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A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study

FDR Hobbs, DA Fitzmaurice, S Jowett, J Mant, E Murray, S Bryan, J Raftery, M Davies and G Lip

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The research reported in this monograph was commissioned by the HTA Programme as project number 96/22/11. The contractual start date was in June 2000. The draft report began editorial review in August 2004 and was accepted for publication in May 2005. 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

A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study

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Objectives: To determine the most cost-effective method of screening for atrial fibrillation (AF) in the population aged 65 years and over, as well as its prevalence and incidence in this age group. Also to evaluate the relative cost-effectiveness of different methods of recording and interpreting the electrocardiogram (ECG) within a screening programme.
Design: Multicentred randomised controlled trial. Purposefully selected general practices were randomly allocated to 25 intervention practices and 25 control practices.
Setting: Fifty primary care centres across the West Midlands, UK.
Participants: Patients aged 65 years and over.
Interventions: GPs and practice nurses in the intervention practices received education on the importance of AF detection and ECG interpretation. Patients in the intervention practices were randomly allocated to systematic (n = 5000) or opportunistic screening (n = 5000). Prospective identification of pre-existing risk factors for AF within the screened population enabled comparison between targeted screening of people at higher risk of AF and total population screening.
Main outcome measures: AF detection rates in systematically screened and opportunistically screened populations in the intervention practices were compared with AF detection rate in 5000 patients in the control practices. The screening period was 12 months.
Results: Baseline prevalence of AF was 7.2%, with a higher prevalence in males (7.8%) and patients aged 75 years and over (10.3%). The control population demonstrated higher baseline prevalence (7.9%) than either the systematic (6.9%) or opportunistic (6.9%) intervention population. In the control population 47 new cases were detected (incidence 1.04% per year). In the opportunistic arm 243 patients without a baseline diagnosis of AF were found to have an irregular pulse, with 177 having an ECG, yielding 31 new cases (incidence 0.69% per year). A further 44 cases were detected outside the screening programme (overall incidence 1.64% per year). In the systematic arm 2357 patients had an ECG yielding 52 new cases (incidence 1.1% per year). Of these, 31 were detected by targeted screening and a further 21 by total population screening. A further 22 cases were detected outside the screening programme (overall incidence 1.62% per year). In terms of ECG interpretation, computerised decision support software (CDSS) gave a sensitivity of 87.3%, a specificity of 99.1% and a positive predictive value (PPV) of 89.5% compared with the gold standard (cardiologist reporting). GPs and practice nurses performed less well. The only difference in performance between intervention populations and controls was that practice nurses from the control arm performed less well than with intervention practice nurses on interpretation of limb-lead (PPV 38.8% versus 20.8%) and single-lead (PPV 37.7% versus 24.0%) ECGs. The within-trial economic evaluation results showed the lowest incremental cost

to be for the opportunistic arm, with an incremental cost-effectiveness ratio of £337 for each additional case detected compared to the control arm. Opportunistic screening dominated both more intensive screening strategies. Model-based analyses showed small differences in cost and quality-adjusted life-years for different methods and intensities of screening, but annual opportunistic screening resulted in the lowest number of ischaemic strokes and greatest proportion of cases of AF diagnosed. Probabilistic sensitivity results indicated that there was a probability of approximately 60% that screening from the age of 65 years was cost-effective in both men and women.

Conclusions: The results of the study indicated that in terms of a screening programme for atrial fibrillation in patients 65 and over, the only strategy that improved on routine practice was opportunistic screening, model-based analyses indicated that there was a probability of approximately 60% of annual opportunistic screening being cost effective. It is suggested that the following topics are worthy of further investigation: the effect of the implementation of a screening programme for AF on the uptake and maintenance of anticoagulation in patients aged 65 years and over; an evaluation of the role of CDSS in the diagnosis of cardiac arrythmias; the best method for routinely detecting paroxysmal AF; ways of improving healthcare professionals' performance in ECG interpretation; development of a robust economic model to incorporate data on new therapeutic agents for use as thromboprophylactic agents for patients with AF, and an evaluation of the relative risk of stroke for patients with incident as opposed to prevalent AF.

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List of abbreviations

AF	atrial fibrillation
CDSS	computerised decision support software
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
DES	discrete event simulation
df	degrees of freedom
EAFT	European Atrial Fibrillation Trial
EcHoES	Echocardiographic Heart of England Screening
EQ-5D	EuroQol 5 Dimensions
GI	gastrointestinal
GMS	general medical services
ICER	incremental cost-effectiveness ratio
INR	international normalised ratio
IQR	interquartile range
ISM	individual sampling model
ITT	intention-to-treat
MidReC	Midlands Research Practices Consortium
NPV	negative predictive value
NRAF	non-rheumatic atrial fibrillation
OCSP	Oxford Community Stroke Project
OR	odds ratio
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
QSE	quasi-standard error
RCT	randomised controlled trial
RR	relative risk
SAFE	Screening for Atrial Fibrillation in the Elderly
SPAF	Stroke Prevention in Atrial Fibrillation
TIA	transient ischaemic attack
VAS	visual analogue scale

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

Atrial fibrillation (AF) is a major risk factor for stroke. This risk can be reduced through treatment with antithrombotic therapy, with a risk reduction of up to 68% observed with warfarin therapy. Guidelines for treatment of AF recommend ages 65 years and over as an indication for treatment with antithrombotic therapy in the presence of AF. This raises the question of whether screening for AF would be a useful policy, and if so what would be the best method for screening. There are no good data on the prevalence of AF in the UK. One small UK study (four practices, $n = 3001$) demonstrated that systematic nurse-led screening detected more cases than opportunistic case finding; however, most of those cases detected were already diagnosed. Two further single practice-based studies investigated the role of practice nurses in the screening process and whole population screening, but were too small to be meaningful.

Objectives

- To evaluate the incremental cost-effectiveness of targeted, population and opportunistic screening with prompts compared with routine clinical practice.
- To evaluate the relative cost-effectiveness of different methods of recording and interpreting the ECG within a screening programme.
- To identify the prevalence and incidence of AF in patients aged 65 years and over.

Methods

This multicentred randomised controlled trial involved patients aged 65 years and over from 50 primary care centres across the West Midlands. These purposefully selected general practices were randomly allocated to 25 intervention practices and 25 control practices. GPs and practice nurses in the intervention practices received education on the importance of AF detection and ECG interpretation. Patients in the intervention practices were randomly allocated to systematic ($n = 5000$) or opportunistic screening ($n = 5000$). Prospective identification of pre-existing risk factors for AF within the screened population enabled comparison between targeted screening of people at higher risk of AF and total population screening. AF detection rates in systematically screened and opportunistically screened populations in the intervention practices were compared with AF detection rate in 5000 patients in the control practices. The screening period was 12 months.

Results

The total number of patients included in each arm was: control 4936, opportunistic screening 4933 and systematic screening 4933. Baseline prevalence of AF was 7.2%, with a higher prevalence in males (7.8%) and patients aged 75 years and over (10.3%). The control population demonstrated higher baseline prevalence (7.9%) than either the systematic (6.9%) or opportunistic (6.9%) intervention population. In the control population 47 new cases were detected (incidence 1.04% per year). In the opportunistic arm 243 patients without a baseline diagnosis of AF were found to have an irregular pulse, with 177 having an ECG, yielding 31 new cases (incidence 0.69% per year). A further 44 cases were detected outside the screening programme (overall incidence 1.64% per year). In the systematic arm 2357 patients had an ECG yielding 52 new cases (incidence 1.1% per year). Of these, 31 were detected by targeted screening and a further 21 by total population screening. A further 22 cases were detected outside the screening programme (overall incidence 1.62% per year).

In terms of ECG interpretation, computerised decision support software (CDSS) gave a sensitivity of 87.3%, a specificity of 99.1% and a positive predictive value (PPV) of 89.5% compared with the gold standard (cardiologist reporting). GPs and practice nurses performed less well. The only difference in performance between intervention populations and controls was that practice nurses from the control arm performed less well than intervention practice nurses on interpretation of limb-lead (PPV 38.8% versus 20.8%) and single-lead (PPV 37.7% versus 24.0%) ECGs.

The within-trial economic evaluation results showed the lowest incremental cost to be for the opportunistic arm, with an incremental cost-effectiveness ratio of £337 for each additional case detected compared to the control arm. Opportunistic screening dominated both more intensive screening strategies. Model-based analyses showed small differences in cost and quality-adjusted life-years for different methods and intensities of screening, but annual opportunistic screening resulted in the lowest number of ischaemic strokes and greatest proportion of cases of AF diagnosed. Probabilistic sensitivity results indicated that there was a probability of approximately 60% that screening from the age of 65 was cost-effective in both men and women.

Conclusions

The prevalence of AF in this population was found to be 7.2%. The incidence ranged from 1.04 to 1.64% per annum. Within the trial, in terms of a screening programme, the only strategy that improved on routine practice was opportunistic screening, at a cost of £337 per additional case detected. Model-based analyses indicated that there was a probability of approximately 60% of annual opportunistic screening being cost effective. Use of CDSS may be considered for analysis of ECGs for detection of AF.

Recommendations for research

It is suggested that the following topics are worthy of further investigation.

- How does the implementation of a screening programme for AF influence the uptake and maintenance of anticoagulation in patients aged 65 years and over?
- An evaluation of the role of CDSS in the diagnosis of cardiac arrythmias.
- What is the best method for routinely detecting paroxysmal AF?
- How can healthcare professionals' performance in ECG interpretation be best improved?
- The development of a robust economic model to incorporate data on new therapeutic agents for use as thromboprophylactic agents for patients with AF.
- An evaluation of the relative risk of stroke for patients with incident as opposed to prevalent AF.

Chapter 1
Introduction

The association between mitral valve disease, atrial fibrillation (AF) and the incidence of embolic stroke is well known. The incidence of systemic embolism (including embolic stroke) is seven times greater in patients with mitral valve disease and AF.[1] Despite a lack of randomised controlled trials (RCTs), the case for oral anticoagulation prophylaxis in patients with these indications is well established.[2,3] The Framingham Study, however, identified AF as an independent risk factor for cerebrovascular accidents, even in the absence of mitral valve disease.[4] AF without mitral valve disease was originally termed lone AF,[5] but is now referred to as non-rheumatic atrial fibrillation (NRAF). Lone AF is now defined in terms of echocardiographic as well as clinical findings. The relative risk for stroke associated with NRAF must be of primary consideration, given that oral anticoagulation carries its own risks. The Whitehall study[6] and the British Heart Study[7] confirmed the increased risk of stroke associated with NRAF.[8]

Comparison of results between studies is difficult owing to differing rates of follow-up, outcome measures and definitions of stroke. It is clear, however, that NRAF represents an independent risk factor for stroke. Thrombotic risk is increased with age, hypertension, diabetes and previous history of embolic event, but not with duration of NRAF.

There have been several attempts to define the community prevalence of NRAF in the UK. Meta-analysis of four community-based studies reveals some consistency of findings between investigations even in different countries.[4,9–12] The prevalence of AF increases with age, from 2.3% in those aged 40 years or over, to 6% in those 60 or over, to 10% in those over 80.[9] Overall UK community prevalence has been estimated at 0.89%.[9] The prevalence is higher in men at all ages, although because of unequal death rates, the overall number of patients with AF is approximately equal between the genders. In overall terms, approximately 50% of patients with AF are aged 75 or over, and over half of these are women. The elderly remain the most controversial with regard to oral anticoagulant therapy.[9]

Several RCTs have attempted to investigate the role of anticoagulation in stroke prevention in NRAF. Eight randomised studies were identified from a MEDLINE search using several search strategies.[13–20] These studies have informed the debate over the selection of patients for anticoagulation, the relative merits of antiplatelets versus anticoagulation, and risk stratification for patients with AF with and without other risk factors for stroke.

These studies were all based in secondary care and caution is needed in interpreting the data for primary-care patients, particularly given the highly selected populations chosen for investigation.[21] Despite excluding up to 97% of potentially eligible patients,[14] there remained a large percentage of patient withdrawals in all trials. The highest withdrawal rate occurred in the study that used a population most similar to that found in UK primary care.[13] There are problems in interpreting the results of these studies, as different levels of anticoagulant intensity were used, actual levels of intensity achieved were either not stated or not subject to direct comparison [using prothrombin ratios rather than international normalised ratio (INR)], and different doses of antiplatelet therapy were used. Other methodological difficulties arise if it is considered that the risk of haemorrhagic side-effects is increased on initiation of therapy, with thrombotic side-effects artefactually low, owing to survival bias. Thus, those patients with NRAF who had already undergone a thrombotic episode such as stroke would be excluded from these studies.

It is clear that there are patients with AF who would benefit from treatment with oral anticoagulation, patients who would benefit from antiplatelet therapy and patients in whom no therapy would be the best option. Meta-analysis of the five primary prevention studies[13–16,18] was undertaken by the Atrial Fibrillation Investigators, the authors of these studies.[22] Notwithstanding concerns regarding the selection of patients for these studies, it is clear that there are different risk factors that influence the therapeutic decision. The five studies cover 1889 patient-years for those receiving warfarin and 1802 in the control group. For the aspirin–placebo comparison there were

1132 patient-years receiving aspirin and 1133 receiving placebo. The primary end-points were ischaemic stroke and major haemorrhage, as assessed by each study.

Patients within the control groups who gave no history of transient ischaemic attack (TIA) or stroke, hypertension or congestive heart failure, diabetes, angina or myocardial infarction had an annual incidence of stroke of 1.5%. Warfarin was found to be consistently effective for the prevention of ischaemic stroke with a reduction in the incidence of all strokes of 68% [95% confidence interval (CI) 50 to 79%], representing an absolute annual reduction of 3.1% ($p < 0.001$). This risk reduction has to be viewed in the light of a reported low incidence of side-effects, particularly haemorrhagic stroke, which may reflect selection bias. The absolute reduction in risk may have been underestimated as the analysis was performed on an intention-to-treat (ITT) basis, when in fact eight of the 27 patients in the warfarin group who had a stroke were not receiving warfarin at the time. Warfarin decreased the rate of death by 33% (95 CI 9 to 51%, $p = 0.10$) and the rate of the combined outcome of stroke, systemic embolism or death by 48% (95% CI 34 to 60%, $p < 0.001$). These results do not take into account any quality of life issues, particularly with regard to individual disutility of warfarin monitoring, which may have a bearing on an individual patient's decision to accept anticoagulant treatment.[23]

Four studies randomised patients to receive aspirin.[13,14,17,19] The Danish Atrial Fibrillation, Aspirin and Anticoagulation (AFASAK) trial,[13] using a dose of 75 mg per day, showed a statistically non-significant reduction in stroke rate compared with placebo. The Stroke Prevention in Atrial Fibrillation (SPAF) study,[14] however, showed a reduction of 44% (95% CI 7 to 66%) in the incidence of stroke at a dose of 325 mg per day. Meta-analysis of these studies with the SPAF II study[19] confirmed that anticoagulation is 50% more effective than aspirin therapy for the prevention of ischaemic stroke in patients with AF. Furthermore, the beneficial effects of aspirin do not appear to be dose related.[24]

The European Atrial Fibrillation Trial (EAFT)[17] was a secondary prevention study and used aspirin at a dose of 300 mg per day compared with warfarin or placebo. No statistically significant reduction in thromboembolic disease was observed in the aspirin-treated group compared with placebo, with warfarin achieving statistically significant improvement. Treatment with aspirin or other platelet inhibitors may have benefits in terms of safety, cost and convenience (no need for regular blood tests), but from the current evidence aspirin alone is not adequate for stroke prevention in patients with AF, compared with warfarin.

Even in combination with warfarin, aspirin has little value in the prevention of stroke for patients with AF.[25] In this study, 1044 patients with AF and at least one other risk factor for thromboembolic disease were randomised to receive either warfarin to achieve a target INR of 2.0–3.0 or a fixed dose of warfarin to achieve an INR of 1.2–1.5 plus a fixed dose (325 mg) of aspirin. The study had to be discontinued after a mean follow-up period of 1.1 years because of the increased incidence of primary events (ischaemic stroke and systemic embolism) in patients given combination therapy ($p < 0.0001$). Furthermore, cost-effectiveness analysis using US data supports the view that warfarin is to be preferred to aspirin or no treatment in terms of quality-adjusted life-years (QALYs) for all patients with NRAF, although for patients under 65 with no other risk factors there is minimal benefit from warfarin compared with no therapy, because of the low underlying risk of stroke. Treatment decisions would ultimately depend on the patients' perception of the disutility associated with taking warfarin.[26]

This study was commissioned to identify the most cost-effective method to identify AF in a community population aged 65 years and over. The rationale for this was that patients identified as having AF through this process are by definition at high risk of having a stroke by virtue of their age. In a sense, this is only half the process required as cost-effectiveness of an overall screening programme would be dependent on treatment; however, this project was restricted by the funding body to simply the case identification side of the problem.

The above notwithstanding, screening for AF in the elderly fulfils many of the Wilson–Jungner criteria for a screening programme.[27] It is a common and important condition that may be diagnosed by means of a simple, low-cost and acceptable test, and the risk of serious sequelae such as stroke can be dramatically reduced by treatment.

A MEDLINE search using a broad range of search strategies identified four relevant previous studies,

with a further modelling paper identified by contacting experts in the field. These are summarised below.

As part of a population survey of elderly people, two methods of detecting patients with AF or flutter were examined.[28] These were identification of patients taking digoxin and pulse palpation by a trained nurse. Although described as a general practice-based study, this was outside routine practice, with patients merely identified from practice lists, and really constituted a public health intervention. Of a sample of 1235 patients aged 65 years and over, recruited from nine practices in Northumberland, 916 (74%) attended a central clinic for a screening limb-lead ECG. No data were given on ECG interpretation; however, the sensitivity of pulse palpation was stated as over 90% with a specificity of 71%. This was not improved by including the data for digoxin searching. The conclusion was that controlled trials of the effect of screening on clinical outcomes were required.

The earliest reported primary care-based screening study for AF was based in a single, four-physician practice.[29] Patients were identified from a computerised database. From a practice population of 7526, 1422 (18.9%) were identified as being aged 65 years or over. All of these patients were sent a written invitation to attend the surgery for a 12-lead ECG, with written and telephone reminders for non-responders. ECG interpretation was undertaken by a hospital cardiologist. Patients with AF or other significant abnormalities (e.g. heart block) were asked to attend the hospital for further investigation. This study was therefore looking at a population-based approach while also assessing the eligibility of patients identified for oral anticoagulation therapy. A total of 1207 (85%) patients had an ECG, with 65 cases identified (5.4% of those screened, 4.6% of those invited). Only five (7.7%) of these cases, however, were previously undiagnosed, giving an approximate incidence of 3.5 cases per 1000 patients (aged 65 years and over) per annum. Of these 65, 56 underwent further cardiological investigation, including cross-sectional and Doppler echocardiography. A wide range of both clinical and echocardiographic co-morbidities was found; however, it is not clear from the data presented how these were distributed, and the proportion of patients without, particularly echocardiographic, morbidities is also unclear. Only 12 (21%) patients were taking warfarin before the screening process, although 32/44 (73%) of those not receiving warfarin were willing to take it following discussion with a physician. The conclusion of the study is that routine echocardiography is not worthwhile in these patients as the decision to anticoagulate or not can be made on clinical grounds alone (predominantly age in this population), while the low incidence rate mitigates against the routine introduction of ECG screening. The caveat to these conclusions was that AF can be a disease of insidious onset and prospective studies were required to establish the need for a screening programme. This study therefore questions the value of a screening programme while recognising the potential for such a scheme and the limitations of scale of the study undertaken.

A further single practice-based study investigated the use of pulse-taking in combination with either 12-lead or limb-lead ECG recording to improve the efficiency of practice-based screening for AF.[30] Patients aged 65 years or over were identified by searching computerised records using READ codes for AF and digoxin prescription. An equal number of patients aged 65 years and over, without either code in their computer records, was sampled. All patients were invited to attend the surgery by appointment (presumably by post). All attending patients were seen by a nurse blind to their medical history who palpated the pulse and recorded the result as either regular or irregular. Limb-lead (or bipolar) and 12-lead ECGs were then performed. Two further nurses reviewed a random sample of patients. At a later date these ECGs were interpreted independently by one GP and one nurse, while all 12-lead ECGs were interpreted by a cardiologist. Different combinations of pulse palpation and ECG interpretation by nurses and GP were analysed to determine the most efficient method of screening. Of 154 patients invited, 86 (56%) attended. Of these, 26 (30%) had AF, according to the cardiologist's interpretation of the 12-lead ECG. Sensitivity for the various methods of diagnosis, for example nurse pulse-taking, and GP 12-lead ECG interpretation, ranged from 92 to 100%, and specificity ranged from 76 to 100%. Looking at combining strategies, for example inexperienced nurse pulse-taking combined with GP interpretation of limb-lead ECG, demonstrated sensitivities of 85–100% and specificities of 95–100%. The optimum strategy appeared to be an experienced nurse undertaking pulse palpation combined with a GP interpreting a 12-lead ECG (100% sensitivity, 98% specificity). This was calculated to cost 60 pence. These data suggested that pulse palpation to exclude patients without

irregular pulses, combined with a 12-lead ECG interpreted by a GP, was more efficient than screening all patients with a 12-lead ECG. It was acknowledged, however, that selection bias and participation rates would need to be considered in judging overall usefulness. It was also felt that the possibility of using limb-lead ECGs should be considered as the differences in sensitivity and specificity were altered only by the misclassification of one case.

Building on the findings of these single practice-based studies, a further UK study has compared systematic nurse-led screening with prompted opportunistic case finding for AF in primary care.[31] This small study (four practices, $n = 3001$) recruited practices from the Medical Research Council (MRC) general practice framework, each selected from one quartile after ranking all framework practices according to the small area standardised mortality ratio of the geographical area served. In total, 7493 patients aged between 65 and 100 years were identified. Approximately 750 patients from each general practice list were randomised to receive an invitation to either a nurse-led systematic screening appointment, or opportunistic screening prompted by a reminder flag in their medical records. Within a screening appointment the nurse examined the radial pulse for a minimum of 20 seconds, to determine irregularity. Following pulse assessment a lead rhythm strip was obtained and read centrally by an academic GP. Opportunistic patients entered the screening appointment if their pulse was found to be irregular by either a GP or practice nurse, over a 6-month period through the flagging system. Within the systematic screening arm, 1099 out of 1499 (73.3%) patients underwent pulse palpation, of whom 67 were found to have AF. Within the opportunistic arm, 439 out of 1502 (29.2%) underwent pulse palpation, of whom 19 were found to have AF. The number needed to screen to detect one additional patient with AF was 31; however, only 12 new cases were found in the systematic arm, with seven in the opportunistic arm. Among systematically screened patients, nurses were able to achieve high sensitivity (91%) using the threshold 'any irregularity' and high specificity (98%) using the threshold 'continuously irregular'.

In a sense this study was not formally screening in that most of the cases detected were already diagnosed. No data were provided on the accuracy or otherwise of AF as a recorded diagnosis, for example how many patients with a diagnosis of AF were found to be in sinus rhythm in the study. Based on these data it was concluded that if systematic screening were introduced to detect only cases that had previously been undiagnosed, the number needed to screen would have been 91, with a minimum cost per case detected of £550.

A Japanese study considered the cost-effectiveness of community-based screening in Japan using a decision modelling approach alone.[32] A Markov model was used to investigate an annual ECG screening programme and an annual pulse-taking programme in a hypothetical population aged 65 followed until they were 85 years old. Results showed both types of annual screening programme to be more costly and marginally more effective than no screening. Incremental cost-effectiveness ratios (ICERs) were approximately US$8000 per QALY in men and US$10,000 in women (2001 prices), and the authors concluded that in the context of conventional cost-effectiveness criteria, screening was favourable.

Five per cent of total NHS expenditure can be attributed to stroke, and there would be expected to be about 1000 new cases of stroke per annum in a typical health authority with a population of half a million. Therefore, any programme that may lead to an important reduction in stroke incidence needs serious consideration, because of both the potential for health gain and the potential for reduced overall NHS expenditure. Screening for AF may be one such programme since, in population terms, AF is an important risk factor for stroke (associated with 15% of all strokes) and anticoagulation provides a highly effective treatment to reduce this risk. Meta-analysis of RCTs has shown a 68% relative risk reduction in patients with AF receiving oral anticoagulation.[22] It has been estimated that optimal treatment of AF in the population may reduce the overall incidence of stroke by 10%. However, as highlighted above, before implementing screening programmes, unresolved questions over how the screening should be conducted must be answered.

The appropriate screening strategy to be used

Opportunistic screening

The simplest strategy is opportunistic case finding, where a healthcare professional could take the opportunity to feel a patient's pulse during a consultation. If the pulse is irregular, they may make a clinical diagnosis of AF, or request or

perform an ECG as a confirmatory test. However, opportunistic case finding is likely to miss a significant proportion of people who would otherwise have benefited from treatment. For example, detection of hypertension in general practice was traditionally detected in an opportunistic way until the introduction of health checks with the 1990 GP contract. The Health Survey for England shows that in 1991, 42% of the population over the age of 75 years had hypertension for which they were not taking any medication.[33] This figure had fallen to 31% by 1994, probably due at least partly to the requirements of the GP contract taking effect.

Targeted screening

Another possible approach is to screen patients who are at higher risk of AF, in a targeted screening programme. Cardiac failure, hypertension and rheumatic heart disease are important precursors of AF.[7] AF is more common in people with a history of myocardial infarction, angina, diabetes mellitus, hyperthyroidism, stroke or TIA than in people without these conditions.[34] Most general practices are computerised, and some have disease registers. A targeted screening programme could exploit these to identify such high-risk patients, either through disease registers or through prescribing information on the computerised records.

Whole population screening

Another approach is to screen everyone aged 65 years and over for AF: a whole population screening programme.

A modelling exercise using decision analysis to inform on the methodology for this study indicated that there are insufficient primary data available to recommend which of these (targeted or whole population) would be the optimum policy

The most appropriate screening test for AF

A 12-lead ECG interpreted by a specialist is recognised as the gold-standard test, but this test though simple is time consuming (taking at least 15 minutes to perform in an outpatient setting). Therefore, it is important to consider simpler tests. This study assessed simpler methods compared with the gold standard, in terms of accuracy, time taken and patient acceptability. These include taking the pulse and simpler ECGs.

Interpreting the ECG

Cardiologists offer the most accurate readings of ECGs, but can satisfactory interpretations be obtained by the GP, the practice nurse or computerised diagnostic software? This study assessed the accuracy of these different approaches to interpreting the ECG.

The value of echocardiography

The main treatment options to reduce risk of stroke in patients with AF are currently warfarin or aspirin. Aspirin is much less effective than warfarin; it achieves a barely significant 21% reduction in stroke risk.[35] However, it is safer to use, since it confers a lower risk of serious haemorrhage. Therefore, in practice, the clinical decision as to which treatment to use depends on the balance of risks and benefits for the individual patient. Thromboembolic risk is currently determined primarily on clinical criteria. Data from the SPAF study[36] suggest that echocardiography may inform on risk stratification, assisting in therapeutic decision-making. The role of routine echocardiography for patients with AF identified in the community remains to be proven. Data also need to be quantified regarding the cost-effectiveness of echocardiography versus clinical impression alone. Studies have suggested that the clinical utility in people aged over 74 is poor.[37,38] Therefore this study focused on patients aged 65–74 years.

Once somebody has been identified as having AF, should they also receive an echocardiogram to assess their risk of stroke, or is clinical assessment of risk adequate?

Optimum strategy

This study, by providing answers to these questions, allowed the optimum strategy for introducing a screening programme for AF in those aged 65 and over to be determined. However, before a decision is made as to whether to institute a screening programme, not only must the question of the best strategy be considered, but also the question of whether any screening programme at all should be introduced. This study provided data to assist in answering this fundamental question by providing:

- an RCT of different screening strategies for AF in people aged 65 and over
- an accurate estimate of the community prevalence and incidence of AF in those aged 65 and over
- an assessment of the health economic implications of screening for AF
- an assessment of the service provision implications of implementing such a programme
- an assessment of the impact on patient quality of life and anxiety after various screening methodologies.

Health economics of screening

This study compared the incremental cost per case detected for different methods of AF screening. This does not refer to the average cost, but rather approximates the incremental cost per case detected in moving from one of the screening options to another. Use of incremental cost per case detected by option shows how the cost per additional case detected is likely to increase as the intensity of screening increases. This method has been used to deal with similar uncertainties about the cost-effectiveness of screening for other diseases, including breast and colorectal cancer, and has been recommended by the US guidelines.[39]

The cost-effectiveness of different approaches to screening is often put in terms of the average cost per case detected, and such an approach ignores the sensitivity and specificity of the screening test. This is because average cost per case detected focuses entirely on true positives, paying no attention to false positives, false negatives and true negatives. False positives and false negatives impose costs on patients and health services that would be neglected if the focus were confined to true positives.[40] An undue emphasis on the average cost per case detected could justify opportunistic screening of a small number of high-risk patients who present, with no consideration of the number of cases missed.

Objectives

Primary objective

- To determine the rate of new cases of AF detection based on a variety of screening strategies and in doing so to evaluate the incremental cost-effectiveness, in terms of cost per case identified, of the different screening strategies (targeted, whole-population screening and opportunistic screening with prompts) compared with routine clinical practice for detection of AF in people aged 65 years and over.

Secondary objectives

- To evaluate the relative cost-effectiveness of screening methods for AF diagnosis, comparing 12-lead ECG (gold standard) with pulse-taking, lead II rhythm strip from standard ECG limb leads alone and single-lead thoracic placement ECG.
- To evaluate the most cost-effective method of test interpretation, comparing cardiologist (gold standard), with GP, practice nurse or computerised diagnostic software (CDSS).
- To assess the differing combinations of screening strategies and procedures in terms of patient acceptability and impact on patient quality of life, including any psychological effects of screening.
- To determine the community prevalence and incidence of AF in people over 65.
- To evaluate the value of clinical assessment and echocardiography as additional methods of risk stratification for thromboembolic disease in patients with AF.
- To evaluate the service provision implications should screening for AF become a national programme, and identify the optimum screening algorithm for identification of patients with AF.

Outcome measures

Primary outcomes

- The incidence of new cases of AF detected according to a variety of screening strategies.
- The incremental cost per case detected. The cost data were collected from an NHS and a patient perspective, and focused on resources required to establish screening, time taken to complete screening and the cost of the equipment.

Secondary outcomes

- The cost-effectiveness of four different methods of screening for AF. The cost data focused on the difference in the cost of the equipment and the time taken for each of the different methods of screening to be completed. This was from both an NHS and a patient perspective.
- The cost-effectiveness of four different methods of ECG interpretation. The cost data focused on the difference in the cost of the grade of staff interpreting the ECG and the accuracy of their interpretation.

- The overall community prevalence and incidence of AF.
- Patient acceptability to AF screening was measured using an adapted version of the screening specific questionnaire used in the Colorectal Screening Programme. Patient uptake of screening was also monitored. The impact on quality of life was assessed using EuroQol 5 Dimensions (EQ-5D). Patient anxiety was measured using the Spielberger 6-item Anxiety Questionnaire.
- Modelling techniques were used to identify the implications of AF screening on health service provision nationally. This includes the effect on echocardiography and anticoagulation clinic provision.

Chapter 2
Methods

This was a multicentred RCT. The study schema, based on Consolidated Standards of Reporting Trials (CONSORT), is shown in *Figure 1*. Fifty computerised general practices in the West Midlands were recruited through the Midlands Research Practices Consortium (MidReC). This was undertaken by writing to all practices in the West Midlands and surrounding counties explaining the study and asking whether they were interested in participating. Practices showing an interest were given further information about the study and invited to attend an investigators' meeting. Following the investigators' meetings 60 practices interested in participating in the project were randomised (stratified based on Townsend score and practice list size): 25 as intervention and 25 as control practices, with ten reserve practices.

Randomisation and patient selection

Patients aged 65 years or over were recruited into the trial; however, patients who were terminally ill were excluded from the study. Randomisation of practices and patients was performed by statisticians from the Department of Primary Care and General Practice at The University of Birmingham. Cluster randomisation of practices to intervention or control was stratified by Townsend quartiles and practice size. Computer searches were carried out to identify cases of known AF, within the sample of patients identified above, using a published strategy.[41] The randomisation of patients within the intervention practices ensured that the study patients in each practice were divided equally between systematic and opportunistic screening arms, and also that there was an even distribution of patients with known AF between the two arms. Random allocation was performed using computer-generated random numbers that were mapped to previously assigned unique patient identifiers.

A computerised list of all patients aged 65 and over was obtained from each practice, and from this a random sample of 10,000 patients from the intervention practices (representing approximately 33% of the total population of patients aged 65 or over in this group) and 5000 from the control practices (representing approximately 16% of the total population of patients aged 65 or over in this group) was identified.

Following initial sampling of the total population, the list of patients from each practice was returned to the practices to enable them to remove any patients who had died or moved or were terminally ill. Patients removed following this process were replaced with patients from a reserve list, which had been randomised at the same time as the initial lists. Once baseline note searches had been undertaken, patients from intervention practices were randomised, to either opportunistic or systematic groups, ensuring the even distribution of known AF patients in both arms. Random allocation was performed using computer-generated random numbers.

Computerised note searches of GP records

Patients in the systematic screening arm were identified by computerised record searching as being at either high risk (target population) or moderate risk (non-target population) of AF by recognised criteria.[11,42] The criteria to identify the target population were: cardiac failure, hypertension, rheumatic heart disease, previous myocardial infarction, angina, diabetes mellitus, hyperthyroidism, previous stroke or previous TIA. These were identified using practice disease registers.

Prevalence and incidence data

Computer searches were carried out to identify cases of probable AF in the 15,000 study patients using a published strategy (*Table 1*).[33] Searches were tailored towards the information that is held on computer in each practice. If practices hold AF registers, or use READ diagnosis coding, then these were used. In addition, a search was carried out to identify prescriptions of digoxin, a β-blocker, a class 1, 3 or 4 antiarrhythmic agent, aspirin or warfarin. This information was recorded on computerised case report forms.

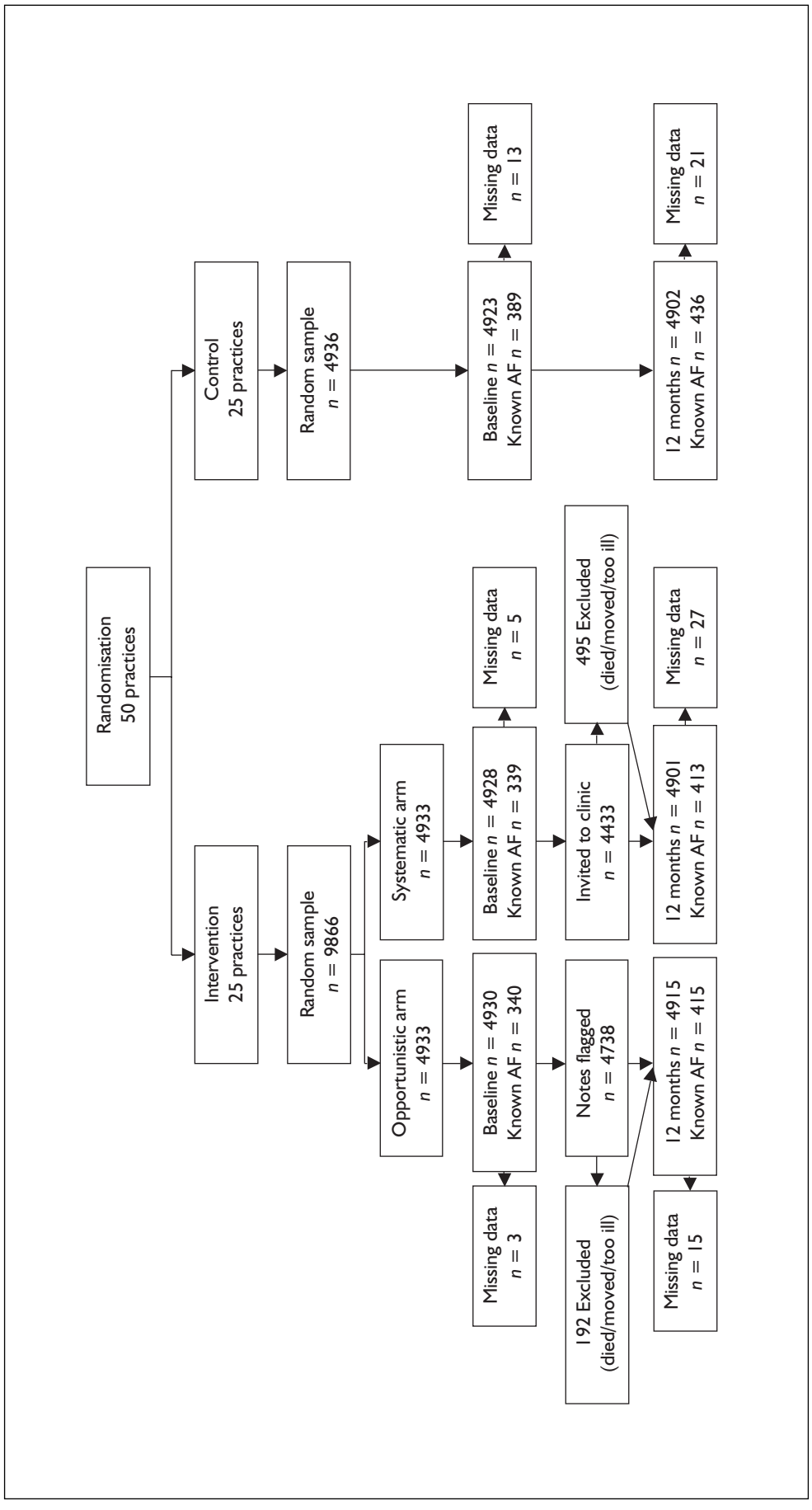

FIGURE 1 *Study CONSORT chart*

TABLE 1 *Computer searches undertaken*

Search
G573 atrial fibrillation/flutter
327 ECG supraventricular arrhythmia
181 Palpitations
Digoxin
Amiodarone
Verapamil
Sotalol
Metoprolol
Warfarin
Aspirin

Case notes of patients identified as 'known' or 'probable' AF in any of these computer searches were reviewed for mention of a diagnosis of AF. AF diagnoses were drawn from hospital letters stating the existence of the condition or ECG recordings from the past 5 years.

An additional 5% random sample of case notes of patients not identified as 'known' or 'probable' AF by computer searching was reviewed (750 in all) to estimate how many other patients who are known to have AF were not identified by the computer searches. If this had revealed a significant number of extra cases of known AF, then the sample size for manual searching would have been increased to allow a precise estimate of the baseline rate of known AF. Unidentified extra AF cases were not found to be significant (a total of three was found), so no additional note search was required. The same computer searches on both intervention and control practice patients notes were performed before and 12 months after commencement of screening.

Practice staff education and ECG training

GPs and other members of the primary healthcare team in the intervention practices attended investigator days at which they were given educational materials informing them of the importance of detection of AF, and the treatment options that are available. The materials encouraged them to consider opportunistic screening of patients. Members of the primary healthcare team in control practices received no educational input from the research staff. Practice nurses attended an ECG training day before starting the ECG screening clinics. Training included how to perform an ECG (using the Biolog) to ensure a standardised high-quality tracing and basic ECG interpretation (specifically how to identify AF).

Screening

Systematic screening

All patients in the systematic screening arm, including those with a history of AF, were invited by letter to attend a screening clinic. Non-responders were sent a reminder. Patients who were selected to the systematic screening arm received an information sheet with their invitation letter.

Opportunistic screening

Patients in the opportunistic arm had their notes flagged. In the majority of practices, a paper flag was inserted into the patient notes, and for the remainder, computer notes had a flag attached. The aim of the flag was to encourage practice staff to undertake pulse recording during routine consultation. Patients with an irregular pulse were given an information sheet and invited to attend a screening clinic. Once this process had been undertaken, the paper flag was completed with details of pulse type and the member of staff taking the pulse. The flag was then removed from the notes and returned to the research team. In addition, computerised flags were deactivated and a list of patients screened was sent to the research team.

Screening clinics

The screening clinics were run by practice nurses. Entry to the trial was discussed and the practice nurse explained the aims of the study and answered any questions. The practice nurse then obtained written consent from those patients who were willing to participate. The nurse recorded baseline information on age, gender, present smoking and alcohol status and past medical history, including previous diagnosis of AF, and any treatment the patient may be receiving for AF. Radial pulse rate, and whether regular or irregular, was noted. A 12-lead ECG, the gold standard by which other traces were compared, was then recorded using the Biolog machine, which was also able to produce a trace corresponding to the single-lead thoracic placement and a rhythm strip of lead II using limb leads from the standard ECG. Finally, the patient was asked to complete an acceptability questionnaire.

ECG interpretation and patient diagnosis

All 12-lead ECGs were sent to two cardiologists for reporting (GL, MD). Where there was disagreement

over the diagnosis a third blinded cardiologist made the decision. The cardiologists were asked to state whether the ECG showed AF or not, and to state whether there were any other significant abnormalities. Patients were informed of the result within 2 weeks. Patients with normal ECGs were informed of this, whereas patients with any abnormality were asked to make an appointment with their GP.

Echocardiography

The value of clinical assessment and echocardiography in risk stratification was determined in patients aged 65–74 years. This compared GP assessment based on the Birmingham guidelines for thromboprophylaxis in AF with any changes in recommendations for treatment once echocardiography results were available to the GP. At the GP appointment patients with AF aged 65–74 years were offered echocardiography. GPs were asked to make a clinical decision as to thromboprophylaxis both before and after the echocardiogram. Patients with other ECG abnormalities were managed as clinically indicated.

Alternative types of ECG and interpretation

At the end of the screening process, GPs and practice nurses from both intervention practices (who had received education on ECG interpretation) and control practices (who had received no education) were sent ECGs to interpret for the presence or absence of AF. All ECGs recorded within the study were printed off as 12-lead, single-lead thoracic placement or limb-lead recordings. Allocation to ECG type was random and resulted in three equal ECG groups. In order for each interpreter to read all three types of ECG, batches of 100 ECGs were collated with the same numbers of each type of ECG. Allocation to a batch was also random. In total, there were 25 batches of ECGs to match the number of practices in each arm. The GP and practice nurse from the same practice read the same batch of ECGs and each batch was read by one control practice and one intervention practice. Therefore, each ECG was read by two GPs and two practice nurses. All ECGs were anonymised, and practices did not receive any ECGs from their own practice. The interpreters were given a sheet to fill in to indicate for each ECG the presence or absence of AF. A smaller scale process was undertaken with the study cardiologists. They were given a small sample of limb-lead and single-lead ECGs (50 of each) to diagnose in order to calculate diagnostic statistics. All ECGs (as 12-lead) were also analysed by the specific software package accompanying the electronic ECG and results recorded.

Patient questionnaires

Patient acceptability and quality of life for different screening strategies were established using the EQ-5D combined with the Spielberger 6-item Anxiety Questionnaire. EQ-5D allowed the measurement of broad aspects of quality of life. The shortened Spielberger anxiety questionnaire also has proven validity and is more specific to anxiety than is the Short Form 12 (SF-12).[43] An adapted version of the screening-specific tool used in the Colorectal Screening Programme[44] was used to assess the acceptability of the screening process, impact of screening on patients and quality of life.

A random sample of 750 patients (375 screened patients and 375 opportunistically screened patients) was sent postal versions of the psychological instruments (EQ-5D and Spielberger) on entry to the study (i.e. before the intervention group had received their invitation to attend for screening). One reminder was sent a month later to non-responders. The same questionnaires were sent to the same groups plus those patient who had screened positive at the end of the screening period, approximately 17 months later. This allowed a non-randomised comparison between the effects on quality of life and anxiety in screen-positive and screen-negative patients. In addition, all patients who were screened were asked to complete the acceptability and Spielberger questionnaire immediately after screening.

Sample size and power calculations

The assumptions for the power calculations were that patients aged 65 and over represent 17% of the total population, and that 40% of study population will be in the targeted high-risk group. It was also assumed that:

- the minimum worthwhile change in detection rate is 1% for targeted screening versus routine practice. It is estimated that this change would

equate to £10,000 per life-year gained. This is based on the following assumptions:
  - 60% of new cases of identified AF would be suitable candidates for warfarin
  - the annual risk of stroke in this population is 5%, reduced by 60% to 2% if treated
  - costs: £25 to screen a patient; £100 to treat with warfarin per annum; £6000 NHS costs to treat a stroke
- 50% of patients with AF will be already known to their GP (estimates range from 30%[45] to 76%[46])
- Community prevalence of AF in this population is 6%.[3]

It was assumed that the baseline prevalence of AF known to the practice would be 3% (i.e. half of the real prevalence of 6%) and that the prevalence of known AF in the control practices would remain constant over the screening period (*Figure 1*). Thus, the change in the prevalence of known AF in the control practices between baseline and follow-up should be approximately 0%. The change in the GP educated arm should be marginally higher and is assumed to be between 0 and 1%. The change in the systematic screening arm should, on average, be between 0 and 3% and is assumed to be approximately 3% for the total screening arm and in the high-risk arm approximately 2%.

All sample size calculations are for 90% power and 5% significance levels unless otherwise stated.

(a) To detect a 1% difference in detection rate between opportunistic screening with prompts and control practices

This required 1236 patients. However, since this is a difference based at the practice level of randomisation, it needs to be inflated by the design factor. Based on AF prevalence data from the Echocardiographic Heart of England Screening (EcHoES) study,[47] the between-practice variance is 3.7 and the within-practice variance is 246. This gives an intracluster correlation coefficient of 0.015. The most efficient design in this circumstance would be a cluster size of 200, which gives a design factor of 4. Therefore, 5000 patients were needed in 25 practices in both intervention (GP educated, opportunistic and systematic screening) and control groups.

(b) To detect a 1% difference in detection rate between total population screening control practices

This required 1236 patients, but when scaled by the design factor of 4 required 5000 patients.

(c) To detect a 1.8% difference in detection rate between intervention (systematic screening high-risk arm) and control practices

This required 684 patients. However, since this is a difference based at the practice level of randomisation, it also needs to be inflated by the design factor. This means that 2736 patients were needed in each arm. Since the ratio of patients in the two arms is 2:5 this means that 1916 patients were needed in the high-risk arm and 4789 in the control arm. With the 2000 patients expected to be at high risk in this arm, resulting from the 5000 needed for the previous comparison, there were enough patients recruited to detect the required difference.

Although comparison (b) required fewer patients to detect the expected difference (2%) stated in the assumptions, it was possible to detect differences as low as 1%, should the detection rate not be as high as expected.

Comparisons (a), (b) and (c) are all at practice-level randomisation.

(d) To detect a 1% difference in detection rate between targeted screening strategy and opportunistic screening

This required 1236 patients in both the high-risk systematic screening and the GP educated (opportunistic) screening arms of the intervention practices, assuming that high-risk screening detects a 1% increase and opportunistic screening detects 0% increase. If the increased detection rates were higher in each arm (1.7% in the high-risk arm and 0.7% in the opportunistic arm) then this could require 2686 patients in each arm. However, since there is a ratio of 2:5 patients in these arms there were sufficient patients as only 1880 are needed in the high-risk arm and 4700 in the opportunistic arm to be able to detect this 1% difference.

(e) To detect a 1% difference in detection rate between total population screening strategy and opportunistic screening

This required 3300 patients in both the total screening and the GP educated (opportunistic) screening arms of the intervention practices.

(f) To detect a relative risk of 2 (1% detection rate difference) between total population and targeted screening

It was assumed that 40% of the study population will fall into the high-risk group, and the prevalence of undetected AF is 3%. This meant that 1434 patients would be needed in each of the

two risk groups to detect a two-fold difference in risk [i.e. the relative risk (RR) of AF in the high-risk compared with the low-risk group is 2]. This RR of 2 equates to an increase in AF detection rate from 3% in the total population arm to 4% in the high-risk arm. Since there is a 40:60 split in the two risk groups unequal sample size calculations only required a minimum of 1200 patients in the high-risk group and 1800 in the moderate/low-risk group. This was achievable with a screening arm of 5000 patients, as there would actually be 1320 in the high-risk group and 1980 in the moderate-risk group if a 66% screening acceptance rate was assumed.

Sample size for quality of life assessment

Although some of the variances are from North American populations there is no reason to suspect that the variation will be different in a British population since data from the EcHoES study on the SF-36 gives variations very similar to the North American norms.

Spielberger

The shortened (6-item) version of the Spielberger state anxiety questionnaire has been validated and used in populations different to that under consideration in Screening for Atrial Fibrillation in the Elderly (SAFE); namely, it tends to have been used in young and mostly female populations.[43,48,49] The variance obtained from these papers appears to be approximately 144 for Marteau and Bekker[43] but higher for the Ubhi[49] paper. However, the women in the latter paper were being informed of major illness outcomes (either benign or malignant breast cancer). A full Spielberger on people undergoing physiological tests also gave a variance in the order of 144.[23] The full version of the Spielberger state anxiety when used with an elderly population also seems to give a variance that is not too far from the previously mentioned papers, being 188.8.[50] Taking this latter value as being the nearest to the present population, it is possible to detect a 4-point difference in the mean values obtained with 249 patients in each arm.

EQ-5D

Visual analogue

The visual analogue scale (VAS) variance as reported for an elderly population aged 75 and over was 365,[51] but for a group of recovered stroke patients (ages not given) it was approximately 100.[52] Taking the former value as a worst case this means that it will be possible to detect a 6% difference between groups on the VAS with 213 patients in each group.

Utility index

Using the utility values from the Dorman paper,[52] the variance is approximately 0.066 and this allows a 0.1 difference to be detected with 139 patients.

Statistical analysis

ITT analysis was used. Any previously known AF cases were subtracted from the totals obtained at the end of the study to prevent double counting in the incidence figures.

Proportions and rates were used as the measures of prevalence and incidence. General linear modelling was used to compare community prevalence and incidence at 12 months at the practice level in the control and intervention arms. The χ^2 test was used to compare overall 12-month prevalence and incidence rates between arms. Patients were compared using a non-linear mixed model, with binomial error, and effect of practice conditioned using a Gaussian error distribution, implemented in Proc Nlmixed in SAS 8.2. Effects of high-risk patients, age (modelled as above the median age 73.66 years) and gender were examined as main effects and interaction with treatment in further exploratory models. Simple models fitted in Proc Genmod were used to check for consistency over method.

Non-linear mixed modelling was used to compare incidence rates per practice in the control and intervention arms, to describe the odds ratio of incident cases. Practice was defined as a random effect to account for extra binomial variability at the practice level. Any differences in practice-level baseline prevalence were accounted for with the inclusion of the log odds of baseline AF. The denominator degrees of freedom were derived from the practice level. The primary analysis was conducted using Proc Nlmixed, in SAS (Version 8.2) (SAS Institute, Cary NC, USA). The analysis was repeated without the inclusion of the covariate describing baseline prevalence.

Secondary analyses included repeating the primary model without the inclusion of the covariate describing baseline prevalence of AF. In addition, the analysis was repeated accounting for overdispersion (extra binomial variability) by inflating the scale factor by the ratio of the deviance and the degrees of freedom on the

appropriate strata, using the ideas of quasi-likelihood. The latter analysis was implemented in Proc Genmod, again in SAS Version 8.2. The mean difference in practice incidence of cases of AF was described using Proc Means in SAS 8.02.

Patient anxiety and quality of life scores were analysed using general linear modelling to examine the differences between the intervention screening strategies on the Spielberger and EuroQol EQ-5D.

To assess the value of echocardiography in risk stratification for thromboembolic disease in patients with AF, data were analysed using simple frequencies and proportions.

Cost-effectiveness is covered in the economic section. However, the use of sensitivity, specificity, positive and negative predictive values allowed for comparison of the various methods for detecting AF between the GPs, nurses and consultants. Multivariate and logistic modelling analyses were undertaken to determine which markers are the best predictors of the presence of AF. Statistical analysis was carried out using SAS Version 8.2 and SPSS Version 10.

Economic evaluation

There are two distinct components to the economic analysis conducted as part of the SAFE project: a within-trial analysis and a longer term model-based analysis. Both have adopted an incremental approach to assess the additional costs and benefits associated with the introduction of a screening programme for AF.

All base-case analyses (undertaken for both the within-trial and model-based analyses; and for opportunistic, systematic high-risk and systematic screening scenarios) assumed screening using a 12-lead ECG interpreted by a consultant cardiologist. Additional analyses were undertaken where the form of ECG (12-lead, limb-lead rhythm strip or single-lead thoracic placement) and the interpreter (consultant cardiologist, GP, practice nurse or CDSS) were varied.

The trial evaluated a large number of alternative screening scenarios for identifying AF: three screening strategies (target, population and opportunistic), three types of ECG and four screening test interpretations (CDSS interpretation only possible with a 12-lead ECG), making 30 plus control, resulting in 31 strategies.

The within-trial analysis has used only data collected as part of the trial, and focused on the performance of screening strategies in terms of true-positive cases detected, so the results are reported as a cost-effectiveness analysis (CEA): cost per additional true-positive case detected. In contrast, the longer term analysis is based on a simulation model, draws on other published data and has assessed outcomes in terms of life-years gained and QALYs. Therefore, the model-based analysis involves both a CEA (cost per life-year gained) and a cost–utility analysis (cost per QALY gained). The detail of the methods for both analyses is given below.

Both sets of analyses used unit costs at 2003 prices. Health professional costs were calculated on the basis of salary scale midpoints (including qualification costs).[53] Administration costs included 40% overheads.[54] Equipment costs were based on purchase prices and amortised over a 3-year period, using the current Treasury recommended discount rate of 3.5%.[55] Straight-line depreciation and no residual value were assumed. All longer term costs and effects were discounted at 3.5%.

Within-trial analysis

If screening for AF, compared with no formal screening programme, was shown to be associated with positive outcomes (i.e. increases in the number of true-positive cases of AF detected), this would have important cost implications both for the healthcare sector and for individuals. For example, early diagnosis and treatment will take place in some people who otherwise would have remained undiagnosed until later in the course of their disease. Therefore, the economic evaluation adopted a broad perspective and considered costs falling both on the NHS and on patients.

Key resource-use data were collected to estimate the short-term costs associated with the alternative approaches to screening. Resource-use data were collected prospectively under two headings: screening process and private costs.

Screening process

Data were collected on the process of implementing and running the screening programmes related to: the patient pulse flags (opportunistic screening), the flagging of high-risk patients (targeted systematic screening), the invitation to patients and reminder invitations to non-responders (population and targeted systematic screening), the ECG clinic, the ECG interpretation and communication of results. The

TABLE 2 *Resource-use data and estimates*

Variable/parameter	Value	Applicable screening scenarios	Source
ECG interpretation time	1 minute	All screening scenarios	Trial data
Pads required per ECG	12-lead: 10 Limb-lead: 4 Single-lead: 1	All screening scenarios	Trial data
Practice nurse time per ECG (without interpretation)	12-lead: 7 minutes Limb-lead: 3 minutes Single-lead: 4 minutes	All screening scenarios	Trial data
Administration time per patient per ECG	2 minutes	All screening scenarios	Trial data
% Patients flagged by computer	100%	Opportunistic screening	Assumption
Time to take pulse	1 minute	Opportunistic screening	Trial data
Additional administration time per patient for flagging notes	1 minute	Opportunistic screening	Trial data
Additional administration time per patient for high-risk search	1 minute	Systematic high-risk screening	Estimate
Additional administration time per patient for invitation letter	1 minute	Systematic population and systematic high-risk screening	Estimate

cost of a patient pulse flag included administrative staff time for flagging patient notes on the computer. The cost of an invitation and the communication of results by letter included administrative staff time, postage and stationery, and obtaining patients' details from practice records. The cost per ECG clinic attendance included staff costs, administrative costs, equipment costs, disposables and any clinic overheads. Costs to interpret an ECG consisted of the time taken by the interpreter. The time taken for a 12-lead ECG was recorded on the computer for the majority of ECGs undertaken and a separate time-and-motion study was undertaken in a single general practice. Expert opinion and a survey of a sample of study practice nurses were used to estimate the average time for a limb-lead rhythm strip ECG and single-placement thoracic ECG. The average time taken by each interpreter (i.e. cardiologist, GP, practice nurse) to read an ECG, in order to detect AF, was estimated using data collected from study subjects interpreting ECGs and from expert opinion.

Private costs

Given the broad perspective being adopted, a sample of patients in all arms of the study were asked to complete a patient-cost questionnaire which recorded the private costs to patients and their companions in attending for screening. Questionnaires were administered to all practices and patients were asked to fill in the questionnaire before their appointment. Data were collected on the time taken to travel to the clinic, the mode and cost of transport where applicable, time spent waiting before the appointment and whether the patient was accompanied. Information was also collected on activities forgone in order to attend the screening clinic, including leisure activities, care of relatives and employment.

Data on some key resources and unit costs used in the economic analyses are reported in *Tables 2* and *3*. The base-case analysis for opportunistic screening assumes flagging by computer, pulse taking for 1 minute in a routine consultation and a 12-lead ECG recorded and read by a cardiologist. To calculate the machine cost per patient, it was estimated (using study data) that at least 94 ECGs would be carried out during a year per practice, including routine ECGs. The base-case analysis for targeted and systematic screening also includes costs of sending out an invitation letter and, where applicable, a reminder letter, and the time taken to carry out a high-risk search in the case of systematic high-risk screening only.

Costs were calculated for all intervention patients taking into account the type of screening and whether screening was undertaken. For opportunistic screening, if the health professional taking the pulse was not recorded, an average of the GP and practice nurse cost was used. In systematic screening, the cost of an invitation was

TABLE 3 *Unit cost estimates*

Cost parameter	Value (£)	Source
12-lead ECG machine (including warranty)	2010.43	Trial data
Electrode pad	0.06	Trial data
Alcohol wipe	0.02	Trial data
Stationery and postage per ECG	0.30	Trial data
Clinic overheads (per hour)	13.16	Trial data
Employment cost per hour		
Consultant (non-patient contact)	82.00	Netten and Curtis, 2003[53]
GP (patient contact)	116.00	Netten and Curtis, 2003[53]
GP (GMS)	73.00	Netten and Curtis, 2003[53]
Practice nurse (patient contact)	29.00	Netten and Curtis, 2003[53]
Practice nurse (GMS)	26.00	Netten and Curtis, 2003[53]
Administration	10.93	Whitley Council, 2003[54]
Paper flag for notes	0.05	Estimate
Invitation letter	0.30	Estimate

GMS, general medical services.

averaged over all patients taking into account the proportion (i.e. 45%) sent a reminder.

The main measure of effect in the trial was the number of new cases of AF detected by each screening method. For all alternative approaches to screening an estimate of sensitivity and specificity was calculated. The economic analysis involved estimating the mean incremental costs and the gain in case detection for each of the screening strategies separately. Given the short time horizon for this CEA, costs were not discounted. CEA was undertaken to relate mean incremental costs to the change in detection rate associated with alternative screening strategies, with results presented using the cost-effectiveness plane.

Model-based analysis

The results of the empirical work, described above, indicate whether the screening alternatives being compared in the study are associated with differences in the key study outcomes. The main purpose of the modelling component of this project is to allow for extrapolation beyond these observed outcomes (i.e. the use of a modelling framework provides the opportunity to predict longer term screening outcomes based on the study results). Such longer term outcomes include the incidence of major events (e.g. strokes), health-related quality of life, patient survival, and the full costs associated with screening and long-term events.

As part of this project an individual sampling model (ISM) was developed; this is a form of discrete event simulation (DES) in which only one individual is considered at a time. Virtually all previous modelling work in the area of AF has used a Markov approach.[26,32,56] One key difference between a Markov and a DES is that in a DES the times of events are recorded to full computer accuracy rather than simply being regarded as taking place in a given cycle (e.g. in a 12-month period). In addition, this type of modelling can take into consideration patient attributes and avoids the problem of having a large number of health states. This ISM model is written in Borland Delphi 7 and uses an event-based executive. Individual patients pass through the model, their status being changed at various times according to the natural history of AF, thrombotic and haemorrhagic events, and the effects of a screening programme. The aim of the model is to produce a realistic set of virtual patient histories, from which estimates of population means, costs and effects (e.g. QALYs) can be estimated.

The model provides the framework for the longer term economic analysis. Using the model to extrapolate beyond observed study outcomes has allowed for the possibility of alternative policies to be compared in terms of an ICER, expressed as the additional costs incurred per life-year gained and the additional costs incurred per QALY gained.

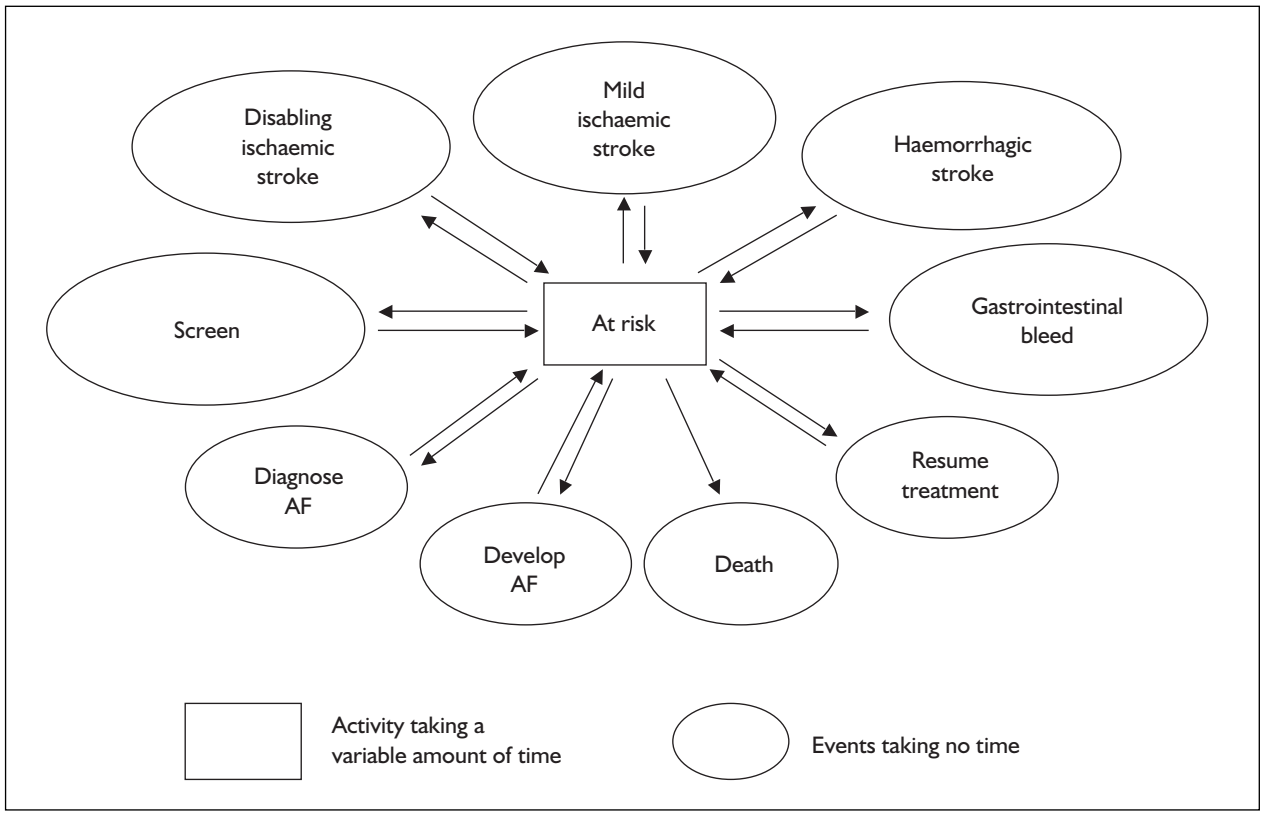

FIGURE 2 *Individual sampling model*

The results of these economic analyses are also presented using cost-effectiveness acceptability curves (CEACs) to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. Both simple and probabilistic sensitivity analyses have been used to explore the robustness of the results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.[57]

The model was constructed to consider the possible outcomes of a screening programme for AF and subsequent treatment decisions (*Figure 2*). The model can be run for any combination of male and female patients. Age is incorporated into the model in one of two ways. The model can be run for patients aged 65 years at the beginning until death, or patients are sampled from a population distribution for ages 65 and over. The model can also be run for the general population or for high-risk patients alone. Patient attributes such as gender, age and medical history are carried through the model and these attributes impact on the risk of any of the events occurring. Each possible event has associated risk estimates and the time to each event is sampled according to these risk estimates. When the event with the earliest time to event occurs, the attributes are updated and all other events are resampled. Each event takes no time, and between events patients are at risk. Events may have an impact on quality of life, temporarily or permanently, and have associated one-off or long-term costs.

The model can consider a single individual, but can also simulate a population over time. In this case, the model was run for 500,000 patients for screening frequency and 1 million patients for screening type to reduce the variability of model results. When reporting the results from a run of virtual patients, the mean and a quasi-standard error (QSE) can be reported. This standard error reflects the uncertainty due to the sampling within the model rather than the parameter uncertainty. Therefore, by increasing the number of virtual patients in the model, the QSE is reduced. The model has been run for a general population only and high-risk (targeted) screening is not addressed here, as the trial results did not demonstrate any benefits from this screening method. In all model runs, costs and QALYs are discounted at 3.5%.

Simple sensitivity analyses were carried out to investigate the effect on results when a key variable is changed. Previous papers have

suggested that the utility value of being on warfarin has an impact on final results; therefore, the model was also run with no reduction of quality of life. The base case assumes all patients are given warfarin treatment; therefore, analyses were also undertaken with patients treated with aspirin, where efficacy is lower but adverse haemorrhagic effects are reduced. Finally, the model uses values for compliance with screening from the trial. To take into account the fact that these values may be lower than observed outside trial conditions (owing to patients' being unwilling to be trial participants), the analysis was also run with compliance values at 10% and 20% higher. For example, a compliance of 41% would be changed to 51% and then 61% in the analyses.

Probabilistic sensitivity analysis (PSA) was undertaken using distributions for variables where variation around the point estimates used in the model was available. For each patient group and screening type, plus no screening, a total of 10,000 replications was performed, with summary data for each replication representing 10,000 patients. This number of patients was chosen to represent a typical number of 65-year-olds (in each gender group) in a typical strategic health authority. The difference in costs and QALYs between no screening and each screening option was calculated for each replication. For each type of screening, these data were plotted on a cost-effectiveness plane. To present the uncertainty in the cost-effectiveness of the alternative strategies, CEACs were used. The curves show the probability that any particular strategy is more cost-effective than current practice (no screening) using alternative values for the maximum value that the health service is willing to pay for an additional QALY in these patients.

Individual patient pathways

Development of AF

The proportion of patients already having AF is determined at baseline by prevalence data, which take into account age and gender. An individual without AF at baseline may or may not develop AF during the course of his or her lifetime and the risk is determined by incidence data, also related to age and gender.

Detection of AF

Without screening

If individuals are specified as having AF before the model has been run, the proportion who already have the condition can be specified. Once an individual in the model has the attribute of having the condition AF, where there has not been any prespecified diagnosis, the condition remains undiagnosed until one of two possible events. An individual may have their AF diagnosed as part of routine care, or if an individual experiences a non-fatal ischaemic or haemorrhagic stroke event it is assumed that tests will be carried out, including an ECG to determine the presence of AF. Once diagnosed, a patient will not be part of any screening programme.

With screening

Patients may be diagnosed through a screening process whereby a patient will have an ECG to detect the presence or absence of the condition. There is a one-off cost for every screening event. Within the model, type of screening, screening interval and the age at which screening begins can be specified. The proportion of patients screened can also be specified, to account for screening take-up.

Type of screening

The model can be run for opportunistic or systematic screening, as well as a no-screening option.

Opportunistic screening

Screening for AF opportunistically involves a patient attending a routine GP or practice nurse consultation, and if their notes are flagged (paper or computer flag) they will also have their pulse taken during the consultation. If the pulse is irregular, the patient is invited to attend for an ECG. This type of screening can be as a one-off screen or carried out several times in the patient's lifetime. Costs associated with opportunistic screening are having a flag put into the notes, the extra time taken to carry out a 1-minute pulse-check and the cost of an ECG, including interpretation costs.

Systematic screening

Screening for AF systematically involves sending a letter to all patients in a target group (e.g. patients aged 65 and over) to invite them to have an ECG. Systematic screening can be a one-off event or be repeated over regular intervals (e.g. annual screen or every 5 years). Costs associated with systematic screening include sending out invitations and the cost of an ECG, including interpretation costs.

Screening method

ECG type

A 12-lead ECG is the gold-standard method of detection of AF; however, AF can also be detected

from a limb-lead rhythm strip ECG or a single-lead thoracic placement ECG. Both are less time consuming to perform, and therefore less costly, but they are also less sensitive and specific than the 12-lead ECG. Within the model, the type of ECG carried out on the patient can be specified, with the likelihood of detection dependent on the associated sensitivity and specificity. If a patient has been diagnosed using a limb-lead or single-lead ECG, then confirmation will be carried out with an additional 12-lead ECG to ensure that the diagnosis is certain, otherwise a wrongly diagnosed patient could be given potentially harmful treatment. The additional ECG will also result in additional cost.

Interpretation type
The gold-standard method of ECG interpretation is by a consultant cardiologist and carried out on a 12-lead ECG. Other options for diagnosis are by a GP, a practice nurse and CDSS, all less costly options but with the trade-off of lower sensitivity and specificity. CDSS can only diagnose from 12-lead ECGs, but GPs and practice nurses can attempt a diagnosis from any type of ECG. If a 12-lead ECG has been interpreted by means other than a cardiologist, any ECG thought to show a diagnosis of AF will subsequently be reread by a cardiologist for confirmation. There will be an additional cost of consultant time. It is assumed that a consultant will only diagnose from a 12-lead ECG. As stated in the previous section, any patient diagnosed using a limb-lead or single-lead ECG will have an additional 12-lead ECG carried out which will be read by a cardiologist for confirmation.

Treatment of AF
Once an individual patient has been diagnosed with AF, treatment can begin. The model can be run for four different treatment options: warfarin only, aspirin only, aspirin followed by warfarin in the event of an ischaemic stroke, and no treatment. Each treatment option (except for no treatment) has an associated annual cost. Treatment with warfarin also results in a small reduction in quality of life.

Ischaemic events
Individuals are at risk of having an ischaemic stroke, the risk of which is dependent on age, gender, presence of AF, associated risk factors, treatment and previous stroke history. Ischaemic stroke incidence tables are used, with separate tables for men and women. The model changes the risk of stroke in the presence of an attribute affecting the incidence by multiplying the risk by a hazard ratio. The presence of AF, associated risk factors and having suffered an ischaemic stroke previously increase the risk of an ischaemic stroke event. Treatment reduces the risk of ischaemic stroke. An ischaemic stroke event can have three possible outcomes: death, mild stroke and disabling stroke. If a non-fatal event occurs, this information is then held for an individual, as it will affect the risk of a future event. Where the first stroke is mild, a second stroke will be disabling, and a further stroke will result in death. In the event of an initial disabling stroke, the second stroke will be fatal. Fatal and mild stroke events result in a one-off cost, and a disabling stroke event results in both one-off and long-term annual costs. Non-fatal events also reduce quality of life permanently.

Haemorrhagic events
Individuals are also at risk of haemorrhagic events, the risk of which is dependent on age, gender and treatment. Events that can occur are haemorrhagic strokes and gastrointestinal bleeds, and treatment increases the risk of these events occurring. Haemorrhagic strokes can only have the outcome of death or disability and a second haemorrhagic stroke results in death. Once a non-fatal haemorrhagic event occurs, any treatment is discontinued. A fatal stroke results in a one-off cost, and a non-fatal stroke both one-off and long-term annual costs. Any major gastrointestinal bleeds require hospitalisation, are non-fatal and result in a one-off cost, temporary reduction (1 month) in quality of life and the discontinuation of treatment. Aspirin treatment is permanently discontinued and warfarin discontinued for 1 month only. If a second gastrointestinal bleed event occurs, warfarin is also permanently discontinued.

Other-cause mortality
As the model runs, individuals in the model can die from other causes, in line with data contained in the standard UK life tables. Presence of AF has an associated increase in risk of death and this is incorporated into the model.

Data and assumptions

Incidence and prevalence of AF, stroke and bleed rates by age and gender are shown in *Table 4*. Risks and probabilities, utility values and costs are listed in *Table 5*. Data specific to each screening method in terms of sensitivity, specificity and cost are shown in *Table 6*, and compliance rates for opportunistic and systematic screening by age group and gender in *Table 7*.

TABLE 4 *Model parameter: general population*

Parameter; age (years)	Males (%)	Females (%)
Prevalence of AF		
65–69	3.0	1.7
70–74	5.0	3.4
75–79	7.3	5.0
80–84	10.3	7.2
⩾85	11.1	9.1
Incidence of AF		
65–74	1.8	1.0
75–84	4.3	2.2
⩾85	3.8	3.1
First ischaemic stroke		
65–74	0.7	0.5
75–84	1.3	1.1
⩾85	1.5	1.6
Haemorrhagic stroke		
65–69	0.3	0.3
70–79	0.4	0.4
80–89	0.9	0.9
⩾90	2.1	2.1
Gastrointestinal bleed (rate at age)		
65	1.0	1.0
70	1.2	1.2
80	1.6	1.6
90	1.9	1.9

TABLE 5 *Model parameters: probabilities, relative risks, utilities and costs*

Parameter	Value
Risks and probabilities	
Disabling stroke	0.35
Fatal ischaemic stroke	0.23
Fatal haemorrhagic stroke	0.40
Ischaemic stroke relative risk with AF	5
Recurrent ischaemic stroke relative risk	3.1
Haemorrhagic stroke relative risk with warfarin	2
Gastrointestinal bleed relative risk with warfarin	3
Stroke risk reduction from warfarin	68%
Stroke risk reduction from aspirin	22%
All-cause mortality relative risk with AF	1.92
Utilities	
Mild ischaemic stroke	0.75
Disabling ischaemic stroke	0.39
Disabling haemorrhagic stroke	0.39
Warfarin treatment	0.986
Gastrointestinal bleed	0.88
Costs (£)	
Mild ischaemic stroke	6,820
Disabling ischaemic stroke	4,550
Disabling haemorrhagic stroke	4,550
Annual (long-term) disabling stroke costs	13,240
Fatal stroke	8,830
Gastrointestinal bleed	1,130
Warfarin treatment	100
Flag in notes (opportunistic screening)	0.18
Invitation/reminder (systematic screening)	0.70
12-lead ECG interpretation by consultant	2.05

TABLE 6 *Screening model parameter values*

Screening method	Sensitivity	Specificity	Cost per patient screened (£)
Pulse	87.2	81.3	1.83
12-lead consultant	100	100	16.25
12-lead CDSS	87.3	99.1	14.20
12-lead GP	79.8	91.6	16.03
12-lead practice nurse	77.1	85.1	14.85
Limb-lead GP	82.5	88.4	12.86
Limb-lead practice nurse	73.3	83.3	11.68
Single-lead GP	85.4	86.4	13.38
Single-lead practice nurse	68.7	82.7	12.20

TABLE 7 *Screening model compliance rates by age, gender and screening type*

	Systematic (%)		Opportunistic (%)	
Age group (years)	Men	Women	Men	Women
65–74	61	61	67	72
75–84	52	46	67	71
85+	34	21	56	58

Patient selection

Within the model the user can specify for which patient group the model is being run, either 'new' 65-year-olds or sampling from a distribution of a population aged 65 and over. Using data from the UK mid-2002 population estimates (Office for National Statistics), a cumulative population distribution for ages 65 and over was constructed. For ages 90 and over, individual age data were not available. The SAFE study data set contained the ages of almost 15,000 patients aged 65 and over. The observed distribution for patients aged 90 and over for each individual age was smoothed and used in conjunction with the published data.

Prevalence of AF

The prevalence rates of AF at baseline were derived from published data,[58] with separate prevalence rates for males and females for five age groups (65–69, 70–74, 75–79, 80–84 and ≥ 85 years). When the model was run for patients aged 65 it was assumed that at the point of the first screen none of the prevalent cases had been previously diagnosed. As prevalence rates at the age of 65 are very low, the effect on final results will be very small. However, for a first screen of patients aged 65 and over, using trial estimates, it was assumed that 70% of prevalent cases had already been diagnosed.

Development of AF

The incidence of AF in the model population was derived from published data,[59] with separate incident rates for men and women for three age groups (65–74, 75–84 and ≥ 85 years).

Diagnosis of AF

Once a patient has developed AF, diagnosis can be from poststroke investigations, by screening or during routine practice in the absence of screening. The gold-standard method of diagnosis is a 12-lead ECG, read by a cardiologist. In the case of a screening programme, the start age, frequency of screening, type of screening, ECG and interpretation method and take-up rate are specified. Take-up rates have been obtained from the study data set for both opportunistic pulse-taking and attendance for systematic screening. For systematic screening, a screening event occurs immediately when a patient reaches the age at which screening is due to happen. For opportunistic screening, pulse-taking occurs at the screening age plus a proportion of that year taken at random from a standard uniform distribution. The sensitivity and specificity of every screening option were obtained from the trial data. Routine detection of AF is also incorporated into the model. In the absence of published data, an arbitrary length of time is specified and an undiagnosed patient is diagnosed when routine detection becomes the next event. The length of time chosen was 3 years plus or minus a random proportion of that year, specified in the model as the negative natural log of 1 minus a random number between 0 and 1 from a standard uniform distribution.

Treatment of AF

In the model it is assumed that any patient diagnosed with AF will begin treatment to reduce the risk of ischaemic stroke. Treatment is specified before the model is run. Once a patient is on treatment, the probability of ischaemic and haemorrhagic events occurring is adjusted to take into account the effect of treatment. Patients remain on the specified treatment until death unless a subsequent event results in its discontinuation. Information on data used to estimate the reduction or increase in risk of thrombotic and haemorrhagic events will be covered within the subsection for that event. Other treatments available for AF, including cardioversion and drugs for rate control (e.g. β-blockers, digoxin) and rhythm control (soltalol, amiodarone), are not included in this model. In base-case runs of the model, warfarin is the treatment of choice.

Ischaemic events

Data for first ischaemic stroke without AF are derived from the Oxfordshire Community Stroke Project (OCSP),[60] with separate incident rates for men and women for three age groups (65–74, 75–84 and ≥ 85 years). Within the study, the stroke rates were for any type of stroke; therefore, the estimate of 81% of strokes being of an ischaemic nature[61] was used and the stroke rates were adjusted accordingly. A previous ischaemic stroke results in an increased risk of a further stroke; therefore, probabilities are adjusted to account for this. The three-fold increase in risk of stroke was derived from the pooled results of the AF treatment trials.[22] Once a patient has AF (diagnosed or undiagnosed), the probability of an ischaemic stroke is adjusted to take into account the increased risk of this event occurring. The five-fold increase in stroke risk is well documented from data generated by the Framingham Study.[4] The reduction in risk of an ischaemic stroke by taking warfarin or aspirin was taken from the AF treatment trials data.[22]

The risk of having a fatal stroke was estimated using data from several studies.[13–19] A simplifying assumption was made that risk would be the same for subsequent strokes.[56] The probability of having a disabling stroke was obtained from the OCSP data[61] and is defined as being "functionally dependent after 1 year". If a stroke is not fatal or disabling it is defined as a non-disabling stroke.

Haemorrhagic events

The incidence of haemorrhagic stroke has not been well documented as it is much less prevalent than ischaemic stroke; therefore, data quoted by a previous modelling study and assumptions made have been used.[62] The annual rate of intracranial bleeding in anticoagulated patients was reported in the SPAF II study[19] to be 0.5% in patients aged 75 and younger (average 64) and 1.8% in those older than 75 (average 80). The risk was extrapolated for older ages, as the risk of haemorrhagic stroke increases with age. There were no reliable data on estimates for non-anticoagulated patients. Data from a systematic review of patients without AF who were anticoagulated reported that anticoagulation doubled the risk of death from intracranial haemorrhage.[63] In addition, a cohort study of patients with AF reported a hazard ratio of approximately 2 in those taking warfarin compared with those not taking warfarin. Therefore, the assumption was made that the risk of intracranial haemorrhage with anticoagulants was double, and the SPAF II estimates were halved. The risk of having a fatal haemorrhagic stroke was estimated using OCSP data,[61] taking into account both intracerebral haemorrhage and subarachnoid haemorrhage. An assumption was made that all strokes would be disabling and a further stroke would be fatal.

Gastrointestinal bleed

The incidence of major gastrointestinal bleed is not well documented in non-anticoagulated patients. The rate for patients on aspirin reported in SPAF II, 1 per 100 persons per year at age 65 increased by 3% per year, was used.[19] Results from the EAFT[17] indicate a three-fold increase in the risk of major extracranial haemorrhage in anticoagulated patients; therefore, this increased risk was assumed in the model.

Other-cause mortality

Mortality data were obtained from standard UK life tables (Government Actuary's Department). A relative risk of 1.92 was used for all-cause mortality in patients with AF,[10] with adjustment made to the life tables to avoid double counting of fatal strokes. The percentage of all deaths attributable to cerebrovascular diseases [International Classification of Disease (ICD)-10 codes I60–I69] in three age groups (65–74, 75–84 and ≥ 85 years) was calculated using data available on underlying causes of death for 2003 registrations for England and Wales.[64] The proportion of cerebrovascular disease deaths was then multiplied by the overall mortality rate (for every age) to calculate the proportion of mortality rate attributable to cerebrovascular disease. This was then deducted from the overall mortality rate to give an adjusted mortality rate.

Costs

Screening costs were obtained from the economic evaluation of the trial. The estimated mean one-off cost of a mild ischaemic stroke event taking into account outpatient and primary care, and the cost of a fatal stroke (ischaemic or haemorrhagic) were obtained from a previous UK modelling study[56] that used published data from Scotland.[65,66] The estimated mean acute cost of a disabling ischaemic or haemorrhagic stroke event taking into hospital care and rehabilitation only, and annual long-term care costs of disabling ischaemic and haemorrhagic stroke events were obtained from estimates from a published stroke care model.[67] The one-off cost of a major gastrointestinal bleed was obtained from NHS Reference Costs for 2003. The estimated cost of warfarin treatment in terms of INR monitoring for 1 year is an average of hospital and primary care-based monitoring for ten visits, where data were collected from local NHS providers. Owing to the very small cost of warfarin and aspirin tablets, they were not included in the model. All costs were inflated to 2003 prices. Costs are discounted at 3.5% per year, in line with current UK Treasury guidance.

Quality of life

The assumption was made that warfarin treatment reduces quality of life because of the inconvenience of having frequent blood tests; however taking aspirin does not. The utility score associated with warfarin treatment and the short-term utility loss for a gastrointestinal bleed were derived from a standard gamble study.[68] Values for mild ischaemic stroke, and disabling ischaemic and haemorrhagic stroke were obtained from a previous time trade-off study.[26] QALYs are discounted at 3.5% per year, in line with current UK Treasury guidance.

Chapter 3
Results

Trial results

Practice characteristics

Fifty practices participated in the study and were randomised to control or intervention, stratified by list size and deprivation (Townsend score). The two arms were not significantly different in terms of number of partners (2.92 versus 3.52), mean list size (5489 versus 5961) or deprivation score (1.40 versus 1.27). The characteristics of every participating practice are shown in *Tables 8* and *9*, and data are for the period when randomisation took place (2001).

In total, 4936 patients were recruited to the control arm, and 4933 patients to the opportunistic and systematic screening arms. Patient age was calculated using 1 January 2001 as the reference date, as this date was used in selecting patients aged 65 and over from practice lists. Forty-three per cent of patients were male, and the average age of patients was approximately 75 years in all arms, with the distribution of age non-normal and highly positively skewed towards younger ages. The number of patients in each arm of the trial and their overall characteristics are shown in *Table 10*.

In the control arm, the number of patients randomised per practice was 200, except for one practice with a small practice list size where only 136 patients could be randomised. The gender and age characteristics of each control practice are shown in *Table 11*.

In the intervention practices, 400 patients were required, equally randomised to opportunistic screening and systematic screening. The number of patients randomised per practice was balanced to take into account list size and proportion of list size aged 65 and over, as some practices did not

TABLE 8 *Control practices*

Practice number	Partners	Townsend score	List size
1	4	6.55	7,481
2	6	2.02	8,200
3	5	–0.50	6,700
4	2	–1.98	3,928
5	2	0.15	2,601
6	3	3.38	5,440
7	3	1.97	6,418
8	3	5.56	3,745
9	6	1.89	12,096
10	4	0.40	7,208
11	2	–3.21	5,606
12	2	–2.50	3,800
13	1	–3.83	2,600
14	2	–3.23	5,390
15	4	0.66	4,454
16	2	1.55	3,149
17	1	0.29	3,352
18	3	–3.85	6,875
19	1	3.76	3,715
20	1	1.98	1,589
21	6	6.61	5,911
22	2	3.27	5,400
23	1	4.82	3,515
24	2	5.08	6,263
25	5	4.10	11,800
Mean	2.92	1.40	5,489

TABLE 9 *Intervention practices*

Practice number	Partners	Townsend score	List size
26	4	–0.03	8,098
27	1	4.25	2,100
28	3	–1.07	4,642
29	2	–2.94	2,295
30	3	5.70	4,891
31	1	5.54	2,285
32	4	0.83	8,364
33	5	2.73	6,300
34	3	2.94	4,913
35	4	–2.66	6,357
36	6	–5.52	11,000
37	4	2.58	7,137
38	1	3.65	3,125
39	2	–0.14	4,590
40	7	4.47	10,536
41	2	0.65	2,070
42	2	–0.64	3,610
43	5	6.68	7,672
44	4	–2.12	6,092
45	2	–1.46	3,900
46	1	3.99	2,400
47	4	0.01	6,800
48	9	1.79	16,000
49	4	–3.48	6,703
50	5	6.10	7,135
Mean	3.52	1.27	5,961

TABLE 10 *Practice population*

	All	Control	Intervention	
			Systematic	Opportunistic
Number of patients	14802	4936	4933	4933
Male (%)	6302 (42.6)	2079 (42.1)	2119 (43.0)	2104 (42.7)
Mean age (SD)	75.3 (7.2)	75.5 (7.2)	75.2 (7.3)	75.1 (7.1)
Median age	74.1	74.5	73.8	74.0
Age <75 (%)	8059 (54.4)	2597 (52.6)	2710 (54.9)	2755 (55.8)

TABLE 11 *Control patients*

Practice number	Patients	Male (%)	Age <75 (%)
1	200	107 (53.5)	110 (55.0)
2	200	78 (39.0)	104 (52.0)
3	200	77 (38.5)	120 (60.0)
4	200	88 (44.0)	122 (61.0)
5	200	74 (37.0)	95 (47.5)
6	200	85 (42.5)	107 (53.5)
7	200	90 (45.0)	110 (55.0)
8	200	95 (47.5)	78 (39.0)
9	200	68 (34.0)	98 (49.0)
10	200	73 (36.5)	73 (36.5)
11	200	75 (37.5)	102 (51.0)
12	200	85 (42.5)	116 (58.0)
13	200	93 (46.5)	128 (64.0)
14	200	86 (43.0)	96 (48.0)
15	200	77 (38.5)	91 (45.5)
16	200	84 (42.0)	98 (49.0)
17	200	79 (39.5)	103 (51.5)
18	200	97 (48.5)	126 (63.0)
19	200	88 (44.0)	106 (53.0)
20	136	50 (36.8)	65 (47.8)
21	200	86 (43.0)	103 (51.5)
22	200	94 (47.0)	126 (63.0)
23	200	80 (40.0)	122 (61.0)
24	200	79 (39.5)	102 (51.0)
25	200	91 (45.5)	97 (48.5)
Total	4936	2079 (42.1)	2597 (52.6)

TABLE 12 *Opportunistic patients*

Practice number	Patients	Male (%)	Age <75 (%)
26	220	98 (44.5)	133 (60.5)
27	41	19 (46.3)	25 (61.0)
28	210	96 (45.7)	112 (53.3)
29	164	61 (37.2)	81 (49.4)
30	220	108 (49.1)	120 (54.5)
31	134	68 (50.7)	103 (76.9)
32	220	93 (42.3)	128 (58.2)
33	220	108 (49.1)	124 (56.4)
34	210	79 (37.6)	123 (58.6)
35	210	79 (37.6)	120 (57.1)
36	220	89 (40.5)	126 (57.3)
37	220	95 (43.2)	124 (56.4)
38	210	95 (45.2)	106 (50.5)
39	210	86 (41.0)	118 (56.2)
40	220	87 (39.5)	130 (59.1)
41	210	86 (41.0)	97 (46.2)
42	107	48 (44.9)	61 (57.0)
43	220	84 (38.2)	114 (51.8)
44	220	102 (46.4)	124 (56.4)
45	210	91 (43.3)	117 (55.7)
46	157	72 (45.9)	79 (50.3)
47	220	91 (41.4)	106 (48.2)
48	220	96 (43.6)	141 (64.1)
49	220	81 (36.8)	122 (55.5)
50	220	92 (41.8)	121 (55.0)
Total	4933	2104 (42.7)	2755 (55.8)

have enough eligible patients. In the systematic arm, computer searches were also carried out to identify patients with associated risk factors, as listed in Chapter 2. A total of 2128 (43.1%) patients had one or more of these associated conditions and were therefore considered to be high-risk patients. *Tables 12–14* show the gender and age distribution of opportunistic, systematic and high-risk systematic patients, respectively.

Baseline note searches

Computer searches of drugs and appropriate disease registers were undertaken to identify patients most likely to have a diagnosis of AF. In total, ten computer searches were undertaken and are listed in *Table 1* (see Chapter 2). Once a patient was identified on a computer search list, their paper and computer notes (where applicable) were searched for a diagnosis of AF and the evidence of diagnosis was noted.

A random sample of patients not found on one of the computer searches (negatives) also had their records checked for a diagnosis of AF. This was done to check whether the computer searches were missing any patients diagnosed with AF. In each study arm, 5% of patients in each practice not found on any computer search had their notes searched. In total, only three patients in this sample were found to have a diagnosis of AF.

TABLE 13 *Systematic patients*

Practice number	Patients	Male (%)	Age <75 (%)
26	220	100 (45.5)	127 (57.7)
27	41	17 (41.5)	15 (36.6)
28	210	71 (33.8)	106 (50.5)
29	164	72 (43.9)	84 (51.2)
30	220	90 (40.9)	114 (51.8)
31	134	76 (56.7)	96 (71.6)
32	220	93 (42.3)	113 (51.4)
33	220	96 (43.6)	134 (60.9)
34	210	99 (47.1)	116 (55.2)
35	210	70 (33.3)	109 (51.9)
36	220	94 (42.7)	130 (59.1)
37	220	94 (42.7)	120 (54.5)
38	210	98 (46.7)	113 (53.8)
39	210	92 (43.8)	113 (53.8)
40	220	94 (42.7)	140 (63.6)
41	210	83 (39.5)	97 (46.2)
42	107	48 (44.9)	55 (51.4)
43	220	85 (38.6)	114 (51.8)
44	220	85 (38.6)	124 (56.4)
45	210	88 (41.9)	116 (55.2)
46	157	67 (42.7)	86 (54.8)
47	220	92 (41.8)	106 (48.2)
48	220	97 (44.1)	122 (55.5)
49	220	98 (44.5)	121 (55.0)
50	220	120 (54.5)	139 (63.2)
Total	4933	2119 (43.0)	2710 (54.9)

TABLE 14 *High-risk systematic patients*

Practice number	Patients (% of all patients)	Male (%)	Age <75 (%)
26	99 (45.0)	47 (47.5)	53 (53.5)
27	12 (29.3)	4 (33.3)	1 (8.3)
28	102 (48.6)	34 (33.3)	50 (49.0)
29	47 (28.7)	20 (42.6)	22 (46.8)
30	89 (40.5)	33 (37.1)	49 (55.1)
31	74 (55.2)	42 (56.8)	52 (70.3)
32	85 (38.6)	30 (35.3)	42 (49.4)
33	91 (41.4)	39 (42.9)	57 (62.6)
34	88 (41.9)	38 (43.2)	48 (54.5)
35	108 (51.4)	30 (27.8)	59 (54.6)
36	95 (43.2)	44 (46.3)	64 (67.4)
37	84 (38.2)	38 (45.2)	48 (57.1)
38	83 (39.5)	30 (36.1)	48 (57.8)
39	105 (50.0)	43 (41.0)	58 (55.2)
40	88 (40.0)	35 (39.8)	57 (64.8)
41	144 (68.6)	60 (41.7)	62 (43.1)
42	38 (35.5)	21 (55.3)	22 (57.9)
43	75 (34.1)	24 (32.0)	46 (61.3)
44	93 (42.3)	33 (35.5)	49 (52.7)
45	108 (51.4)	46 (42.6)	59 (54.6)
46	73 (46.5)	31 (42.5)	40 (54.8)
47	94 (42.7)	38 (40.4)	44 (46.8)
48	86 (39.1)	43 (50.0)	47 (54.7)
49	82 (37.3)	37 (45.1)	47 (57.3)
50	85 (38.6)	40 (47.1)	67 (78.8)
Total	2128 (43.1)	880 (41.4)	1191 (56.0)

TABLE 15 *Prevalence of AF of all study patients*

Patients	Notes searched	Missing notes	Diagnosis of AF	Prevalence (%) (95% CI)	No diagnosis of AF in notes
14,802	5216 (35.2%)	21	1068	7.2 (6.8 to 7.7)	4,127

Baseline prevalence (known AF)

The baseline prevalence refers to the cases of AF that are known and diagnosed, as there may also be undiagnosed cases. If a patient was found on one of the ten computer searches, an attempt was made to search their notes for evidence of AF. Prevalence estimates for each practice are calculated omitting those patients whose notes were missing. In total, 5216 (35%) patient notes were searched and 1068 (7.2%, 95% CI 6.8 to 7.7%) of the study population had a diagnosis of AF. Data were missing for 21 patients, six male and 15 female; four were aged 65–74 years and 17 were 75 or older (*Table 15*).

The overall individual level baseline prevalence in the control arm was 7.9% (95% CI 7.2 to 8.7%), and it was 6.9% (95% CI 6.2 to 7.6%) in both the opportunistic and systematic arms. Individual baseline prevalence in the high-risk subgroup was 8.7% (95% CI 7.6 to 10.0%). In total, 186 (54.9%) of the 339 AF patients in the systematic arm were in the high-risk subgroup. In all trial arms, prevalence was higher in males than in females, and higher in patients aged 75 years and over than in those aged 65–74 years. The breakdown of baseline prevalence, by arm, gender and age can be found in *Tables 16* and *17*. In all three trial arms a small proportion of patient notes could not be located. If all of the patients did not have AF the prevalence did not change. However, if all were patients with AF then prevalence estimates would be slightly higher, especially in the control arm

TABLE 16 *Prevalence of AF by gender, age and study group*

Group	Patients	Prevalence (%)				
		Overall	Males	Females	Age <75	Age ≥75
All	14,802	7.2 (1068/14,781)	7.8 (491/6296)	6.8 (577/8485)	4.6 (373/8055)	10.3 (695/6729)
Control	4936	7.9 (389/4923)	8.8 (183/2075)	7.2 (206/2848)	4.5 (118/2594)	11.6 (271/2329)
Opportunistic	4933	6.9 (340/4930)	7.5 (157/2102)	6.5 (183/2828)	4.3 (118/2752)	10.2 (222/2181)
Systematic	4933	6.9 (339/4928)	7.1 (151/2119)	6.7 (188/2809)	5.1 (137/2709)	9.1 (202/2219)
High risk	2128	8.7 (185/2127)	4.5 (85/1880)	8.0 (100/1247)	7.0 (83/1191)	10.9 (102/936)

Denominators are minus the patients with missing note search data.

TABLE 17 *Prevalence of AF by age and gender groups and study group*

Group	Patients	Prevalence (%)				
			Age <75		Age ≥75	
		Overall	Males	Females	Males	Females
All	14,802	7.2 (1068/14,781)	5.5 (213/3838)	3.8 (160/4217)	11.3 (278/2458)	9.8 (417/4268)
Control	4936	7.9 (389/4923)	6.1 (74/1216)	3.2 (44/1378)	12.7 (109/859)	11.0 (162/1470)
Opportunistic	4933	6.9 (340/4930)	5.4 (70/1304)	3.3 (48/1448)	10.9 (87/795)	9.8 (135/1380)
Systematic	4933	6.9 (339/4928)	5.2 (69/1318)	4.9 (68/1391)	10.2 (82/801)	8.5 (120/1418)
High risk	2128	8.7 (185/2127)	8.0 (45/561)	6.0 (38/630)	12.5 (40/319)	10.0 (62/617)

Denominators are minus the patients with missing note search data.

TABLE 18 *Maximum and minimum prevalence*

Group	Missing notes	AF	Minimum prevalence	Maximum prevalence
Control (n = 4936)	13	389	7.9%	8.1%
Opportunistic (n = 4933)	3	340	6.9%	7.0%
Systematic (n = 4933)	5	339	6.9%	7.0%

(*Table 18*). The baseline prevalence ranged from 4.0 to 12.0% in the control practices (*Table 19*), 2.2 to 11.3% in the opportunistic arm (*Table 20*) and 2.2 to 10.5% in the systematic arm (*Table 21*). Prevalence estimates for high-risk systematic patients ranged from 1.4 to 16.7% (*Table 22*).

In total, 5216 study patients were found on at least one of the ten computer searches, and 20.5% of these had a diagnosis of AF (*Table 23*). The success rate of a search is the percentage of patients found on a note search with an actual diagnosis of AF. Overall, the most successful searches were those indicating supraventricular arrhythmia (90.2%) and AF/flutter (85.6%), and the most successful drug searches were digoxin (76.0%) and warfarin (62.9%). The sensitivity and specificity of each search were also calculated, with digoxin having the highest sensitivity at 59.2%. Except for aspirin (79.3%), all searches had a specificity of at least 98%. A breakdown of computer search success rate by trial arm can be found in *Table 24*.

Twelve-month note searches

Twelve months after the baseline searches took place, the same computer searches of drugs and appropriate disease registers were undertaken to identify new diagnoses of AF.

TABLE 19 *Control patients: baseline prevalence of AF*

Practice number	Patients	Notes searched	Missing notes	Diagnosis of AF	Prevalence (%)	No diagnosis of AF
1	200	73	1	14	7.0	58
2	200	59	0	14	7.0	45
3	200	79	0	21	10.5	58
4	200	84	0	17	8.5	67
5	200	69	1	10	5.0	58
6	200	65	1	21	10.6	43
7	200	57	0	17	8.5	40
8	200	66	2	23	11.6	41
9	200	57	1	8	4.0	48
10	200	84	0	24	12.0	60
11	200	43	0	9	4.5	34
12	200	62	0	14	7.0	48
13	200	49	0	16	8.0	33
14	200	55	1	12	6.0	42
15	200	79	0	19	9.5	60
16	200	80	0	24	12.0	56
17	200	95	2	15	7.5	78
18	200	61	0	16	8.0	45
19	200	53	1	14	7.0	38
20	136	54	0	12	8.8	42
21	200	74	1	14	7.0	59
22	200	72	0	12	6.0	60
23	200	83	1	15	7.5	67
24	200	89	0	15	7.5	74
25	200	78	1	13	6.5	64
Total	4936	1720 (34.8%)	13	389	7.9	1318

TABLE 20 *Opportunistic patients: baseline prevalence of AF*

Practice number	Patients	Notes searched	Missing notes	Diagnosis of AF	Prevalence (%)	No diagnosis of AF
26	220	65	0	13	5.9	52
27	41	7	0	2	4.9	5
28	210	63	0	19	9.0	44
29	164	66	0	14	8.5	52
30	220	75	0	13	5.9	62
31	134	43	0	3	2.2	40
32	220	56	0	15	6.8	41
33	220	92	0	15	6.8	77
34	210	77	1	15	7.2	61
35	210	85	0	18	8.6	67
36	220	78	1	14	6.4	63
37	220	61	0	13	5.9	48
38	210	76	0	15	7.1	61
39	210	73	0	17	8.1	56
40	220	80	0	20	9.1	60
41	210	115	0	6	2.9	109
42	107	50	1	12	11.3	37
43	220	67	0	14	6.4	53
44	220	73	0	17	7.7	56
45	210	72	0	8	3.8	64
46	157	80	0	14	8.9	66
47	220	78	0	23	10.5	55
48	220	82	0	14	6.4	68
49	220	75	0	13	5.9	62
50	220	58	0	13	5.9	45
Total	4933	1747 (35.4%)	3	340	6.9	1404

TABLE 21 *Systematic patients: baseline prevalence of AF*

Practice number	Patients	Notes searched	Missing notes	Diagnosis of AF	Prevalence (%)	No diagnosis of AF
26	220	66	0	14	6.4	52
27	41	9	0	4	9.8	5
28	210	60	0	19	9.0	41
29	164	66	0	14	8.5	52
30	220	79	0	13	5.9	66
31	134	48	0	3	2.2	45
32	220	60	1	12	5.5	47
33	220	87	1	13	5.9	73
34	210	75	0	14	6.7	61
35	210	86	0	19	9.0	67
36	220	80	0	16	7.3	64
37	220	66	0	14	6.4	52
38	210	74	0	14	6.7	60
39	210	65	0	16	7.6	49
40	220	85	0	23	10.5	62
41	210	112	0	8	3.8	104
42	107	49	0	10	9.3	39
43	220	60	1	12	5.5	47
44	220	76	1	17	7.8	58
45	210	78	1	9	4.3	68
46	157	80	0	12	7.6	68
47	220	75	0	21	9.5	54
48	220	79	0	15	6.8	64
49	220	72	0	14	6.4	58
50	220	62	0	13	5.9	49
Total	4933	1749 (35.5%)	5	339	6.9	1405

TABLE 22 *High-risk systematic patients: baseline prevalence of AF*

Practice number	Patients	Diagnosis of AF	High-risk patients	High-risk patients with AF	Prevalence (%)
26	220	14	99	8	8.1
27	41	4	12	2	16.7
28	210	19	102	14	13.7
29	164	14	47	5	10.6
30	220	13	89	10	11.2
31	134	3	74	1	1.4
32	220	12	85	8	9.4
33	220	13	91	5	5.5
34	210	14	88	7	8.0
35	210	19	108	9	8.3
36	220	16	95	10	10.5
37	220	14	84	7	8.3
38	210	14	83	9	10.8
39	210	16	105	9	8.6
40	220	23	88	7	8.0
41	210	8	144	7	4.9
42	107	10	38	3	7.9
43	220	12	75	3	4.1
44	220	17	93	12	12.9
45	210	9	108	4	3.7
46	157	12	73	5	6.8
47	220	21	94	15	16.0
48	220	15	86	11	12.8
49	220	14	82	6	7.3
50	220	13	85	8	9.4
Total	4933	339	2128 (43.1%)	186	8.7

TABLE 23 *Computer search strategy and diagnosis of AF*

Search	Notes searched	Missing notes	Diagnosis of AF (%)	Sensitivity (%)	Specificity (%)
G573 atrial fibrillation/flutter	662	2	567 (85.6)	53.1	99.3
327 ECG supraventricular arrhythmia	41	0	37 (90.2)	3.5	100.0
181 Palpitations	264	0	64 (24.2)	6.0	98.5
Digoxin	832	5	632 (76.0)	59.2	98.6
Amiodarone	181	0	111 (61.3)	10.4	99.5
Verapamil	339	1	105 (31.0)	9.8	98.3
Sotalol	121	0	72 (59.5)	6.7	99.6
Metoprolol	198	0	33 (16.7)	3.1	98.8
Warfarin	732	4	453 (61.9)	42.2	98.0
Aspirin	4208	15	625 (14.9)	57.8	79.3
All ten searches	5216	21	1068 (20.5)	100	100

TABLE 24 *Computer search strategy: diagnosis of AF by trial arm*

Search	Overall (%)	Control (%)	Opportunistic (%)	Systematic (%)
G573 atrial fibrillation/flutter	567 (85.6)	192 (88.1)	184 (85.6)	191 (83.0)
327 ECG supraventricular arrhythmia	37 (90.2)	13 (92.9)	8 (80.0)	16 (94.1)
181 Palpitations	64 (24.2)	18 (24.3)	25 (25.3)	21 (23.1)
Digoxin	632 (76.0)	241 (77.2)	205 (73.7)	186 (76.9)
Amiodarone	111 (61.3)	33 (55.0)	38 (61.3)	40 (67.8)
Verapamil	105 (31.0)	35 (36.8)	38 (29.2)	32 (27.4)
Sotalol	72 (59.5)	29 (58.0)	19 (61.3)	24 (60.0)
Metoprolol	33 (16.7)	9 (13.0)	14 (21.2)	10 (15.9)
Warfarin	453 (62.9)	171 (70.1)	134 (56.5)	148 (59.0)
Aspirin	625 (14.9)	226 (16.5)	208 (14.6)	191 (13.5)
All ten searches	1068 (20.5)	389 (22.6)	340 (19.5)	339 (19.4)

Twelve-month incidence

Incidence rates were calculated after removing those patients diagnosed with AF at baseline and patients where notes could not be found. In this case incidence refers to the number of new cases of AF that were known and diagnosed within the study period. Data were missing for patients where notes were no longer available as a result of death or their no longer being at the practice. Data are presented for the high-risk subset of the systematic arm alone, and also for the systematic group assuming that only high-risk patient screening has occurred. Therefore, any cases detected by the screening programme for systematic patients not in the high-risk group are not included, but cases found routinely are included.

At the practice level, the mean incidence of AF in the control arm was 0.99% (95% CI 0.71 to 1.27%) per year, 1.71% (95% CI 1.23 to 2.19%) in the opportunistic arm and 1.52% (95% CI 1.13 to 1.92%) in the systematic arm. There was a significant difference in the mean incidence of AF between the three arms ($F_{2,72} = 3.90$, $p = 0.025$). Using a Bonferroni adjustment to account for multiple testing, a significantly increased incidence was found in the opportunistic arm compared with the control arm ($p = 0.027$).

At the patient level the incidence rates were 1.04% (95% CI 0.78 to 1.38%) for the control arm, 1.64% (95% CI 1.31 to 2.05%) for the opportunistic arm and 1.62% (95% CI 1.29 to 2.03%) for the systematic arm (*Table 25*). There was a significant difference between the three arms ($\chi^2 = 7.417$, df = 2, $p = 0.025$). Significant differences were found between the control arm and the opportunistic arm ($p = 0.013$) and the control arm and the systematic arm ($p = 0.016$), taking into account multiple testing.

Overall, screening practices identified substantially more cases of AF than the control practices [odds ratio (OR) 1.61, 95% CI 1.14 to 2.29, $p = 0.0085$], and similar results were obtained when baseline prevalence was removed from the model (OR 1.58, 95% CI 1.12 to 2.22, $p = 0.0103$). Similar results were also gained for the replication of the analysis in Proc Genmod (OR 1.61, 95% CI 1.15 to 2.30).

TABLE 25 *Incidence of AF by group*

Group	Patients	Baseline AF	Missing notes		12-month incidence denominator	Incident cases	Incidence (%)
			Baseline	12 months			
Control	4936	389	13	21	4513	47	1.04
Opportunistic	4933	340	3	15	4575	75	1.64
Systematic	4933	339	5	27	4562	74	1.62
High risk only	2128	185	1	9	1933	42	2.18
High-risk screening only	4933	339	5	27	4562	53	1.16

TABLE 26 *Incidence of AF by gender, age and study group*

Group	Patients	Incidence (%)			
		Males	Females	Age <75	Age ≥75
Control	4936	0.85 (16/1880)	1.18 (31/2633)	0.73 (18/2472)	1.42 (29/2041)
Opportunistic	4933	1.96 (38/1941)	1.41 (37/2634)	1.18 (31/2628)	2.23 (44/1947)
Systematic	4933	2.25 (44/1958)	1.15 (30/2604)	1.17 (30/2562)	2.20 (44/2000)
High risk alone	2128	3.16 (25/791)	1.49 (17/1142)	1.36 (15/1103)	3.25 (27/830)
High-risk screening only	4933	1.63 (32/1958)	0.81 (21/2604)	1.09 (28/2562)	1.75 (35/2000)

The opportunistic screening group had 75 new cases of AF and the systematic screening group 74 new cases. Differences in screening method had no effect on the rate of detection between the groups (OR 0.99, 95% CI 0.72 to 1.37, $p = 0.95$).

The effect of screening on the incidence of AF in high-risk cases was investigated with practice-level random effects by age and by gender. In the systematic arm there were 42 incident cases in 1933 patients and 37 incident cases out of 1924 patients in the opportunistic arm. There was no systematic difference between detection of cases among those identified to be at high risk between the groups. The odds ratio for interaction between systematic screening and high-risk patients on incident cases was 1.34 (95% CI 0.70 to 2.57, $p = 0.38$). There was no effect of age on outcome; the odds ratio for interaction between age greater than median and systematic screening on incident cases was 1.06 (95% CI 0.53 to 2.10, $p = 0.88$), and similarly there was no effect of gender on outcome; the odds ratio for interaction between gender (male) and systematic screening on incident cases was 1.41 (95% CI 0.73 to 2.70, $p = 0.31$). Analyses undertaken without fitting random effects gave very similar results.

In all trial arms, 12-month incidence was higher in patients aged 75 years and over than in those aged 65–74 years. In the intervention arms, males had a higher incidence than females, but a lower incidence in the control arm. Incidence was also higher in all age and gender groups for the high-risk patients (*Table 26*). The same relationship with incidence was also observed for the combined age/gender subgroups (*Table 27*).

The incidence rates ranged from 0 to 2.67% in the control practices (*Table 28*), 0 to 5.13% in the opportunistic arm (*Table 29*) and 0 to 3.88% in the systematic arm (*Table 30*). Incidence estimates for high-risk systematic patients ranged from 0 to 5.49% (*Table 31*). In total, 42 (56.8%) of the 74 incident cases of AF in the systematic arm were patients in the high-risk subgroup.

Twelve-month prevalence

Prevalence of AF at 12 months takes into account the cases of AF identified from searches at baseline and 12 months. Data were missing for patients where notes were no longer available as a result of death or their no longer being at the practice.

At the practice level, the mean 12-month prevalence in the control arm was 8.9% (95% CI 7.9 to 8.9%), 8.5% (95% CI 7.6 to 9.4%) in the opportunistic arm and 8.4% (95% CI 7.6 to 9.3%) in the systematic arm. There was no significant difference in the mean community prevalence of

TABLE 27 *Incidence of AF by age and gender groups and study group*

Group	Patients	Incidence (%)			
		Age <75		Age ≥75	
		Males	Females	Males	Females
Control	4936	0.61 (7/1139)	0.83 (11/1333)	1.21 (9/741)	1.54 (20/1300)
Opportunistic	4933	1.62 (20/1233)	0.79 (11/1395)	2.54 (18/708)	2.10 (26/1239)
Systematic	4933	1.69 (21/1243)	0.68 (9/1319)	3.22 (23/715)	1.63 (21/1285)
High risk	2128	1.95 (10/514)	0.85 (5/589)	5.42 (15/277)	2.17 (12/553)
High-risk screening	4933	1.05 (13/1243)	0.38 (5/1319)	2.66 (19/715)	1.25 (16/1285)

TABLE 28 *Control patients: incidence of AF*

Practice number	Patients	Baseline missing notes	Baseline diagnosis of AF	Missing notes 12 months	Incident cases	Incidence (%)
1	200	1	14	2	2	1.09
2	200	0	14	0	2	1.08
3	200	0	21	1	2	1.12
4	200	0	17	2	1	0.55
5	200	1	10	1	3	1.60
6	200	1	21	0	3	1.69
7	200	0	17	0	1	0.55
8	200	2	23	2	1	0.58
9	200	1	8	1	1	0.53
10	200	0	24	0	1	0.57
11	200	0	9	0	1	0.52
12	200	0	14	1	2	1.08
13	200	0	16	0	1	0.54
14	200	1	12	0	1	0.53
15	200	0	19	3	4	2.25
16	200	0	24	0	4	2.27
17	200	2	15	1	1	0.55
18	200	0	16	0	1	0.54
19	200	1	14	0	2	1.08
20	136	0	12	0	0	0.00
21	200	1	14	0	1	0.54
22	200	0	12	1	5	2.67
23	200	1	15	0	1	0.54
24	200	0	15	4	2	1.10
25	200	1	13	2	4	2.17
Total	4936	13	389	21	47	1.04

AF at 12 months between the three arms ($F_{2,72} = 0.320$, $p = 0.728$).

At the patient level the 12-month prevalence rates were 8.9% (95% CI 8.1 to 9.7%) for the control arm and 8.4% for both the opportunistic (95% CI 7.7 to 9.3%) and systematic arms (95% CI 7.7 to 9.2%). There was no significant difference between arms ($\chi^2 = 0.879$, df = 2, $p = 0.644$). The overall 12-month prevalence was 8.6% (95% CI 8.2 to 9.1%) (*Table 32*).

In all trial arms, the 12-month prevalence was higher in males than in females, and in patients aged 75 years and over than in those aged 65–74 years. Prevalence was also higher in all age and gender groups for the high-risk patients compared with all patients. These relationships were also observed for the combined age/gender subgroups, and the highest prevalence was found in males aged 75 and over (*Table 33*).

TABLE 29 *Opportunistic patients: incidence of AF*

Practice number	Patients	Baseline missing notes	Baseline diagnosis of AF	Missing notes 12 months	Incident cases	Incidence (%)
26	220	0	13	0	3	1.45
27	41	0	2	0	2	5.13
28	210	0	19	0	3	1.57
29	164	0	14	0	2	1.33
30	220	0	13	1	5	2.43
31	134	0	3	0	0	0.00
32	220	0	15	0	3	1.46
33	220	0	15	2	3	1.48
34	210	1	15	0	4	2.06
35	210	0	18	0	5	2.60
36	220	1	14	1	2	0.98
37	220	0	13	0	8	3.86
38	210	0	15	0	3	1.54
39	210	0	17	1	4	2.08
40	220	0	20	0	3	1.50
41	210	0	6	0	4	1.96
42	107	1	12	1	1	1.08
43	220	0	14	1	1	0.49
44	220	0	17	0	1	0.49
45	210	0	8	0	2	0.99
46	157	0	14	0	2	1.40
47	220	0	23	0	1	0.51
48	220	0	14	0	2	0.97
49	220	0	13	0	8	3.86
50	220	0	13	8	3	1.51
Total	4933	3	340	15	75	1.64

TABLE 30 *Systematic patients: incidence of AF*

Practice number	Patients	Baseline missing notes	Baseline diagnosis of AF	Missing notes 12 months	Incident cases	Incidence (%)
26	220	0	14	0	8	3.88
27	41	0	4	0	0	0.00
28	210	0	19	0	4	2.09
29	164	0	14	1	3	2.01
30	220	0	13	0	1	0.48
31	134	0	3	3	0	0.00
32	220	1	12	1	6	2.91
33	220	1	13	0	3	1.46
34	210	0	14	2	5	2.58
35	210	0	19	1	1	0.53
36	220	0	16	0	3	1.47
37	220	0	14	1	4	1.95
38	210	0	14	1	3	1.54
39	210	0	16	0	3	1.55
40	220	0	23	2	3	1.54
41	210	0	8	1	3	1.49
42	107	0	10	0	1	1.03
43	220	1	12	1	2	0.97
44	220	1	17	2	3	1.50
45	210	1	9	0	4	2.00
46	157	0	12	2	1	0.70
47	220	0	21	0	3	1.51
48	220	0	15	1	5	2.45
49	220	0	14	1	5	2.44
50	220	0	13	7	0	0.00
Total	4933	5	339	27	74	1.62

TABLE 31 *High-risk systematic patients: incidence of AF*

Practice number	High-risk patients	Missing notes	Baseline diagnosis of AF	Missing notes 12 months	Incident cases	Incidence (%)
26	99	0	8	0	5	5.49
27	12	0	2	0	0	0.00
28	102	0	14	0	3	3.41
29	47	0	5	0	3	7.14
30	89	0	10	0	1	1.27
31	74	0	1	1	0	0.00
32	85	0	8	1	3	3.95
33	91	0	5	0	1	1.16
34	88	0	7	1	1	1.25
35	108	0	9	1	1	1.02
36	95	0	10	0	2	2.35
37	84	0	7	0	2	2.60
38	83	0	9	0	0	0.00
39	105	0	9	0	2	2.08
40	88	0	7	0	1	1.23
41	144	0	7	0	2	1.46
42	38	0	3	0	1	2.86
43	75	1	3	1	1	1.43
44	93	0	12	1	1	1.25
45	108	0	4	0	3	2.88
46	73	0	5	2	1	1.52
47	94	0	15	0	3	3.80
48	86	0	11	1	3	4.05
49	82	0	6	0	2	2.63
50	85	0	8	0	0	0.00
Total	2128	1	185	9	42	2.18

TABLE 32 *Twelve-month prevalence of AF by gender, age and study group*

Group	Patients	Prevalence (%)				
		Overall	Males	Females	Age <75	Age ≥75
All	14,802	8.6 (1264/14,718)	9.4 (589/6270)	8.0 (675/8448)	5.6 (452/8035)	12.2 (812/6683)
Control	4936	8.9 (436/4902)	9.6 (199/2063)	8.3 (237/2839)	5.3 (136/2590)	13.0 (300/2312)
Opportunistic	4933	8.4 (415/4915)	9.3 (195/2098)	7.8 (220/2817)	5.4 (149/2746)	12.3 (266/2169)
Systematic	4933	8.4 (413/4901)	9.2 (195/2109)	7.8 (218/2792)	6.2 (167/2699)	11.2 (246/2202)
High risk	2128	10.7 (227/2118)	12.6 (110/876)	9.4 (117/1242)	8.3 (98/1186)	13.8 (129/932)

Denominators are minus the patients with missing note search data.

TABLE 33 *Twelve-month prevalence of AF by age and gender groups and study group*

Group	Patients	Prevalence (%)				
			Age <75		Age ≥75	
		Overall	Males	Females	Males	Females
All	14,802	8.6 (1264/14,718)	6.8 (261/3828)	6.4 (191/2967)	13.4 (328/2442)	11.4 (484/4241)
Control	4936	8.9 (436/4902)	6.7 (81/1213)	4.0 (55/1377)	13.9 (118/850)	12.4 (182/1462)
Opportunistic	4933	8.4 (415/4915)	6.9 (90/1303)	4.1 (59/1443)	13.2 (105/795)	11.7 (161/1374)
Systematic	4933	8.4 (413/4901)	6.9 (90/1312)	5.6 (77/1387)	13.2 (105/797)	10.0 (141/1405)
High risk	2128	10.7 (227/2118)	9.8 (55/559)	6.9 (43/627)	17.4 (55/317)	12.0 (74/615)

Denominators are minus the patients with missing note search data.

TABLE 34 *Maximum and minimum 12-month prevalence*

Group	Missing notes	AF	Minimum prevalence	Maximum prevalence
Control (n = 4936)	34	436	8.8%	9.5%
Opportunistic (n = 4933)	18	415	8.4%	8.8%
Systematic (n = 4933)	32	413	8.4%	9.0%

TABLE 35 *Control patients: 12-month prevalence of AF*

Practice number	Patients	Missing data	Diagnosis of AF	Prevalence (%)
1	200	3	16	8.1
2	200	0	16	8.0
3	200	1	23	11.6
4	200	2	18	9.1
5	200	2	13	6.6
6	200	1	24	12.1
7	200	0	18	9.0
8	200	4	24	12.2
9	200	2	9	4.5
10	200	0	25	12.5
11	200	0	10	5.0
12	200	1	16	8.0
13	200	0	17	8.5
14	200	1	13	6.5
15	200	3	23	11.7
16	200	0	28	14.0
17	200	3	16	8.1
18	200	0	17	8.5
19	200	1	16	8.0
20	136	0	12	8.8
21	200	1	15	7.5
22	200	1	17	8.5
23	200	1	16	8.0
24	200	4	17	8.7
25	200	3	17	8.6
Total	4936	34	436	8.9

A small proportion of patient notes could not be located. If all of these patients did not have AF the prevalence would not change a great deal. However, if all were patients with AF then prevalence estimates would be somewhat higher, with 9.5% in the control arm, 8.8% in the opportunistic arm and 9.0% in the systematic arm (*Table 34*).

The 12-month prevalence rates ranged from 4.5 to 14.0% in the control practices (*Table 35*), 2.2 to 12.4% in the opportunistic arm (*Table 36*) and 2.3 to 11.0% in the systematic arm (*Table 37*). Prevalence estimates for high-risk systematic patients ranged from 1.4 to 19.1% (*Table 38*). In total, 227 (55.0%) of the 413 AF patients in the systematic arm were in the high-risk subgroup.

Screening

Opportunistic screening

Of 4933 patients in the opportunistic screening arm, 195 (4.0%) were excluded during the 12-month period as they were no longer eligible for screening because of dying, moving practice or being terminally ill (*Table 39*). A pulse was taken from 69.2% of patients and 11.0% of these were judged as having an irregular pulse; 65.9% agreed to have an ECG, with 84 (35.3%) diagnosed as having AF, representing 2.6% of the total number of patients who had their pulse taken. Of the 123 patients who had an irregular pulse but did not have an ECG, 56 (45.5%) were already confirmed as having AF. Overall, there were 75 new cases of AF in the 12-month period in the opportunistic arm, of whom 24 had a regular pulse recorded.

TABLE 36 *Opportunistic patients: 12-month prevalence of AF*

Practice number	Patients	Missing data	Diagnosis of AF	Prevalence (%)
26	220	0	16	7.3
27	41	0	4	9.8
28	210	0	22	10.5
29	164	0	16	9.8
30	220	1	18	8.2
31	134	0	3	2.2
32	220	0	18	8.2
33	220	2	18	8.3
34	210	1	19	9.1
35	210	0	23	11.0
36	220	2	16	7.3
37	220	0	21	9.5
38	210	0	18	8.6
39	210	1	21	10.0
40	220	0	23	10.5
41	210	0	10	4.8
42	107	2	13	12.4
43	220	1	15	6.8
44	220	0	18	8.2
45	210	0	10	4.8
46	157	0	16	10.2
47	220	0	24	10.9
48	220	0	16	7.3
49	220	0	21	9.5
50	220	8	16	7.5
Total	4933	18	415	8.4

TABLE 37 *Systematic patients: 12-month prevalence of AF*

Practice number	Patients	Missing data	Diagnosis of AF	Prevalence (%)
26	220	0	22	10.0
27	41	0	4	9.8
28	210	0	23	11.0
29	164	1	17	10.4
30	220	0	14	6.4
31	134	3	3	2.3
32	220	2	18	8.3
33	220	1	16	7.3
34	210	2	19	9.1
35	210	1	20	9.6
36	220	0	19	8.6
37	220	1	18	8.2
38	210	1	17	8.1
39	210	0	19	9.0
40	220	2	26	11.9
41	210	1	11	5.3
42	107	0	11	10.3
43	220	2	14	6.4
44	220	3	20	9.2
45	210	1	13	6.2
46	157	2	13	8.4
47	220	0	24	10.9
48	220	1	20	9.1
49	220	1	19	8.7
50	220	7	13	6.1
Total	4933	32	413	8.4

TABLE 38 *High-risk systematic patients: 12-month prevalence of AF*

Practice number	High risk patients	Missing notes	Diagnosis of AF	Prevalence (%)
26	99	0	13	13.1
27	12	0	2	16.7
28	102	0	17	16.7
29	47	0	8	17.0
30	89	0	11	12.4
31	74	1	1	1.4
32	85	1	11	13.1
33	91	0	6	6.6
34	88	1	8	9.2
35	108	1	10	9.3
36	95	0	12	12.6
37	84	0	9	10.7
38	83	0	9	10.8
39	105	0	11	10.5
40	88	0	8	9.1
41	144	0	9	6.3
42	38	0	4	10.5
43	75	2	4	5.5
44	93	1	13	14.1
45	108	0	7	6.5
46	73	2	6	8.5
47	94	0	18	19.1
48	86	1	14	16.5
49	82	0	8	9.8
50	85	0	8	9.4
Total	2128	10	227	10.7

TABLE 39 *Opportunistic screening*

Practice number	Patients	Excluded (%)	Notes flagged	Pulse (%)	Irregular pulse (%)	ECG (%)	AF (%)	New cases
26	220	10 (4.5)	210	165 (78.6)	23 (13.9)	19 (82.6)	5 (26.3)	1
27	41	1 (2.4)	40	32 (80.0)	3 (9.4)	2 (66.7)	2 (100.0)	2
28	210	12 (5.7)	198	127 (64.1)	12 (9.4)	8 (66.7)	3 (37.5)	0
29	164	3 (1.8)	161	81 (50.3)	11 (13.6)	6 (54.5)	3 (50.0)	0
30	220	13 (5.9)	207	130 (62.8)	22 (16.9)	17 (77.2)	7 (41.2)	4
31	134	1 (0.7)	133	97 (72.9)	28 (28.9)	18 (64.3)	1 (5.6)	0
32	220	9 (4.1)	211	152 (72.0)	12 (7.9)	6 (50.0)	2 (33.3)	1
33	220	0 (0.0)	220	105 (47.7)	13 (12.4)	9 (69.2)	5 (55.6)	1
34	210	11 (5.2)	199	185 (93.0)	26 (14.1)	21 (80.8)	8 (38.1)	2
35	210	9 (4.3)	201	143 (71.1)	12 (8.4)	9 (75.0)	5 (55.6)	1
36	220	0 (0.0)	220	98 (44.5)	5 (5.1)	2 (40.0)	0 (0.0)	0
37	220	4 (1.8)	216	176 (81.5)	24 (13.6)	21 (87.5)	10 (47.6)	6
38	210	11 (5.2)	199	165 (82.9)	20 (12.1)	6 (30.0)	1 (16.7)	1
39	210	8 (3.8)	202	173 (85.6)	23 (13.3)	18 (78.3)	5 (27.8)	2
40	220	4 (1.8)	216	112 (51.9)	3 (2.7)	2 (66.7)	0 (0.0)	0
41	210	17 (8.1)	193	156 (80.8)	12 (7.7)	9 (75.0)	4 (44.4)	3
42	107	7 (6.5)	100	67 (67.0)	10 (14.9)	8 (80.0)	3 (37.5)	0
43	220	20 (9.1)	200	128 (64.0)	13 (10.2)	5 (38.5)	0 (0.0)	0
44	220	2 (0.9)	218	179 (82.1)	17 (9.5)	13 (76.5)	3 (23.1)	0
45	210	14 (6.7)	196	145 (74.0)	13 (9.0)	4 (30.8)	1 (25.0)	1
46	157	8 (5.1)	149	121 (81.2)	19 (15.7)	14 (73.7)	7 (50.0)	2
47	220	0 (0.0)	220	149 (67.7)	7 (4.7)	3 (42.9)	2 (66.7)	1
48	220	5 (2.3)	215	162 (75.3)	14 (8.6)	9 (64.3)	3 (33.3)	1
49	220	3 (1.4)	217	164 (75.6)	12 (7.3)	8 (66.7)	4 (50.0)	2
50	220	23 (10.5)	197	66 (33.5)	7 (10.6)	1 (14.3)	0 (0.0)	0
All	4933	195 (4.0)	4738	3278 (69.2)	361 (11.0)	238 (65.9)	84 (35.3)	31

TABLE 40 *Opportunistic screening: patients without AF at baseline*

Practice number	Notes flagged	Pulse (%)	Irregular pulse (%)	ECG (%)	AF
26	198	154 (77.7)	15 (9.7)	14 (93.3)	1
27	38	31 (81.6)	3 (9.7)	2 (66.7)	2
28	181	115 (63.5)	6 (5.2)	5 (83.3)	0
29	147	71 (48.3)	5 (7.0)	3 (60.0)	0
30	195	122 (62.6)	14 (11.5)	13 (92.9)	4
31	130	95 (73.1)	27 (28.4)	17 (63.0)	0
32	197	141 (71.6)	8 (5.7)	4 (50.0)	1
33	205	93 (45.4)	8 (8.6)	5 (62.5)	1
34	185	171 (92.4)	17 (9.9)	14 (82.4)	2
35	185	129 (69.7)	6 (4.7)	5 (83.3)	1
36	205	90 (43.9)	4 (4.4)	2 (50.0)	0
37	203	167 (82.3)	19 (11.4)	17 (89.5)	6
38	185	151 (81.6)	11 (7.3)	6 (54.5)	1
39	186	161 (86.6)	16 (9.9)	13 (81.3)	2
40	197	104 (52.8)	2 (1.9)	2 (100.0)	0
41	187	150 (80.2)	10 (6.7)	8 (80.0)	3
42	88	58 (65.9)	6 (10.3)	5 (83.3)	0
43	188	117 (62.2)	10 (8.5)	5 (50.0)	0
44	201	164 (81.6)	12 (7.3)	9 (75.0)	0
45	188	138 (73.4)	11 (8.0)	4 (36.4)	1
46	136	108 (79.4)	10 (9.3)	8 (80.0)	2
47	197	132 (67.0)	3 (2.3)	2 (66.7)	1
48	201	150 (74.6)	9 (6.0)	7 (77.8)	1
49	204	155 (76.0)	7 (4.5)	6 (85.7)	2
50	186	63 (33.9)	5 (7.9)	1 (20.0)	0
All	4413	3030 (68.7)	244 (8.1)	177 (72.5)	31

In total, 3278 patient pulses were taken, of which 2027 (61.8%) were by a GP and 910 (27.8%) by a practice nurse. The remaining 10.4% of pulses lack specific data on the health professional who took the pulse. There were two main reasons: the name of the pulse-taker was not entered onto the flag or the flagging was computerised and there was no facility to enter the details of the pulse-taker. Practice nurses reported 15.9% of pulses to be irregular compared with 8.8% of pulses taken by the GPs. The success rate of pulse-taking, in terms of a subsequent ECG reporting the presence of AF following an irregular pulse, was 39.8% (43 out of 108 ECGs) for GPs and 31.4% (33 out of 72 ECGs) for practice nurses. This compares with the overall rate of 35.3%.

At the practice level, there was wide variation in the proportion of patients who had a pulse taken, with the lowest take-up of screening at 33.5% and the highest at 93.0%. There were also practice-level differences in the take-up of an ECG when the pulse was judged to be irregular, from 14.3 to 87.5%.

Take-up rates were also calculated for patients without a diagnosis of AF at baseline, as this reflects what would happen in an actual screening programme. Of the patients who had their notes flagged, 68.7% also had their pulse taken. Of these, 244 (8.1%) had an irregular pulse and 177 (72.5%) agreed to have an ECG. In total, 31 new cases of AF were detected by opportunistic screening, 17.5% of those who agreed to have an ECG (*Table 40*).

Gender and age differences in the take-up of screening were apparent. Taking into account all patients in the opportunistic arm, a higher proportion of women than men had their pulse taken (70.5% versus 67.4%) (*Table 41*), and this was the case for both age groups (*Table 42*). However, once a pulse was found to be irregular, a higher proportion of men accepted the invitation to have an ECG (73.4% versus 57.8%), and this was the case for both age groups. A larger proportion of patients in the younger age group had their pulse taken (70.3% versus 67.7%) and agreed to have an ECG (70.4% versus 62.3%). Patterns of take-up of screening by gender and age were similar in patients without a baseline AF diagnosis (*Tables 43* and *44*).

Systematic screening

Five-hundred (10.1%) patients were excluded from systematic screening because of death, moving

TABLE 41 *Opportunistic screening: all patients by gender and by age group*

	Males *n* = 2028 (%)	Females *n* = 2710 (%)	Age <75 *n* = 2700 (%)	Age ≥75 *n* = 2038 (%)
Pulse taken	1367 (67.4)	1911 (70.5)	1899 (70.3)	1379 (67.7)
Irregular pulse	188 (13.8)	173 (9.1)	162 (8.5)	199 (14.4)
Had ECG	138 (73.4)	100 (57.8)	114 (70.4)	124 (62.3)
AF	49 (35.5)	35 (35.0)	35 (30.7)	49 (39.5)

TABLE 42 *Opportunistic screening: all patients by gender and age group combined*

	Age <75		Age ≥75	
	Males *n* = 1276 (%)	Females *n* = 1424 (%)	Males *n* = 752 (%)	Females *n* = 1286 (%)
Pulse taken	869 (68.1)	1030 (72.3)	498 (66.2)	881 (68.5)
Irregular pulse	92 (10.6)	70 (6.8)	96 (19.3)	103 (11.7)
Had ECG	68 (73.9)	46 (65.7)	70 (72.9)	54 (52.4)
AF	20 (29.4)	15 (32.6)	29 (41.4)	20 (37.0)

TABLE 43 *Opportunistic screening: patients without AF diagnosis at baseline by gender and age group*

	Males *n* = 1876 (%)	Females *n* = 2537 (%)	Age <75 (%) *n* = 2585	Age ≥75 (%) *n* = 1828
Pulse taken	1249 (66.6)	1781 (70.2)	1806 (69.9)	1224 (67.0)
Irregular pulse	129 (10.3)	115 (6.5)	117 (6.5)	127 (10.4)
Had ECG	100 (77.5)	77 (67.0)	85 (72.6)	92 (72.4)
AF	16 (16.0)	15 (19.5)	9 (10.6)	22 (23.9)

TABLE 44 *Opportunistic screening: patients without AF diagnosis at baseline by gender and age group combined*

	Age <75		Age ≥75	
	Males *n* = 1208	Females *n* = 1377	Males *n* = 668	Females *n* = 1160
Pulse taken	813 (67.4)	992 (72.0)	435 (65.1)	789 (68.0)
Irregular pulse	67 (8.2)	50 (5.0)	62 (14.3)	65 (8.2)
Had ECG	51 (76.1)	34 (68.0)	49 (79.0)	43 (66.2)
AF	6 (11.8)	3 (8.8)	10 (20.4)	12 (27.9)

practice or address or being deemed unsuitable (e.g. terminally ill) by practice staff. In total, 246 had died, 245 had moved and nine were unsuitable to be invited. A total of 4433 was invited for screening; 20.4% returned the reply slip or contacted research staff to decline the invitation for an ECG. Of those originally invited, 53.2% attended a screening clinic, and 135 (5.7%) were diagnosed with AF. Three of the patients screened had an ECG considered too poor (by the study cardiologists) to ascertain the presence of AF. Although the patients were invited to have a repeat ECG, all three declined. The remaining patients did not respond to the invitation or reminder. At a practice level, there was wide variation in the take-up of screening, from 22.2 to 67.9% (*Table 45*).

Compliance rates were also calculated for patients without a diagnosis of AF at baseline. In a routine

TABLE 45 *Systematic screening*

Practice number	Patients	Excluded (%)	Invited	Refused (%)	Screened (%)	AF (%)	New cases
26	220	24 (10.9)	196	33 (16.8)	130 (66.3)	10 (7.7)	7
27	41	8 (19.5)	33	4 (12.1)	14 (42.4)	0 (0.0)	0
28	210	19 (9.0)	191	60 (31.4)	78 (40.8)	5 (6.4)	3
29	164	12 (7.3)	152	23 (15.1)	100 (65.8)	6 (6.0)	3
30	220	15 (6.8)	205	37 (18.0)	84 (41.0)	2 (2.4)	0
31	134	8 (6.0)	126	13 (10.3)	28 (22.2)	1 (3.6)	0
32	220	17 (7.7)	203	55 (27.1)	82 (40.4)	9 (11.0)	5
33	220	21 (9.5)	199	35 (17.6)	84 (42.2)	2 (2.4)	1
34	210	14 (6.7)	196	46 (23.5)	133 (67.9)	11 (8.3)	3
35	210	15 (7.1)	195	45 (23.1)	114 (58.5)	7 (6.1)	0
36	220	31 (14.1)	189	35 (18.5)	103 (54.5)	6 (5.8)	3
37	220	14 (6.4)	206	44 (21.4)	123 (59.7)	7 (5.7)	3
38	210	26 (12.4)	184	32 (17.4)	101 (54.9)	3 (3.0)	1
39	210	24 (11.4)	186	37 (19.9)	117 (62.9)	6 (5.1)	2
40	220	20 (9.1)	200	43 (21.5)	81 (40.5)	5 (6.2)	2
41	210	15 (7.1)	195	43 (22.1)	101 (51.8)	6 (5.9)	2
42	107	6 (5.6)	101	15 (14.9)	68 (67.3)	3 (4.4)	1
43	220	29 (13.2)	191	47 (24.6)	84 (44.0)	2 (2.4)	1
44	220	16 (7.3)	204	46 (22.5)	128 (62.7)	8 (6.3)	3
45	210	22 (10.5)	188	27 (14.4)	123 (65.4)	4 (3.3)	2
46	157	21 (13.4)	136	36 (26.5)	71 (52.2)	5 (7.0)	0
47	220	18 (8.2)	202	41 (20.3)	123 (60.9)	6 (4.9)	2
48	220	29 (13.2)	191	41 (21.5)	113 (59.2)	13 (11.5)	4
49	220	16 (7.3)	204	33 (16.2)	137 (67.2)	7 (5.1)	4
50	220	60 (27.3)	160	33 (20.6)	37 (23.1)	1 (2.7)	0
Total	4933	500 (10.1)	4433	904 (20.4)	2357 (53.2)	135 (5.7)	52

systematic screening programme, patients with a diagnosis of AF are unlikely to be invited. The take-up rates were very similar to those of patients in the systematic screening arm as a whole, with 53.4% of patients having an ECG and a further 20.1% declining the invitation. Again, at the practice level, there was wide variation in the take-up of screening, from 22.0 to 70.7% (*Table 46*). In total, 52 new cases of AF were detected by systematic screening, 2.4% of those who agreed to have an ECG.

In total, 2128 (43.1%) systematic patients were classified as high-risk patients, owing to the presence of one or more associated conditions, as specified previously. Of 2098 patients who were sent an invitation, 19.7% responded to decline the invitation for an ECG; 57.7% attended a screening clinic, and 89 (7.3%) were diagnosed with AF. Again, wide variation in the take-up of screening was evident, with screening rates ranging from 30.4 to 76.8% (*Table 47*). Considering only those patients with no prior diagnosis of AF, 58.2% of the 1915 invited were screened, with 31 new cases diagnosed (*Table 48*).

Gender and age differences in the take-up of systematic screening were evident. Considering all patients in the systematic arm, a higher proportion of men attended a screening clinic (57.0% versus 50.3%) (*Table 49*). However, the difference was more evident in patients aged 75 and over (49.9% versus 39.9%), with little difference between genders in the younger age group (*Table 50*). As expected, a larger proportion of patients in the younger age group attended screening (60.7% versus 43.0%). Similar patterns were seen in those patients with no prior diagnosis of AF, with more males overall attending screening (56.4% versus 51.1%) and younger patients more likely to attend (60.8% versus 42.9%) (*Table 51*). Again, there was very little difference between men and women in the 65–74-year-old age group, but for those aged 75 and over, a higher proportion of men was screened (48.6% versus 39.9%) (*Table 52*).

Considering both opportunistic and systematic screening arms, 679 intervention patients were found to have AF at baseline and 136 of these had this confirmed by a study ECG. A further 69 patients had a study ECG showing sinus rhythm.

TABLE 46 *Systematic screening: patients without AF at baseline*

Practice	Invited	Refused (%)	Screened (%)	AF
26	184	29 (15.8)	125 (67.9)	7
27	31	4 (12.9)	14 (45.2)	0
28	175	56 (32.0)	71 (40.6)	3
29	141	19 (13.5)	95 (67.4)	3
30	193	35 (18.1)	79 (40.9)	0
31	123	13 (10.6)	27 (22.0)	0
32	191	50 (26.2)	75 (39.3)	5
33	191	33 (17.3)	81 (42.4)	1
34	182	44 (24.2)	121 (66.5)	3
35	178	45 (25.3)	99 (55.6)	0
36	175	31 (17.7)	97 (55.4)	3
37	193	41 (21.2)	116 (60.1)	3
38	172	29 (16.9)	96 (55.8)	1
39	175	35 (20.0)	111 (63.4)	2
40	183	40 (21.9)	74 (40.4)	2
41	187	40 (21.4)	97 (51.9)	2
42	92	12 (13.0)	65 (70.7)	1
43	180	42 (23.3)	82 (45.6)	1
44	187	42 (22.5)	118 (63.1)	3
45	180	26 (14.4)	118 (65.6)	2
46	129	35 (27.1)	66 (51.2)	0
47	184	34 (18.5)	114 (62.0)	2
48	178	40 (22.5)	103 (57.9)	4
49	192	30 (15.6)	133 (69.3)	4
50	148	30 (20.3)	35 (23.6)	0
Total	4144	835 (20.1)	2212 (53.4)	52

TABLE 47 *Systematic screening: high-risk patients*

Practice number	Patients	Excluded	Invited	Refused (%)	Screened (%)	AF (%)	New cases
26	99	2	97	17 (17.5)	64 (66.0)	6 (9.4)	4
27	12	0	12	1 (8.3)	4 (33.3)	0 (0)	0
28	102	0	102	28 (27.5)	47 (46.1)	5 (10.6)	3
29	47	0	47	8 (17.0)	33 (70.2)	5 (15.2)	3
30	89	0	89	16 (18.0)	41 (46.1)	2 (4.9)	0
31	74	1	73	7 (9.6)	23 (31.5)	0 (0)	0
32	85	2	83	25 (30.1)	35 (42.2)	5 (14.3)	2
33	91	1	90	14 (15.6)	45 (50.0)	1 (2.2)	1
34	88	1	87	15 (17.2)	70 (80.5)	6 (8.6)	1
35	108	2	106	23 (21.7)	67 (63.2)	4 (6.0)	0
36	95	2	93	13 (14.0)	57 (61.3)	4 (7.0)	2
37	84	0	84	15 (17.9)	54 (64.3)	4 (7.4)	1
38	83	1	82	15 (18.3)	55 (67.1)	2 (3.6)	0
39	105	1	104	24 (23.1)	64 (61.5)	5 (7.8)	2
40	88	1	87	18 (20.7)	37 (42.5)	3 (8.1)	1
41	144	1	143	32 (22.4)	79 (55.2)	5 (6.3)	1
42	38	0	38	5 (13.2)	27 (71.1)	2 (7.4)	1
43	75	0	75	20 (26.7)	35 (46.7)	0 (0)	0
44	93	0	93	24 (25.8)	62 (66.7)	5 (8.1)	1
45	108	2	106	15 (14.2)	72 (67.9)	3 (4.2)	2
46	73	3	70	16 (22.9)	40 (57.1)	4 (10.0)	0
47	94	3	91	22 (24.2)	57 (62.6)	5 (8.8)	2
48	86	1	85	16 (18.8)	56 (65.9)	10 (17.9)	3
49	82	0	82	9 (11.0)	63 (76.8)	2 (3.2)	1
50	85	6	79	16 (20.3)	24 (30.4)	1 (4.2)	0
Total	2128	30	2098	414 (19.7)	1211 (57.7)	89 (7.3)	31

TABLE 48 *Systematic screening: high-risk patients without AF at baseline*

Practice	Invited	Refused (%)	Screened (%)	AF
26	89	14 (15.7)	62 (69.7)	4
27	10	1 (10.0)	4 (40.0)	0
28	88	24 (27.3)	41 (46.6)	3
29	42	7 (16.7)	29 (69.0)	3
30	79	15 (19.0)	37 (46.8)	0
31	72	7 (9.7)	23 (31.9)	0
32	75	23 (30.7)	29 (38.7)	2
33	86	13 (15.1)	43 (50.0)	1
34	80	14 (17.5)	64 (80.0)	1
35	97	23 (23.7)	58 (59.8)	0
36	83	10 (12.0)	53 (63.9)	2
37	77	13 (16.9)	50 (64.9)	1
38	73	14 (19.2)	50 (68.5)	0
39	95	22 (23.2)	59 (62.1)	2
40	80	17 (21.3)	33 (41.3)	1
41	136	30 (22.1)	75 (55.1)	1
42	35	5 (14.3)	25 (71.4)	1
43	72	19 (26.4)	35 (48.6)	0
44	81	20 (24.7)	55 (67.9)	1
45	102	14 (13.7)	70 (68.6)	2
46	65	16 (24.6)	36 (55.4)	0
47	77	17 (22.1)	50 (64.9)	2
48	74	15 (20.3)	48 (64.9)	3
49	76	7 (9.2)	62 (81.6)	1
50	71	14 (19.7)	23 (32.4)	0
Total	1915	374 (19.5)	1114 (58.2)	31

TABLE 49 *Systematic screening: all patients by gender and age group*

	Males (%)	Females (%)	Age <75 (%)	Age ≥75 (%)
Invited	1890	2543	2542	1891
Refused	305 (16.1)	599 (23.6)	350 (13.8)	554 (29.3)
No response	507 (26.8)	665 (26.2)	649 (25.5)	523 (27.7)
Screened	1078 (57.0)	1279 (50.3)	1543 (60.7)	814 (43.0)
AF	84 (7.8)	51 (4.0)	64 (4.0)	71 (8.7)

TABLE 50 *Systematic screening: all patients by gender and age group combined*

	Age <75		Age ≥75	
	Males (%)	Females (%)	Males (%)	Females (%)
Invited	1220	1322	670	1221
Refused	151 (12.4)	199 (15.1)	154 (23.0)	400 (32.8)
No response	325 (26.6)	324 (24.5)	182 (27.1)	341 (27.9)
Screened	744 (61.0)	799 (60.4)	334 (49.9)	480 (39.3)
AF	42 (5.7)	22 (2.8)	42 (12.6)	29 (6.0)

TABLE 51 *Systematic screening: patients without AF diagnosis at baseline by gender and age group*

	Males (%)	Females (%)	Age <75 (%)	Age ≥75 (%)
Invited	1763	2381	2418	1726
Refused	280 (15.9)	555 (23.3)	327 (13.5)	508 (29.4)
No response	488 (27.7)	609 (25.6)	620 (25.6)	477 (27.6)
Screened	995 (56.4)	1217 (51.1)	1471 (60.8)	741 (42.9)
AF	33 (3.3)	19 (1.6)	24 (1.6)	28 (3.8)

TABLE 52 *Systematic screening: patients without AF diagnosis at baseline by gender and age group combined*

	Age <75		Age ≥75	
	Males (%)	Females (%)	Males (%)	Females (%)
Invited	1158	1260	605	1121
Refused	140 (12.1)	187 (14.8)	140 (23.1)	368 (32.8)
No response	317 (27.4)	303 (24.0)	171 (28.3)	306 (27.3)
Screened	701 (60.5)	770 (61.1)	294 (48.6)	447 (39.9)
AF	17 (2.4)	7 (0.9)	16 (5.4)	12 (2.7)

A total of 904 patients replied to decline screening (*Table 53*); 38.9% of these did not give a reason for their refusal. Where reasons were given, an inability to get to the surgery was a major issue, either generally (9.4%) or for a more specific reason such as illness (6.9%) or old age (5.8%). Other patients did not want to be screened because of current relevant health issues, and stated they were already part of the NHS system (9.2%), had had a recent ECG (7.9%) or had AF (1.5%).

TABLE 53 *Reasons for refusal of systematic screening*

Reason	Number (%) *n* = 904
No reason given	352 (38.9)
Can't get to surgery	85 (9.4)
Already in NHS system	83 (9.2)
Had recent ECG	71 (7.9)
Illness	62 (6.9)
Old age	58 (6.4)
Not interested	38 (4.2)
Mental health problems (e.g. dementia)	27 (3.0)
No health problems	14 (1.5)
Has AF	14 (1.5)
Away at the moment	12 (1.3)
Anxiety	11 (1.2)
Not convenient	9 (1.0)
Nursing home	8 (0.9)
Carer	7 (0.8)
Communication problems	7 (0.8)
Personal reasons	5 (0.6)
Considered not suitable by practice	4 (0.4)
Difficult to make appointment	3 (0.3)
NHS resource worries	1 (0.1)
Signed up to another study	1 (0.1)
Insurance concerns	1 (0.1)

Echocardiography

In total, 83 patients were aged 65–74 at the time of their screening and were found to have AF, of whom 31 (37.3%) took up the offer of having an echocardiogram. A further six refused as they had already had an echocardiogram in the past. The remainder were not offered this test by their GP, with the main reason also being a previous echocardiogram having taken place. Of 31 patients who had an echocardiogram, 26 pre-echocardiogram questionnaires and 23 post-echocardiogram questionnaires were returned by the GPs. The GPs were asked to assess the patient's risk of stroke and the treatment they would offer to the patient.

Pre-echocardiogram questionnaire

Thirteen patients were assessed as being at a high risk of stroke, with nine to be treated with warfarin and the remaining four with aspirin. Ten patients had a medium stroke risk, eight to be treated with aspirin and two with warfarin. Two were of low risk, one to be treated with warfarin, the other with aspirin. One patient did not have their stroke risk assessed, but warfarin was the treatment of choice.

TABLE 54 *GP pre- and postechocardiography (echo) treatment decisions*

	Pre-echo treatment		
Postecho treatment	**Aspirin**	**Warfarin**	**Total**
Aspirin	5	0	5
Warfarin	5	10	15
Missing data	3	3	6
Total	13	13	26

Postechocardiogram questionnaire

Reassessment of stroke risk once an echocardiogram had been carried out resulted in 16 patients being assessed as high risk, three as medium risk and two as low risk. Information on stroke risk was missing from two questionnaires. Thirteen of the high-risk patients were treated with warfarin. In terms of change in treatment decision, four patients were to be given warfarin instead of aspirin and 17 patients were to be given the same treatment as stated in the pre-echocardiogram questionnaire. Data on treatment decision for pre- and postechocardiogram was not available for ten patients. *Table 54* reports the number of patients on aspirin and warfarin pre- and postechocardiogram where data at both time-points were available.

AF detection

All study 12-lead ECGs were read independently by two cardiologists. The agreed diagnosis from the cardiologists was considered to be the gold standard. A total of 2595 ECGs was undertaken. A cardiologist diagnosis was available for 2592 ECGs owing to three ECGs being of too poor quality for diagnosis. The patients were recalled for a repeat ECG but did not attend a further clinic. Study ECGs were also interpreted using diagnostic software (CDSS). A comparison of the diagnosis given by the cardiologists and the computer software was undertaken for 2592 ECGs (*Table 55*). A diagnosis was not possible for 145 ECGs (5.6%) as they were of too poor quality to be read by the computer package. Of the 219 cardiologist diagnoses of AF, CDSS correctly diagnosed 179 cases. Twenty-one patients with sinus rhythm were incorrectly diagnosed as having AF by the software.

All patients had their pulse taken at the ECG clinic by a practice nurse. Pulse data were missing for 15 patients and an additional two patients were not given a cardiologist diagnosis owing to poor-quality ECG. A comparison of the diagnosis given by the cardiologists and the practice nurse pulse-taking was undertaken for 2578 ECGs (*Table 56*). Twenty-eight of 218 patients diagnosed with AF had a regular pulse, and 441 of the 2360 patients in sinus rhythm had an irregular pulse.

TABLE 55 *Comparison of CDSS with cardiologist diagnosis*

	Cardiologist		
CDSS	**AF**	**Sinus rhythm**	**Total**
AF	179	21	200
Sinus rhythm	26	2221	2247
No diagnosis	14	131	145
Total	219	2373	2592

TABLE 56 *Comparison of pulse-taking with cardiologist diagnosis*

	Cardiologist		
Pulse	**AF**	**Sinus rhythm**	**Total**
Irregular	190	441	631
Regular	28	1919	1947
Total	218	2360	2578

All study ECGs were also sent to GPs and practice nurses from control and intervention practices to be read for the presence or absence of AF. They were read as a 12-lead, limb-lead rhythm strip or single-lead thoracic placement ECG. One control practice was not sent any ECGs as they had withdrawn from the study before the ECGs were sent out. After several reminders, 20 GPs and 21 practice nurses from 24 control practices returned the interpretations, and 21 GPs and 20 practice nurses from 25 intervention practices responded. In some cases the GP or practice nurse was uncertain of the correct diagnosis; therefore, it was coded as 'no diagnosis'.

Using 12-lead ECGs, GPs did not diagnose 20 out of 99 cases of AF and incorrectly diagnosed 114 of the 1355 sinus rhythm ECGs as having AF. Diagnoses were not returned for 242 ECGs, 14.3% of the total sent out. With the limb-lead rhythm strip ECGs, 22 out of 126 cases of AF were missed, and 156 of 1358 patients in sinus rhythm were given an AF diagnosis. A further 232 diagnoses (13.5%) were not returned. Reading single-lead thoracic placement ECGs resulted in 19 of 132 cases of AF and 180 of 1325 sinus rhythm ECGs having a wrong diagnosis. No diagnosis was

TABLE 57 *Comparison of GP and cardiologist diagnosis*

(a) 12-lead ECG

	Cardiologist		
GP diagnosis	**AF**	**Sinus rhythm**	**Total**
AF	79	114	193
Sinus rhythm	20	1239	1259
No diagnosis	0	2	2
Total	99	1355	1454

Diagnoses were not returned for 242 (14.3%) ECGs.

(b) Limb-lead rhythm strip ECG

	Cardiologist 12-lead		
GP diagnosis	**AF**	**Sinus rhythm**	**Total**
AF	104	156	260
Sinus rhythm	22	1194	1216
No diagnosis	0	8	8
Total	126	1358	1484

Diagnoses were not returned for 232 (13.5%) ECGs.

(c) Single-lead thoracic placement ECG

	Cardiologist 12-lead		
GP diagnosis	**AF**	**Sinus rhythm**	**Total**
AF	112	180	292
Sinus rhythm	19	1141	1160
No diagnosis	1	4	5
Total	132	1325	1457

Diagnoses were not returned for 237 (14.0%) ECGs.

TABLE 58 *Comparison of practice nurse and cardiologist diagnosis*

(a) 12-lead ECG

	Cardiologist 12-lead		
Practice nurse diagnosis	**AF**	**Sinus rhythm**	**Total**
AF	74	198	272
Sinus rhythm	22	1127	1149
No diagnosis	0	5	5
Total	96	1330	1426

Diagnoses were not returned for 270 (15.9%) ECGs.

(b) Limb-lead rhythm strip ECG

	Cardiologist 12-lead		
Practice nurse diagnosis	**AF**	**Sinus rhythm**	**Total**
AF	85	220	305
Sinus rhythm	31	1095	1126
No diagnosis	2	12	14
Total	118	1327	1445

Diagnoses were not returned for 271 (15.8%) ECGs.

(c) Single-lead thoracic placement

	Cardiologist 12-lead		
Practice nurse diagnosis	**AF**	**Sinus rhythm**	**Total**
AF	92	222	314
Sinus rhythm	42	1060	1102
No diagnosis	0	6	6
Total	134	1288	1422

Diagnoses were not returned for 272 (16.1%) ECGs.

returned for 237 ECGs (14.0%). *Table 57* presents analyses for all three types of ECG.

Practice nurses did not identify 22 out of 96 cases of AF from 12-lead ECGs and 198 of the 1330 patients in sinus rhythm were diagnosed as having AF. Diagnoses were not returned for 270 ECGs, 15.9% of the total sent out. Using limb-lead rhythm strip ECGs, 31 out of 118 cases of AF were misdiagnosed, and 220 of 1445 patients in sinus rhythm were given an AF diagnosis. No diagnosis was returned for 271 ECGs (15.8%). Diagnosis using single-lead thoracic placement ECGs resulted in wrong diagnoses for 42 of 134 cases of AF and 222 cases of 1288 sinus rhythm. No diagnosis was returned for 272 ECGs (16.1%). *Table 58* presents the analyses for all three types of ECG.

The diagnostic performance of each method of ECG reading was calculated, in terms of the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) (*Table 59*). Only ECGs with an actual diagnosis were included in the calculations; therefore, the ECGs that the CDSS was unable to diagnose were not included. Not including cardiologist diagnoses, interpretation by the computer software had the best diagnostic performance, with 87.3% sensitivity, 99.1% specificity, a PPV of 89.5% and an NPV of 98.8%. The sensitivity of pulse-taking was high (87.2%), but specificity was lower (81.3%) than for all other methods. GPs performed better than the practice nurses for all types of ECG, but there was no consensus of opinion over which type of ECG performed best. Diagnostic performance of individual GPs and practice nurses varied widely, with sensitivity ranging from 0 to 100% for both groups, for all types of ECG. Specificities ranged from 46.9 to 100% for GPs and from 30.0

TABLE 59 *Interpretation of ECGs by reader and ECG type*

Reader	ECG type	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
CDSS	12-lead	87.3 (82.1 to 91.2)	99.1 (98.6 to 99.4)	89.5 (84.5 to 93.0)	98.8 (98.3 to 99.2)
Pulse	–	87.2 (82.1 to 91.1)	81.3 (79.7 to 82.8)	30.1 (26.7 to 33.8)	98.6 (97.9 to 99.0)
GP	12-lead	79.8 (70.9 to 86.5)	91.6 (90.0 to 92.9)	40.9 (34.2 to 48.0)	98.4 (97.6 to 99.0)
	Limb-lead	82.5 (75.0 to 88.2)	88.4 (86.6 to 90.0)	40.0 (34.2 to 46.1)	98.2 (97.3 to 98.8)
	Single-lead	85.4 (78.5 to 90.5)	86.4 (84.4 to 88.1)	38.4 (33.0 to 44.1)	98.4 (97.5 to 99.0)
Practice nurse	12-lead	77.1 (67.7 to 84.4)	85.1 (83.0 to 86.9)	27.2 (22.3 to 32.8)	98.1 (97.1 to 98.7)
	Limb-lead	73.3 (64.6 to 80.5)	83.3 (81.2 to 85.2)	27.9 (23.1 to 33.2)	97.2 (96.1 to 98.1)
	Single-lead	68.7 (60.4 to 75.9)	82.7 (80.5 to 84.7)	29.3 (24.5 to 34.6)	96.2 (94.9 to 97.2)
Consultant[a]	Limb-lead	92.9	98.8	92.9	98.8
	Single-lead	100	100	100	100

[a] 95% CIs not applicable.

TABLE 60 *GP and practice nurse interpretations*

Reader	ECG type	Sensitivity (%)	Sensitivity range (%)	Specificity (%)	Specificity range (%)
GP	12-lead	79.8	0–100	91.6	57.6–100
	Limb-lead	82.5	0–100	88.4	46.9–100
	Single-lead	85.4	0–100	86.4	53.1–100
Practice nurse	12-lead	77.1	0–100	85.1	30.0–100
	Limb-lead	73.3	0–100	83.3	34.5–100
	Single-lead	68.7	0–100	82.7	40.6–100

to 100% for practice nurses (*Table 60*). In addition, two cardiologists were given a small sample of limb-lead and single-lead ECGs (50 of each) to diagnose in order to calculate diagnostic statistics. However, both cardiologists reported that, in routine care, the preference of a cardiology consultant is to read a 12-lead ECG rather than an ECG with less detail.

Screened patients (opportunistic and systematic)

In total, 2595 patients had an ECG as part of the study, 238 opportunistic patients and 2357 systematic patients. Thirty-six (1.4%) had a domiciliary ECG. Patients attending for screening were between 65 and 98 years old, with a mean age of 73.5. Men comprised 46.9% of patients seen (*Table 61*). A total of 219 (8.4%) patients had a diagnosis of AF, with the remainder in sinus rhythm. In addition, three patients had an ECG where no diagnosis was possible and the patient did not reattend for a further ECG. The ethnicity of the majority of patients screened was white British (93.2%), 3.2% were of black Caribbean origin and 2.3% of patients stated their ethnicity as white Other. Only 32 (0.1%) patients of Asian origin (Chinese, Indian, Pakistani and Asian other) were screened.

TABLE 61 *Details of screened patients*

Demographic data	*n* = 2595
Mean age (SD)	73.5 (6.02)
Age range (years)	65–98
Male	1216 (46.9%)
Ethnicity, *n* (%)	*n* = 2584
White British	2409 (93.2)
White other	60 (2.3)
Black African	1 (0.0)
Black Caribbean	82 (3.2)
Chinese	2 (0.1)
Indian	23 (0.9)
Pakistani	5 (0.2)
Asian other	2 (0.1)
Diagnosis, *n* (%)	*n* = 2595
AF	219 (8.4)
Sinus rhythm	2373 (91.4)
No diagnosis	3 (0.1)

Patient questionnaires

Baseline questionnaire

In total, 750 questionnaires were sent to randomly selected patients in the intervention arm. Questionnaires were sent out before baseline note searching, before patients were randomised to systematic or opportunistic screening. As this randomisation took into account who had been sent a questionnaire (in addition to presence of AF), numbers were equal in the two groups. Altogether, 620 were returned, 311 from opportunistic patients, where 55 were not completed, and 309 from systematic patients, where 72 were not completed.

Six-hundred and twenty questionnaires (84.1%) were returned, with 493 of these completed; 295 (59.8%) completed the 6-item Spielberger state anxiety questions correctly and 473 (95.9%) completed the 5-item EQ-5D questions correctly. The state anxiety scores and EQ-5D scores were both non-normally distributed. No significant difference was found between the two intervention arms at baseline for anxiety ($z = –0.392$, $p = 0.695$) or quality of life ($z = –0.334$, $p = 0.739$). Descriptive statistics for anxiety scores and EQ-5D at baseline are given in *Table 62*. A breakdown of EQ-5D responses by dimension showed that almost half of respondents (47.9%) reported problems with mobility, and two-thirds (67.5%) had problems with pain/discomfort (*Table 63*).

Postscreening questionnaire

Postscreening questionnaires were administered to all patients ($n = 2595$) undergoing an ECG. In total, 1962 (75.6%) were returned, with 1940 completed giving a response rate of 74.8%. The mean state anxiety score was calculated for 1769 (91.2%) of respondents as 171 did not complete one or more of the six items. The data were highly skewed, with 683 (38.6%) of respondents recording the lowest score (least anxiety). No significant difference was found between the two intervention arms at screening for anxiety scores ($z = –0.343$, $p = 0.732$). Descriptive statistics for anxiety scores are given in *Table 64*.

Patients also completed a general section concerning the acceptability of the screening programme and whether they had any previous knowledge of the study (*Table 65*). Less than half of respondents (43.6%) considered themselves to be perfectly healthy, but 61.0% stated they had no trouble with their heart. Three-hundred and twenty-four patients (17.1%) did not know what

TABLE 62 *Baseline questionnaire scores*

	All patients	Intervention	
		Systematic	Opportunistic
Mean state anxiety score (95% CI)	36.11 (34.68 to 37.54) *n* = 295	35.78 (33.80 to 37.76) *n* = 148	36.44 (34.35 to 38.53) *n* = 147
Median state anxiety score (IQR)	36.67 (26.67–43.33) *n* = 295	33.33 (26.67–43.33) *n* = 148	36.67 (26.67–43.33) *n* = 147
Mean EQ-5D score (95% CI)	0.69 (0.66 to 0.72) *n* = 473	0.68 (0.64 to 0.72) *n* = 246	0.70 (0.67 to 0.74) *n* = 227
Median EQ-5D score (IQR)	0.73 (0.62–0.85) *n* = 473	0.73 (0.62–0.85) *n* = 246	0.73 (0.62–0.85) *n* = 227

IQR, interquartile range.

TABLE 63 *EQ-5D dimensions: baseline*

All responses (*n* = 493)	No problems *n* (%)	Some problems *n* (%)	Severe problems *n* (%)	Missing data *n* (%)
Mobility	255 (51.7)	233 (47.3)	3 (0.6)	2 (0.4)
Self-care	407 (82.6)	71 (14.4)	7 (1.4)	8 (1.6)
Usual activities	282 (57.2)	172 (34.9)	33 (6.7)	6 (1.2)
Pain/discomfort	154 (31.2)	291 (59.0)	42 (8.5)	6 (1.2)
Anxiety/depression	289 (58.6)	186 (37.7)	10 (2.0)	8 (1.6)

TABLE 64 *Postscreening questionnaire scores*

	All patients *n* = 1769	Intervention	
		Systematic *n* = 1603	Opportunistic *n* = 166
Mean state anxiety score (95% CI)	28.72 (28.25 to 29.19)	28.77 (28.27 to 29.26)	28.25 (26.78 to 29.73)
Median state anxiety score (IQR)	26.67 (20.00–33.33)	26.67 (20.00–33.33)	26.67 (20.00–33.33)

TABLE 65 *Patient screening acceptability questionnaire (n = 1940)*

Statement	*n* (%)
	n = 1897
I'm perfectly healthy	828 (43.6)
I've never had trouble with my heart	1157 (61.0)
I didn't know what was involved	324 (17.1)
It wasn't convenient	70 (3.7)
I think health screening is important	1810 (95.4)
	n = 1889
The letter/information sheet explained tests properly	1784 (94.4)
I would have liked:	*n* = 1892
Someone to discuss it more first	91 (4.8)
To talk about the tests with doctor first	60 (3.2)
To come to a clinic appointment for more information	76 (4.0)
	n = 1876
I had heard about the screening before the study	265 (14.1)
	n = 265
Information from friend/relative/neighbour	122 (46.0)
Information from doctor/surgery/clinic	112 (42.3)
Information from other source	29 (10.9)
Information source not specified	7 (2.6)

was involved in the screening, but 94.4% thought that the tests were explained properly through written materials and only 3.7% considered the screening inconvenient. Almost all patients (95.4%) thought that health screening was important. In terms of gaining more information about screening, 4.8% would have liked someone to discuss it with, 3.2% would have liked to have talked to their doctor first and 4.0% would have liked a clinic appointment to obtain more information. Before their invitation to be part of the study, 14.1% had heard about the screening, mainly through friends, relatives or neighbours (46.0%) or their doctor's surgery (42.3%).

End of study questionnaire

Of the 750 patients sent a baseline questionnaire, 14 were not randomised and were therefore not sent a further questionnaire. A further 130 were excluded as they had moved or died during the study period or were unsuitable to receive a questionnaire. In total, 606 of the original 736 randomised to receive a quality of life questionnaire were sent a follow-up questionnaire. In addition, 186 patients (who did not receive a baseline questionnaire) were eligible to be sent a questionnaire as they had been screened as part of the study and diagnosed with AF. Fifteen of these were excluded as they had moved or died since the screening had occurred.

In total, 630 (81.1%) of the 777 questionnaires were returned and 535 were returned completed; 479 (89.5%) completed the 6-item Spielberger state anxiety questions correctly and 520 (97.2%) completed the 5-item EQ-5D questions correctly. The state anxiety scores and EQ-5D scores were both non-normally distributed. No significant difference was found between the two intervention arms at the end of the study for anxiety

($z = -1.699$, $p = 0.089$) or quality of life ($z = -1.166$, $p = 0.244$). Adjusting for baseline score, there was no significant difference in anxiety outcomes at the end of the study between opportunistic and systematic arms ($F_{1,197} = 4.02$, $p = 0.844$). Similarly, there was no significant difference in quality of life ($F_{1,317} = 0.019$, $p = 0.473$). Descriptive statistics for anxiety scores and EQ-5D are given *Table 66*. EQ-5D responses were analysed for each dimension. Mobility was a problem in 54.2% of respondents, almost half had problems with usual activities (48.8%) and 69.5% reported problems with pain/discomfort (*Table 67*).

End of study anxiety scores for screen-positive and screen-negative patients were significantly different ($F_{1,268} = 4.883$, $p = 0.028$), and patients diagnosed with AF had a higher anxiety score. EQ-5D scores were also significantly different ($F_{1,290} = 0.360$, $p = 0.020$), with screen-positive patients reporting a lower quality of life score. Adjustment for baseline scores was not possible owing to too few responses to both questionnaires. The descriptive statistics for anxiety and EQ-5D scores of screen-positive and screen-negative study patients can be found in *Table 68*.

TABLE 66 *End of study questionnaire*

	All patients	Intervention	
		Systematic	Opportunistic
Mean state anxiety score (95% CI)	36.65 (35.48 to 37.82) *n* = 479	35.92 (34.29 to 37.55) *n* = 259	37.50 (35.82 to 39.18) *n* = 220
Median state anxiety score (IQR)	36.67 (26.67–43.33) *n* = 479	33.33 (23.33–43.33) *n* = 259	36.67 (26.67–46.67) *n* = 220
Mean EQ-5D score (95% CI)	0.69 (0.67 to 0.71) *n* = 520	0.69 (0.66 to 0.73) *n* = 277	0.69 (0.65 to 0.72) *n* = 243
Median EQ-5D score (IQR)	0.73 (0.62–0.85) *n* = 520	0.73 (0.62–0.80) *n* = 277	0.71 (0.62–0.85) *n* = 243

TABLE 67 *EQ-5D dimensions: end of study*

All responses (*n* = 535)	No problems *n* (%)	Some problems *n* (%)	Severe problems *n* (%)	Missing data *n* (%)
Mobility	241 (45.0)	288 (53.8)	2 (0.4)	4 (0.7)
Self-care	426 (79.6)	93 (17.4)	9 (1.7)	7 (1.3)
Usual activities	270 (50.5)	224 (41.9)	37 (6.9)	4 (0.7)
Pain/discomfort	157 (29.3)	344 (64.3)	28 (5.2)	6 (1.1)
Anxiety/depression	339 (63.4)	178 (33.3)	11 (2.1)	7 (1.3)

TABLE 68 *End of study questionnaire scores: screened patients*

	Screen positive	Screen negative
Mean state anxiety score (95% CI)	38.12 (35.89 to 40.35) *n* = 142	34.61 (32.41 to 36.81) *n* = 128
Median state anxiety score (IQR)	36.67 (26.67–46.67) *n* = 142	30.00 (23.33–43.33) *n* = 128
Mean EQ-5D score (95% CI)	0.66 (0.62 to 0.70) *n* = 156	0.73 (0.68 to 0.77) *n* = 136
Median EQ-5D score (IQR)	0.69 (0.59–0.80) *n* = 156	0.76 (0.69–1.00) *n* = 136

TABLE 69 *Base-case cost-effectiveness estimates*

Strategy	Cases detected (95% CI)	Incremental cases detected	Incremental cost (95% CI)	Incremental cost per additional case detected	
				Comparison with no screening	Comparison with previous strategy
No screening (control)	47 (35 to 62)	–	–	–	–
Opportunistic	75 (59 to 94)	28	£9429 (£8938 to 9920)	£337	£337
Systematic high risk	53 (40 to 69)	6	£21,119 (£20,408 to 21,831)	£3520	Dominated by opportunistic screening
Systematic population	74 (58 to 93)	27	£40,882 (£39,790 to 41,974)	£1514	Dominated by opportunistic screening

Economic evaluation

Within-trial analysis

NHS perspective

The base-case analysis results from an NHS perspective (excluding private costs) indicate that opportunistic screening detected more new cases of AF, compared with both systematic population and systematic high-risk screening (*Table 69*). In addition, opportunistic screening was associated with a lower incremental cost of £9429. Therefore, opportunistic screening dominates both more intensive screening strategies of systematic high-risk screening and population screening. The incremental cost of systematic high-risk screening was £21,119 and for systematic population screening was £40,882. If the ICER of £337 per additional case of AF detected is considered acceptable, the relevant policy question then concerns which form of opportunistic screening should be implemented. The ICER of £337 is based on consultant interpretation of a 12-lead ECG. The screening strategies considered here use different ECG technologies (i.e. single-, limb- or 12-lead) and/or different interpreters (i.e. consultant, GP, nurse or computer). The costs and effects of each alternative screening strategy are shown in *Table 70*. When compared with no screening, the incremental gain in cases detected is positive for all strategies and the incremental cost is positive for all strategies.

NHS plus patient perspective

A total of 632 screened patients completed a patient private cost questionnaire (*Table 71*). As expected for patients aged 65 and over, the activity forgone for the majority (89.9%) was leisure time. Only 15 patients reported that they gave up work time to come to the clinic. The average total time spent travelling was 25 minutes, ranging from 2 minutes to 2 hours. Over half of respondents (57.9%) reported travelling to the clinic by car, and the mean total distance travelled by this group was 3.47 miles (5.58 km). A further 27.7% either walked or cycled to the practice, with only a minority (11.4%) using public transport. The mean time waiting in the clinic for their ECG was 6.1 minutes, with 18.2% of patients having no wait at all. Using the questionnaire data, the mean patient cost was calculated. For patients with complete data (n = 532), the mean cost was £3.13 (95% CI £2.97 to 3.29), with a median of £2.52. The costs ranged from £0.65 to 14.53.

Using the mean estimate of the patient private cost and applying this to all visits, the cost-effectiveness estimates were recalculated to assess the incremental cost of screening from a broader perspective. This broadening of the perspective does not change the overall cost-effectiveness results and the incremental cost per additional case detected for opportunistic screening increased to £363 (*Table 72*). On the basis of the within-trial analysis results above, it is difficult to judge how attractive screening is: should the NHS be willing to pay £363 to detect an extra case of AF? This question cannot be answered without considering the longer term consequences associated with screening and treatment, and so model-based analysis is crucial.

Model-based analysis

The base-case model runs were undertaken on a general population to address two different policy

TABLE 70 *Cost-effectiveness of alternative opportunistic screening strategies*

Strategy	Interpretation	Compared to no screening			Compared to consultant-read 12-lead ECG	
		Additional cases detected (95% CI)	Additional cost (95% CI)	Incremental cost per additional case detected	Additional cases detected[a]	Additional cost[a]
12-lead ECG	Consultant	28[a]	£9429 (£8938 to 9920)	£337	–	–
	GP	22 (20 to 25)	£9377 (£8892 to 9861)	£426	–6	–£52
	Practice nurse	22 (19 to 24)	£9095 (£8645 to 9546)	£413	–6	–£334
	CDSS	24 (23 to 26)	£8941 (£8508 to 9373)	£372	–4	–£488
Limb-lead rhythm strip ECG	Consultant	26[a]	£8675 (£8274 to 9075)	£333	–2	–£754
	GP	23 (21 to 25)	£8622 (£8228 to 9017)	£374	–5	–£807
	Practice nurse	21 (18 to 23)	£8341 (£7980 to 8703)	£397	–7	–£1088
Single-lead thoracic placement ECG	Consultant	28[a]	£8798 (£8383 to 9213)	£314	0	–£631
	GP	24 (22 to 26)	£8748 (£8337 to 9155)	£364	–4	–£681
	Practice nurse	19 (17 to 21)	£8465 (£8089 to 8841)	£445	–9	–£964

[a] 95% CIs not applicable.

TABLE 71 *Patient cost questionnaire*

Main activity forgone, *n* (%)	
Work	15 (2.4)
Looking after relatives	36 (5.7)
Leisure time/housework	568 (89.9)
Missing	13 (2.1)
Total travel time (minutes)	
Mean (SD)	25.1 (17.7)
Range	2–120
Missing	26 (4.1)
Travel mode, *n* (%)	
Walking/bike	175 (27.7)
Private car	366 (57.9)
Bus/train	73 (11.4)
Taxi	11 (1.7)
Motorbike/moped	3 (0.5)
Missing	5 (0.8)
Total distance travelled (miles)[a] (car or motorbike), *n* = 334	
Mean (SD)	3.47 (2.68)
Range	0.06–15.5
Missing	34
Waiting time in clinic (minutes)	
Mean (SD)	6.1 (7.7)
Range	0 to 60
No wait	115
Missing	45

[a] 1 mile = 1.61 km.

TABLE 72 *Base-case cost-effectiveness estimates including patient costs*

Strategy	Cases detected (95% CI)	Incremental cases detected	Incremental cost (95% CI)	Incremental cost per additional case detected (£)	
				Comparison with no screening	Comparison with previous strategy
No screening (control)	47 (35–62)	–	–	–	–
Opportunistic	75 (59–94)	28	£10,174 (£9593 to £10,755)	£363	£363
Systematic high risk	53 (40–69)	6	£24,530 (£23,678 to £25,382)	£4088	Dominated by opportunistic screening
Systematic population	74 (58–93)	27	£48,260 (£46,952 to £49,567)	£1787	Dominated by opportunistic screening

questions. The first set of model runs (*Table 73*) was carried out to look at different screening intervals for opportunistic screening for men and women, for a 65-year-old cohort and a general population of patients aged 65 and over. Screening used a 12-lead ECG read by a cardiology consultant, the gold standard, and subsequent treatment was warfarin. A no-screening option was also included. The second set of model runs (*Table 74*) was carried out to look at different screening intervals for systematic screening. The third set of model runs (*Table 75*) addressed the alternative ways in which screening could be organised, in terms of the initial ECG (12-lead, limb-lead rhythm strip or single-lead thoracic placement) and method of interpretation (GP, practice nurse or CDSS). Here, the runs were only carried out for opportunistic screening, for the 65-year-old male cohort. Screening frequency was fixed at annual screening and treatment was warfarin. The results have been ordered by cost, with the least cost option appearing first in the table.

In the model runs concerned with screening type or interval (*Tables 73* and *74*), 500,000 simulated patients were used. The model runs concerned with screening organisation used one million simulated patients (*Table 75*). The tables show mean costs and QALYs for each option and the associated quasi-standard errors, which demonstrate the stochastic nature of the model. By doubling the sample size, the standard errors were reduced. In addition, for each model run the numbers of ischaemic strokes, haemorrhagic strokes and gastrointestinal bleeds were recorded to check the consistency and validity of the model results. The number of patients with AF and cases diagnosed were also recorded, to calculate the percentage of AF patients actually diagnosed. The expectation was, in the case of more intense, more frequent or more sensitive screening (therefore more patients treated), the number of AF cases diagnosed and ischaemic strokes would be reduced. However, because of the risks of haemorrhage with warfarin, the number of haemorrhagic strokes and gastrointestinal bleeds would increase.

On the basis of the study findings from the within-trial analysis, let us focus initially on opportunistic screening (*Table 73*). Compared with no screening, for all cohorts opportunistic screening brings increases in the percentage of AF detected, the most marked increase being achieved by annual screening. In line with prior expectations, the introduction of screening is associated with large reductions in the number of ischaemic strokes, but an increase in both haemorrhagic strokes and gastrointestinal bleeds. The combined effect of these benefits and disbenefits is that, overall, the QALY scores for the opportunistic screening options are not significantly different to those for the no-screening option. The cost results suggest that, at worst, opportunistic screening is cost neutral and, at best, is associated with a small reduction in overall costs. These cost analysis findings reflect the balance between up-front costs of screening and treatment and future costs associated with thrombotic and haemorrhagic events. Model runs for systematic screening (*Table 74*) in the same patient groups also demonstrate a reduction in ischaemic strokes and highest proportion of diagnosed AF cases for annual screening, but no pattern can be observed for mean costs and QALYs. Model runs were also carried out for both types of screening every 2, 4 or 5 years but, again, differences in costs and QALYs are small.

Table 75 reports model results for alternative opportunistic screening approaches. They suggest that, if opportunistic screening is to be undertaken, then use of a 12-lead ECG with interpretation by either a consultant cardiologist or CDSS is performed. These two approaches appear to be associated with lower numbers of ischaemic strokes and lower costs, compared with no screening and compared with other screening scenarios. Analyses were carried out for men and women and both patient cohorts, but no differences were observed, therefore only the results for the male 65-year-old cohort are shown here.

Sensitivity analyses

Simple one-way sensitivity analyses were initially undertaken on key variables to investigate the effect on model results. In the base-case analysis, there was a slight reduction in quality of life for patients on warfarin; therefore, in the sensitivity analysis the model was run for no quality of life decrease. For the 65-year-old cohorts, QALYs increased slightly in both opportunistic and systematic screening, with annual screening having the highest values. General population (age ≥ 65 years) screening also saw a slight increase in QALYs, but values were very similar for all screening frequencies.

Base-case runs assumed warfarin as treatment of choice; therefore, the model was also run for aspirin, which is less effective in ischaemic stroke

TABLE 73 *Base-case opportunistic screening results for screening strategy by cohort*

Cohort	Screening type	Cost (£)		QALYs		Ischaemic strokes	Haemorrhagic strokes	GI bleeds	% AF diagnosed
		Mean	QSE	Mean	QSE				
Males aged 65	Annual	6653	31.48	10.4255	0.0063	96,572	39,895	121,824	90.4
	3 yearly	6773	31.80	10.4169	0.0063	100,441	39,625	119,680	83.0
	One-off	6772	31.56	10.4152	0.0063	104,028	39,419	116,730	75.7
	No screen	6812	31.86	10.4136	0.0063	104,759	38,723	116,166	74.8
Males aged ≥ 65	Annual	4906	24.52	7.0914	0.0061	73,585	35,484	90,440	87.3
	3 yearly	4998	24.77	7.0876	0.0061	78,074	35,191	88,462	78.3
	One-off	5003	24.79	7.0693	0.0061	79,739	34,453	87,051	71.5
	No screen	5040	24.83	7.0751	0.0061	80,900	34,449	85,937	69.3
Females aged 65	Annual	8370	36.76	12.3945	0.0066	109,512	57,954	154,042	91.1
	3 yearly	8349	36.62	12.3937	0.0066	111,975	57,300	152,160	84.5
	One-off	8323	36.56	12.3795	0.0066	114,723	56,547	148,855	77.5
	No screen	8366	36.61	12.3806	0.0066	114,640	56,901	148,786	77.2
Females aged ≥ 65	Annual	6389	29.00	8.1614	0.0067	85,176	51,624	108,599	88.1
	3 yearly	6404	29.05	8.1547	0.0067	87,859	50,693	108,328	80.0
	One-off	6410	29.08	8.1455	0.0067	89,285	50,222	106,440	73.2
	No screen	6429	29.07	8.1686	0.0067	90,057	50,151	106,595	71.7

GI, gastrointestinal.

TABLE 74 *Base-case systematic screening results for screening strategy by cohort*

Cohort	Screening type	Cost (£)		QALYs		Ischaemic strokes	Haemorrhagic strokes	GI bleeds	% AF diagnosed
		Mean	QSE	Mean	QSE				
Males aged 65	Annual	6777	31.59	10.4334	0.0063	97,819	39,611	122,337	88.2
	3 yearly	6814	31.72	10.4307	0.0063	102,002	39,303	119,358	81.2
	One-off	6763	31.55	10.4153	0.0063	104,574	38,603	116,710	75.4
	No screen	6812	31.86	10.4136	0.0063	104,759	38,723	116,166	74.8
Males aged ≥ 65	Annual	5004	24.72	7.0775	0.0061	74,654	35,255	88,944	84.0
	3 yearly	5065	24.87	7.0857	0.0061	78,678	35,255	87,553	76.3
	One-off	5035	24.84	7.0774	0.0061	80,160	34,296	86,420	70.4
	No screen	5040	24.83	7.0751	0.0061	80,900	34,449	85,937	69.3
Females aged 65	Annual	8486	36.86	12.3876	0.0066	110,284	58,182	153,034	86.5
	3 yearly	8389	36.73	12.3866	0.0066	112,668	57,374	150,761	81.6
	One-off	8318	36.46	12.3824	0.0066	114,719	56,657	149,227	77.6
	No screen	8366	36.61	12.3806	0.0066	114,640	56,901	148,786	77.2
Females aged ≥ 65	Annual	6476	29.09	8.1629	0.0068	86,622	50,978	108,599	81.4
	3 yearly	6469	29.24	8.1665	0.0067	88,636	50,549	107,090	75.6
	One-off	6490	29.23	8.1735	0.0067	90,303	50,352	107,085	72.2
	No screen	6429	29.07	8.1686	0.0067	90,057	49,463	103,516	71.7

TABLE 75 *Base-case annual opportunistic screening results for screening type for a 65-year-old male cohort*

Screening type	Cost (£)		QALYs		Ischaemic strokes	Haemorrhagic strokes	GI bleeds	% AF diagnosed
	Mean	QSE	Mean	QSE				
12-lead consultant	6648	22.24	10.4258	0.0044	193,028	79,695	243,909	90.3
12-lead CDSS	6678	22.31	10.4248	0.0044	195,506	79,173	242,449	87.9
Limb-lead practice nurse	6696	22.22	10.4233	0.0044	199,088	78,711	240,121	85.1
Single-lead practice nurse	6699	22.19	10.4211	0.0044	200,741	78,393	238,539	84.1
Limb-lead GP	6708	22.25	10.4288	0.0044	197,690	78,896	241,378	86.8
12-lead GP	6717	22.30	10.4246	0.0044	198,510	78,908	241,025	86.5
Single-lead GP	6719	22.30	10.4250	0.0044	197,279	79,706	241,678	87.6
12-lead practice nurse	6725	22.33	10.4234	0.0044	199,261	78,512	240,403	85.8
No screen	6756	22.36	10.4153	0.0045	209,448	77,148	232,159	74.8

reduction but has fewer side-effects and no reduction of quality of life in the model. Mean costs were higher and mean QALYs lower for men and women in the 65-year-old cohort.

Compliance rates were varied in the analysis for the 65-year-old cohorts as trial-based rates were used in the base case. Both an additional 10% and 20% compliance made very little difference to overall results, with no marked change in costs or QALYs for gender or for different types and frequencies of screening. The only exception was a slight increase in QALYs in males for an additional 20% compliance with opportunistic screening.

In the base-case model runs for 65-year-olds, all cases of AF at baseline were undiagnosed; therefore, the effect on results for annual and one-off screening (at the age of 65) and no screening with 70% diagnosed AF at baseline was explored. Again, there was very little difference in the overall results.

PSA was carried out for male and female cohorts aged 65 years and opportunistic and systematic screening separately, resulting in four different analyses. The results for opportunistic screening are included here. As stated in Chapter 2, for each analysis a graphical representation of the uncertainty in incremental costs and effects was shown on a cost-effectiveness plane, and a CEAC curve drawn showing the probability of a screening programme being cost-effective compared with no screening for a range of threshold values that the NHS might be willing to pay for an additional QALY.

The scatters on the cost-effectiveness planes, as outputs from the PSA, are reported in *Figures 3* and *4*. The scatters span all four quadrants of the cost-effectiveness plane, indicating the considerable uncertainty about whether screening is beneficial or not, and whether it is cost-saving or not. The simulation for opportunistic screening for men suggests that at any threshold ICER, this type of screening has a probability of approximately 60% of being cost-effective (*Figure 5*). The CEAC for opportunistic screening in women (*Figure 6*) suggests that screening has a probability slightly less than 60% of being cost-effective, at all ICER levels.

Model limitations

The limitations of the data concern the uncertainty around the estimates used in the model. The model uses data on prevalence and incidence of AF and this will be an underestimate

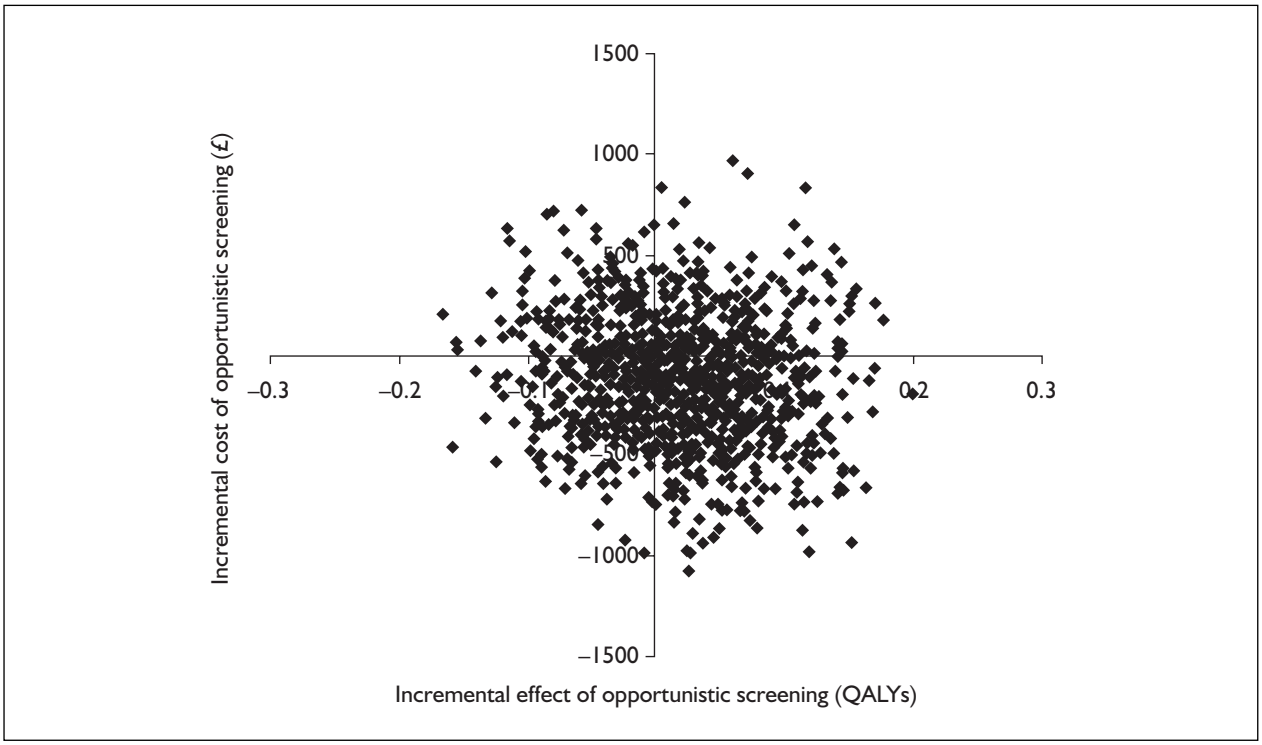

FIGURE 3 *Incremental cost-effectiveness plane for annual opportunistic screening compared with no screening in men, start age 65 years*

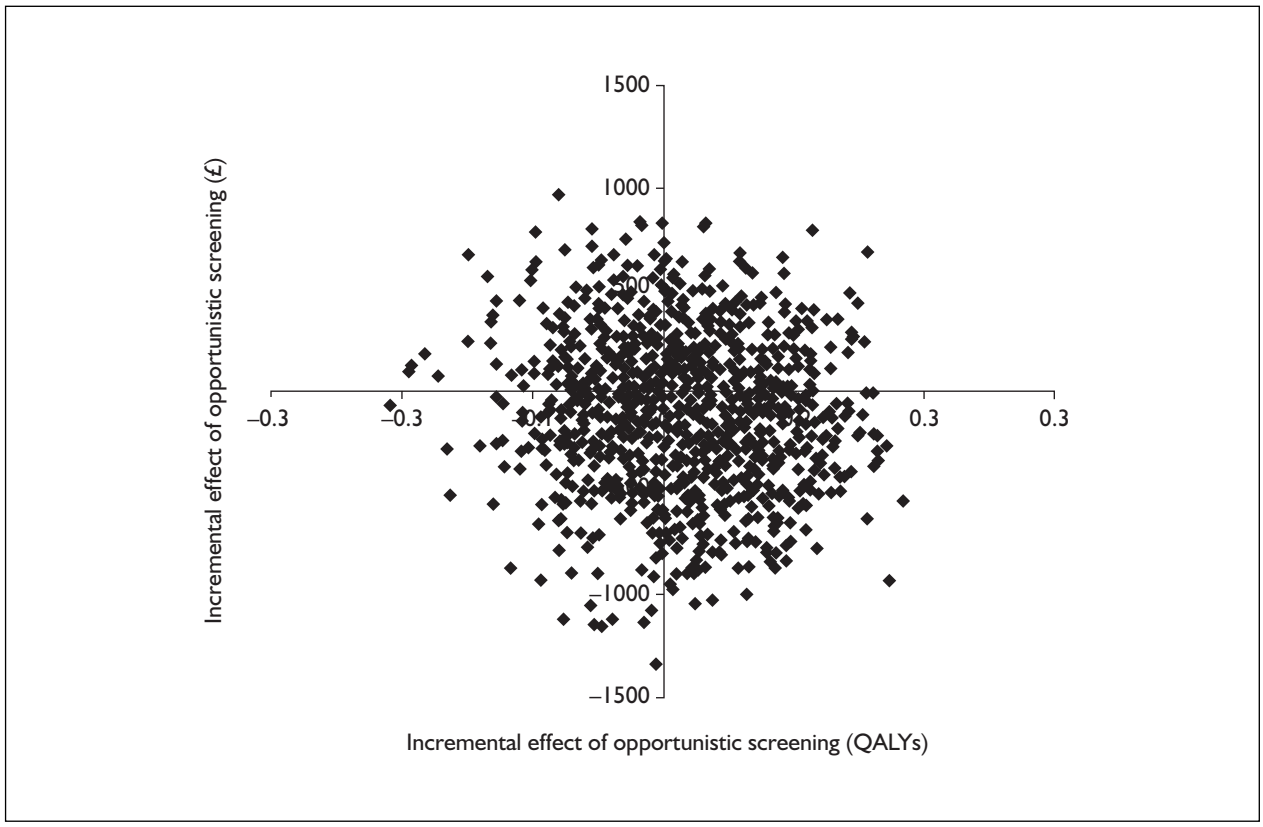

FIGURE 4 *Incremental cost-effectiveness plane for annual opportunistic screening compared with no screening in women, start age 65 years*

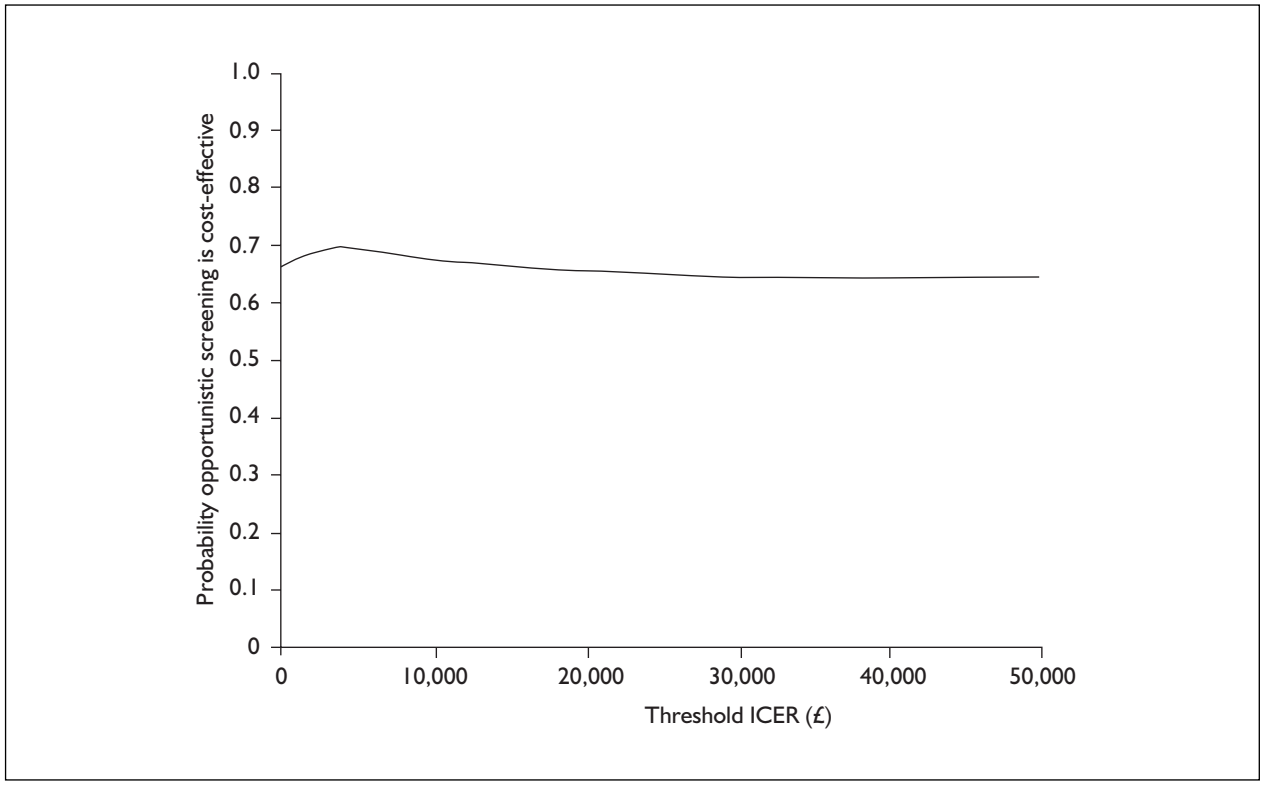

FIGURE 5 *CEAC for annual opportunistic screening compared with no screening in men, start age 65 years*

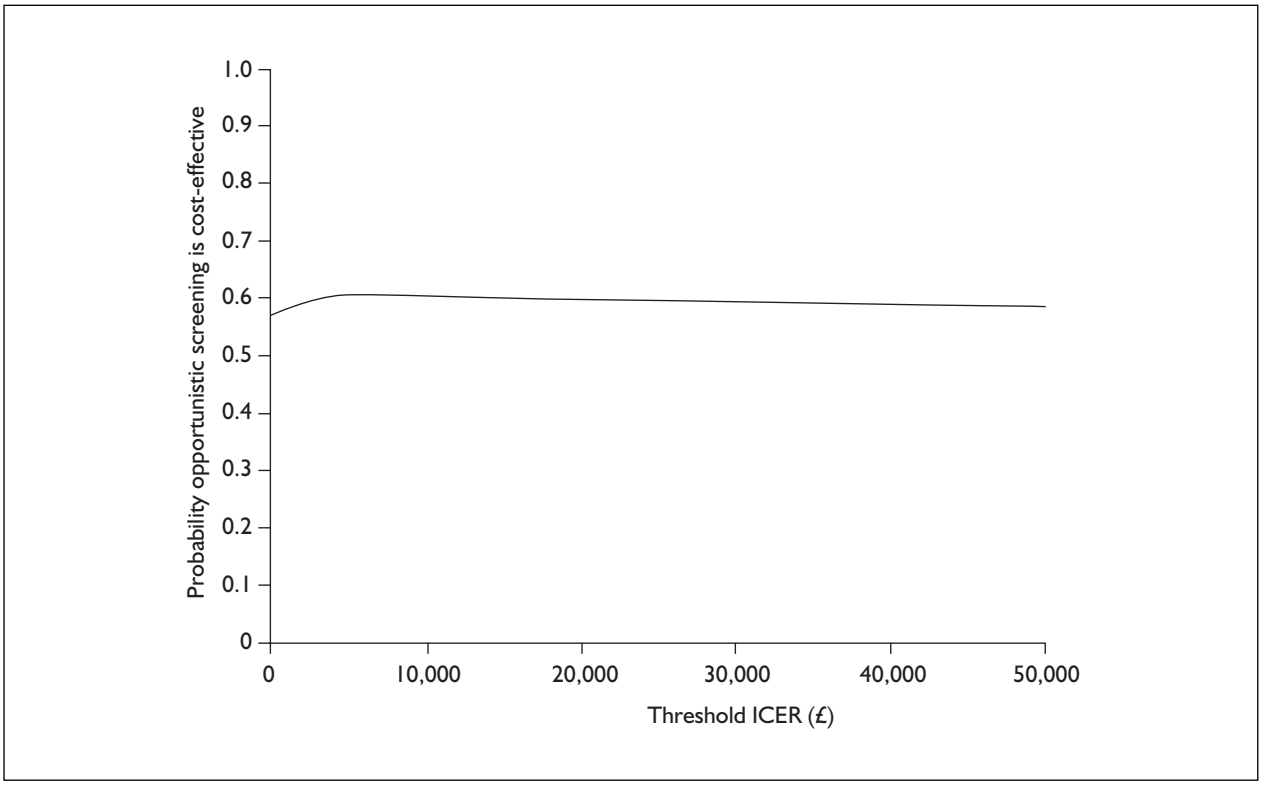

FIGURE 6 *CEAC for annual opportunistic screening compared with no screening in women, start age 65 years*

of the true values owing to unknown undiagnosed cases. In addition, within the model, prevalent cases at baseline are assumed to be undiagnosed for the screening programme for 65-year-olds, but in reality many of the cases will already have been diagnosed. Therefore, the results for one-off screening will overestimate the benefit of this type of screening, although the effect of changing the proportion diagnosed has been tested by simple sensitivity analyses. In some cases, for example, the sensitivity and specificity of screening and compliance rates, no published data were available so study data were used, which underestimate or overestimate parameter values. In terms of time to routine detection of AF, an arbitrary value had to be used.

In addition, there were structural limitations, for example artificially specifying disablement or death from stroke after previous stroke events, and assuming that all gastrointestinal bleeds were non-fatal and resulted in an arbitrary length of time for reduction in quality of life.

The model was simplified by considering only one treatment at a time, either warfarin or aspirin. In reality, some patients with AF will be on warfarin, some on aspirin, and others will receive treatment such as cardioversion to revert them back to sinus rhythm. In this model, patients will only have their treatment discontinued if a serious adverse haemorrhagic event occurs. However, real patients will have their treatment discontinued for many reasons. This is particularly the case of warfarin, where regular monitoring is required and therefore treatment is likely to be changed if the patient is non-compliant. In addition, treatment received is dependent on both doctor and patient preferences, and a change in circumstances (e.g. development of another condition) or when the patient becomes very old and/or frail may result in a change in treatment.

Chapter 4
Discussion

This multicentred primary care-based study was commissioned by the NHS HTA Board to determine the most cost-effective method of screening for AF in the population aged 65 years and over. The underlying principles behind this question were: (1) AF is an independent risk factor for stroke; (2) this risk can be reduced substantially by treatment with warfarin; (3) patients aged 65 and over with AF are at high risk of stroke and would benefit most from warfarin therapy; and (4) AF is underdiagnosed in the community.

In ascertaining the cost-effectiveness of various screening strategies it was necessary to achieve a series of linked objectives involving case identification to establish baseline prevalence and incidence in this population, the effectiveness of combinations of screening strategies with different personnel (including interpretation of tests) and the utility of additional tests, followed by a modelling approach to determine implications for further research and policy implementation.

Fifty practices were involved in the study, reflecting the whole spectrum of socioeconomic and demographic parameters within the UK. Practices were recruited from the MidReC, the largest independent primary care network in the UK. The scale and diversity of the practices involved ensures generalisability of the results. Just under 15,000 patients were included in the study from a total population of 286,250, with an average age of 75 years, and 43% were male.

Baseline prevalence of AF was determined using a two-stage process: computer identification of patients with a possible diagnosis followed by a manual search to confirm or refute the diagnosis. The computer searches included a number of both clinical and pharmacological terms and identified around one-third of all patients as having possible AF. The most accurate search terms were 'supraventricular tachycardia', 'atrial fibrillation/flutter', 'digoxin', and 'warfarin'. Aspirin was not particularly useful as a search term, perhaps reflecting the ubiquity of its use. The accuracy of this approach was confirmed by searching manually a 5% sample of notes not selected by the computer search. This revealed only a further three cases. The authors are confident, therefore, that these findings are accurate.

The prevalence of AF was found to be 7.9% in the control population and 6.9% in the intervention population at baseline. This difference must be accounted for in one of two ways: either there was a real difference in prevalence or the control practices were identifying more cases of AF through routine practice than the intervention practices. Given the similarities of the practices in terms of demographics this is unlikely to reflect a real difference and is more likely to reflect a higher detection rate within these practices. This caused some difficulties with interpretation of the incidence data. The annual incidence of AF was found to be 1.04% (95% CI 0.78 to 1.38%) in the control population compared with 1.64% (95% CI 1.31 to 2.05%) for the opportunistic arm and 1.62% (95% CI 1.29 to 2.03%) for the systematic arm. Does this reflect a real difference in detection or merely reflect the fact that more patients had already been identified within the control population? Using a patient-level analysis, screening was demonstrated to be more effective, even taking into account the difference in baseline prevalence. It is clear therefore that screening is effective in detecting more cases of AF than routine care.

If screening is effective, which screening method should be used? In terms of choosing between opportunistic screening and systematic screening, the effects were very similar, with almost identical numbers of new cases detected. From a societal perspective, the cost per case detected for systematic screening was £1787 compared with £363 for patients identified opportunistically. High-risk screening was even less cost-effective (£4088 per case detected). One reason why opportunistic screening was so effective was that approximately 70% of patients eligible had a pulse taken during the 12 months. Pulse-taking has previously been shown to be highly sensitive for detecting AF; thus, if a high proportion of patients receives a simple prescreening test before having an ECG, opportunistic screening would be more cost-effective owing to the reduced number of ECGs performed.

These findings contrast with previously published general practice data where systematic screening combining pulse-taking with rhythm strip ECG was suggested as the optimum strategy.[31] The earlier study was smaller (four practices, 3001 patients) and crucially only screened over a 6-month period. Thus, while 1099/1499 (73%) of patients underwent systematic screening, only 439/1502 (29%) were seen opportunistically. It is clear from the present findings that the majority of patients in the eligible age group are seen at least once within a 12-month period, and the figure is likely to be even higher in a 2-year period. Thus, as long as practitioners are reminded to take a pulse on patients in the eligible age group, the majority of patients would be identified opportunistically, requiring far fewer ECGs and hence reducing cost.

The base-case analysis indicates that opportunistic screening (with a 12-lead ECG and consultant interpretation) is more cost-effective than systematic screening (either high risk or population). However, the results reported in *Table 70* suggest that cost-savings can be achieved by moving away from opportunistic screening with 12-lead ECG and consultant interpretation to other configurations of opportunistic screening. For example, cost-savings can be achieved through the use of limb or single-lead ECGs, and through the use of GP, practice nurse or CDSS interpretation of the ECG. There is, however, a price to be paid in that such alternative opportunistic strategies almost all have a smaller gain in new cases of AF detected. Although consultant-read limb or single-lead ECGs detect similar numbers of cases to 12-lead ECGs, and are cheaper, advice from the study cardiologists suggests that this is not an appropriate option because of the strong cardiologist preference for a gold-standard ECG. The feasibility of routine interpretation of ECGs by cardiologists may be challenged because of workload and capacity constraints. Therefore, the alternative of CDSS interpretation looks attractive in terms of its relatively high yield.

The cost-effectiveness ratios of alternative opportunistic screening scenarios, relative to opportunistic screening with a 12-lead ECG and consultant interpretation, can be plotted, as shown in *Figure 7*. All ratios fall in the south-west quadrant, indicating that the trade-off to be considered is a reduction in both cost and effectiveness.

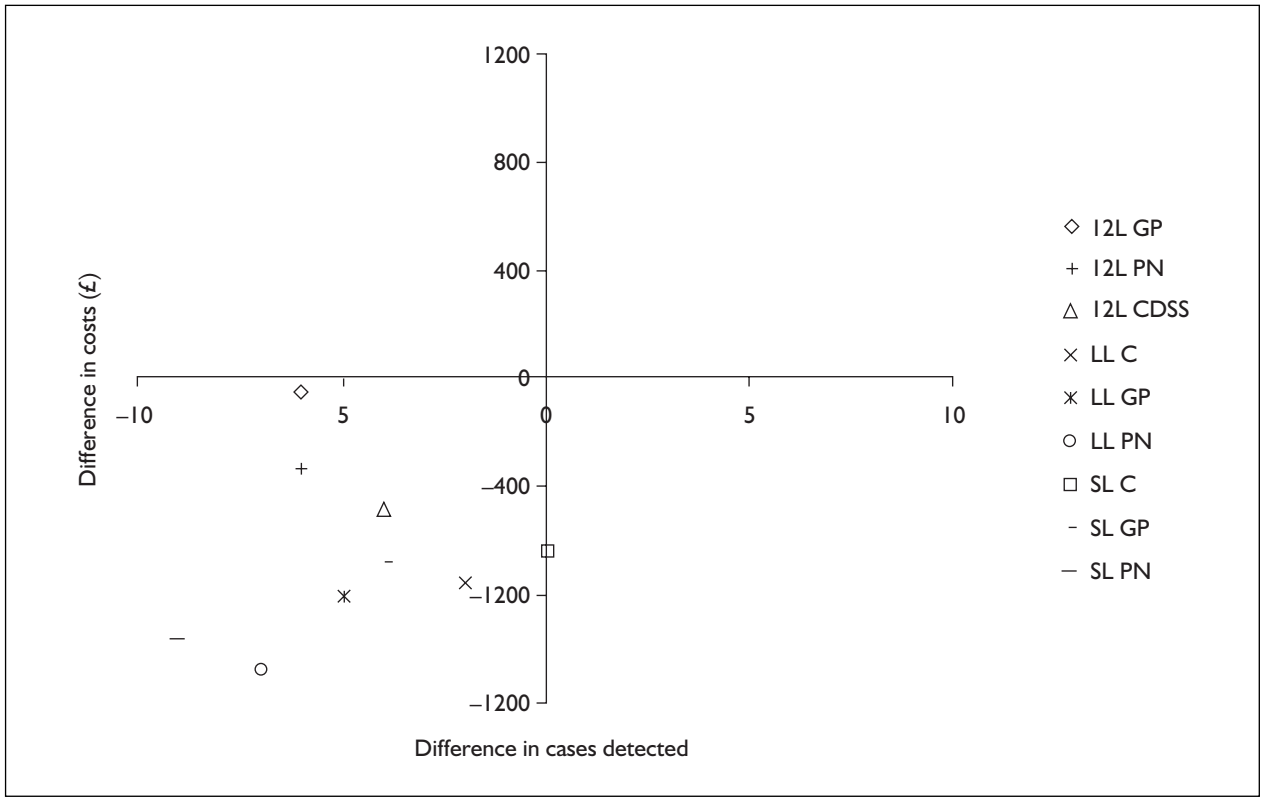

FIGURE 7 *Cost-effectiveness plane: alternative opportunistic screening strategies compared with 12-lead ECG and consultant interpretation. 12L, 12-lead ECG; LL, limb-lead ECG; SL, single-lead ECG; PN, practice nurse; C, consultant.*

Having determined in overall terms that opportunistic screening combining pulse-taking with an ECG is the most cost-effective screening strategy, the personnel, expertise and equipment required remain to be determined. In terms of pulse-taking, the majority of pulses were taken by doctors, and pulse-taking compared with the gold standard of a cardiologist-interpreted ECG had a sensitivity of 87% and specificity of 81%, compared with practice nurse figures of 91% and 74% from a previous study.[31] Thus, whoever performs the initial pulse-taking, it will result in around a 2% false-negative rate and a 70% false-positive rate.

Having been identified as having possible AF as a result of having an irregular pulse, the options that remain are to have a single-lead, limb-lead or 12-lead ECG, which is then interpreted by either a cardiologist, GP, practice nurse or computerised software. In calculating the possible alternative strategies, the gold standard has been defined as a cardiologist interpretation of a 12-lead ECG. The different options have been investigated to outline the different diagnostic approaches that may be possible. *Table 70* summarises the findings from SAFE. If a GP had interpreted 12-lead ECGs, six cases of AF would have been missed, with an overall cost-saving of £52. Similarly, if a 12-lead ECG had been interpreted by computerised software, only four cases would have been missed, with an overall cost-saving of £488. Thus, in comparing these alternatives, the computerised software option is dominant, detecting more cases less expensively. Using these data the worst case scenario would be GP interpretation of the 12-lead ECG, which saves only £8.67 for each case missed, whereas a consultant reporting a single-lead ECG misses no cases and saves £631.

The within-trial economic results suggest that opportunistic screening is the most cost-effective option. However, it was also important to consider costs and effects over a longer period, particularly to identify the most appropriate frequency of screening and to consider the full range of benefits and disbenefits of screening and treatment. Previous modelling work suggested that there was little difference between ECG screening and pulse-taking, both methods were cost-effective using standard cost-effectiveness criteria, and sensitivity analyses showed less frequent screening to be more cost-effective.

The results from the base-case ISM runs demonstrated only very small differences in costs and QALYs for different methods and intensities of screening. However, annual opportunistic screening for all patient groups resulted in the lowest number of ischaemic stroke events and the greatest number of cases of AF diagnosed, with annual systematic screening the next most effective method using these criteria. The additional costs required to screen patients appear to be offset by the reduction in treatment and long-term costs of ischaemic stroke events. The results from the PSAs indicate that there is a probability of approximately 60% that annual opportunistic screening in both men and women from the age of 65 is cost-effective.

These data are the most robust yet produced for the UK. The screening process did not raise anxiety (although screen-positive patients were more anxious than screen-negative patients) and was acceptable to patients. Based on these data, a systematic approach to screening cannot be justified.

In terms of diagnosis, the gold standard remains 12-lead ECG interpreted by an expert. The performance of GPs and practice nurses in terms of ECG interpretation was disappointing; however, the computerised software performed well and represents a realistic alternative to expert interpretation.

The study was complicated by the fact that the control population had a higher baseline prevalence of AF. This was accounted for in the analysis. The echocardiographic aspect of the study was not revealing, as too few patients underwent the procedure.

In conclusion, this study has demonstrated that if screening is to be introduced, opportunistic pulse screening for AF with computer-reported ECG assessment is more likely to be considered cost-effective than other methods for identifying new cases of AF in the population aged 65 years and over.

Chapter 5

Recommendations for further research

There are clearly some implications for policy arising from the SAFE study. Should a screening programme be implemented through primary care, based on the results of SAFE, an opportunistic approach, using pulse-taking followed by ECG for those with irregular pulses, is probably the most cost-effective option. There are, however, several issues that could form the basis of future research to help to define further the optimum patient pathway.

- How does the implementation of a screening programme for AF influence the uptake and maintenance of anticoagulation in patients aged 65 and over?
  It is clear from current data that not all patients identified with AF receive optimum treatment with thromboprophylactic agents. It is not clear what effect the introduction of a screening programme would have on this process.
- An evaluation of the role of computerised decision support software in the diagnosis of cardiac arrythmias.
  The data for software interpretation of ECGs were very encouraging. There are few data on the performance of interpretive software in routine care.
- What is the best method for routinely detecting paroxysmal AF?
  The data on incidence of AF may be an underestimate owing to the contribution of patients with paroxysmal AF who may not have been detected. These patients may be at higher risk of thrombotic disease. It remains unclear how best to detect these patients routinely.
- How can healthcare professionals' performance in ECG interpretation be best improved?
  GP and practice nurse performance in interpreting ECGs was not very encouraging, even in those who had received some training. Given the moves to transfer more care delivery into primary care, further research into how best to improve health professionals' performance is required.
- The development of a robust economic model to incorporate data on new therapeutic agents for use as thromboprophylactic agents for patients with AF.
  As part of this study a sophisticated model to simulate the treatment effect of thromboprophylactic agents was developed. A new class of drugs, the oral direct thrombin inhibitors, is currently arousing interest as an alternative to warfarin therapy. Any new agent will have to be subjected to rigorous evaluation within a similar model.
- An evaluation of the relative risk of stroke for patients with incident as opposed to prevalent AF.
  This study provided robust data on both incident and prevalent cases of AF. It is not clear whether these populations have similar or different risks for thromboembolic disease. Further research on cohorts of patients identified as incident or prevalent could further assist in risk stratification of patients with AF.

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We would also like to thank all the staff at the following practices, recruited through MidReC, who participated in the study.

Medical centres

The Park Medical Centre, 691 Coventry Road, Small Heath, Birmingham B10 0JL

Bridge House Medical Centre, Scholars Lane, Stratford-Upon-Avon, Warwickshire CV37 6HE

The Moorcroft Medical Centre, Bottleslow Street, Hanley, Stoke-on-Trent ST1 3NJ

Bulkington Surgery, School Road, Bulkington, Bedworth, Warwickshire CV12 9JB

The Surgery, Lower Quinton, Near Stratford-Upon-Avon, Warwickshire CV37 8SJ

Hawkesley Medical Practice, 375 Shannon Road, Hawkesley, Birmingham B38 9TJ

Weoley Park Surgery, 112 Weoley Park Road, Selly Oak, Birmingham B29 5HA

The Surgery, Selcroft Avenue, Quinton, Birmingham B32 2BX

The Health Centre, Wrekin Drive, Donnington, Telford, Shropshire TF2 8QN

Harborne Medical Practice, 4 York Street, Harborne, Birmingham B17 0HG

The Surgery, 108 Bunbury Road, Northfield, Birmingham B31 2DN

Warwick Gates Family Health Centre, Cressida Close, Heathcote, Warwick CV34 6DZ

Masefield Road Surgery, Masefield Road, Lower Gornal, Dudley DY3 3BU

Richmond Medical Centre, 179 Richmond Road, Solihull, West Midlands B92 7SA

River Brook Medical Centre, 3 River Brook Drive, Stirchley, Birmingham B30 2SH

Victoria Road Surgery, 21 Victoria Road, Acocks Green, Birmingham B27 7XZ

Moor Green Lane Medical Centre, 339 Moor Green Lane, Moseley, Birmingham B13 8QS

The Surgery, 287 Haslucks Green Road, Shirley, Solihull, West Midlands B90 2LW

The Health Centre, Dunning Street, Tunstall, Stoke-on-Trent ST6 5AP

Pendeford Health Centre, Whitburn Close, Pendeford, Wolverhampton WV9 5NJ

Bellevue Medical Centre, 6 Bellevue, Edgbaston, Birmingham B5 7LX

The Surgery, 111 Church Lane, Stechford, Birmingham B33 9EJ

Moxley Medical Centre, 10 Queens Street, Moxley, Wednesbury WS10 8TE

Kingsdale Surgery, 422–424 Kings Road, Kingstanding, Birmingham B44 0UJ

The Harlequin Surgery, 160 Shard End Crescent, Shard End, Birmingham B34 7BP

Kingsway Lodge, King Street, Much Wenlock, Shropshire TF13 6BL

Belgrave Surgery, 108 Medway, Belgrave, Tamworth, Staffordshire B77 2JW

Keelinge House Surgery, 176 Stourbridge Road, Holly Hall, Dudley, West Midlands DY1 2ER

The Surgery, Fentham Hall, Marsh Lane, Hampton-in-Arden, Solihull, West Midlands B92 0AH

Lea Road Medical Practice, 35 Lea Road, Pennfields, Wolverhampton WV3 0LS

Old Mill Surgery, 22 Speedwell Road, Edgbaston, Birmingham B5 7QA

Horseley Heath Surgery, 14 Horseley Heath, Tipton, West Midlands DY4 7QU

Handsworth Wood Medical Centre, 110 Church Lane, Handsworth Wood, Birmingham B20 2ES

Stockwell Surgery, Park Medical Centre, Ball Haye Road, Leek, Staffordshire ST13 6QP

The Surgery, 1 Goodrest Croft, Yardley Wood, Birmingham B14 4JU

Monkspath Surgery, Farmhouse Way, Shirley, Solihull, West Midlands B90 4EH

Bilbrook Medical Centre, Brookfield Road, Bilbrook, Wolverhampton WV8 1DX

Kingsbury Road Surgery, 273 Kingsbury Road, Erdington, Birmingham B24 8RD

DeMontfort Medical Centre, Burford Road, Bengeworth, Evesham, Worcestershire WR11 5AG

The Medical Centre, Craig Croft, Chelmsley Wood, Birmingham B37 7TR

The Surgery, 89 Blurton Road, Blurton, Stoke-on-Trent ST3 2BS

Tysoe Surgery, Main Street, Tysoe, Warwickshire CV35 0SE

Duncan Street Primary Care Centre, Duncan Street, Blakenhall, Wolverhampton WV2 3AN

Henley-in-Arden Medical Centre, Prince Harry Road, Henley-in-Arden, Solihull B95 5DD

The Surgery, 265 Baldwins Lane, Hall Green, Birmingham B28 0RF

Aylesbury Surgery, Warren Farm Road, Kingstanding, Birmingham B44 0DX

Greenbank Surgery, 1025 Stratford Road, Hall Green, Birmingham B28 8BG

The Westgate Practice, Greenhill Health Centre, Church Street, Lichfield, Staffordshire WS13 6JL

Park Surgery, 278 Stratford Road, Shirley, Solihull, West Midlands B90 3AF

The Wand Medical Centre, 279 Gooch Street, Highgate, Birmingham B5 7JE

Contribution of authors

FDR Hobbs (Professor of Primary Care and General Practice) and DA Fitzmaurice (Professor of Primary Care Research) were the principal investigators. J Mant (Senior Lecturer in Primary Care and General Practice) prepared the design and analysis. E Murray (Project Officer) was project manager. S Jowett (Clinical Services Manager) was project manager and health economist. S Bryan (Professor of Health Economics) and J Raftery (Professor of Health Economics) were responsible for the economic evaluation. M Davies (Consultant Cardiologist and Senior Lecturer) and G Lip (Professor of Cardiovascular Medicine) worked on the study design and interpreted the ECG results.

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Appendix 1

National Screening Committee criteria for appraising the viability, effectiveness and appropriateness of a screening programme

The criteria, which are set out below, are based on the classic criteria first promulgated in a WHO report in 1966, but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the adverse effects of healthcare; regrettably, some people who undergo screening will suffer adverse effects without receiving benefit from the programme.

These criteria have been prepared taking into account international work on the appraisal of screening programmes, particularly that in Canada and the USA. It is recognised that not all of the criteria and questions raised in the format will be applicable to every proposed programme, but gathering as much information as possible will obviously assist the NSC to make better evidence-based decisions.

All of the following criteria should be met before screening for a condition is initiated:

The condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, or disease marker and a latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

The test

4. There should be a simple, safe, precise and validated screening test.
5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
6. The test should be acceptable to the population.
7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The treatment

8. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
9. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
10. Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme.

The screening programme

11. There must be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
13. The benefit from the screening programme should outweigh the physical and

psychological harm (caused by the test, diagnostic procedures and treatment).

14. The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
15. There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme.
17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.
18. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
19. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

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