Study protocol

SMART: Self-Management of Anticoagulation, a Randomised Trial [ISRCTN19313375]

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Abstract

Background: Oral anticoagulation monitoring has traditionally taken place in secondary care because of the need for a laboratory blood test, the international normalised ratio (INR). The development of reliable near patient testing (NPT) systems for INR estimation has facilitated devolution of testing to primary care. Patient self-management is a logical progression from the primary care model. This study will be the first to randomise non-selected patients in primary care, to either self-management or standard care.

Method: The study was a multi-centred randomised controlled trial with patients from 49 general practices recruited. Those suitable for inclusion were aged 18 or over, with a long term indication for oral anticoagulation, who had taken warfarin for at least six months. Patients randomised to the intervention arm attended at least two training sessions which were practice-based, 1 week apart. Each patient was assessed on their capability to undertake self management. If considered capable, they were given a near patient INR testing monitor, test strips and quality control material for home testing. Patients managed their own anticoagulation for a period of 12 months and performed their INR test every 2 weeks. Control patients continued with their pre-study care either attending hospital or practice based anticoagulant clinics.

Discussion: The methodology used in this trial will overcome concerns from previous trials of selection bias and relevance to the UK health service. The study will give a clearer understanding of the benefits of self-management in terms of clinical and cost effectiveness and patient preference.

Introduction

Increasing numbers of patients are receiving anticoagulation therapy, primarily driven by increased indications for warfarin therapy, particularly for non rheumatic atrial fibrillation.[1] Oral anticoagulation monitoring has traditionally taken place in secondary care because of the need for a laboratory blood test, the International Normalised Ratio (INR).[2] The INR measures the level of the induced clotting defect and there is good evidence that the incidence of adverse events is directly related to the intensity of treatment, with thrombotic events increasing exponentially as the INR decreases below a value of 2.0 and haemorrhagic events increasing exponentially as the INR increases above a value of 4.5.[3]

Table 1:

Study author	Country	Nature of study	Patient Numbers intervention/control	Results intervention v control
White et al [12]	USA	RCT	23/23	93% v 75% *
Sawicki [15]	Germany	RCT	90/89	53% v 34% **
Hasenkam et al [16]	Denmark	Matched	21/20	77% v 55% *
Ansell et al [17]	USA	Matched	20/20	89% v 68% *
Anderson et al [18]	Canada	Observational	40/self-control	74% ***
Barnado [19]	Germany	Observational	216/No control	83.1% ***
Massicotte et al [20]	Canada	Observational	23/No control	63% ***
Korfer and Kortke[21]	Germany	RCT	279/303	80% v 54% ***

• % time in range, **% patients in range, ***% tests in range

The rapid and continuing rise in the number of patients receiving warfarin has meant that traditional hospital based clinics are increasingly unable to cope with the throughput of patients.[4] This has led to the investigation of alternative models of care for anticoagulation management, in particular primary care management using Near Patient Testing (NPT) devices for INR estimation.[5] Near patient testing can be defined as the performance of a diagnostic test, usually performed in a hospital pathology laboratory outside the usual setting. The development of reliable NPT for INR estimation has facilitated devolution of testing to general practice.[6] NPT machines for INR estimation have now been subject to rigorous evaluation in the hospital laboratory and primary care settings.[7–10]

The Birmingham model of primary care anticoagulation monitoring[4] (developed by the study investigators) using NPT and computerised decision support software (CDSS) was created as a result of this progress and the efficacy, safety and efficiency of the model has been accepted as a credible alternative to hospital based care.[11]

A further advance for anticoagulation services is the investigation of patients' ability to manage their own therapeutic monitoring. Patient self-management (PSM) of INR is a logical progression from the NPT primary care anticoagulation model. PSM offers increased patient empowerment to control therapy with a model analogous to home glucose monitoring using a portable glucometer.[12] It is essential, however, that the INR can be reliably measured within home settings, and also that patients are able to interpret the INR result and alter therapy as appropriate.

We have previously demonstrated in a pilot study involving 49 patients from 6 general practices that PSM is feasible within the UK, with PSM patients achieving satisfactory levels of therapeutic control (74% of time spent in range compared to 77% in routinely managed patients).[13,14]

Earlier studies, predominantly from Germany and the USA have addressed the feasibility of allowing orally anticoagulated patients to undertake self-management.[12,15–21] (Table 1). These studies offer some observational evidence to suggest that PSM is a relevant model of care for long term anticoagulation management in terms of reliability, convenience and reduced risks. Also treatment quality is comparable or even better than conventional management.

The studies, however, used highly selected populations and suffered methodological weaknesses since patients were usually not randomly selected. Patients selected for self-management within these studies were inherently more likely to have better therapeutic control as eligibility would include levels of 'intelligence', manual dexterity and previously stable control. Furthermore, these eligibility criteria were applied subjectively, with no objective measures of compliance or cognitive ability stated.

The health economic analyses from Germany are furthermore not relevant to the NHS as patient self-management is 100% reimbursed (subject to satisfactory completion of a training programme) through private health insurance. Cost-effectiveness of PSM within the NHS will be sensitive to the reduction in patient contact with medical services afforded by the model balanced against the increased capital costs associated with providing patients with their own NPT and reagents, and ultimately the incidence of serious adverse events, particularly stroke.

Major haemorrhagic or thrombotic complications from warfarin therapy are relatively rare (haemorrhagic 1–3 per 100 patient years and thrombotic 4–6 per 100 patient years [22,23]) so it is unlikely that a significant difference between the groups will be shown in this study. The main implication of the German studies is that self-management required only a modest amount of dexterity and skills. However it is recognised that practical training and

conceptual education on self-management is essential for the success of the self-management programme.

It can be concluded from the published studies that while self-management appears a credible alternative to existing models of care, there are currently no data from the UK to support its use. There are no clinical outcome data in any of the published studies to support its use either. Evidence is required from UK trials regarding both clinical and cost-effectiveness before it can be introduced in the UK on a wide scale.

The main criticism of studies published thus far is that standard care within them was poor in comparison to published UK data.[15,24,25]. This means that any improvement in therapeutic control and reduction in serious adverse events associated with self-management will be exaggerated in comparison to UK models of care.

Therefore, based on the success of observational studies to date, this study was the first to randomise non-selected patients in primary care, to receive either PSM or standard care.

The current study aims to evaluate the clinical and cost-effectiveness of PSM. It is currently accepted practice that adequate clinical performance is represented by a level of 60% spent within the therapeutic range.[26]

The intervention, in terms of patient education and PSM, was therefore be accurately evaluated against standard care. Standard care being the patients' previous management, either attending a hospital or general practice based anticoagulation clinic. Based upon pre study data collected for this study, frequency of testing on average for patients participating in standard care is 10 INR tests per year. There are various models involving a wide range of health professionals. Patients either attended;

• Hospital based clinics using both venous samples with laboratory testing or NPT systems.

• Primary care based clinics with three models of care including

  • Phlebotomy only, samples are sent to the hospital laboratory for INR estimation and dosing decisions,

  • or phlebotomy and dosing in practice with INR testing performed by the laboratory,

  • or phlebotomy with INR estimation and dosing decisions being made in the primary care clinic.

This study focused on the practicalities of the PSM model within the NHS with particular emphasis on training, cost, and clinical effectiveness. It was important for self-management of oral anticoagulation to prove that compared to routine management and including all follow up costs, it is cost effective and gives at least equally good clinical outcomes. Monitoring costs and the cost of treating thromboembolic and haemorrhagic complications were therefore compared.

Hypothesis
There is no difference in therapeutic control of patients self managing their oral anticoagulation therapy in comparison with standard care in patients on long term oral anticoagulation therapy.

Aim
To determine the clinical and cost effectiveness of patient self-management (PSM) in comparison with standard care in patients on long term oral anticoagulation therapy.

Objectives
☐ To assess whether patients (or a carer) manage their own anticoagulation therapeutic control in terms of percentage of time spent within therapeutic range, as effectively as patients receiving standard care.

☐ To investigate the cost effectiveness of PSM with regard to monitoring costs (with cost-modelling for the treatment of serious adverse events, particularly stroke).

☐ To provide information on the types of patient who may potentially benefit or who may be unsuitable for this model of care.

☐ To determine patient preferences and utilities with regard to patient self-management.

Method
The study was a multi-centred randomised controlled trial. Patients on long term warfarin therapy from 48 general practices within the West Midlands and surrounding areas were recruited with support from the Midlands Research Consortium (MiDReC). Practices were selected to represent a geographic spread of rural/suburban centres and to cover a wide socio-economic range of patients. (Figure 1).

Patient recruitment
Patients' suitable for trial inclusion were identified from a practice-generated computer list. The inclusion criteria was patients aged 18 or over, with a long term (greater than 12 months) indication for oral anticoagulation, who had taken warfarin for at least six months and were willing (or in the case of dependent patients both they and their
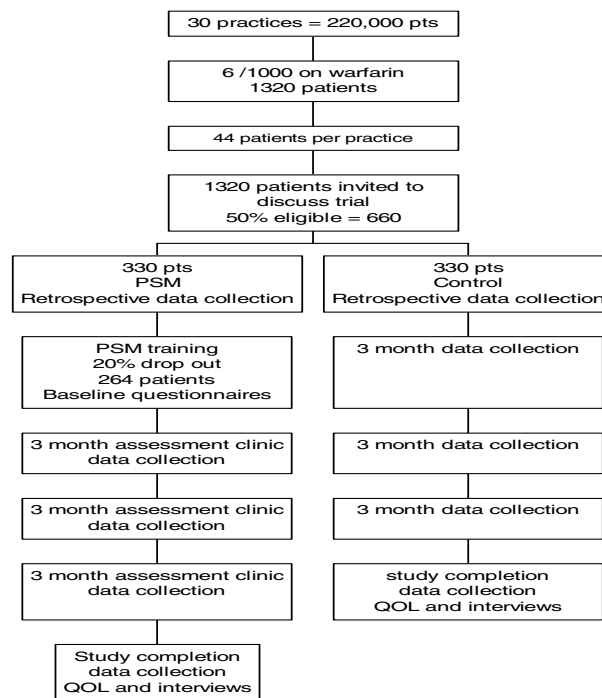
Figure 1
Summary of study design

carer were willing) to participate in the study. A 'carer' is defined as someone who takes care of the patient, but is not employed to do so, e.g., partner, spouse, other relative.

Exclusion criteria for the trial was patients with a short-term indication (less than 12-months) for warfarin therapy:aged under 18 years of age; resident in a nursing home; or physically unable to attend the surgery. Patients who had moved out of the area, become terminally ill, discontinued warfarin or died were also excluded.

There were are no other absolute exclusion criteria, but patients were only invited to enter into the study if both the research team and the patients own GP agreed that there was uncertainty as to which model of care would provide the best therapeutic control. Thus, if a GP felt that

a patient would be unable to cope with PSM, the patient was not invited to enter into the study.

All remaining patients were sent letters from their GP inviting them to participate in the study; together with information sheets, reply slips and free post envelopes. They were asked to complete the reply slip regardless of whether they wished to participate as it informed on education and ethnicity and the reason why they did not wish to take part. A follow up letter was sent if no response was received after 2 weeks.

This method of selection was as inclusive as possible and allowed no room for subjectivity based on previous control or compliance.

Outcome measures
Primary outcome measure
Therapeutic INR control in terms of percentage of time spent within therapeutic range. Percentage time in range was calculated according to Rosendaal's equation [27] which assumes a linear change between INR results through a specific software programme (BAP-PC, Birmingham University).

Secondary outcome measure
Major bleeding and thrombotic complications and associated deaths

Cost- effectiveness

Patient satisfaction and attitudes to self management.

Information sessions
Patients giving a positive response to the invitation letter were asked to attend an information session at their practice to explain the purpose of the study, potential advantages (personal and societal); and the implications of taking part.

Patients willing to participate who gave written informed consent were randomly allocated to either PSM or control.

Patient training
Patients randomised to the intervention arm (i.e. PSM) attended at least two training sessions, with the option of a third session. The training sessions were based on those used in Germany [28] but were less formal and intensive. A number of trained anticoagulation nurses were employed to help with patient training. The training sessions were practice-based, held for a maximum of 6 patients at a time (limited to 4 if possible) held 1 week apart.

Each patient was individually assessed to satisfy the research team that they were capable of undertaking PSM. A certificate was given to each patient to certify that they had successfully completed the training course. For those patients who did not meet the assessment criteria, an additional session was arranged. Patients then not considered capable of PSM were asked to return to their usual care and followed-up within the PSM arm, with the reason for withdrawal documented. Identical data for withdrawn patients were monitored as for the control patients for the period of the trial intervention. The NPT device used in this study was the 'Coaguchek S' (Roche Diagnostics).

Trial procedure
The intervention patients managed their own anticoagulation for a period of 12 months. Throughout the trial the patient performed their INR test once every 2 weeks,

unless a dosage change was made then they performed the test after 1 week. Senior research personnel were available for support and advice as necessary via a pager.

Intervention patients were asked to attend a practice-based clinic every 3 months for assessment of their progress and to perform quality control procedures. These clinics were managed by research personnel and involved enquiries regarding general health and haemorrhagic or thrombotic complications. If at the 3-month assessment any patient was deemed not to be managing self-management effectively they were asked to undertake further training. If they were still not competent in self-management following further training they were required to withdraw from the study.

Data were collected from all participating hospital laboratories and practice based clinics regarding the technique and reagents used for measuring INR. Baseline INR and demographic data were collected retrospectively for 6 months on all patients at study entry. Intervention (PSM) patients recorded INR results and warfarin dose on a case report form.

Control patients continued with their pre-study care either attending hospital or practice based anticoagulant clinics. Research personnel collected control and excluded patients' INR results and warfarin dose from the responsible anticoagulation clinic (hospital or practice). At six monthly intervals and at the end of the study GP records of PSM, control and excluded patients were reviewed for any mention of hospital admission, to ascertain any adverse events including fatalities, and whether they were still taking warfarin. If a major haemorrhagic or thrombotic event was identified patients were withdrawn from the study.

Data on any complications related to oral anticoagulation therapy for patients in the control arm of the study were collected from patient records held at the general practice. Control patients were not asked to self report adverse events. Data on adverse events for patients in the intervention arm were collected from the GP records and patients were asked to self report events by completing an adverse events clinical report form.

Patients names were flagged at the central register by NHS number, to facilitate collection of mortality data. Postal questionnaires were sent to study participants at baseline, six months and 12 months. A random sample of patients in both the PSM and control groups were also asked to complete a cost questionnaire and invited to participate in focus groups to inform conjoint analysis centred around willingness to pay for this model of care. Standardised, validated and reliable measures were used for collecting

patient self-reported changes in levels of psychological well-being. The use of the SF-12 allowed the measurement of changes in broad aspects of health status. Similarly the use of EQ-5D allowed the measurement of broad aspects of quality of life.[29,30] The EQ-5D not only allowed changes in health status to be measured but also valued, using the University of York Measurement and Valuation of Health general population survey tariff.[31]

The cost analysis adopted a broad perspective to include costs incurred within the health sector and by patients and carers. Data collection was undertaken on all trial patients in order to allow a stochastic cost analysis to be conducted. The focus of the data collection was upon the key cost drivers which included; anticoagulation clinic attendances in primary and secondary care, contact with GPs; contact with secondary care, both outpatient and inpatient; consumables used in treatment provision and drugs. The analysis adopted an incremental approach such that data collection was concentrated on resource use differences between trial arms.

Unit costs were collected from published sources and a representative sample of NHS providers in order to increase generalisability. The methods used to collect data included patient questionnaires and a review of patient records (both GP and hospital). Data on private costs was collected from a survey of a sub-cohort of the trial population.

Statistical analysis

For the primary outcome that INR control, in terms of percentage of time spent in range in both groups to be equivalent at a level of 10%, with 5% significance and 80% power, 261 patients were needed in each group (total 522). This was also sufficient for the secondary outcomes for patient satisfaction on either EQ-5D or SF-12. These patients numbers provided sufficient power to show a four point difference in the two groups with a significance of 5% at 80% power. These numbers were also able to detect a 13% change in those reporting a problem with pain and discomfort on the EQ-5D and a five point increase in mean score on the visual analogue scale, at the same power and significance. This sample size also allowed the detection of a drop from 4 events per hundred patient years to 0.2 events per hundred patient years at the same power and significance. Because of an estimated 20% drop-out rate from the PSM arm, the study proposed to recruit 660 patients.

The types of analysis proposed were Chi-square, log-linear models, logistic regression and survival analysis, t-tests, ANOVA and non-parametric equivalents.

The t-tests or a non-parametric equivalent was used to examine the differences between the two main groups for the percentage of time spent within therapeutic range and ANOVA or its non-parametric equivalent for detecting changes in time spent within range for more than 2 target therapeutic groups. Chi-squared and log-linear models were used to examine demographic data. Logistic regression was used to search for predictors of adverse events. Survival analysis was used to see whether there is a difference in time to the 1st adverse event (assuming there are sufficient events).

Discussion

This is an important study in terms of developing an evidence base for the utility of patient self-management of oral anticoagulation in the UK. Previous studies have used highly selected populations in observational non-randomised trials.

This study aimed to recruit all patients aged 18 and over who take oral anticoagulant therapy, although a small proportion of patients were excluded by practice staff or GPs for reasons of co-morbidity or immobility.

The principle contentious issue within this methodology was the role of training. It could be argued that all patients should be trained and that randomization should only occur once patients have been trained. In this way any confounding effect produced by training would be negated. We felt that this process would be unethical and training patients for a service that they would not receive seemed inequitable. As training focused primarily on the ability to perform the INR test accurately, and to interpret this into a warfarin dose, this should not affect their INR control. Similarly all patients receiving warfarin should have received the basic level of education provided when they first started.

The methodology used in this trial will overcome concerns of selection bias and relevance to the UK health service. Based on a pilot study, it was anticipated that 50% of patients invited to participate would be recruited but, in fact, there was just 25% response. Also there was a 30% drop out during or immediately following training instead of the 20% anticipated. The study will give a clearer understanding of who might benefit from this model of care.

Study completion is anticipated for July 2003, with results available by November 2003.

Abbreviations

PSM Patient Self-management

NPT Near Patient Testing

QC Quality control

CDSS Computerised decision support software

Competing interests

DA Fitzmaurice is funded by an NHS Career Scientist Award

ET Murray has an MRC Research Fellow

Roche diagnostics have contributed towards conference fees.

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