that the period of follow-up should be long enough to reveal the difference in death between groups. However, this result was dominated by a large trial that had a long-term follow-up (>2 years).[33]

Association between anticoagulation control, complications and death

Pooling of results from all individual trials suggested that compared with usual care, PST/PSM significantly reduced the risk of thromboembolic events (*Figure 4*) and deaths (*Figure 5*), although there were no significant differences in the risk of major bleeding events (*Figure 3*). These findings appear to be supported by observed differences in time below and above the INR target range between the PST/PSM and control groups (*Figure 2*). However, across all trials the differences in complication events and deaths were not consistently associated with the differences in the control of anticoagulant therapy (time or INR values in the therapeutic range) between PST/PSM and usual care (*Figure 7*). Thus in the trial by Menendez-Jandula and colleagues,[34] thromboembolic events and deaths were significantly lower in the PSM group despite the fact that the quality of AC was similar between the PSM and AC clinic groups. Most complication events occurred while the INRs were within the target range.[34] For example, in Beyth and colleagues' trial, only 11 of the 25 major bleeding events occurred in patients with INR value >3.5.[26]

A further difficulty is a lack of consistent association between the complication events and deaths (*Figures 3–5*). In the trial by Sidhu and O'Kane,[35] the complication events were not reduced in the PST/PSM group, although there was a reduction in the number of deaths. In contrast, complication events and deaths in the PST/PSM group were both reduced (although statistically non-significant) in the trials by Beyth and colleagues[26] and Menendez-Jandula and colleagues.[34] However, only three of the 21 deaths in the latter trial were directly related to anticoagulation therapy.[34]

Therefore, the observed reduction in complications and deaths in some trials may be attributable to other explanations, including other components of the interventions or systematic or chance errors.

Other components of interventions

Patients need to receive training in order to conduct self-testing or self-management of their anticoagulant therapy. Such training usually aims to ensure that patients understand relevant theories and are able to use a portable INR monitor correctly, to interpret INR findings correctly and to adjust the dose of warfarin

correctly. Hence patients in the PST/PSM group are more knowledgeable than those in the usual care group. Gadisseur and colleagues found only a slight benefit for INR control in patients receiving usual care who had received extra education compared with usual care patients who had not.[30] Improved knowledge and the empowerment of patients may reduce the risk of complications and deaths without a measurable improvement in the quality of AC.

Two trials compared the results for patients who performed PST/PSM and patients who received similar training in the usual care.[27,30,32] Gadisseur and colleagues compared PSM and patient training only (without self-monitoring after training), and found no difference between the two groups in the quality of AC (*Table 5*).[30] Patients who received training but did not perform self-monitoring showed improved quality of AC compared with a non-randomised usual care group without training.[30] In the trial by Khan and colleagues,[27,30,32] patients who received training without performing self-monitoring had similar quality of AC to patients in the self-monitoring group (*Table 5*). However, available data from these two trials contributed very little to the meta-analyses of complications and deaths (*Figures 3–5*). There is a lack of evidence about whether patient education alone is sufficient to reduce the risk of bleeding and thromboembolic complications and deaths in patients who receive long-term anticoagulation therapy.

Summary of RCT effectiveness results

PSM of oral anticoagulation therapy is more effective than poor-quality usual care provided by family doctors. Poor quality of AC managed by family doctors is particularly associated with a great proportion of time spent below the target therapeutic range, which could be much reduced by PSM. PSM is as effective as good-quality specialised anticoagulation clinics in maintaining the quality of anticoagulation therapy.

There was no significant difference in risk of major bleeding events between PST/PSM and usual care controls. Pooled analyses found that PST/PSM was statistically significantly associated with fewer thromboembolic events and deaths compared with primary care or AC clinics. However, the reduction in complication events and deaths was not consistently associated with the improvement of AC. The observed reduction in complications and deaths in some trials may be due to alternative explanations, including patient education and patient empowerment. In addition, random or systematic errors could not be ruled out from the included trials. More importantly, findings of meta-analyses by pooling results from all trials may not be applicable to the UK setting. The improved AC and the reduction of major complications and deaths by PSM were mainly observed in trials conducted outside the UK.

Clinical effectiveness: non-randomised controlled studies

The inclusion of a usual care control within a non-randomised study makes it possible to evaluate the relative effect of PSM, although the comparability between groups may be questionable. This section focuses on eight non-RCTs.[39,43–49] One study, by Gardiner and colleagues,[39] was a trial that randomly compared PSM and PST, but also provided data to make before–after comparison of PST/PSM and usual care control. Two duplicate papers of non-RCTs were excluded.[17,50] Studies that only compared INR values measured by self-monitoring and laboratory for the same sample were not included. Basic data from excluded non-RCTs of PSM were extracted and are presented in Appendix 3 for the purpose of reference.

Main characteristics of non-RCTs

The main study characteristics of non-RCTs are presented in *Table 10*. The studies were conducted in Germany, Austria, Israel, the USA, Denmark, Switzerland and the UK. Five of the eight studies were at least partly industry sponsored. Funding was unreported or unclear in three studies. The indications for AC treatment were AF in one study, MHV replacement in three studies and mixed in four studies. Patients had received anticoagulation therapy previously. PSM was compared with management by family doctors in two studies[43,48] and compared with AC clinics in six studies.[39,44–47,49]

Studies were generally of small size. The number of patients ranged from 34 to 156 in five parallel controlled studies. The before–after studies included 700 and 154 patients.[48] The period of follow-up ranged from 1 to 43 months.

Quality of included non-RCTs

Quality of non-RCTs is presented in *Table 11*. One study was published in German and quality assessment is incomplete.[43]

Four studies were prospective by design, and the selection of control patients was matched to patients in the self-monitoring group in five studies (*Table 11*). Patient inclusion criteria were provided in most studies but the source population for patients and methods of their

TABLE 10 *Main study characteristics of non-randomised controlled studies*

Study (design)	Country	Indication; age, % male; use of AC	Usual care	Follow-up	Sample size		Study sponsor
					Control	PSM	
Watzke, 2000[49] (parallel)	Austria	Mixed; 54 years; 46%; ⩾6 months previous stable AC	AC clinic	12 months	49	53	Industry
Eldor, 2002[46] (parallel)	Israel	AF; 70.4 years; 88%; ⩾3 months, previous AC	AC clinic	12 months	17	17	Industry
Cosmi, 2000[47] (parallel)	Italy	Mixed; 53.7 years; 60%; mean 5.6 years previous AC	AC clinic	6 months	78	78	Industry
Schmidtke, 2001[43] (unclearl)	Germany	MHV; 59.5 years; 70%; unclear	Doctor	20 weeks	20	20	Unclear
Ansell, 1995[44] (parallel)	USA	Mixed; 45 years; 60%; previous AC	AC clinic	43.6 months	20	20	Unclear
Christensen, 2001[45] (parallel)	Denmark	MHV; 19–70 years; 71%; >9 months previous AC	AC clinic	38.6 months	24	24	Partly industry
Preiss, 2001[48] (before–after)	Switzerland	MHV; 55 years; NR; previous AC	Doctor	>30 days	355	355	Unclear
Gardiner, 2006[39] (before–after)	UK	Mixed; 59.9 years; 61%; >8 months previous AC	AC clinic	6 months	77	77	Partly industry

TABLE 11 *Quality assessment of non-randomised controlled studies*

Quality criterion	Watzke, 2000[49]	Eldor, 2002[46]	Cosmi, 2000[47]	Schmidtke, 2001[43]	Ansell, 1995[44]	Christensen, 2001[45]	Preiss, 2001[48]	Gardiner, 2006[39]
Study design	Prosp.	Prosp.	Prosp.	Prosp.	Retro.	Retro.	Retro	Retro
Comparison groups	Match.	Match.	Match.	Unclear	Match.	Match.	Before–after	Before–after
Follow-up (months)	12	12	6	4.6	43.6	38.6	>1	6
Were eligibility criteria explicit?	Yes	Yes	Yes		No	Yes	Yes	Yes
Was sample source/ selection described?	Yes	No	Yes		No	Yes	Yes	Yes
Were patients assembled at same time?	Yes	Yes	Yes		No	No	No	No
Were individual patient data reported?	Yes	Yes	No		No	Yes	No	No
Was outcome assessment blinded?	No	No	No		No	No	No	No
Were withdrawals explicitly stated or excluded?	Yes	Yes	Yes		Yes	Yes	NA	Yes

Match., matched controls; Prosp., prospective design; Retro, retrospective.

selection were generally poorly described. Masking of patients and investigators was probably impossible in these studies. The withdrawals were explicitly described in all studies.

Non-randomised studies: anticoagulation control

The results of AC control reported in non-RCTs are presented in *Table 12*. In five of the six parallel controlled non-randomised studies, INR values were tested 2–4.7 times more frequently by the PSM group than the usual care control. In Cosmi and colleagues' trial,[47] the testing of INR by the PSM group was as frequent as the testing by the usual care control.

TABLE 12 *Quality of anticoagulation control – results of non-randomised studies that compared patient self-monitoring and usual care control*

Study	Follow-up (months)	Sample size (tests)		Control group: INR in range (%)			PSM group: INR in range (%)		
		Control	PSM	Below	In	Above	Below	In	Above
Watzke, 2000[49]	12	49 (539)	53 (2733)		73.8			84.5	
Eldor, 2002[46]	12	17 (268)	17 (780)	17.9	72.4	9.7	11.8	80.5	7.7
Cosmi, 2000[47]	6	78 (897)	78 (913)	9.8	80.5	9.5	13.6	80.0	6.4
Schmidtke, 2001[43]	4.6	20 (135)	20 (344)	36.3	52.6	11.1	20.3	69.8	9.9
Ansell, 1995[44]	43.6	20 (1608)	20 (2153)	21.8	68.0	10.3	6.3	88.6	5.2
Christensen, 2001[45]	38.6	24 (1219)	24 (2498)		61.0			78.0	
Preiss, 2001[48]	>1	355	355		62.5			73.5	
Gardiner, 2006[39]	6	77 (1124)	77 (NR)		62.5 (95% CI 56.1 to 74.0)			71.0 (95% CI 64.7 to 76.4)	

The outcome measure used was percentage of INR values in the therapeutic range, which ranged from 52.6 to 80.5% in the control group and from 69.8 to 88.6% in the PSM group. In two before–after comparison studies, the proportion of time in the therapeutic range in the PSM group was significantly greater than that by the usual care control.[39,48] Pooling results from studies with a parallel control (and weighted by the number of INR values), it was found that the pooled proportion of INR values in the therapeutic range was 69.5% in the control group and 82.9% in the PSM group. The pooled difference in percentage values in the range was 13.4% between the control and the PSM group.

Four studies provided percentage of INR values below, in and above therapeutic range (*Table 12*). The pooled percentage of INR values below the range was 18.4 and 10.1% in the control and PSM group, respectively, with a rate difference of 8.4%, and above the range 10.0 and 7.1% in the control and PSM group, respectively, with a rate difference of only 3.0%.

Findings from non-RCTs on the quality of AC are similar to those from RCTs reviewed in the previous section. Using data on INR values in the therapeutic range from RCTs (*Table 5*), the pooled estimate was 59.6 and 69.9% in the control and the PST/PSM group, respectively. The overall rate difference in percentage of INR values in the therapeutic range between the PSM and the control group was 10.3% in RCTs and 13.4% in non-RCTs. According to data from RCTs (*Table 7*), the proportion of INR time below the therapeutic range was considerably reduced by PSM as compared with poor-quality usual care control. This phenomenon was also observed in non-RCTs. The rate difference between the PSM and the control group was 8.4% for INR below the range and 3.0% for INR above the range, according to data from non-RCTs.

There were only two non-RCTs that used doctor management as the control, including one before–after study that did not give the number of INR values. Hence subgroup analysis was not conducted to compare the results for AC clinics and family doctors.

Non-randomised studies: major complications and deaths

Six studies reported major complication events and deaths (*Table 13*). The classification of 'severe' or 'major' events is unlikely to have been wholly consistent between studies. When data from non-RCTs were combined with data from RCTs, the results of meta-analyses were not materially different from those for only RCTs. The pooled RDs by combining RCTs and non-RCTs were –0.00396 (95% CI –0.0149 to 0.00699) for major bleeding events, –0.0199 (95% CI –0.0302 to –0.00964) for thrombotic events and –0.01544 (95% CI –0.02634 to –0.004546) for deaths (forest plots not prepared). Hence the impact of including these non-RCTs in analyses was negligible.

Summary of effectiveness results from non-randomised studies

Sample sizes in non-RCTs were generally small, and the period of follow-up was similar to that in

TABLE 13 *Serious complications in non-randomised controlled studies that compared PSM and usual care control*[a]

Study	Follow-up (months)	Sample size		Major bleeding		Thromboembolic event		Death	
		Control	PSM	Control	PSM	Control	PSM	Control	PSM
Watzke, 2000[49]	12	49	53	0	1	0	1	0	0
Eldor, 2002[46]	12	17	17	0	0	0	0	0	0
Cosmi, 2000[47]	6	78	78	0	0	0	1	0	1
Schmidtke, 2001[43]	4.6	20	20	4	0	1	0	0	0
Ansell, 1995[44]	43.6	20	20	0	2	1	1	0	0
Christensen, 2001[45]	38.6	24	24	1	1	1	1	1	0

[a] Preiss and colleagues[48] reported the incidence of serious complications per 100 patient-years: 4.67 in the control group and 3.28 in the PSM group.

RCTs. Results from non-RCTs were generally similar to those from RCTs. According to data from non-RCTs, PSM allowed good AC in terms of INR values within the therapeutic range for highly selected patients. The contribution of data from non-RCTs had a negligible effect on the results of meta-analyses of major complications and death outcomes.

Quality of life

Six trials reported QoL data (*Table 14*).[12,27–30,32] Three of the trials used a questionnaire designed by Sawicki that was based on statements about patient feelings towards anticoagulation treatment.[12,27,30] Two trials[28,32] used a questionnaire designed to measure QoL in patients receiving anticoagulation treatment.[51] Other QoL measures employed were the Schedule for the Evaluation of Individual Quality of Life (SEIQoL) tool for quality of life estimation,[28] the UK Short Form with 36 Items (SF-36)[32] and EuroQol questionnaires.[29,32] Fitzmaurice and colleagues also reported results from patient interviews.[28]

In the Sawicki study, both control and intervention groups showed improvements in self-efficacy and reduced feelings of distress but the PSM group showed significantly greater improvement.[12] There were also improvements in general treatment satisfaction and daily hassles scores, but only in PSM patients. Using Sawicki's questionnaire, Cromheecke and colleagues found significantly greater improvements in treatment satisfaction, self-efficacy, distress and daily hassles for patients who self-managed their treatment compared with usual care.[27] The same questionnaire was also used by Gadisseur and colleagues, who found increased distress in patients who received more education about their treatment but did not self-monitor or manage their therapy, increased feelings of self-efficacy in patients who self-monitored their INR values, and increased treatment satisfaction, self-efficacy and decreased perceptions of daily hassles and distress in patients who self-managed their anticoagulant therapy.[30,41]

In semi-structured interviews with patients, the themes of concern were knowledge and management of condition and self-empowerment, increased anxiety and obsession with health, self-efficacy, relationship with health professionals and societal and economic costs.[28] Results from the SF-36 questionnaire[32] found a significant change from baseline to study end in only one domain – emotional role limitation ($p = 0.04$). There were no significant differences in measured QoL between intervention and control groups using SEIQoL and 'quality of life in anticoagulated patients' questionnaires.[28,32] The changes in the EuroQol score were similar between the PSM and the control group.[29,32,52]

In summary, the Sawicki questionnaire found increased distress about treatment in patients given education but no control over their monitoring or dosing, increased self-efficacy in patients who self-monitored their INR levels, and increased treatment satisfaction, self-efficacy and reduced perception of daily hassles for patients who self-managed their treatment compared with usual care. There were no significant differences in measured QoL between intervention and control groups using the EuroQol, SEIQoL and 'quality of life in anticoagulated patients' questionnaires. Referring to data presented in *Table 5*, it can be seen that trials that reported favourable results on clinical outcomes also reported favourable results on QoL by PSM.[12,27] Trials that found no significant difference in AC between PST/PSM and

TABLE 14 *Quality of life results from randomised controlled studies: patients self-monitoring versus usual care of oral anticoagulation control*

Study	Methods	Results	Conclusions
Sawicki, 1999[12]	Using a structured questionnaire, covering 5 topics, and scored from 1 to 6 for each topic. The QoL assessor was blinded to the treatment arm	Mean difference (SD) between baseline and follow-up: **Control** / **PSM** / ***p*** General treatment satisfaction: +0.24 (1.48) / +1.54 (1.38) / <0.001 Self-efficacy: +0.38 (0.96) / +0.83 (0.92) / 0.003 Strained social network: –0.23 (0.79) / –0.40 (0.83) / 0.19 Daily hassles: –0.03 (0.53) / –0.49 (0.83) / 0.01 Distress: –0.21 (0.93) / –0.61 (–/87) / 0.01	Self-management results in improved treatment-related QoL measures
Cromheecke, 2000[27]	Using Sawicki's questionnaire covering 5 categories. Each category scored from 1 (total dissatisfaction) to 6 (complete satisfaction). This is a cross-over trial. Control patients for QoL assessment were matched for age, sex and indications	Mean (SD) scores at follow-up: **Control** / **PSM** / ***p*** General treatment satisfaction: 4.0 (1.5) / 4.8 (1.2) / 0.015 Self-efficacy: 4.5 (1.0) / 5.4 (0.6) / <0.001 Daily worries: 2.6 (0.5) / 1.8 (0.5) / <0.001 Distress: 2.9 (1.1) / 2.5 (0.8) / 0.022 Social issues: 2.7 (0.9) / 1.7 (0.6) / <0.001	A patient satisfaction assessment showed superiority of self-management over conventional care
Gadisseur, 2003[30]	Using Sawicki's questionnaire covering 5 categories. Each category scored from 1 to 6. Improved QoL was indicated by rising scores for general satisfaction and self-efficacy, and by diminishing scores for daily hassles, distress and strains on the social network	Mean difference between baseline and follow-up: **Control** / **PST** / **PSM** General treatment satisfaction: –0.23 / +0.19 / +0.49 Self-efficacy: +0.02 / +0.31 / +0.32 Strained social network: +0.21 / –0.02 / –0.21 Daily hassles: +0.23 / –0.09 / –0.31 Distress: +0.33 / +0.06 / –0.44	General treatment satisfaction was already high under routine care and increased further through self-monitoring and full self-management. Distress, perceived daily hassles and strain on social network were reduced through PSM
Khan, 2004[32]	SF-36 and EuroQol questionnaires, and Lancaster's instrument (for warfarin users) were used in interviews of patients by a blinded assessor	Baseline/24-week scores **Control** / **PST** *UK SF-36* Physical functioning: 52/53 / 61/57 Physical role limitation: 48/52 / 57/45 Bodily pain: 60/65 / 70/65 General health perceptions: 55/56 / 52/53 Vitality: 48/52 / 55/53 Social functioning: 70/72 / 78/71 Emotional role limitation: 62/63 / 81/63 Mental health: 76/76 / 80/78 *EuroQol five dimension score*: 0.74/0.70 / 0.82/0.75	QoL measurements and health beliefs about warfarin were unchanged (apart from emotional role limitation) with education (control group) or education plus self-monitoring

continued

TABLE 14 *Quality of life results from randomised controlled studies: patients self-monitoring versus usual care of oral anticoagulation control (cont'd)*

Study	Methods	Results	Conclusions
Fitzmaurice, 2002[28]	A sample of patients (8 PSM and 8 control) were given a semi-structured interview covering relevant themes generated from a series of focus groups. Lancaster's instrument was also used	Five common themes emerged from the patient interview: 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	No significant difference in QoL was found between the two groups
Fitzmaurice, 2005[29] Jowett, 2006[52]	Postal questionnaires sent to trial participants at baseline 6 and 12 months, which contained the EQ-5D	QALYs over 12 months: **Control** / **PSM** Complete case 0.738 / 0.739 Imputed 0.712 / 0.721	There was no significant difference in QoL between the groups

SD, standard deviation.

usual care tended to report similar results on QoL.[28,29,32] However, one trial found that PSM improved patients' QoL, although AC was not significantly different between groups.[30]

Patient acceptability

This section describes patient acceptability in terms of the proportions of patients who agreed to enter the studies included in this review, and the proportion who refused or withdrew and their reasons for doing so. RCTs that were fully published and gave details on selection and patient characteristics were included in this section. Three trials did not provide detailed data on patient acceptability.[27,31,37]

Patients not previously treated with AC therapy

Two trials included patients who had not previously been treated with anticoagulant therapy.[26,38] At recruitment these patients were hospitalised and receiving intravenous heparin treatment. One of these trials required that patients demonstrated their ability to use a portable coagulometer and were known to be compliant with previous therapy.[38] In this study, the mean age of trial participants was 50 years. Of 125 patients eligible, 40% (n = 50) agreed to participate. Four patients (~5%) refused due to fear of sampling their own blood; 23 of 26 (88%) who were randomised to PSM completed. Two patients withdrew due to difficulties when blood sampling and one-third returned to clinic care. In the other trial,[26] patients over 65 years of age (mean 75 years) for whom treatment with warfarin was planned for 10 or more days were selected and approval sought once they had been randomised to treatment group. A total of 132 patients (81% of 163 randomised to PSM) agreed and were able to participate in PSM; of the 163 patients, 46 (28%) monitored the PT themselves, 50 (31%) had a spouse, other relative or visiting nurse help with their monitoring and 36 (22%) were monitored conventionally (20 had physical limitations such as arthritis or decreased vision; 12 preferred venipuncture; three stopped warfarin; and one was discharged to a nursing home where a portable coagulometer could not be used). Thirty-one patients (19%) declined to participate; their reasons were not reported.

Patients with mechanical heart valves or atrial fibrillation

Three trials included patients from a narrower patient population; two trials enrolled patients with implanted MHVs[33,35,42] (mean 61–68 years), and the third enrolled patients with AF.[32] Sidhu and Kane enrolled the first 100 patients who consented to enter the trial (100/231 patients, 43%); patient refusals were not reported.[35] Kortke and colleagues reported a subanalysis from a larger trial[33] of 1200 patients in the ESCAT study; the investigators evaluated data from the first 600 patients to complete a 2-year follow-up visit.[42] In the study reported by Khan and colleagues,[32] eligible patients were first selected by computer (249 selected, total population not stated). Patients eligible to enter the trial were those aged over 65 years (mean 71–75 years) with at least 12 months of warfarin therapy and a stable INR

value for the previous 6 months. A total of 154 patients were randomised to the intervention group, and their consent was sought to continue with the trial; 85 patients (55%) agreed to participate. Patients who refused to participate were concerned about self-testing, use of needles or preferred to continue at their usual anticoagulation clinic. There was no significant difference in the patient characteristics of those who refused to participate and those who entered the study.

During the study period of the Sidhu trial, of 51 patients 10 (20%) dropped out and another six were transferred to clinic management;[35] similarly, four patients (9%) withdrew from the Khan trial.[32] During training, patients withdrew or were unsuitable to continue due to difficulties with managing dosing or blood sampling. Discontinuation of warfarin therapy was another reason for withdrawal.

A further trial planned to recruit 2000 patients with non-valvular AF, but was terminated prematurely with 202 patients, because of difficulty in obtaining patients' consent to participate.[37]

Warfarin therapy for patients with mixed indications

In four studies, about 10–25% of eligible patients agreed to participate (mean age 58–66 years).[16,29,30,39] These came from large primary care or clinic outpatient populations (≥800 patients) who had been treated with anticoagulation therapy for at least 3–8 months. The majority of patients who declined were reluctant to enter a clinical trial and were satisfied with current services. Other reasons included feeling too old, nervousness, uncertainty about trial participation and a preference not to contemplate illness.

Fitzmaurice and colleagues[28] selected patients on long-term anticoagulation therapy whose condition was stable and who were considered capable of performing self-testing and self-dosing (mean age 63–69 years). Sunderji and colleagues[36] also selected patients who had been treated for at least 1 month with anticoagulant therapy and were likely to be able to perform self-monitoring or management according to their pharmacists or physicians (mean ages 58–62 years). Of these patients, 72–92% agreed to participate in the studies. In the Sunderji study, 60 out of 96 excluded patients (25% of total population screened) refused treatment because they preferred physician management.[36] During these two studies, a further 23–24% of patients withdrew or were withdrawn from treatment.[28,36] Reasons for withdrawal included difficulties with blood sampling, operation of the coagulometer, dosing and a preference to return to physician management.

Menendez-Jandula and colleagues[34] randomly selected 1500 patients from a population of 5000 at an anticoagulation clinic and included those over 18 years of age on long-term anticoagulation treatment (mean age 65 years). About 63% of patients agreed to enter the study. A further 68 (19%) of patients withdrew, lacking in confidence or unable to cope with self-testing.

Sawicki[12] enrolled patients who needed life-long anticoagulation therapy starting treatment at specialist, secondary care anticoagulation departments; 179 patients agreed to enter the study (69%, mean age 55 years). During the study, 12 patients (13%) withdrew from the self-management group and a further two chose not to self-monitor; seven patients in the usual care group, however, opted to self-monitor. Reasons for withdrawal were not reported.

Gardiner and colleagues[39] reported that 13% of 800 eligible patients agreed to participate in a trial that compared PSM and PST in the UK, and 26% of those randomised dropped out for reasons mainly such as difficulties with finger-prick testing and nervousness about self-management.

Three studies reported that patients randomised to self-monitoring or self-management groups were younger than the general anticoagulant population.[16,29,30] Gadisseur and colleagues[30] also found that the patients in their active intervention groups (education only, self-monitoring or self-management) included more men. Fitzmaurice and colleagues[29] found that in the intervention group, the mean age of those completing training was significantly lower than that of those initially randomised (61 versus 64, $p = 0.012$). In one study, however, individuals who refused to participate did not differ in age or gender distribution from the studied group.[32]

In summary, the proportion of patients agreeing to enter trials ranged from 10 to 95% of those invited to participate. Three trials had little or no prior patient selection, and the remaining trials were more specific in their selection criteria (newly treated patients, specific indication or more information on patient competence before enrolment). Where stated, the main reasons for refusing trial entry were fear of blood sampling, satisfaction with current service provision, lack of

TABLE 15 *Patient acceptability of PST/PSM – data from included randomised trials*

Study	Eligible or screened patients	Agreed and accepted to participate	Agreed/eligible (%)	Randomised to PST/PSM (before training)	Able and conducted PST/PSM	Able/randomised (%)	Completed PST/PSM	Completed/ conducted (%)
Beyth, 2000[26]		426		163	132	81.0	96	72.7
Cromheecke, 2000[27]				50	49	98.0	49	100.0
Fitzmaurice, 2002[28]	298	56	18.8	30	26	86.7	23	88.5
Fitzmaurice, 2005[29]	2530	617	24.4	337	242	71.8	193	79.8
Gadisseur, 2003[30]	720	184	25.6		99			
Gardiner, 2005[16a]	800	84	10.5	44	39	88.6	30	76.9
Gardiner, 2006[39a]	800	104	13.0	104			77	(74)
Horstkotte, 1998[31]							75	
Khan, 2004[32]	209	85	40.7		44		40	90.9
Kortke, 2001[33]					579			
Menendez-Jandula, 2005[34]	1198	737	61.5	368	300	81.5	289	96.3
Sawicki, 1999[12]	260	179	68.8	90			74	
Sidhu, 2001[35]		100		51	41	80.4	35	85.4
Sunderji, 2004[36]	236	140	59.3	70	57	81.4	53	93.0
Voller, 2005[37]					101			
White, 1989[38]	125	50	40.0	26	24	92.3	23	95.8
Total			**33.4**			**79.9**		**87.1**
Combined Fitzmaurice trials[28,29] (Birmingham)	**2828**	**673**	**23.8**	**367**	**268**	**73.0**	**216**	**80.6**

[a] The Gardiner (2005) and Gardiner (2006) studies may have used the same patient population, so data from the Gardiner (2006) study were not used in the pooled analyses.

confidence and a preference not to contemplate illness. During the studies, a further 6–25% of patients withdrew, for reasons including difficulties with blood sampling or operation of the coagulometer, lack of confidence in ability to self-monitor or self-manage treatment or a preference to return to physician management. One study found no significant difference in the characteristics of patients who refused to participate compared with those who entered the study. Three studies, however, found that patients randomised to self-monitoring or who successfully completed training were younger than the general anticoagulant population.

Data from the included trials are represented in *Table 15*. Pooling of available data from all trials suggested that, on average, 33% of eligible patients agreed to participate in the trials. Some 80% of patients randomised to the PST/PSM group were successfully trained and/or able to conduct PST/PSM, and 87% of those who started PST/PSM completed the allocated intervention. These figures vary greatly across individual trials because of different eligibility and inclusion criteria used in these trials. The two UK Birmingham trials perhaps provided the most relevant data.[28,29] Results of these trials indicated that for every 100 eligible patients in the UK, 24 would agree to conduct PSM, 17 of those 24 patients could be successfully trained and able to carry out PSM, and only 14 would conduct long-term PSM. However, the patient acceptability estimated by data from trials may or may not be generalisable to usual practice settings.

Chapter 5

Economic evaluation

This chapter first presents a review of existing studies on the economic evaluation of PSM of oral anticoagulation therapy. Then a Markov-type model was developed to estimate the cost-effectiveness of PSM versus usual care of oral AC in the UK.

Review of economic evaluation studies

MEDLINE, NHS EED and HEED were searched for relevant studies on economic evaluation of PST or PSM of oral anticoagulation therapy. References of retrieved articles were also examined. Study inclusion was conducted by one reviewer. Data from included studies were extracted to tables by one reviewer and checked by another. Studies of full economic evaluation that compared costs and effects of PSM and usual care control were included. A search of MEDLINE yielded 205 references, from which four relevant studies were identified.[19,53–55] No additional studies were identified by searching NHS EED and NEED database. One study published in Catalan was identified by a search of Internet and it was only partially translated into English.[56] Two studies that were published after the formal literature search was undertaken were also identified.[52,57] The data extraction and assessment of relevance were carried out by one reviewer and checked by another. Main study characteristics, methods and results of included studies are presented in Appendix 3.

There were some methodological limitations, but the main concern is the questionable applicability of findings from studies conducted outside the UK to the setting of the UK.[19,53–57] The study methods and main findings from these studies are narratively described and commented upon below.

Taborski and colleagues' study (1999)[53]

This study in Germany compared the cost-effectiveness of PSM and AC management by family physicians. The study covered only costs relevant to the government-controlled health insurance. Costs of performing PSM and family physician management, and costs of treating complications were estimated using data collected from patients and the published literature. If costs of treating complications (DM 618.86 versus 20.70 per patient-year) were ignored, it was found that, on average, PSM cost more than the conventional approach. Findings from published literature were then used to estimate the risk of minor or serious bleeding and thromboembolic complications separately for PSM and family physician's management. Due to an assumed reduction in serious bleeding and thromboembolic complications, PSM reduced overall costs as compared with conventional management by family physicians (DM 1342.46 vs 2061.48 per patient-year). Since AC management by German family physicians was used as the comparator, findings from this study have limited relevance to the UK setting.

Lafata and colleagues' study (2000)[19]

This study was conducted in the USA and the model structure, assumptions and data sources were explicitly presented. A 5-year Markov model was built to examine the cost-effectiveness of three anticoagulation management approaches: usual care (family doctor), AC clinic testing with a capillary monitor and PST with a capillary monitor. It was assumed that a different AC management resulted in a different proportion of time below or above the target range, and consequently resulted in a different risk of serious bleeding and thromboembolic complications.

The model's input values were estimated from the published literature, data from a large health system and, when necessary, expert opinion. In the base case, it was assumed that time below and above the therapeutic range was 33 and 17%, respectively, for usual care, 26 and 9%, respectively, for AC clinic and 6 and 5%, respectively, for PST. The risk of bleeding and thromboembolic complications specific to time spent below, in or above the therapeutic range was estimated according to data from a cohort study.[58] Complications were classified into three categories: serious, life-threatening or fatal. Data from the published literature were used to assign utility values to complications associated with anticoagulation therapy.

Costs were estimated using data from the published literature, data from the authors' institution and, when necessary, expert opinion. The analysis was conducted from two perspectives: (1) medical provider and (2) patients and their carers. PST was associated with the highest 5-year medical care costs per 100 patients (US$, 1997) among the three management approaches ($526,014 versus $419,514 for usual care and $405,560 for AC clinic). However, the patients' and carers' costs (5-year per 100 patients) were lowest with PST, because of reduced costs of time and travelling ($96,713 versus $110,223 for usual care and $240,110 for AC clinic). AC clinic testing was the cost-effective alternative when only direct medical care costs were considered. When patient and carer costs were also included, PST became the most cost-effective alternative, and it was cost saving when PST was compared with AC clinic.

Sensitivity analyses found that results were sensitive to assumptions regarding time spent below and above the therapeutic range and annual testing frequency. The assumed advantage of PST in terms of time in the therapeutic range (89% for PST versus 65% for AC clinic) did not correspond to findings from trials in the UK (e.g. 70% for PSM versus 68% for hospital or primary AC clinic[29]).

Muller and colleagues' study (2001)[54]

The objective of this study was to conduct an economic analysis of the coagulation-related complications following heart valve replacement. Stroke incidence in a hypothetical cohort of 10,000 patients with heart valve replacement was estimated based on data from the German Experience with Low Intensity Anticoagulation study.[59] Lifetime costs of a stroke were estimated according to US data.[60] It was assumed that PSM of oral anticoagulation reduced severe complications by 30% compared with usual management by family doctors. Costs per life-year gained were estimated to be DM 105,000.

Samsa and colleagues' study (2002)[55]

This study described an interactive mathematical model, the Anticoagulation Management Event/Cost Model (ACME). The model compared four anticoagulation management policies: (1) no anticoagulation therapy, (2) physician management, (3) AC clinics and (4) PSM. The input values were estimated based on data from the published literature. The estimated time within therapeutic range was 46.83% for physician management, 51.68% for anticoagulation clinics and 77.12% for PSM. The results showed that making PSM available was the most cost-effective management policy.

Sola-Morales and Elorza's study (2003)[56]

The study was published by the Catalan Agency for Health Technology Assessment in Spanish and Catalan.[56] We assessed this study according to a partial English translation of the economic section provided by Dr Allan Brown of Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

The study compared the cost-effectiveness of five possible alternatives: (1) PSM, (2) PST, (3) use of portable coagulometers by family doctors (POC-doctor), (4) use of portable coagulometers at hospital (POC-hospital) and (5) usual hospital care (blood test with venopuncture). A 5-year Markov model was built using data from literature reviews. In the model, the different AC management approaches were directly linked to the risk of complications (without an intermediate variable of time in therapeutic range). It was assumed that all four approaches using portable coagulometer (PSM, PST, POC-doctor, and POC-hospital) had the same clinical outcomes (i.e. bleeding and thromboembolic complications), which was lower than that by the usual care. From a health insurer perspective, a comparison of costs associated with each of the alternatives found that hospital-based portable coagulometer testing was the most efficient.

Regier and colleagues' study (2006)[57]

A Bayesian Markov model was developed to compare the cost-effectiveness of PSM and physician management of long-term anticoagulation therapy from a Canadian healthcare payer's perspective. The basic structure of the model is similar to that of previous models in which the quality of oral anticoagulation therapy determined the risk of clinical complications and deaths. Input parameters in the model were estimated based on the published literature. Results indicated that PSM is a cost-effective strategy for long-term oral anticoagulation therapy. However, the data on the percentage of INR time below, in or above the therapeutic range in the model, were from a single trial[36] and the quality of usual care control (physician management) used in the model was much poorer than the current usual care (specialised anticoagulation clinics) in the UK.

Jowett and colleagues' study (2006)[52]

This was a cost–utility analysis alongside a randomised trial conducted in Birmingham, UK.[29]

The cost-effectiveness of PSM was determined in comparison with routine primary or secondary clinic-based AC management over 12 months in 617 patients receiving long-term anticoagulation therapy. Quality-adjusted life-years (QALYs) were calculated from utility scores elicited using the EQ-5D questionnaire at baseline, 6 months and 12 months. Multiple imputation was employed to address the issue of missing data and a regression-based adjustment was carried out to adjust for baseline differences. It was found that the mean difference in QALYs between the groups (favouring PSM) was 0.009 (95% CI –0.012 to 0.03), which was not statistically significant.

Costs were measured from both a healthcare and a societal perspective.[52] Healthcare costs consisted of PSM costs including training and assessment, the cost of routine AC management and primary and secondary care contacts for thrombotic and haemorrhagic complications. Overall mean healthcare costs were £417 (95% CI £394 to £442) in the PSM group and £122 (95% CI £103 to £144) in the routine care group. After including patient costs, they were on average £463 and £180, respectively. According to the cost-effectiveness acceptability curves (CEACs) (*Figure 8*), the probability that PSM was cost-effective was 46% at a threshold of £30,000 per QALY and 30% at a ceiling of £20,000 per QALY.

Summary of findings from identified studies

Complication events were the key outcomes in literature-based studies. In three studies the quality of AC control (time in therapeutic range) was explicitly linked to the subsequent changes in complication events.[19,55,57] Three studies linked AC management alternatives directly to complication events.[53,54,56]

Costs were estimated from an insurer perspective in three studies,[53,54,56] from a societal perspective by two studies[19,52] and medical care perspective in one study.[55] PSM was associated with a higher healthcare cost compared with AC clinics. After including patient and carer costs, the overall costs by PST/PSM were lower in the study by Lafata and colleagues,[19] but higher in the study by Jowett and colleagues.[52]

Results of cost-effectiveness analysis favoured PSM in five studies,[19,53–55,57] but superiority was not clear in the Catalan study[56] or in the UK study.[52] In studies that provided favourable cost-effectiveness analyses, it was assumed that PSM significantly reduced the risk of major complications.

The most relevant data were from the study by Jowett and colleagues.[52] The economic evaluation

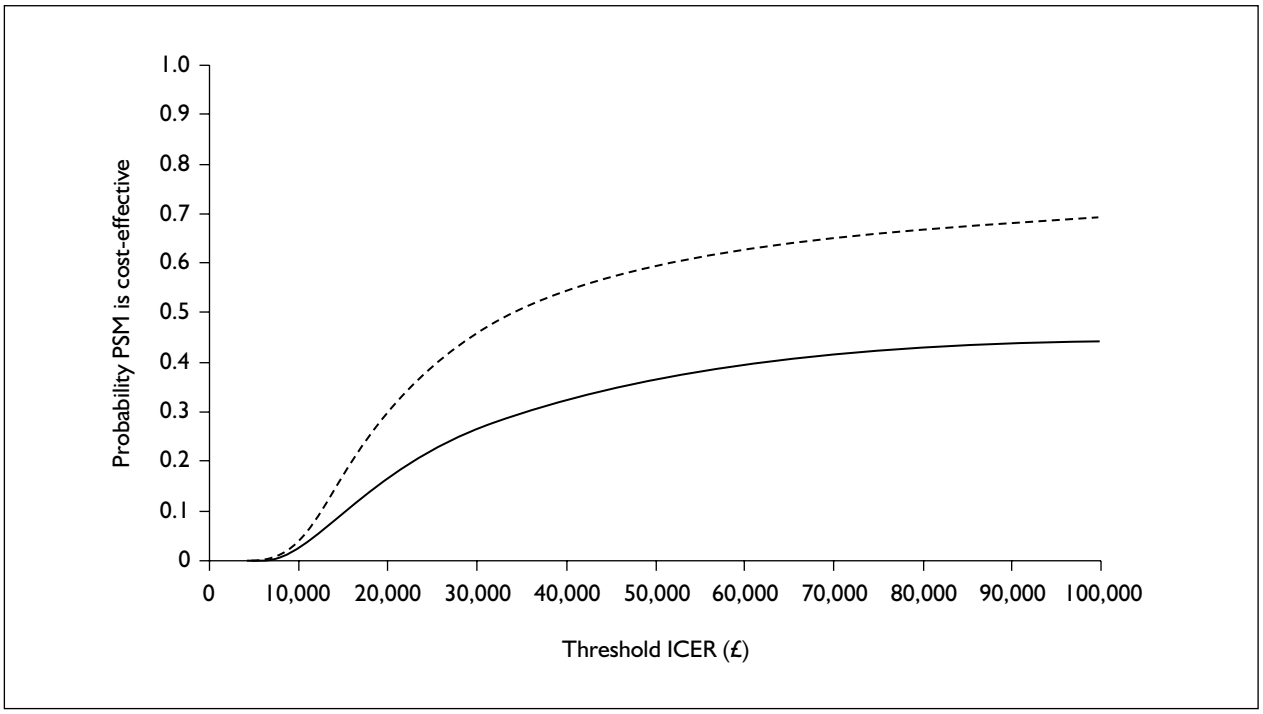

FIGURE 8 *CEAC for PSM compared to routine care. Dashed line, imputed data; solid line, complete case. Data taken from Jowett and colleagues.*[52]

was part of a clinical trial in the UK, and was conducted from both NHS and societal perspectives. Patients included in the trial were from primary care settings and less selected. All important outcomes were measured in the trial, including complications and QoL. Clearly, PSM is more expensive in terms of cost to the NHS than current routine care in the UK (£417 versus £122 per patient-year). It was concluded that using a cost-effectiveness threshold of £30,000 per QALY gained, PSM does not appear to be cost-effective.

Cost-effectiveness of PSM for oral anticoagulation therapy in the UK: a modelling approach

Objectives and model structure

The objective was to develop a computer model for the evaluation of cost-effectiveness of PSM of oral anticoagulation therapy compared with usual care in the UK. A Markov-type, state-transition model was developed using Microsoft Excel [henceforth called the UK oral anticoagulation model (UK OAC model) (*Figure 9*)]. The structure of the model was similar to previously published models of PSM of oral anticoagulation therapy.[19,55,57] It was assumed that the risk of haemorrhagic and thrombotic complications was determined by the quality of AC (percentage of INR time in, below or above the therapeutic range). The model allowed comparison of PSM of AC with usual care in the UK. The model was run deterministically and stochastically.

Five health states were specified: no disability, disability due to major haemorrhagic events, disability due to thrombotic events, disability due to both haemorrhagic and thrombotic event and death. Cycle length was 1 year. The risk of new haemorrhagic and thrombotic events for patients was specific to AC in terms of the proportion of time in, below or above the therapeutic range. Consequences of major complication events included death, alive without permanent disability and alive with permanent disability. It was assumed that 50% of those patients disabled due to major haemorrhagic events would stop oral anticoagulation therapy. Hence, the risk of both haemorrhagic and thrombotic complications was increased in patients with disability due to previous major haemorrhagic events.

Input values for effectiveness parameters

According to data from the Birmingham trial (SMART), the average age of patients receiving anticoagulation therapy is about 65 years.[29] In the UK OAC model, the base-case patient was aged 65 years, with an increased risk of death compared

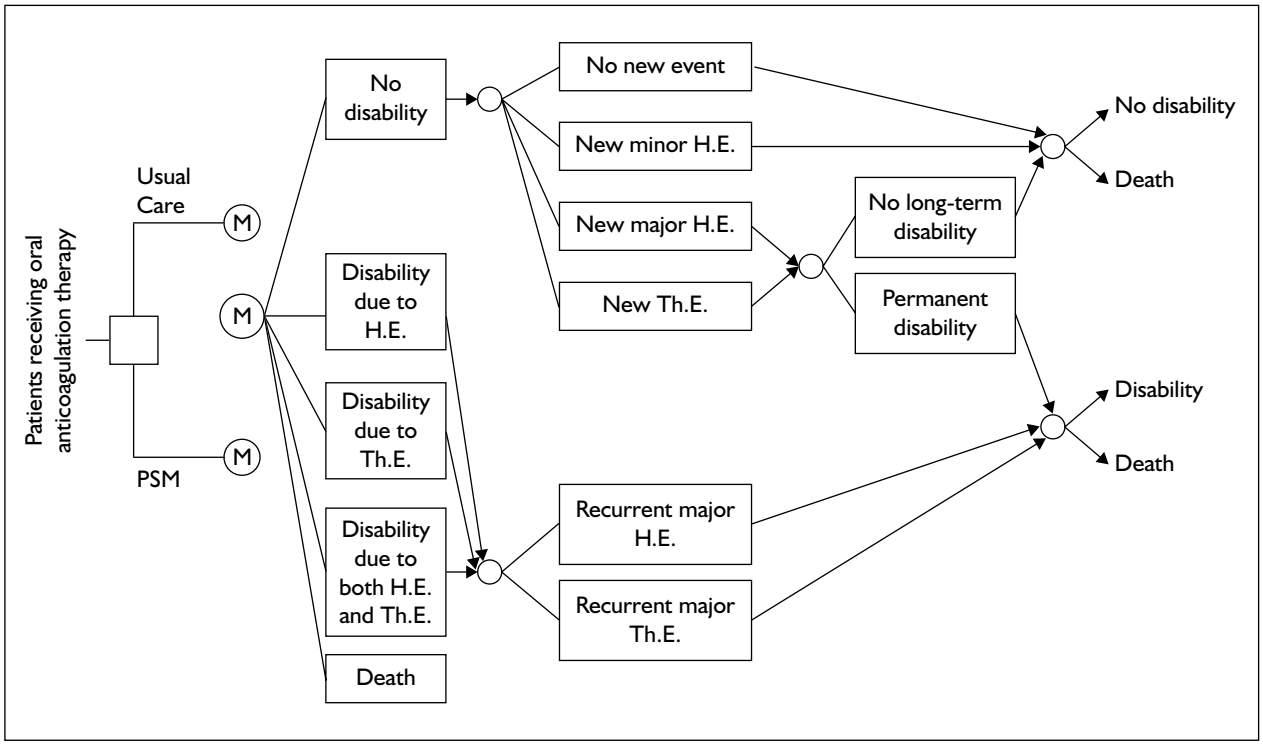

FIGURE 9 *Schematic structure of the UK OAC model for the evaluation of the cost-effectiveness of PSM of AC in the UK. H.E., haemorrhagic event; Th.E., thrombotic event.*

with the general population of the same age (risk ratio of 1.2 arbitrarily decided but equally applied to both the PSM and usual care conditions). *Table 16* shows input values for effectiveness parameters in the model. The proportion of time in, below or above the INR therapeutic range by PSM and usual care in the UK was based on data from the SMART trial in Birmingham, which was the most relevant to the UK setting.[29] Risk of haemorrhagic and thrombotic events specific to the quality of AC was estimated from review of published literature.[61–64] Risk of death after an acute event was based on Regier and colleagues[57] and risk of disability in patients who survived an acute event was based on Gage and colleagues.[65] It was assumed that risk of death was also increased in patients with minor haemorrhagic events and disabled patients due to haemorrhagic or thrombotic events. Utility values for different health states or clinical events were estimated according to data from the SMART trial, Regier and colleagues[57] and Thomson and colleagues.[66]

Evidence from RCTs reviewed in Chapter 4 indicated that the risk of complications in PSM patients may be reduced because of patient education and patient empowerment, and that the quality of AC by PSM was not significantly different from usual care. The model assumed that the risk of complications in PSM patients was on average reduced non-specifically by 5% (range: 0–10%).

To reflect uncertainty or imprecision of input values, a range of values was provided mostly by assuming 25% smaller or greater than the point estimate. For risk ratio or utility values, the range of possible values was assumed mostly to be 0.5 smaller or greater than the point estimate (*Table 16*). For stochastic simulations, we used a β distribution for categorical data values and triangular distribution for risk ratios and utility values.

Input values for cost parameters

Estimates of input cost values are shown in *Table 17*. The cost analysis was from the NHS perspective (including Personal Social Services for long-term care of disability and Chambers and colleagues[69]). All costs were updated to 2005.

Data from the Birmingham (SMART) trial and methods described by Jowett and colleagues[52] were used to estimate testing and related costs of PSM and usual care of anticoagulation therapy in the UK. Cost of GP consultation was based on the assumption of 10 minutes of GP's time and the unit cost from Curtis and Netten.[70] The unit costs for acute complication events were from the NHS Reference Costs 2005 (NHS Trust, non-elective), Department of Health, England.[71] The procedure weightings for acute events were estimated according to data from the SMART trial when available. The cost per fatal stroke was from Youman and colleagues[72] and costs for short-term rehabilitation and long-term care of disability were from Chambers and colleagues.[69]

According to data from the SMART trial, it is assumed that 40% of patients who received PSM training would not perform PSM, for various reasons. Costs related to patient training and CoaguChek machine were applied only to the first year. We also assumed that the CoaguChek machine would be used by other patients in three-quarters of PSM cases after patients stop performing PSM.

The assumed ranges for input cost values were mostly 25% smaller or greater than the point estimate, except where interquartile ranges were available from the NHS reference costs 2005.[71] Stochastic simulations were conducted by assuming a normal distribution for cost input values, triangular distribution for procedure weightings and beta distribution for the success rate of PSM training.

Both costs and effectiveness were discounted by 3.5% (range 0–6%).

Main findings

The results of base case deterministic evaluation are shown in *Table 18*. Over a 5-year period, the incremental cost per QALY is £122,365 by PSM. The relative cost-effectiveness of PSM improved for longer follow-up, because the costs of PSM training and CoaguChek machine only occur in the first year. Over a 10-year period, the estimated cost per QALY gained by PSM was £63,655.

The base case evaluation used data from the Birmingham (SMART) trial for model inputs for proportions of time that INR was in and out of the therapeutic range. In this trial, there were no differences between the PSM and usual care control for these parameters (*Table 16*). The small difference in estimated effectiveness was all attributable to the utility values (0.738 versus 0.739) based on an assumed 2.5% reduction in major complications in the PSM group because of patient training (i.e. improved knowledge and patient empowerment). When the average estimates derived by pooling results from all

TABLE 16 *Model input data for estimating effectiveness*

	Point estimate	Lower estimate	Upper estimate	Data sources and notes
Anticoagulation control				
Usual care				
Above	0.1450	0.109	0.181	Source: Birmingham (SMART) trial[29]
Within	0.6880	0.766	0.610	Note: lower and upper estimate 25% smaller or greater than the point estimate
Below	0.1670	0.125	0.209	
PSM				
Above	0.1230	0.092	0.154	
Within	0.7040	0.778	0.630	
Below	0.1730	0.130	0.216	
Risk of events specific to time in therapeutic range				
Minor haemorrhagic event rate by time within range				
Above	0.1129	0.085	0.141	Source: Palareti *et al*., 1996[61]
Within	0.0475	0.036	0.059	Note: lower and upper estimate 25% smaller or greater than the point estimate
Below	0.0610	0.046	0.076	
Major haemorrhagic event rate by time within range				
Above	0.0337	0.025	0.042	Source: pooled from Cannegieter *et al*., 1995,[62] EAFTSG, 1995,[63] Palareti *et al*., 1996,[61] and Tangelder *et al*., 2001[64]
Within	0.0092	0.0069	0.012	
Below	0.0117	0.009	0.015	
Thromboembolic event rate by time within range				
Above	0.0081	0.0061	0.0101	Source: pooled from Cannegieter *et al*., 1995,[62] EAFTSG, 1995[63] and Tangelder *et al*., 2001[64]
Within	0.0073	0.0055	0.0091	
Below	0.0272	0.020	0.034	
Non-specific effect of PSM	2.5%	0.0%	5.0%	Assumed reduction of complication risk in PSM patients due to training, patient empowerment, etc.
Complication risk ratio for patients with disability due to previous major haemorrhagic event	1.5	1.0	2.0	Assumed. It was assumed that 50% of disabled patients with major haemorrhagic events would stop oral anticoagulation therapy. Thus the risk of complications in these patients will increase
Disability rate in survivors of a major event				
Permanent disability after major haemorrhagic events	0.140	0.105	0.175	Source: Gage *et al*., 1995[65]
Permanent disability after major thrombotic events	0.638	0.478	0.797	Note: lower and upper estimate 25% smaller or greater than the point estimate
Death rate for acute events				
Major haemorrhagic events	0.14	0.105	0.175	Source: Regier *et al*., 2006[57]
Major thrombotic events	0.21	0.1575	0.2625	Note: lower and upper estimate 25% smaller or greater than the point estimate
Death risk ratios (additional to age-specific patients without events or disability)				
Minor haemorrhagic events	1.5	1.0	2.0	Assumed (for 1 year only)
Disabled due to major haemorrhagic events	1.5	1.0	2.0	Assumed
Disabled due to thrombotic events	2.25	1.75	2.75	Sundberg *et al*., 2003:[67] stroke disabled versus high-risk stroke: 2.25 = 3.63/1.61
Disabled with both haemorrhagic and thrombotic events	3	2.5	3.5	Assumed

continued

TABLE 16 *Model input data for estimating effectiveness (cont'd)*

	Point estimate	Lower estimate	Upper estimate	Data sources and notes
Utility values				
No events – usual care	0.738			Source: Birmingham (SMART) trial[29]
Difference between usual care and PSM patients	0.001	–0.027	0.032	Source: Birmingham (SMART) trial[29] Note: utility = 1.0 for no event in Regier *et al*., 2006.[57] Utility values for complication events below were adjusted correspondingly when considered necessary
Minor haemorrhagic events	0.72	0.70	0.74	Assumed
Major haemorrhagic events				
Acute stage	0.54	0.44	0.64	Source: Regier *et al*., 2006[57] and Post *et al*., 2001[68]
Disabled	0.32	0.12	0.52	Ranges assumed
Thromboembolic events				
Acute stage	0.45	0.35	0.55	Source: Regier *et al*., 2006[57] and Post *et al*., 2001[68]
Disabled	0.32	0.12	0.52	Ranges assumed
Both haemorrhagic and thrombotic disabled	0.19	0.09	0.29	Source: Thomson *et al*., 2000[66] (major stroke) Ranges assumed

available trials (*Table 7*) were used, the incremental cost per QALY of PSM versus usual care was £47,387 after 5 years and £19,617 after 10 years.

Incremental utility values and costs over 5 and 10 years, estimated by 5000 stochastic simulations, are shown in *Figure 10 (a)* and *(b)*, respectively. The average incremental cost per patient was £903 (95% CI £705 to £1105) over 5 years and £1004 (95% CI £712 to £1320) over 10 years. The average incremental utility values per patient were 0.010 (95% CI –0.079 to 0.103) over 5 years and 0.021 (95% CI –0.132 to 0.179) over 10 years. Thus PSM was always associated with greater cost than the usual care. PSM was on average more effective than the usual care but the 95% CI overlapped with negative values in terms of QALYs gained.

Figure 11 shows CEACs over 5 and 10 years, generated by 5000 stochastic simulations. Over 10 years, the probability that PSM is cost-effective (threshold incremental cost–utility ratio £30,000/QALY) was 44%.

The estimated incremental cost per QALY by PSM over 10 years (£63,655) by the UK OAC model was less favourable than that by the SMART trial (£31,437–32,716 per QALY).[52] However, the CEAC from the model is similar to that estimated from data from the SMART trial (*Figure 8*). The SMART trial estimated that at £30,000 per QALY the probability of being cost-effectiveness was 46% for the imputed data set and 26% for the complete case analysis.[52]

Additional NHS costs of patient self-monitoring

The average incremental cost of PSM per patient per year was estimated to be £180.21 over 5 years or £100.39 over 10 years (*Table 18*). In the SMART trial, there were approximately six patients who were eligible for self-monitoring of anticoagulation therapy per 1000 general population. Applying this figure to the whole population in England and Wales in 2004 (n = 53,045,600), the total number of eligible patients would be 318,274, and 79,568 (25%) of the eligible patients would accept self-monitoring. It can be estimated that wide adoption of PSM of anticoagulation therapy would cost the NHS an additional £8.0–14.3 million. By excluding the cost of the self-testing machine, the costs to the NHS would be considerably reduced (by about £4.6–6.8 million). However, the acceptability of PSM is likely to be much lower should patients have to pay for the CoaguChek machine.

Summary of modelling findings

The results of the modelling found that the incremental cost per QALY gained by PSM was

TABLE 17 *Model's input data for cost estimation*

		Point estimate (£)	Lower estimate (£)	Upper estimate (£)	Data sources and notes
Anticoagulation control cost (per year)					
Usual care annual costs		98.47	73.86	123.09	Birmingham (SMART) trial[29]
PSM costs					
Training cost		170.23	127.67	212.67	Range: ± 25%
Training success rate		0.60	0.45	0.75	
CoaguChek machine		513.56	385.17	641.95	
Other costs					
GP consultation (×2)		44.14	33.12	55.20	
Internal quality control (×4)		21.92	16.44	27.40	
External quality control (×1)		26.28	19.71	32.85	
Test strip (×26)		71.24	53.43	89.05	
	Weight (range)				
Unit costs per acute events					
Minor haemorrhagic event					National reference costs (2005):[71a]
A&E (high cost – discharged)	0.2 (0.1–0.3)	115.00	104.00	167.00	NHS Trust, TNELIP, V02
A&E (low cost – discharged)	0.3	74.00	64.00	83.00	NHS Trust, TNELIP, V06
GP consultation	0.5 (0.4–0.6)	22.00	16.56	27.60	Curtis and Netten, 2005[70]
Major haemorrhagic event					
Cerebral haemorrhage	0.25 (0.20–0.30)	2,156.00	1,097.00	2,924.00	NHS Trust, TNELIP, A19
GI bleed – major procedures	0.10 (0.05–0.15)	3,948.00	1,354.00	5,262.00	NHS Trust, TNELIP, F61
GI bleed – complications	0.20 (0.15–0.25)	1,266.00	819.00	2,076.00	NHS Trust, TNELIP, F62
GI bleed – no complications	0.325	486.00	300.00	825.00	NHS Trust, TNELIP, F63
Epistaxis day case	0.0625 (0.02–0.10)	627.00	438.00	764.00	NHS Trust, TDC, C56
Epistaxis non-elective inpatients	0.0625 (0.02–0.10)	955.00	621.00	1,190.00	NHS Trust, TNELIP, C56
Major thrombotic event					
Pulmonary embolism	0.3 (0.25–0.325)	1,309.00	1,037.00	2,050.00	NHS Trust, TNELIP, D11
Thrombotic stroke (9 days hospital stay)	0.4 (0.35–0.425)	1,707.00	985.00	2,447.00	NHS Trust, TNELIP, A23
Minor thrombotic stroke	0.125 (0.10–0.15)	667.00	463.00	1,129.00	NHS Trust, TNELIP, A21
Transient ischaemic attack (day case)	0.125	525.00	330.00	536.00	NHS Trust, TDC, A21
Thrombectomy	0.05 (0.025–0.075)	2,173.00	1,116.00	2,806.00	NHS Trust, TELIP, Q06
Fatal stroke costs		8838.30	6628.73	11047.88	Youman *et al.*, 2003[72] Range: ± 25%
Costs for disabled patients					
Rehabilitation for first year disability		932.13	699.10	1165.16	Chambers *et al.*, 1999[69]
Annual cost for long-term care of disability		13802.74	10352.06	17253.43	Range: ± 25%

A&E, accident and emergency; GI, gastrointestinal; HRG, Healthcare Resource Group; TDC, day cases HRG data; TELIP, elective inpatient HRG data; TNELIP, non-elective inpatient HRG data.

[a] Where NHS Trust costs are quoted, lower and upper estimates are from interquartile ranges for data from the National reference costs.[71]

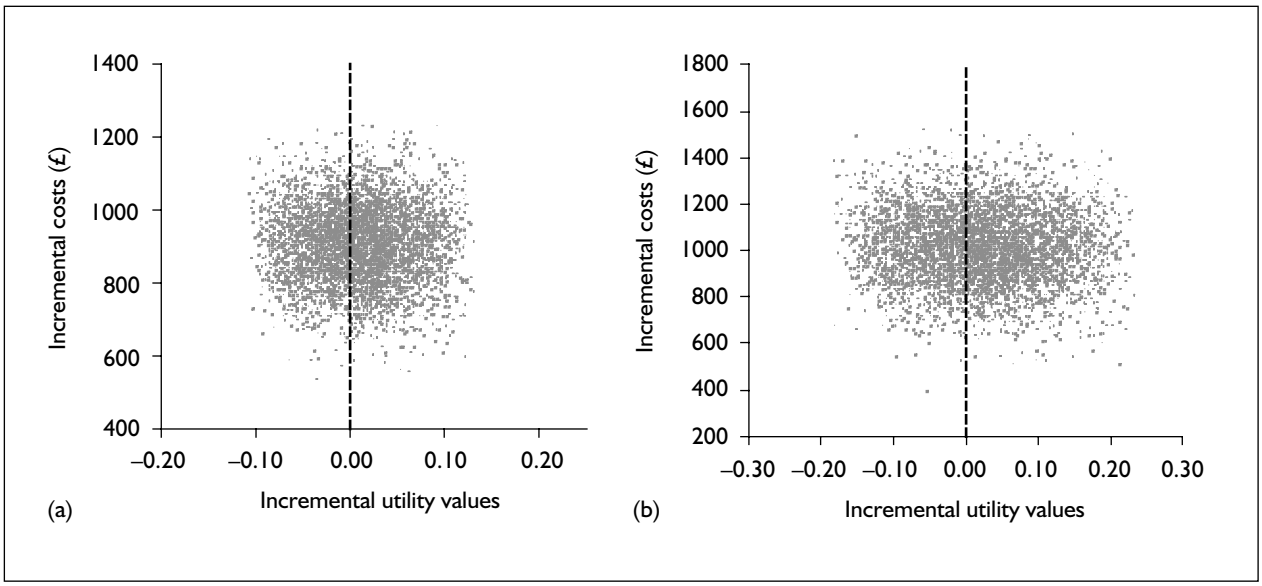

FIGURE 10 *Results of 5000 Monte Carlo simulations (per patient): results at (a) 5 and (b) 10 years*

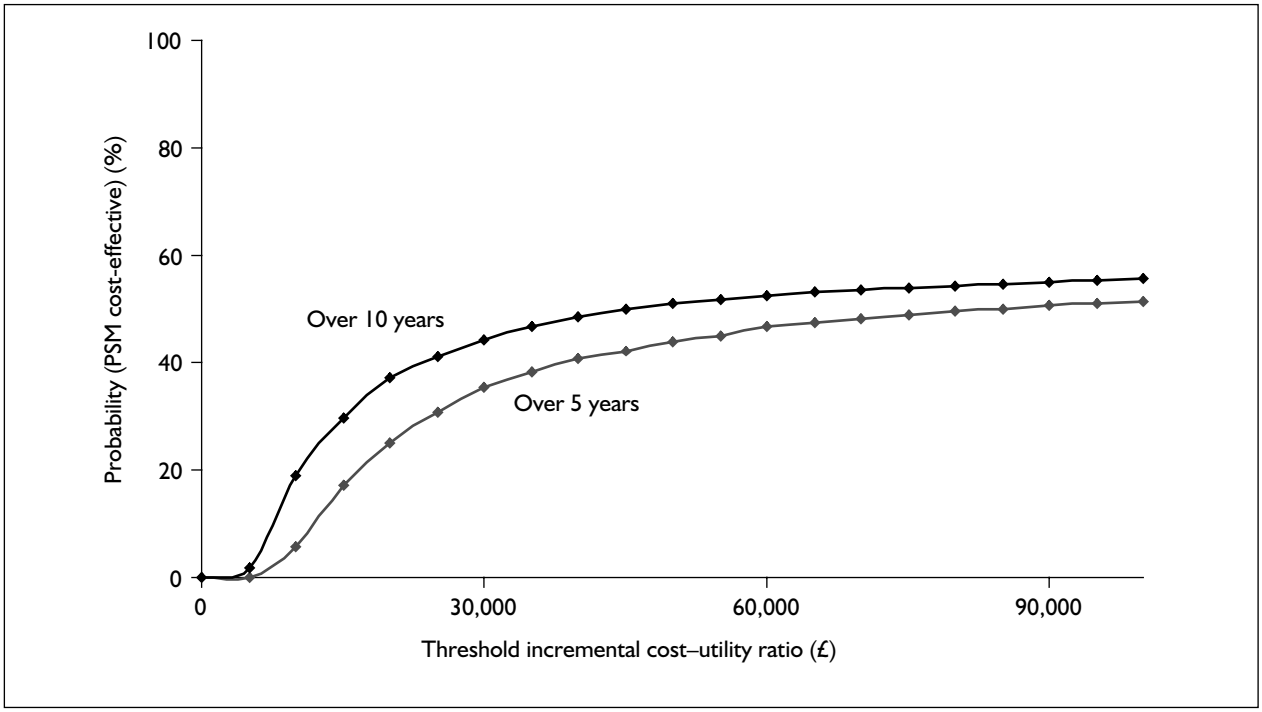

FIGURE 11 *CEACs for PSM versus usual care in the UK, estimated from Monte Carlo simulations of the UK OAC model*

TABLE 18 *Incremental cost-effectiveness of PSM versus usual care for anticoagulation control in the UK – results of deterministic base case evaluation*

Year	Cumulative utility (per 100)	Incremental NHS cost (per 100)	Cost–utility ratio (£)
1	0.129	74,427	577,170
2	0.269	79,060	294,283
3	0.418	83,220	199,239
4	0.574	86,890	151,326
5	0.736	90,104	122,365
6	0.902	92,899	102,938
7	1.071	95,309	88,998
8	1.241	97,368	78,480
9	1.410	99,048	70,249
10	1.577	100,393	63,655

about £122,365 over 5 years and £63,655 over 10 years. The probability that PSM is cost-effective (up to £30,000/QALY) was 44% over a 10-year period. Therefore, self-monitoring by general patients of oral anticoagulation therapy is unlikely to be more cost-effective than current usual care in the UK. However, for patients whose anticoagulation therapy could not be satisfactorily controlled by the usual care, self-monitoring may be a cost-effective alternative.

Chapter 6

Discussion and conclusions

Discussion

Patient self-monitoring and quality of oral anticoagulation

Long-term oral anticoagulation, prescribed to patients with an increased risk of thromboembolism, requires frequent monitoring to maintain a balance between decreased risk of thromboembolic complications and the tendency for increased bleeding complications. One of the important features of PSM of oral anticoagulation therapy is that AC could be more frequently tested by self-monitoring (every 1–2 weeks) than by usual care provided by family doctors or hospital clinics (every 2–4 weeks).

A recent review of quantitative studies found that "patients who have received anticoagulation therapy spend a significant proportion of their time with an INR out of the therapeutic range".[73] Results of controlled trials indicate that PSM is better than poor-quality anticoagulation control provided by family doctors, particularly in the prevention of inadequate anticoagulation (proportion of time INR spent below the therapeutic range). The proportion of time spent below the therapeutic range was on average 19% in patients who underwent self-monitoring compared with 33% in patients managed by family doctors (*Table 7*). PSM was as effective as usual care of specialised clinics for AC.

Patient self-monitoring and major complications

The number of major bleeding and thromboembolic events and deaths reported in reviewed trials is very small (*Table 8*). Meta-analyses could be performed but were sometimes accompanied by methodological difficulties due to the absence of events in both arms of trials. After pooling of data from all trials, no significant differences were found in risk of major bleeding events between PSM and usual care controls. Pooled analyses found that compared with primary care or AC clinics, PSM was statistically significantly associated with fewer thromboembolic events and deaths. The results of the meta-analyses were dominated by two large trials, which together contributed 46.5% of the total weight in meta-analyses.[33,34] These two largest trials reported greater effect in favour of PSM compared with smaller trials in terms of reduced risk of thromboembolic events and of death (*Figure 6*). In one of these large trials, acenocoumarol or phenoprocoumon was used for oral anticoagulation therapy, whereas warfarin is most commonly used in the UK.[34] Since the half-lives of acenocoumarol and phenoprocoumon are different from that of warfarin, it can be questioned whether the results of this trial are applicable to the UK.[34] In the other large trial, data on death outcome were not reported.[33] This trial was fully published only in German; translation difficulties, an incomplete account published in English and lack of details made it difficult to assess adequately for any methodological limitations.

It is difficult to interpret the results of meta-analyses of clinical complications and deaths. First, the reduction in complication events and deaths was not consistently associated with the improvement of AC. Second, random or systematic errors could not be ruled out from the included trials. More importantly, results of meta-analysis by pooling data from all trials may not be generalisable to the setting in the UK.

Data from the trials indicated that PSM is better than poor-quality usual care but as effective as high-quality AC clinics. The improved AC and the reduction of major complications and deaths by PSM were mainly observed in trials conducted outside the UK. Therefore, there is no convincing evidence to indicate that PSM is more effective than the current anticoagulation care provided in the UK.

Patient education and training

Since the reduction in complication events could not be satisfactorily explained by the improvement in AC, the observed reduction in complications and deaths in some trials may be due to alternative explanations. These include improved patient knowledge, enhanced patient compliance and patient empowerment. Patients need to receive training in order to conduct self-testing or self-management of their anticoagulant therapy. Such training usually aims to ensure that patients understand relevant theories, are able to use a

portable INR monitor correctly, to interpret INR findings correctly and possibly (PSM) to adjust the dose of warfarin correctly. With increased knowledge, patients may be more aware of the importance of appropriate AC and common risk factors, so that compliance to treatment may be improved. Two trials compared results for patients who performed PST/PSM and patients who received similar training but usual care.[27,30,32] The limited evidence indicated that the quality of AC for patients who received training without self-monitoring is as high as for similarly trained patients who self-monitor, and may be better than for untrained patients who receive usual care.

Patient selection for self-monitoring

Pooling of available data from all trials suggested that 33% of eligible patients agreed to participate in the trials. About 80% of patients randomised to the PST/PSM group were successfully trained and/or able to conduct PST/PSM, and 87% of those who started PST/PSM completed the allocated intervention. According to data from the two UK trials, for every 100 eligible patients 24 would agree to conduct PSM, 17 of those 24 patients could be successfully trained and able to carry out PSM and only 14 would conduct long-term PSM.[28,29] The relative success of PSM found in trials therefore depends not only on the quality of the comparator (usual care, as discussed above) but also on the proportion of the randomised population capable of efficient PSM. Hence the most favourable results for PSM will be found in trials with poor-quality usual care that enrolled capable populations. The UK trials included in this report had good-quality usual care as comparator and enrolled patients reasonably representative of the general AC population. For this reason, in this report data from UK trials were considered to be of greater relevance to the review question.

Clearly, not all patients are capable of performing self-monitoring and some patients may find it unnecessary because of high-quality care provided by existing anticoagulation clinics. However, selected patients may consider self-monitoring of oral anticoagulation as an invaluable option. For example, self-monitoring may enhance the QoL for some patients who are frequently away from home, who are in employment or education, or those who find it difficult to travel to clinics.[74]

The available clinical trials included participants with a wide range of indications for long-term oral anticoagulation therapy. AF and MHV replacement were the two most common indications. Ten of the 16 RCTs reviewed in the report included patients with mixed indications (*Table 2*). Subgroup analyses found no significant difference in the relative effectiveness of PST/PSM versus usual care control between patients with different clinical indications (*Table 6* and *Figure 6*).

Patient self-testing or self-management

The main difference between the procedures of PST and PSM of oral anticoagulation therapy is who decides about the change in anticoagulation therapy according to INR testing results. In the PST module, patients perform INR test at home and contact clinicians who will interpret the results and decide subsequent changes, whereas PSM requires that patients perform the test and decide what to do according to the INR results. Therefore, it is possible that self-testing may be less difficult for patients than self-management. Patients who perform only self-testing need more time and ways to contact clinicians, and clinicians or nurses need more time to interpret INR results and to make decisions, compared with self-management. Therefore, self-testing may be more expensive than self-management.

A meta-analysis by Heneghan and colleagues conducted subgroup analysis of RCTs on PST/PSM for oral anticoagulation therapy and concluded that patients capable of self-management "have fewer thromboembolic events and lower mortality than those who self-monitor alone".[75] However, two RCTs that directly compared PST and PSM found no significant difference in AC.[30,39] We also conducted subgroup analyses of RCTs and found no significant differences in thromboembolic and death events between the PST and PSM, although trials of PST reported a greater reduction in major bleeding events than trials of PSM (*Figure 6*). The results from subgroup analyses should be considered exploratory and interpreted with great caution.

Cost-effectiveness of patient self-monitoring

Seven studies that evaluated the cost-effectiveness of PSM of AC were identified and assessed in this report. However, only one UK study provided relevant data[52] and indicated that PSM is more expensive in terms of cost to the NHS than is current routine care in the UK (£417 versus £122 per patient-year). The study concluded that using a cost-effectiveness threshold of £30,000 per QALY gained, PSM does not appear to be cost-effective.

A new Markov model was developed to perform further cost-effectiveness analysis for this report.

The results of the modelling found that the incremental cost per QALY gained by PSM is £122,365 over 5 years and £63,655 over 10 years. The probability that PSM is cost-effective (up to £30,000/QALY) is 44% over a 10-year period. Therefore, self-monitoring by general patients of oral anticoagulation therapy is unlikely to be more cost-effective than current usual care in the UK. However, for patients whose anticoagulation therapy could not be satisfactorily controlled by the usual care, self-monitoring may be a cost-effective alternative.

It was estimated that wide adoption of PSM of anticoagulation therapy would cost the NHS an additional £8.0–14.3 million per year.

Conclusions

For selected and successfully trained patients, self-monitoring is effective and safe for long-term oral anticoagulation therapy. In general, PSM is unlikely to be more cost-effective than the current high-quality care provided by specialised anticoagulation clinics in the UK. Self-monitoring may enhance the QoL for some patients who are frequently away from home, who are in employment or education, or those who find it difficult to travel to clinics.

Recommendations for further research

Published values of percentage of time or percentage of tests within the target range indicate that there is scope for further improvement of PSM beyond the performance currently achieved. Different dose algorithms and other procedures that could lead to alternative dosing regimes represent an element of PSM that might be profitably researched with the aim of improving performance.

Limited evidence indicated that patient education and training may improve clinical outcomes of anticoagulation therapy, even without performing PSM of AC. There is a lack of evidence about whether patient education alone is sufficient to reduce the risk of bleeding, thromboembolic complications and deaths in patients who receive long-term anticoagulation therapy. The clinical effectiveness and cost-effectiveness of patient education and training in long-term oral anticoagulation therapy need to be investigated.

Only one economic analysis of PSM of long-term anticoagulation therapy was identified that was directly relevant to the UK. Therefore, further cost-effectiveness research is required to build on the findings of this study, particularly taking into account the costs of PSM outside trial conditions. In addition, further consideration should be given to the measurement of the less tangible benefits of self-management, which the broad health measures used to calculate QALYs may not be able to capture.

Warfarin allows many children with heart disease to survive into healthy adulthood, but this brings families another set of problems. In addition to missing time off school to attend clinics, it makes timing of holidays difficult. For parents this may involve time away from work, with long clinic waits, often with other siblings. The PSM model, where children or carers have knowledge of changes in lifestyle and concurrent medication, may also be effective in reducing risks of adverse events. Although a few studies have been conducted on PSM of anticoagulation therapy in children,[76,77] there is a lack of RCTs and, as far as we are aware, no clinical trials are being undertaken in this area. Future research needs to evaluate the effectiveness of PSM in children.

PSM of anticoagulation therapy arose from development of NPT devices sufficiently user-friendly and compact that some patients satisfactorily control their anticoagulation. Further progress in the design, conception and ease of use of devices may broaden the spectrum of patients able to undertake PSM and provide alternatives for this model of management. It is important that potential future developments are subjected to appropriate quality control and that effectiveness is investigated with well-designed RCTs with sufficient follow-up to capture key outcomes of complication events (thromboembolism, bleeds) and mortality.

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Contribution of authors

Martin Connock (Systematic Reviewer) contributed to background and effectiveness sections and assembled the report. Claire Stevens (Medicines Information Scientist) identified relevant trials and extracted data from included trials and contributed to the background and effectiveness sections. Anne Fry-Smith (Information Specialist) designed the search strategies and searched electronic literature databases. Sue Jowett (Research Fellow) gave general project support, provided data and advice for the calculation of NHS cost, and contributed to the interpretation of evidence (primarily economic evaluation). David Fitzmaurice (Professor of Primary Care Research) provided clinical advice. David Moore (Senior Research Analyst) coordinated the review. Fujian Song (Reader) identified relevant trials, extracted data from included trials, conducted statistical analyses and wrote the economics section. FS, SJ, DF and AFS developed the protocol. All authors contributed to the editing of the report.

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Appendix 1

Search strategies

Clinical effectiveness

Database: MEDLINE (Ovid) – 1966 to September week 1 2005

1 exp anticoagulants/ (121654)
2 (warfin or coumadin or coumarin).mp. (4156)
3 (oral adj anticoagul$).mp. (3709)
4 or/1-3 (123832)
5 self administration/ (5527)
6 drug administration schedule/ (52694)
7 international normalized ratio/ (1240)
8 near patient test$.mp. (169)
9 point of care systems/ (2301)
10 self test$.mp. (303)
11 self manage$.mp. (2321)
12 drug monitoring/ (6673)
13 primary health care/ (29533)
14 (primary care or general practice or general practitioner$).mp. (63897)
15 or/5-14 (148475)
16 4 and 15 (2946)

Database: EMBASE (Ovid) – 1980 to 2005 week 38

1 exp Anticoagulant Agent/ (201600)
2 (warfarin or coumarin or coumadin).mp. (30911)
3 oral anticoagul$.mp. (3596)
4 anticoagulation/ (11177)
5 or/1-4 (209755)
6 drug self administration/ (1788)
7 drug administration/ (25749)
8 international normalized ratio/ (332)
9 drug monitoring/ (23589)
10 self care/ (4004)
11 self medication/ (3971)
12 primary medical care/ (20353)
13 primary health care/ (8027)
14 health center/ (4915)
15 general practice/ (17599)
16 general practitioner/ (21224)
17 (near adj patient test$).mp. (165)
18 (primary care or primary health care or general practice or genral practitioner).mp. (49917)
19 (self test$ or self manage$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2185)
20 or/6-19 (132093)
21 5 and 20 (5690)
22 (systematic adj review$).mp. (11139)
23 meta-analysis.mp. (26284)
24 or/22-23 (33276)
25 21 and 24 (130)
26 randomized controlled trial/ (98438)
27 exp clinical trial/ (358520)
28 exp controlled study/ (2025793)
29 double blind procedure/ (56986)
30 randomization/ (16068)
31 placebo/ (80156)
32 single blind procedure/ (5483)
33 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (2063435)
34 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (96238)
35 (placebo$ or matched communities or matched schools or matched populations).mp. (125615)
36 (comparison group$ or control group$).mp. (124109)
37 (clinical trial$ or random$).mp. (580758)
38 (quasiexperimental or quasi experimental or pseudo experimental).mp. (1197)
39 matched pairs.mp. (1747)
40 or/26-39 (2424859)
41 21 and 40 (1891)

Database CINAHL (Ovid) – 1982 to September week 2 2005

1 exp anticoagulants/ (3628)
2 (warfin or coumadin or coumarin).mp. (72)
3 (oral adj anticoagul$).mp. (216)
4 or/1-3 (3664)
5 self administration/ (864)
6 drug administration schedule/ (759)
7 international normalized ratio/ (229)
8 near patient test$.mp. (29)
9 point of care systems/ (1393)
10 self test$.mp. (10718)
11 self manage$.mp. (2323)
12 drug monitoring/ (1416)
13 primary health care/ (10117)
14 (primary care or general practice or general practitioner$).mp. (19239)
15 or/5-14 (35640)
16 4 and 15 (450)

Database: Cochrane Library (CENTRAL) 2005 Issue 3

#11.(self next manage*)669
#12.DRUG MONITORING single term (MeSH)579
#13.((primary next care) or (primary next health next care) or (general next practice) or (general next practitioner*))8784
#14.(#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)22096

Ongoing studies

National Research Register 2005 Issue 3

The same strategy as for Cochrane Library (CENTRAL) was used.

Economic evaluation

Database: Cochrane Library (NHS EED, DARE and HTA database) (Wiley Internet) 2005 Issue 3

The same strategy as for Cochrane Library (CENTRAL) was used.

MEDLINE (Ovid) 1966 – September week 1 2005

1 exp anticoagulants/ (121654)
2 (warfin or coumadin or coumarin).mp. (4156)
3 (oral adj anticoagul$).mp. (3709)
4 or/1-3 (123832)
5 self administration/ (5527)
6 drug administration schedule/ (52694)
7 international normalized ratio/ (1240)
8 near patient test$.mp. (169)
9 point of care systems/ (2301)
10 self test$.mp. (303)
11 self manage$.mp. (2321)
12 drug monitoring/ (6673)
13 primary health care/ (29533)
14 (primary care or general practice or general practitioner$).mp. (63897)
15 or/5-14 (148475)
16 4 and 15 (2946)
17 economics/ (23997)
18 exp "costs and cost analysis"/ (117766)
19 cost of illness/ (7311)
20 exp health care costs/ (24869)
21 economic value of life/ (4528)
22 exp economics medical/ (9687)
23 exp economics hospital/ (13492)
24 economics pharmaceutical/ (1515)
25 exp "fees and charges"/ (21806)
26 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (210892)
27 (expenditure$ not energy).tw. (9166)
28 (value adj1 money).tw. (385)
29 budget$.tw. (9421)
30 or/17-29 (315368)
31 16 and 30 (174)
32 quality of life/ (48428)
33 life style/ (22136)
34 health status/ (27294)
35 health status indicators/ (9472)
36 value of life/ (4528)
37 quality of wellbeing.tw. (2)
38 or/32-37 (101728)
39 16 and 38 (29)
40 decision support techniques/ (5211)
41 markov.mp. (4333)
42 exp models economic/ (4361)
43 decision analysis.mp. (2069)
44 cost benefit analysis/ (35934)
45 or/40-44 (47242)
46 16 and 45 (49)
47 31 or 39 or 46 (205)
48 from 47 keep 1-205 (205)

HEED September 2005

Anticoagulants OR anticoagulant OR warfarin OR coumadin OR coumarin

Appendix 2

Results of subgroup analyses: patient self-monitoring versus usual care for oral anticoagulation therapy

The results are given in *Tables 19–21*.

TABLE 19 *Major bleeding events*

	Point	Lower CI	Upper CI	Interaction *p*-value	Trials	Patients	I2%	*p*-Value
All trials	–0.0039	–0.0154	0.0077		15	4091	0.0	0.80
2 largest trials	0.0051	–0.0136	0.0238	0.16	2	1892	60.3	0.11
Other trials	–0.0116	–0.0259	0.0027		13	2199	0.0	0.54
Self-testing	–0.0349	–0.0667	–0.0031	0.03	6	800	26.8	0.23
Self-managing	0.0034	–0.0086	0.0155		10	3351	0.0	0.88
Control–doctor	–0.0053	–0.0262	0.0155	0.91	5	1971	43.5	0.13
Control–AC clinic	–0.0040	–0.0157	0.0076		8	1873	0.0	0.97
TR difference ⩽ 0.1	–0.0035	–0.0140	0.0070	0.95	9	2164	0.0	0.94
TR difference > 0.1	–0.0043	–0.0258	0.0172		6	1927	23.4	0.26
Trials in the UK	0.0031	–0.0142	0.0203	0.43	5	911	0.0	0.81
Other countries	–0.0058	–0.0199	0.0082		10	3180	0.0	0.59
Allocation concealment	–0.0053	–0.0168	0.0061	0.81	5	1817	0.0	0.93
Unclear/not	–0.0027	–0.0214	0.0160		10	2274	0.0	0.50
Blinded assessor	–0.0197	–0.0388	–0.0006	0.06	3	1227	55.7	0.11
Unclear/not	0.0030	–0.0114	0.0174		12	2864	0.0	0.93
ITT analysis	–0.0138	–0.0280	0.0003	0.11	5	1868	16.6	0.31
Unclear/not	0.0045	–0.0131	0.0222		10	2223	0.0	0.91
Drop-outs ⩽ 30%	–0.0060	–0.0194	0.0075	0.77	7	1317	0.0	0.95
Drop-outs > 30%	–0.0028	–0.0187	0.0130		8	2774	7.1	0.38
Follow-up <12 months	–0.0149	–0.0334	0.0035	0.17	10	1350	0.0	0.47
Follow-up ⩾ 12 months	0.0016	–0.0131	0.0163		5	2741	0.0	0.44
CoaguChek	0.00072	–0.01192	0.01336	0.05	11	3375	0.0	0.89
ProTime	–0.03919	–0.07794	–0.00044		3	514	32.3	0.23
Industry sponsor	–0.0045	–0.0168	0.0078	0.39	9	1667	0.0	0.94
Not industry	–0.0156	–0.0380	0.0068		3	1021	67.0	0.05

TABLE 20 *Thromboembolic events*

	Point	Lower CI	Upper CI	Interaction *p*-value	Trials	Patients	I2%	*p*-Value
All trials	–0.0224	–0.0334	–0.0115		15	4091	26.2	0.17
2 largest trials	–0.0339	–0.0511	–0.0168	0.06	2	1892	0.0	0.38
Other trials	–0.0125	–0.0264	0.0014		13	2199	0.0	0.84
Self-testing	–0.0254	–0.0564	0.0056	0.81	6	800	0.0	0.45
Self-managing	–0.0213	–0.0324	–0.0102		10	3351	38.2	0.10
Control–doctor	–0.0286	–0.0470	–0.0102	0.40	5	1971	0.0	0.73
Control–AC clinic	–0.0190	–0.0319	–0.0061		8	1873	45.2	0.08
TR difference ⩽ 0.1	–0.0182	–0.0298	–0.0066	0.44	9	2164	36.9	0.12
TR difference > 0.1	–0.0271	–0.0463	–0.0080		6	1927	0.0	0.68
Trials in the UK	0.0034	–0.0117	0.0185	0.001	5	911	0.0	0.96
Other countries	–0.0298	–0.0431	–0.0165		10	3180	1.1	0.43
Allocation concealment	–0.0207	–0.0338	–0.0075	0.77	5	1817	67.2	0.02
Unclear/not	–0.0239	–0.0404	–0.0073		10	2274	0.0	0.73
Blinded assessor	–0.0393	–0.0634	–0.0152	0.08	3	1227	0.0	0.41
Unclear/not	–0.0152	–0.0269	–0.0035		12	2864	0.0	0.58
ITT analysis	–0.0276	–0.0447	–0.0106	0.40	5	1868	69.6	0.01
Unclear/not	–0.0181	–0.0321	–0.0040		10	2223	0.0	0.74
Drop-outs ⩽ 30%	–0.0319	–0.0494	–0.0144	0.22	7	1317	0.0	0.64
Drop-outs > 30%	–0.0179	–0.0317	–0.0041		8	2774	34.8	0.15
Follow-up < 12 months	–0.0196	–0.0397	0.0004	0.73	10	1350	0.0	0.82
Follow-up ⩾ 12 months	–0.0238	–0.0368	–0.0109		5	2741	69.0	0.01
CoaguChek	–0.020603	–0.031714	–0.009492	0.43	11	3375	37.8	0.10
ProTime	–0.039436	–0.08518	0.006308		3	514	0.0	0.90
Industry sponsor	–0.0240	–0.0386	–0.0094	0.46	9	1667	23.0	0.24
Not industry	–0.0133	–0.0374	0.0108		3	1021	49.4	0.14

TABLE 21 *Deaths*

	Point	Lower CI	Upper CI	Interaction *p*-value	Trials	Patients	I2%	*p*-Value
All trials	–0.0170	–0.0287	–0.0053		15	4091	12.6	0.31
2 largest trials	–0.0265	–0.0438	–0.0092	0.14	2	1892	0.0	0.83
Other trials	–0.0088	–0.0247	0.0071		13	2199	0.0	0.85
Self-testing	–0.0105	–0.0437	0.0228	0.67	6	800	0.0	0.76
Self-managing	–0.0183	–0.0302	–0.0063		10	3351	25.0	0.21
Control–doctor	–0.0216	–0.0407	–0.0025	0.39	5	1971	61.0	0.04
Control–AC clinic	–0.0109	–0.0258	0.0041		8	1873	0.0	0.78
TR difference $\leqslant$ 0.1	–0.0094	–0.0224	0.0037	0.18	9	2164	0.0	0.74
TR difference > 0.1	–0.0256	–0.0456	–0.0055		6	1927	38.5	0.15
Trials in the UK	–0.0098	–0.0337	0.0141	0.51	5	911	5.4	0.38
Other countries	–0.0191	–0.0325	–0.0057		10	3180	30.6	0.16
Allocation concealment	–0.0112	–0.0260	0.0036	0.37	5	1817	0.0	0.54
Unclear/not	–0.0216	–0.0391	–0.0042		10	2274	36.2	0.12
Blinded assessor	–0.0230	–0.0483	0.0022	0.55	3	1227	0.0	0.39
Unclear/not	–0.0144	–0.0272	–0.0017		12	2864	9.4	0.35
ITT analysis	–0.0164	–0.0357	0.0030	0.92	5	1868	0.0	0.59
Unclear/not	–0.0176	–0.0317	–0.0034		10	2223	33.9	0.14
Drop-outs $\leqslant$ 30%	–0.0151	–0.0308	0.0007	0.80	7	1317	0.0	0.71
Drop-outs > 30%	–0.0180	–0.0336	–0.0024		8	2774	43.3	0.09
Follow-up < 12 months	–0.0077	–0.0287	0.0134	0.28	10	1350	0.0	0.95
Follow-up $\geqslant$ 12 months	–0.0216	–0.0357	–0.0075		5	2741	35.6	0.18
CoaguChek	–0.017601	–0.02957	–0.005632	0.93	11	3375	13.1	0.32
ProTime	–0.020021	–0.069524	0.029481		3	514	15.6	0.31
Industry sponsor	–0.0149	–0.0286	–0.0012	0.88	9	1667	19.5	0.27
Not industry	–0.0123	–0.0430	0.0184		3	1021	0.0	0.67

Appendix 3

Non-randomised studies: major study characteristics

Study, year, country	Study design, duration	Sample size, *N*	Indication intervention PSM, PST, PMA	Use of AC Mean age (years); % male	Outcomes	Patient selection, [study sponsor], comments
Taborski, 2004[78] and Voller, 2004,[79a] Germany	Prospective cohort 1.5 months; (subgroup 6 months)	76	Mixed PSM	New AC 57.4; 71%	(a) % INR values in range (b) Agreement PST vs ref. lab. results (c) Pre- and post-training knowledge test (MCQ)	Selection method not described [Industry] A 'new' training programme was implemented Very large drop-out/missing values in the subgroup study
Kulinna, 1999,[80] Germany	Prospective cohort 6 months	100	Mixed PST	New AC 57; 68%	(a) % INR values in range (b) QoL questionnaire at 6 months (18 items on 6-point VAS for retrospective assessment of change from start)	Selection method not described [Funding not reported]
Heidinger, 2000,[81] Germany	Retrospective survey Mean 13.5 months	1375 (753 AF, 622 DVT)	AF and DVT PSM	>3 months AC 57; 64.5%	(a) % INR values in range (b) Major bleeding and major embolic events (c) Minor bleeding and minor embolic events (d) Treatment for complications (e) Deaths	Selection method not described [ASMA; industry?] Event rates ascertained through PQ Target INR only based on results for 430 out of 1375 patients No fatal events (how detected from patient questionnaire?)
Sawicki, 2003,[82] Germany	Prospective cohort 5 years	178	AF and MHV PSM	Mean 2 years AC 54.4; 69%	(a) % INR values and time in range (b) Major bleeding and embolic events (c) Minor bleeding or embolic events (d) Hospital admissions, inpatient days (e) Deaths (f) QoL/satisfaction PQ; 32 items, 5 domains	Selection described in previous RCT 178 enrolled, 150 evaluated [Industry] Extension of industry-sponsored RCT Described as prospective ascertainment mainly by interview at end of 5 years follow-up
Bernardo, 1995,[83] Germany	Retrospective analysis by PQ 1.9 years[b]	600 trained, 216 evaluated	MHV (most) PSM	Long-term AC 50.9; 58.5%	(a) % INR values in range, (range = 1.5 INR) (b) Severe and mild bleeding and embolic complications in a randomly selected subsample (c) Comparisons with a PMA sample (d) PQ self-reported complications	Inclusion criteria described but selection method not reported [Funding not reported] Of 600 only 49.5% chose to adopt PSM

continued

Study, year, country	Study design, duration	Sample size, *N*	Indication intervention PSM, PST, PMA	Use of AC Mean age (years); % male	Outcomes	Patient selection, [study sponsor], comments
Morsdorf, 1999,[84] Germany	Prospective cohort Not reported	50	Mixed PSM	50% new AC 57.1; 72%	(a) Agreement of PST INR results with those from ref. lab. (b) Amount of training required to become 'qualified self manager' (c) Manpower costs	Selection reported in previous RCT [Funding not reported] Study found a mean of 12 hours of training required for competent 'PSM' Training was for PSM but the results reported refer to PST at end of training (no patient-determined dose adjustment)
Koertke, 2005,[85] Germany	Prospective cohort [ESCAT II] Mean 1.3 years	1818 (910 low INR range, 908 usual INR range)	MHV PSM	New AC likely 59.7; % not reported	(a) % INR values in range (b) Grade III bleeding and embolic complications (c) Kaplan–Meier analysis of appearance of grade III complications (d) Kaplan–Meier analysis of survival	Selection method not described. Randomisation by 'random masters list' [Funding not reported] 1428 and 1420 patient-years for low INR and conventional INR, respectively. Called an 'extended analysis' of data in an earlier paper,[86] but is a reanalysis (no explanation for the differences in the results)
OAMSG, 2001,[87] USA	Prospective cohort 1.5 months	82	Mixed PST at home PST at clinic	AC use not reported 55; 61%	(a) Comparison of PST–home and PST–clinic test results vs ref. lab. test results (no Bland–Altman plot) (b) PQ on ease of use. 10-point VAS (1 = very easy, 10 = very difficult) (c) Preference 'finger stick' vs venous sampling	Selected volunteers who successfully conducted test without difficulty [Industry in part] Trained and tested for competence before entry so ease of use result not surprising Total number of components in questionnaire unclear
OAMSG, 2001,[88] USA	Prospective cohort Duration unclear	177	Mixed PST at clinic	Previous AC 45; 45%	(a) Agreement between tests. PST at clinic vs physician at clinic vs ref. lab. vs non-AC controls (Bland–Altman plots) (b) PQ on patient satisfaction with PST	Selection method not clearly described [Industry in part] Population trained and tested for competence Structure and administration of PQ unclear
Anderson, 1993,[89] Canada	Prospective cohort 6–24 months	40	DVT (90%) PST	Previous AC 25–74; 47.5%	(a) Agreement PST with ref. lab. INR (b) PQ on complications and AC preferences	Selection from 49 consecutive long-term AC patients; 6 unsuitable, suitability criteria not specified [Industry] PQ structure not described

continued

Study, year, country	Study design, duration	Sample size, *N*	Indication intervention PSM, PST, PMA	Use of AC Mean age (years); % male	Outcomes	Patient selection, [study sponsor], comments
Massicotte, 1995,[77] Canada	Prospective cohort Mean 13 months	23 Home 40 Clinic	Mixed PST at home or NPT device by HCP at clinic	Previous AC >4 weeks Home: median 3; 57% Clinic: median 14; 53%	(a) % INR values in range (b) Agreement between subset of home PST and clinic HCP values and ref. lab. values (c) Complications (d) Patient/family satisfaction	Home PST patients selected for special reasons (e.g. geographical isolation) Clinic patients were consecutive, but did not practice PST [Public funding] Structure of questionnaire or interview not described; unclear if both home testing and clinic testing were interrogated about satisfaction
Sunderji, 1999,[90] Canada	Prospective cohort 3 months	10	Mixed PST then PSM	⩾1 month previous stable AC 55; 80%	(a) Agreement between subset of PST INR values and lab.-determined values (b) Patient satisfaction with PSM (PQ: 5 domains)	Patients selected by HCPs on basis of likely competence and compliance [Industry] Generalisability probably limited, highly motivated, competent population selected. 8 of 10 chose PST. PST for first 2 months, PSM third month
Christensen, 2003,[91] Denmark	Prospective cohort Mean 2.1 years	94	MHV PSM	Previous AC use not reported 47.6; 65%	(a) % time INR in range (b) Major bleeding and embolic complications	All patients enrolled for PSM from University Hospital, selected for competence and likely compliance [Funding not reported] This study includes the patients from previous studies[17,45,92,93] With 197 patient-years of observation it is surprising no deaths were reported. No drop-outs were reported
Christensen, 2004,[76] Denmark	Case series Mean 3.6 years	22	Cardiac surgery for congenital heart disease PSM	Previous AC use not reported Children 10.6; 60%	(a) % time INR in range (b) Major bleeding and embolic complications (c) Deaths (d) Satisfaction with treatment	Method of selection of cases not described, inclusion criteria listed [Public funding] Method for elicitation of patient satisfaction not described

continued

Study, year, country	Study design, duration	Sample size, *N*	Indication intervention PSM, PST, PMA	Use of AC Mean age (years); % male	Outcomes	Patient selection, [study sponsor], comments
Murray, 2003,[94] UK	Prospective cohort 26 weeks	23	Mixed Quality control by PSM patients	⩾6 months previous stable AC 63; % NR	PSM patients' performance using 4 lyophilised samples measured with PST coagulometer vs HCP performance with the same samples and same instrument	Patients selected on basis of a good record of compliance and consistent test results [Industry] Quality control investigation of patient testing
Stigendal, 1998,[95] Sweden	Prospective details unclear 3 months	9	Mixed PSM	Not reported	% INR values in range	Selection of patients not reported [Public funding]
Piso, 2002,[50] Austria	Retrospective before–after study 3 years (1 year PSM)	10	MHV (90%) PSM vs PMA	Previous stable AC 52; 70%	% INR values in range (target range >1 INR some patients) and time in range	Ten patients from trial above (Watzke *et al.*,[49] *N* = 102) 'self-selected' by returning to physician control after 1 year of PSM [Funding not reported] Very small, ill-defined sample; results unlikely to be generalisable to UK

DVT, deep vein thrombosis; MCQ, multichoice questionnaire; PMA, physician managed anticoagulation; PQ, patient questionnaire; VAS, visual analogue scale.
[a] Yearly follow-up by questionnaire.
[b] Calculated from 412 patient-years and 216 patients evaluated.

Appendix 4

Studies of economic evaluation of patient self-monitoring of anticoagulation therapy

Study, country, objectives	Methods	Costs	Effectiveness	Conclusions
Taborski, 1999[53] Germany To compare the cost-effectiveness of AC PSM with the conventional AC by family doctors or a specialist	Data collected from patients, and published studies. Insurer's perspective	Total annual costs (DM, year?): PSM: 618.86 Usual care: 289.80 Costs/thromboembolic event Minor: 97.80 Major: 19,777.00 Costs/bleeding event Minor: 53.90 Major: 20,341.00	Thromboembolic events (/100 patient-years): Minor / Major PSM: 5.14 / 2.49 Control: 9.31 / 4.37 Bleeding complications (/100 patient-years): Minor / Major PSM: 4.4 / 1.10 Control: 17.48 / 4.37	Self-testing saves DM 719.02 per patient per year
Lafata, 2000[19] USA To examine the cost-effectiveness of three anticoagulation management approaches: usual care (traditional office setting), AC clinic testing with a capillary monitor and PST	A 5-year Markov model using data from literature, and data from a large health system and when necessary expert opinion. Model structure: AC management → INR in TR → Complications Societal perspective	5-year costs per 100 patients (US$, 1997): Medical care costs: Usual care 419,514 AC clinic 405,560 PST 526,014 Patient and caregiver costs: Usual care 110,223 AC clinic 240,110 PST 96,713 All costs: Usual care 529,737 AC clinic 645,671 PST 622,727	Serious-fatal events per 100 over 5 years: Thromboembolic events: Usual care 13.46 AC clinic 11.79 PST 7.77 Haemorrhagic events: Usual care 17.19 AC clinic 15.16 PST 14.34	All costs per QALY: Usual care vs AC clinic: $232,226 AC clinic vs PST: cost saving AC clinic testing is the most cost-effective alternative to usual care when costs to patients and their caregivers are ignored, and once these costs are included, PST becomes the most clinically effective and cost-effective alternative
Muller, 2001[54] Germany To conduct an economic analysis of coagulation-related complications, bleeding and thromboembolism following heart valve replacement	Stroke incidence over a period of 10 years was estimated based on data from the German Experience with Low Intensity Anticoagulation study. Lifetime costs of a stroke were based on the US data and adapted to German standards. Insurer perspective	10,000 MHV patients over 10 years (DM): Direct cost of strokes: 14.2 and 14.1 million for thromboembolism and bleeding, respectively Total cost of strokes: 26 and 54 million for thromboembolism and bleeding, respectively	It was estimated that PSM led to a 30% reduction in severe complications (data not shown)	Costs per life-year gained: DM 105,000

continued

Study, country, objectives	Methods	Costs	Effectiveness	Conclusions
Samsa, 2002[55] USA To develop an interactive mathematical model (ACME) to clarify best approach to anticoagulation management	The ACME was a series of linked, nested spreadsheets. Input values were estimated based on literature Model structure: AC management → INR in range → complications Medical care perspective	Total care costs per 1000 patient-years (US$): No AC: 0 Physician+: 225,445 AC clinic+: 293,593 PSM+: 465,220 Total event costs: No AC: 4,544,647 Physician+: 3,329,078 AC clinic+: 3,035,767 PSM+: 2,308,117	Time in range (%): No AC: 0 Physician+: 46.83 AC clinic+: 51.68 PSM+: 77.12 Annual bleeding events (early, late) (%): No AC: 0.07, 0.04 Physician+: 1.30, 0.69 AC clinic+: 0.35, 0.18 PSM+: 0.27, 0.14 Annual thromboembolic events (MHV, AF) (%): No AC: 12.50, 6.59 Physician+: 3.83, 2.02 AC clinic+: 4.21, 2.22 PSM+: 2.98, 1.57	The greatest benefit is obtained by moving patients who are not currently receiving anticoagulation therapy on to warfarin. Additional benefits can be obtained by reducing the number of very high and very low INRs and by reducing the tendency for physicians to under-dose
Sola-Morales, 2003[56] Catalonia, Spain To compare cost-effectiveness of 5 possible alternatives: PSM, POC by family doctors, PST, POC at hospital, usual hospital care Note: only brief translation available. Lack of details	A 5-year Markov model using data from literature review Model structure: AC management → complications Insurer's perspective	5-year costs (€, 2002): Usual care: 8997.40 POC-clinic: 3461.50 POC-hospital: 3305.30 PST: 5188.50 PSM: 4469.50 Note: details on unit costs available from Annex 5	Portable coagulometer by either patients, or doctors or hospital (95% CI): Complications: 0.02041 (0 to 0.3171) Major complications: 0.409026 (0 to 0.5) Mortality: 0.001323 (0 to 0.008197) Time in TR: 0.72494 (0.69 to 0.78) Usual care group: Complications: 0.10204 (0 to 0.1585) Major complications: 0.4 (0 to 0.25) Mortality: 0.0056689 (0 to 0.3) Time in TR: 0.62554 (0.53 to 0.77) Continue AC after major complications: 0.183	Since all portable coagulometer strategies are based on the same effectiveness values, they have the same efficacy at 5 years AC control with the portable coagulometer in the hospital setting is the most efficient

continued

Study, country, objectives	Methods	Costs	Effectiveness	Conclusions
Jowett, 2006[52] UK To determine the cost-effectiveness of PSM of anticoagulation therapy compared with routine primary or secondary clinic-based care	Cost–utility analysis alongside an RCT, 12 months, including 617 long-term AC patients Healthcare and societal perspective	PSM mean (n = 326; UK£, 2003) (95% CI): AC costs: 382 (366 to 398) Additional NHS: 35 (17 to 59) Total NHS cost: 417 (394 to 442) Patient costs: 46 (43 to 49) Overall societal: 463 (439 to 489) Routine care (n = 265): AC costs 90 (83 to 97) Additional NHS 32 (15 to 55) Total NHS cost 122 (103 to 144) Patient costs 57 (54 to 61) Overall societal 180 (160 to 203)	QALYs over 12 months (means) (95% CI): Complete case: PSM: 0.739 Control: 0.738 MD: 0.001 (–0.027 to 0.032) Imputed: PSM: 0.721 Control: 0.712 MD: 0.009 (–0.012 to 0.030)	The probability that PSM is cost-effective, at a threshold of £20,000 and £30,000 per QALY gained, is 30% and 46%, respectively With increasing number of patients requiring AC, PSM may relieve pressure on traditional clinic-based care. Furthermore, the cost-effectiveness of this model of care for some subgroups of anticoagulation therapy patients needs to be explored further
Regier, 2006[57] Canada To compare the incremental cost and health benefits of self-management with those of physician management from the perspective of the Canadian healthcare payer over a 5-year period	A 5-year Bayesian Markov model, using data from a trial and published literature Model structure: AC management → INR in range → complications Healthcare payer's perspective	Incremental mean cost (Can$) (95% CI): 5 years: 989 (310 to 1655) 10 years: 599 (–459 to 1677)	Events avoided per 100 patients: 5 years / 10 years Thrombotic 3.5 / 5.67 Bleeding 0.79 / 1.25 Death 0.12 / 4.1	Incremental cost per QALY saved (Can$): 5 years: 14,129 10 years: 2,995 Self-management is a cost-effective strategy for patients receiving long-term oral anticoagulation therapy for AF or MHV replacement

MD, mean difference.

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We look forward to hearing from you.

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