A community pharmacy based anticoagulant management service (2002-027)

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EXECUTIVE SUMMARY

Background

In Australia, warfarin is a widely used anticoagulant for the prevention and treatment of pulmonary embolism and deep venous thrombosis and for prophylaxis of thromboembolic events in patients with atrial fibrillation, prosthetic heart valves and myocardial infarction. Its use, however, is complicated by the risk of excessive bleeding from over-anticoagulation which can be life threatening and which remains the most significant adverse event for patients receiving the drug. The most important predictor of outcome on warfarin therapy remains the clotting status of the patient (measured by the INR) and its control within the target range selected according to the indication for anticoagulation. Clinical studies have shown that anticoagulant management programs that incorporate patient education and regular monitoring of INR can reduce the incidence of serious misadventure and improve patient outcomes. Patients receiving warfarin report significant impacts on their quality of life associated with their therapy. Constant vigilance of diet and concomitant medications is necessary and significant disruption to daily living and time management can be associated with the requirement for long-term, periodic INR assessment. This study seeks to address the challenges of warfarin therapy through community pharmacists providing education and support to patients receiving warfarin therapy and applying a point-of-care testing device for assessing INR and communicating the INR results in consultation with general practitioners.

Aims and Objectives

This project evaluated the impact of a community pharmacist managed anticoagulant service conducted in collaboration with general practitioners on;

1. INR control, clinical outcome and quality of life of patients receiving warfarin;
2. a cost comparison of a pharmacy based service compared to usual care;
3. the professional links between community pharmacists and general practitioners in providing patient care for persons taking warfarin.

Methods

Setting: This study was conducted in community pharmacies and general practices across the greater Sydney metropolitan area.

Design: An observational study of patients on warfarin maintenance therapy who received a pharmacist-general practitioner-based anticoagulation (*intervention*) management service. Prospectively collected data from the *intervention* arm was compared to retrospectively collected data from patients receiving usual care (*control* and *pre-intervention*).

Pharmacist-general practitioners managed anticoagulation:

- Trained pharmacists provided patient education and support, monitored INR (with a point-of-care testing device) and made warfarin management recommendations.
- INR Results and pharmacist's recommendations were communicated to the patient's general practitioner for vetting, discussion and decision.

Clinical Endpoint: The primary clinical endpoint was the proportion of time INR observations were *within*, *below* and *above* the specified range. This parameter has been closely linked to patient outcome.

Humanistic Endpoints: The main humanistic endpoints included patient satisfaction, quality of life assessment (using a validated structured questionnaire specific for patients receiving warfarin), patient warfarin knowledge assessment (measured using a previously validated questionnaire) and pharmacist experiences.

Economic Endpoint: A comparison was made between the costs of delivering the community pharmacist-managed anticoagulant service compared to the costs of providing usual care. This approach was selected based on the observations that frequency of testing and patient INR control was the same between the intervention and control arms of the study. The Medicare Benefits Schedule expenditure was also compared for a limited number of patients.

Study Comparisons: Slow recruitment was a major issue which affected the size of the final study cohort. In light of this issue, the investigators changed the protocol (with the permission of the Pharmacy Guild of Australia) to allow three sets of clinical and humanistic data to be collected. These are defined below;

- ***Intervention*** – prospectively collected data from patients who received pharmacist-general practitioner based anticoagulant management.

- ***Pre-intervention*** – retrospectively collected data from patients receiving *usual care* prior to the *intervention.*
- ***Control*** – retrospectively collected data from a separate group of patients who received *usual care* over the same timeframe as the *intervention.*

Results

This study combined data from 53 patients, 758 INR measurements and 537 pharmacist recommendations collectively representing approximately 40 years of patient experience on warfarin.

Clinical Outcomes: There were no major (haemorrhagic and thromboembolic) or minor (episodes of bruising or bleeding) warfarin-related adverse events recorded during the trial. The table below presents a summary of all patient data and the primary clinical endpoint for patients in the *control* and *intervention* group (note: *pre-intervention* data were collected from the patients prior to the *intervention).*

Parameter	**Control**	**Intervention cohort**	
		Pre-intervention	***Intervention***
Patients	12[1]	20	41
INR results	92	142	524
INR results per patient	15 (6 – 33) [2]	7 (2 – 21) [2]	13 (1 – 28) [2]
Time in Study (months)	9.5 ± 5.8	4.8 ± 3.3	8.2 ± 3.7
Frequency of monitoring (readings per month)	2.1 ± 0.9 (1.2 -3.5)	1.7 ± 1.1 (0.6 – 5.0)	1.6 ± 0.7 (0.4 – 4.1)
Length of time INR readings were WITHIN range (%)[3]	**81 ± 17 % (52 – 95)**	**75 ± 18 % (35 – 100)**	**81 ± 16 % (45 – 100)**
Length of time INR readings were BELOW range (%)[3]	12 ± 15 % (0 – 32)	6 ± 3 % (2 – 12)	9 ± 3 % (2 – 13)
Length of time INR readings were ABOVE range (%)[3]	8 ± 4 % (3 – 15)	10 ± 14 % (0 – 46)	11 ± 13 % (0 – 44)

[1] INR data only available for 6 patients
[2] median and range (shown in brackets)
[3] Derived from data for 38 patients and 519 INR observations for *Intervention* and 14 patients and 126 INR observations for *Pre-intervention.*

These data show that a pharmacist-managed anticoagulant service conducted in collaboration with the patient's GP using of point-of-care INR testing could maintain safe and efficacious control of patient INR over the course of the study. However, statistical analyses were not conducted on these data because of differences in patient numbers and the combination of retrospective and prospective data.

Fourteen patients provided adequate clinical data for a rigorous comparison between INR control during the *pre-intervention* and *intervention* phases. A summary of the individual and mean results for the 14 patients that contributed adequate *pre-intervention* and *intervention* INR data is summarised below.

Parameter	**Intervention**	
	Pre- *	**During***
Time in Study (months)	4.7 ± 1.6	8.8 ± 4.0
Proportion of time INR readings were WITHIN range (%)	75 ± 17 % (65 – 86)	78 ± 18 % (68 – 89)
Proportion of time INR readings were BELOW range (%)	15 ± 17 % (5 – 25)	8 ± 9 % (2 – 13)
Proportion of time INR readings were ABOVE range (%)	9 ± 14 % (1 – 18)	15 ± 16 % (5 – 25)

Mean ± standard deviation (and 95% confidence intervals) are reported.

These results show that there was no statistically significant difference (p=0.66; paired 2-tailed t-test) between the proportion of time INR readings were within the target range for these 14 patients in the *pre-intervention* and *intervention* period. Furthermore, the proportions of time above and below the INR range were not statistically significant different (p=0.15 and p=0.07, respectively) for the *pre-intervention* and *intervention* periods.

Humanistic endpoints: Patients involved in the pharmacist-general practitioner managed anticoagulant service were very satisfied with the service and highlighted convenience as a major advantage. The quality of life of patients in the *intervention*

group increased over the course of the study (based on a before and after comparison) whereas warfarin related knowledge tended to be higher after the study but did not reach statistical significance. Pharmacists participating in the study recorded a high level of satisfaction in providing the service. This is reflected in the fact that general practitioners actioned 96% of the 537 management recommendations made by pharmacists.

Economic Comparison: A comparison was made of the cost of delivering the community pharmacist-managed anticoagulant service compared to the associate costs of providing usual care. The findings of the cost comparison suggest that in the first year of delivery the community pharmacist-managed anticoagulant service was more expensive to deliver (reflecting the need for set up costs and training) but in subsequent years the pharmacy-based service conducted in collaboration with GPs and using point-of-care INR testing offered considerable cost savings. The Medical Benefits Schedule (MBS) data for 17 patients in this study showed a trend towards lower MBS expenditure on anticoagulant monitoring but a significant difference between the *pre-intervention* and *intervention* expenditure was not observed. The frequency of INR monitoring by general practitioners during the *pre-intervention* and by pharmacists and general practitioner in the *intervention* were not significantly different.

Conclusions

A community pharmacist-general practitioner managed anticoagulant service using point-of-care INR testing can;

- maintain the control of patient INR within the target range to help achieve optimal anticoagulation outcomes;
- improve patient knowledge which, in turn, has been linked to reduced risk of warfarin-related complications;
- improve patient quality of life by reducing treatment related distress;
- foster timely and appropriate inter-professional collaboration between pharmacists and general practitioners;
- be delivered in a manner which is comparable to the cost of existing pathology services.

Furthermore, this study demonstrated that the community pharmacist-general practitioner managed anticoagulant service was acceptable to patients and pharmacists involved in the study. Trained and supported pharmacists were able to make credible management recommendations about anticoagulation that were accepted by general practitioners.

Taken together, the results of this study demonstrate that a community pharmacist-general practitioner managed anticoagulant service is feasible and offers on alternative option for some patients receiving warfarin.

An important note

The "*intervention*" in this study consisted of trained pharmacists working in close collaboration with general practitioners and patients to manage a patient's anticoagulant therapy. The title of this project might lead some readers to conclude that pharmacists were working independently of general practitioners – this is not the case. At all times during this study patients remained in the care of their general practitioner and no clinical decisions (eg dose regimen changes) were made by pharmacists without the prior approval of the patient's general practitioner. This was a fundamental aspect of the study.

Recommendations

1. A community pharmacy based anticoagulant management service that combines point-of-care INR testing, patient education and general practitioner collaboration is feasible for patients receiving maintenance warfarin therapy.
2. The collaborative community pharmacist- general practitioner anticoagulant management model examined in this study provides a suitable alternative (not replacement) for existing anticoagulant management options.
3. We recommend that funding for community pharmacist- general practitioner management of anticoagulation be considered in the future.
4. Future studies should be conducted over a longer time frame involving a larger number of patients and pharmacists to allow an assessment of the long term impact of community pharmacist-general practitioner based anticoagulant management on patient care.
5. The use of point-of-care INR testing in pharmacy should be supported by appropriate training of staff in the use of the device and competency evaluated according to professional standards for near-patient testing procedures.
6. Anticoagulant management using point-of-care INR testing should be conducted in association with an appropriate internal and external quality control program.

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1.0 INTRODUCTION

1.1 Warfarin in the Australian Community

In Australia, warfarin is a widely used anticoagulant for the prevention and treatment of pulmonary embolism and deep venous thrombosis and for prophylaxis of thromboembolic events in patients with atrial fibrillation, prosthetic heart valves and myocardial infarction [*Cardiovascular Drug Guideline*, 2003].

1.2 The Challenges of Anticoagulant Therapy

Warfarin has an important place in cardiology. Its use, however, is complicated by the risk of excessive bleeding from over-anticoagulation which can be life threatening and remains the most significant adverse event for patients receiving the drug. Unfortunately warfarin was responsible for more than 5,000 hospital admissions in Australia in 1999-2000 (*Second National Report on Patient Safety - Improving Medication Safety*, Australian Council for Safety and Quality in Health Care, July 2002). Patients who receive an inadequate dose of warfarin are at risk of thrombotic events which can also have serious outcomes. There is considerable variability in the pharmacokinetics and pharmacodynamics of warfarin [Chan *et al*, 1994a] and a significant risk of drug interactions [Chan *et al*, 1994b; McLachlan, 2000]. Vigilance is required on the part of the patient with respect to regulating dietary intake of vitamin K rich foods and avoiding interacting medications. For these reasons, patients on warfarin also require routine monitoring of blood clotting status (usually measured by the International Normalised Ratio; INR) and careful warfarin dose titration to meet their individual requirements.

Although the risk of bleeding increases as the INR increases, about 50% of episodes occur while the INR is lower than 4.0 [Campbell *et al*, 2001]. This highlights the important role that both regular INR monitoring and patient education can play in avoiding serious outcomes for patients receiving warfarin. Furthermore, as the Australian population ages more "at risk" people are likely to be receiving anticoagulant therapy with warfarin which will require greater care in dose

individualisation to minimise the risk and incidence of serious adverse events [Campbell *et al*, 2001].

Patients receiving warfarin report significant impacts on their quality of life [Lane and Lip, 2005] associated with their therapy. Constant vigilance with respect to diet and concomitant medications is necessary and significant disruption to daily living and time management can be associated with the requirement for long-term, periodic INR assessment. This typically includes regular visits to a pathology collection centre or general practitioner (GP) surgery to provide a venous blood sample. Once transported and analysed by the pathology laboratory the INR result is communicated to the patient's general practitioner who then contacts the patient or is contacted by the patient to discuss dosing recommendations or management options. The patient's perspective in this management approach should not be overlooked and the possible impact on the patient's quality of life could be a contributing factor to adherence to therapy and appropriate monitoring [Das *et al*, 2005; Lane and Lip, 2005]. For example, the discomfort of regular venipuncture might be poorly tolerated or the delay in obtaining INR results and dosing advice might be unacceptable to some patients. So, disruption to a patient's daily living and ultimately their quality of life can be affected by both the blood-collection process and in the process of seeking and receiving the INR-assessment result and associated dosage or management recommendations.

This study seeks to address the challenges of monitoring and optimising warfarin therapy through community pharmacists (working with general practitioners) providing education and support to patients receiving warfarin therapy and applying a point-of-care approach for assessing INR and communicating the INR results and associated recommendations to patients and their general practitioner.

1.3 HYPOTHESIS

A community pharmacy program to manage, monitor and educate patients on anticoagulant therapy improves outcomes in patients receiving warfarin.

1.4 AIM OF THIS STUDY

This study aimed to develop an expanded role for the community pharmacist to work closely with general practitioners in managing, monitoring and educating patients receiving anticoagulant therapy with the overall goal of improving outcomes for patients receiving warfarin.

1.5 OBJECTIVES

This project evaluated the impact of a community pharmacist managed anticoagulant service conducted in collaboration with general practitioners on;

1. INR control, clinical outcome and quality of life of patients receiving warfarin;
2. cost analysis of the pharmacy based service compared to standard or usual care;
3. the professional links between community pharmacists and general practitioners in providing patient care for persons taking warfarin..

2.0 LITERATURE REVIEW

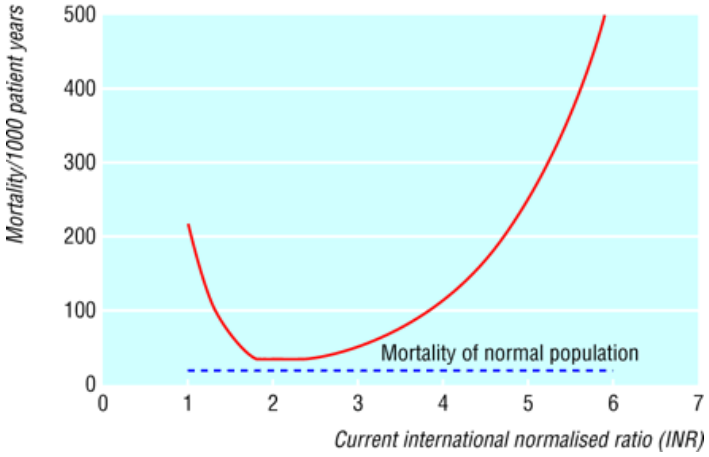
This literature review examines and discusses the benefits and risks of anticoagulant therapy and establishes the basis for monitoring INR in managing patients receiving warfarin. This section also provides a synopsis of models that have been employed to optimise warfarin management with a detailed emphasis on the role of the pharmacist in managing oral anticoagulation.

2.1 The benefits and risks of anticoagulant medicines and the need for routine monitoring of anticoagulant therapy

There is clear and convincing evidence of the benefits of warfarin therapy in reducing the morbidity and mortality associated with a range of thromboembolic conditions [Gallus *et al*, 2000; Levine *et al*, 2001]. This evidence has been accumulated over decades and involves many years of patient experience receiving warfarin. The most compelling evidence has come from outcome studies that have evaluated the predictors of anticoagulant efficacy and the risk factors for anticoagulant related unwanted effects (related to inefficacy or excessive anticoagulation) [e.g. Jones *et al*, 2005]. The major clinical studies have focussed on the risk of bleeding and stroke as key endpoints of concern.

One such study was conducted by the Swedish researchers, Oden and Fahlen [2002], who used a record linkage study design, including 42,451 patients, 3,533 deaths, and 1.25 million INR measurements, to study how mortality differs with different intensities of anticoagulation measured using INR. These researchers showed that mortality from all causes of death was strongly related to level of INR and the minimum risk of death was attained at 2.2 INR for all patients. Furthermore, a high INR was associated with increased mortality with an increase of every 1 unit of INR above 2.5. Figure 1 summarises the risk of mortality as identified by Oden and Fahlen [2002] clearly demonstrating the risks associated with both under and over anticoagulation and the need to control patients INR within the target range.

Figure 1: The risk of mortality associated with INR (adapted from Oden and Fahlen, 2002)



A study by Hylek *et al* [1996] used a hospital-based case-control methodology to evaluate the risk of stroke associated with different INR targets. They found that the risk of stroke rose steeply when INR was below 2.0 and that other (less important but significant) independent risk factors were previous stroke, diabetes, hypertension and current smoking.

There have been a number of comprehensive evaluations of the risks and implications of bleeding related to anticoagulant therapy [Linkins *et al*, 2003] and Levine *et al* [2001] make the important point that anticoagulant management decisions need to find the balance between risks of bleeding and stroke. The most important predictor of outcome on warfarin therapy remains the INR and its control within the target range selected according to the indication for anticoagulation [Samsa and Matchar, 2002].

2.2 Balancing the risks to optimise outcomes for patients

Clinical studies have shown that anticoagulant management programs that incorporate patient education and regular monitoring of INR can reduce the incidence of serious misadventure and improve patient outcomes [Chiquette *et al*, 1998; Knowlton *et al*, 1999; McCrudy, 1993]. Patients who have a poor understanding of the reason for their anticoagulant therapy and the potential adverse events (and how they are

managed) are more likely to be non-compliant when compared to patients who receive appropriate education about anticoagulant therapy [Campbell *et al*, 2001].

2.3 Anticoagulant Management Models

There have been numerous investigations to explore the most appropriate model for anticoagulant management. These models include;

- Physician-based dose adjustment
- Hospital-based anticoagulation clinics
- Community-based anticoagulation services
- Patient self-monitoring

These anticoagulant management models typically incorporate routine INR measurement, dosing protocols, clinical management protocols (eg for excessive anticoagulation) and patient education. The setting has varied from hospital to community and involved a number of health-care practitioners including general practitioners, haematologists, practice nurses and pharmacists, and patients themselves. The stage of anticoagulation (initiation or maintenance) has also varied between different studies.

The evaluation of these models has usually attempted to assess the clinical and economic benefit of each model in comparison to usual care. The key endpoint evaluated is usually the control of a patient's INR estimated as the time the patient's INR is maintained within the target range.

2.4 Pharmacists Role in Anticoagulant Management

A number of studies that have focused on the role that the pharmacist can play in the management of anticoagulant therapy have clearly identified an opportunity for pharmacists to provide a value-added service in this area. To and Pearson [1997] conducted the 'Pharmacist assisted warfarin dosing program' (PAWD) in the hospital setting where on the request of a clinician, patients were initiated on warfarin by a pharmacist using a dosing protocol. The PAWD program was piloted on 240 patients,

and compared to 340 control patients anticoagulated in the "standard" manner. There were no significant differences in the time taken to achieve therapeutic INR and a low incidence of bleeding (6% versus 8%, for "control" and PAWD, respectively) and thromboembolic events (3% versus 0%, for "control" and PAWD, respectively) was observed in both groups. It was concluded that the PAWD program was found to be equally safe and effective as usual care, with an improvement in the administration of doses [To and Pearson, 1997]. Hall and Radley [1994] identified a role for the community pharmacist in the provision of anticoagulant management in a survey of general practitioners. Following from this, Macgregor *et al* [1996] established a pharmacist-led anticoagulation clinic in a general practitioner's surgery. Using point-of-care testing, this service maintained 90% of INR results within the therapeutic range. Elderly and disabled patients felt that they benefited from this service, where tailored counselling by the pharmacist improved their knowledge of treatment, and decreased travel requirements resulted in financial savings for patients [Macgregor *et al*, 1996].

One of the largest studies to evaluate the role of pharmacists in anticoagulant management was recently published by Witt *et al* [2005]. This study explored the impact of a *Clinical Pharmacy Anticoagulation Service* (CPAS) provided in a health maintenance organisation. Witt *et al* [2005] followed 6,645 patients for 6 months using a retrospective observational cohort study design with approximately half of the patients in the *intervention* group that received the CPAS. These researchers found that the involvement of pharmacists lead to a 39% reduction in anticoagulant-related complications and this was a result of improved INR control. For patients receiving the CPAS their INR was within the target range for 64% of the time compared to 55% for the *control* group ($p<0.001$). As a result of these findings this service was recommended for widespread implementation.

Pharmacists have successfully taken on some of the more challenging aspects of anticoagulant management. Dager *et al* [2000] used a prospective study (with a matched historical control cohort) to study the impact of hospital pharmacists on patient outcome during initiation of warfarin. They found that during warfarin initiation in hospital daily consultation by a pharmacist decreased the length of

hospital stay and the need for treatment for excessive anticoagulation in patients starting warfarin for the first time. These observations support the improvement in patients outcome and are likely to translate to economic benefits. Witt and Humphries [2003] (in an earlier study to the one described above) investigated the management that pharmacists provide in dealing with excessively anticoagulated patients (INR>6) as part of the centralised telephone Clinical Pharmacy Anticoagulant Service. These researchers found that the management provided by pharmacists as part of the service lead to improved clinical outcomes when compared with traditional management. These data are supported by a Canadian study which compared the INR control achieved by trained pharmacists (using a warfarin nomogram to make patient management decisions) compared to physician management in 227 patients being initiated on warfarin following prosthetic value surgery [Tschol *et al*, 2003]. Pharmacists were able to achieve equally safe and effective INR control in this patient group.

Boddy [2001] reported on a study which showed that in the hospital setting haematology pharmacists were better than clinicians in maintaining patients within their target INR range during initiation of warfarin therapy. This researcher also found that pharmacists recommendations lead to timely dose administration and the need for few INR measurements which had benefits through associated cost reduction and patient acceptability.

Relatively few studies of anticoagulant management have been conducted in a community pharmacy setting. Holden and Holden [2000] compared pharmacist- and general practitioner-managed anticoagulation in a community outreach service in the United Kingdom. Using a retrospective analysis these researchers compared data on proportion of time within the INR target range for 51 patients using 1782 INR measurements. These researchers found that the pharmacy-managed service, which maintained 73 ± 17 % of the INR readings within the target range (INR 2-3), was not inferior to general practitioner-managed anticoagulation which achieved 65 ± 17 % of INR readings within range. In another community pharmacy-based study, Knowlton *et al* [1999] evaluated the impact of anticoagulant education and monitoring (with a point-of-care INR testing device) in 26 patients using an observational study design.

These workers showed that pharmacist-management could maintain patients within their target INR 75% of the time.

Any anticoagulant management services must be able to be delivered in a cost effective manner. Anderson [2004] conducted a cost analysis of a decentralised outpatient pharmacy anticoagulant service (involving laboratory INR testing). The costs associated with delivering the pharmacy service and the associated effectiveness (based on INR control) was evaluated using data from 92 patients in a managed care setting in the USA. This comprehensive analysis of the costs to deliver such a service and comparison with the costs associated with managing warfarin complications (such as stroke) showed that the pharmacist-managed service was relatively inexpensive compared to managing the complications of ischemic stroke or intracranial bleeding.

In summary, these data provide strong support for pharmacist involvement in anticoagulant management to ensure optimal monitoring and patients' outcomes.

2.5 Point-of-Care testing devices to measure INR

The availability of point-of-care INR testing devices which use capillary blood to determine prothrombin time and INR have facilitated the expansion of available anticoagulant management models into the community. In recent years there have been a number of point-of-care INR testing devices available for use in anticoagulant management. The utility of these devices has been evaluated in a variety of settings including monitoring by pharmacists and self-monitoring by patients.

One of the issues that is central to the clinical utility of point-of-care INR testing devices is the need for acceptable accuracy and reliability of INR readings. There have been a number of important studies which have assessed the performance of the available point-of-care testing devices for INR measurement [including Douketis *et al*, 1998; Murray *et al*, 1999; Jackson *et al*, 2004c, 2004e]. A recent study by Poller *et al* [2003] compared the INR determined using two widely used point-of-care testing (POCT) prothrombin time (PT) monitors (CoaguChek Mini and TAS PT-NC) compared to conventional methods in 600 samples collected from patients. The

authors found that one device over estimated the "true" INR by 15.2 % (95% CI; 13.4 to 17.0%) whereas the other device investigated displayed a deviation of -7.1 % (95% CI; -8.9 to -5.4 %). These deviations from the "true" laboratory determined INR have been attributed to a combination of differences in the calibration of the device (by the manufacture), instrument error and operator error. In real terms these differences equate to a 0.4 and 0.2 unit difference in INR for a patient with an INR reading in the target range of 2 to 3.

An associated BMJ Editorial by Murray and Greaves [2003] puts some of these results into perspective suggesting that the discrepancy in INR between point-of-care systems and laboratory measurements is important but not surprising. These workers confirm that it highlights the need for standardisation of point-of-care testing monitors and improved quality assurance procedures. The balance of published clinical studies that have employed point-of-care testing of INR suggest that these devices can be effective in clinical practice. For example, a study involving 336 tests collected over 6 months by Fitzmaurice *et al* [2002], which used a point-of-care testing device evaluated by Poller *et al* [2003], found no difference in the clinical outcome of patients compared to patients receiving usual care. Murray and Greaves [2003] highlight the importance of considering the difference between statistical and clinical significance in anticoagulant decision making with respect to dose adjustments. This was also discussed by van den Besselaar [2001] who concluded that point-of-care testing devices provide less precise estimates of INR (when compared to automated laboratory standards) but this should be weighed against the "clinical advantages" of near patient testing. This author did highlight the importance that internal and external quality control programs can offer for reliability but acknowledged the different nature of quality control (QC) materials required for point-of-care INR testing devices, which might not reflect a patient sample. All contributors to this debate concede that larger studies are needed to exclude significant clinical differences in outcome from using point-of-care testing devices to monitor anticoagulation. However, at this stage it is clear that these devices do offer great promise for use in the primary-care setting with the opportunity to streamline patient management and improve quality of life [Murray and Greaves, 2003]

2.6 The Australian Experience

There is clear evidence that adverse events related to warfarin represent a significant burden to the Australian healthcare system (Runciman *et al*, 2003) and there are barriers to the increase in utilisation of warfarin in some patient groups (Peterson *et al*, 2002). This has lead to a call by Halstead *et al* (1999) to improve anticoagulant management through actions such as the assessment of home- and practice-based anticoagulant monitoring.

There have been a number of studies that have evaluated the impact of different anticoagulant models in the Australian healthcare setting. Jackson *et al* [2004a] have highlighted the important role that pharmacists can play in monitoring anticoagulant therapy using a point-of-care INR testing device. Using a series of case studies these researchers have made a clear case for "pharmacist-assisted anticoagulant monitoring" in rural communities where there is limited access to pathology services. An essential part of this service has been to evaluate and promote the need for quality use of medicines in this area to optimise the outcome of patients with atrial fibrillation [Jackson *et al*, 2004b; 2004d]. These workers also conducted a systematic evaluation of the accuracy and clinical utility of the Coaguchek S point-of-care testing device used in their studies [Jackson *et al*, 2004c; 2004e]

This "promise" of benefit that point-of-care testing devices can offer for patients on warfarin has been highlighted in another Australian study. Jackson *et al* [2004c] conducted a trial in a rural setting utilising 15 general medical practices involving data from 169 patients to compare the performance of the point-of-care testing device to laboratory-based INR measurements. The authors found that the point-of-care INR testing device was accurate compared to laboratory INR readings. An important aspect of this study was that the authors confirmed that the minor differences in INR readings (90% were with 0.5 INR units) would not have lead to differences in the clinical management decisions for people taking warfarin. Jackson *et al* [2004c] also noted that, when used with appropriate training and a quality assurance program, the point-of-care testing device provided a significant opportunity to optimise

anticoagulant therapy in rural and remote communities where timely access to pathology services may be limited.

Home visitation by a pharmacist after discharge from hospital was evaluated by Jackson *et al* [2004d] using a randomised controlled trial involving 128 patients initiated on warfarin and discharged from hospital into the care of their general practitioner. They studied the impact of home monitoring by a pharmacist compared to usual care. The results of this study highlighted an important role for pharmacists in this area by demonstrating that home visits and the use of point-of care INR testing improved INR control (within the target range) and reduced haemorrhagic complications.

In summary, there is comprehensive evidence supporting the need for regular INR assessment and patient education as key determinants of the clinical outcome for patients receiving anticoagulants. There are a number of anticoagulation management models that have been evaluated and each offers potential benefits to patients. Importantly, there is strong evidence supporting the utility of point-of-care INR testing devices. The role of the pharmacist in anticoagulant monitoring and management has been evaluated in international and Australian studies. However, there are relatively few studies that have evaluated the role of community pharmacists working with general practitioners to deliver anticoagulant management service.

3.0 RESEARCH METHODS

3.1 Study Design

This study was originally designed as a prospective, controlled evaluation of a pharmacist-general practitioner managed anticoagulation service using a staggered parallel design involving pre- and post-intervention assessment of coagulation status (INR) and clinical and quality-of-life endpoints. Patients in the *intervention* group were to receive anticoagulant management from their pharmacist in collaboration with their general practitioner using a point-of-care INR testing device. Patient recruited into the *control* group were to receive their usual care (i.e they were managed essentially by their general practitioner using standard pathology laboratory INR testing). Patients were recruited through community pharmacies and two groups of pharmacies were to be involved; those providing the education, INR-testing and warfarin management service and those who provided usual care.

As the study progress adequate numbers of pharmacies and patients could not be recruited into the ***control*** arm of the study, despite the implementation of a variety of strategies to facilitate and promote control-group recruitment. To allow a comparison between *usual care* and the study ***intervention***, clinical data were collected, pertaining to a period (3-12 months) prior to recruitment into the study, for patients in the *intervention* group. These data provide a ***pre- intervention*** dataset. The limitations of this revised design are discussed later in this report.

3.2 Clinical Setting

This study was conducted in community pharmacies and general practices across the greater Sydney metropolitan area.

3.2.1 Pharmacist and general practitioner recruitment

A random sample of pharmacists in the greater Sydney metropolitan area were sent invitations to participate in the study by letter and also recruited at Pharmacy Continuing Education functions. Pharmacists were provided with a participant information sheet and consent form (Appendix 1). Pharmacists who expressed an interest in participating were invited to an educational seminar on anticoagulation management and provided with information about the project. Before confirmation of participation pharmacists were asked to give assurances that they could:

(a) recruit up to 10 patients receiving warfarin;

(b) ensure a physical environment and pharmacy-staffing profile in their pharmacy that was conducive to providing services to patients participating in the study for 12 months.

The original study plan was to recruit 5 pharmacies each into the *Intervention* and *Control* arms of the study and each pharmacy would recruit 10 patients each. However, due to slow progress in recruiting patients, another 3 pharmacies were recruited to boost patient enrolment into the *Intervention* arm of the study.

General practitioners, of the patients interested in participating in the study, were contacted by the pharmacist and provided with study information sheet and a consent form (Appendix 2). General practitioners were given the opportunity to seek clarification of any aspect of the study and additional information was provided on several occasions by the investigators.

3.2.1.1 Pharmacist Training

Pharmacists participating in the *intervention* arm attended one and half days of specialised pharmacy education which included;

- information about the clinical use of warfarin with a focus on its use in the community, importance of routine monitoring, dose adjustment, patients education aids, dietary factors and drug interactions;

- skills training in counselling patients receiving warfarin;
- instruction on appropriate procedures for collection and disposal of capillary blood samples;
- training in the use of the *INRatio* point-of-care testing device for monitoring INR; and
- an overview of the study protocol and associated data collection forms.

Further details of this training are provided in Appendix 4.

Once pharmacists consented to participate the study Project Officer visited each pharmacy and provided onsite training in the use of the point-of-care INR testing device and the data collection tools used in this study.

3.2.2 Patient Recruitment

It was planned to recruited a total of 100 patients (50 into each study arm) receiving long-term warfarin therapy. Candidates were identified at the pharmacy and recruited *via* referral from their general practitioner. Patients were approached directly by the pharmacist and provided with an approved information sheet and asked to discuss this with their general practitioner and pharmacist (Appendix 3). The study investigators were not directly involved in patient recruitment but did provide further information and resources to participating pharmacists to assist them in responding to questions from patients and general practitioners.

The specific **inclusion criteria** for patients were:

- Patients undergoing long-term warfarin therapy (longer than 12 months);
- Patients receiving community-based care;
- General practitioner referral and consent to participate

The **exclusion criteria** for patients were:

- Patients receiving short term warfarin therapy (less than 12 months);
- Patients with a known contraindication to warfarin;
- Patients for whom their medication is administered and managed by a carer;
- Patients from non-English speaking backgrounds or patients unable to give informed consent in English.

3.3 Role of the Pharmacist

In this study pharmacists actively recruited patients and facilitated the provision of information to patients and general practitioners. Pharmacists co-ordinated the "consenting" of patients and general practitioners. It was planned that pharmacists would see patients at least once per month to check their INR, advise them on dietary and lifestyle issues, and monitor adherence to the prescribed regimen.

During the patient's first visit the pharmacist collected a detailed medical and medication history. The pharmacist also administered a quality of life questionnaire [Sawicki, 1999] and warfarin knowledge assessment tool [Walters and Bajorek, 2005]. The latter was used as a basis for tailoring initial patient education (see Appendices).

The protocol for pharmacist activities in the *intervention* arm of the study is presented in Appendix 6(a).

During each subsequent pharmacy visit the pharmacist provided additional patient education (as required), monitored INR (using the point-of-care INR testing devices) and made dosage recommendations in consultation with the patient's general practitioner. The details of these sessions where documented by pharmacists in each patient's file. Results and pharmacist's recommendations were communicated to the patient's general practitioner for vetting, discussion and decision.

3.3.1 Patient Education

Patient education was provided to patients in this study by the pharmacist. On entry into the study patient warfarin knowledge was assessed and education was provided to fill in the gaps in the patient's knowledge. This was re-enforced at each pharmacy visit. A customised patient education booklet (successfully used in a previous study; Bajorek, 2002) was provided to patients and employed in the patient education sessions. A copy of the booklet is provided in Appendix 5.

3.3.2 INR assessment by the pharmacist and dose considerations

INR results were assessed at least once per month. The frequency of INR monitoring was at the discretion of the pharmacist and general practitioner based on the clinical needs and observations in individual patients. This was dependent on the clinical signs a patient was exhibiting, pharmacist assessment of compliance, whether a dose change had been initiated or concomitant medicines started or stopped.

The result of the INR assessment (and any associate quality control data) was recorded and the pharmacist made a recommendation about patient management which was communicated to the general practitioner for consideration. Dose recommendations were only implemented once they have been approved by the patient's general practitioner. In this study pharmacists were given (and trained in the use of) a previously published warfarin dosing protocol which had been developed and evaluated by Foss *et al* [1999]. A copy of the dosing protocol adapted for this study is presented in Appendix 6(b).

3.3.3 General Practitioner-Pharmacist interaction

Dosing suggestions or monitoring recommendations made by the pharmacist were immediately communicated to the patient's general practitioner for vetting or discussion by fax. No action was taken until the consent of the general practitioner was obtained, even if by phone and later confirmed by fax. The pharmacist recorded the outcome of the recommendations and the action recommendation by the general practitioner. Appendix 7 contains the forms used by the pharmacists in the study to communicate their recommendations to the general practitioners.

3.4 INR measurement and Quality control of the *INRatio* device

In this study the *INRatio* device, made by Hemosense Inc (USA) and supplied by Point-of-care Diagnostics Pty Ltd in Australia, was employed in the *intervention* arm for point-of-care INR testing. This device uses test strips that require capillary blood and the device reports the International Normalised Ratio (INR). The test strips

include a high and low *quality control* (QC) sample to assess prothrombin time which serves as an internal quality control assessment.

Quality control of the device not only covers procedural (operator) error and degradation of test strips, but also environmental factors that may cause sample degradation. The *INRatio* device has an electronic self-checking system to check for errors relating to temperature, humidity, current fluctuation and inadequate sample. The test strip has three testing channels for the (i) patient's sample, and for (ii) high and (iii) low quality controls. These controls test for reagent validity, to ensure that improper storage of the strips has not occurred and does not affect the patient's results. The controls are activated at the same time as the patient test is performed, since the sample is used as a catalyst for activation of the reaction within the controls. If there is any problem with any of the quality control results, the patient's INR will not be displayed by the device. Instead, it will display a "QC" error message.

In November 2004, 9 months after the commencement of the project, the Pharmacy Guild of Australia funded an upgrade of the software of the *INRatio* devices being used in the study. Hence, an internal quality control program was established for the pharmacies involved. Each pharmacy was provided with test strips from an identical batch for use in future INR determination. The low and high prothrombin time QC data were recorded and collected on the EDCNet website (coordinated by National Serology Reference Laboratory, Australia). This provided an independent data management and recording framework for the internal QC program.

The feasibility of using an *External Proficiency Testing* program for pharmacies was investigated but was not available at the time this study was conducted because of the lack of availability of QC capillary (as opposed to venous) blood samples for distribution and evaluation.

INR data were collected retrospectively in the *control* arm and *pre-intervention* period of the study. The INR data were collected retrospectively from general practitioners and their clinical record by pharmacists or the study project officer via a direct approach. Clinical information was not collected from the pathology provider but only

released by the patient's general practitioner under the strict consenting protocol used in this study. Patients were not directly approached by the researchers.

3.5 Adverse Event Reporting and Stopping Rules

The study incorporated checks to assess the possible risks to each patient. It was important to note that;

1. Patients remained the in care of their general practitioner at all times in the study, meaning that any adverse event would be identified by the patient, general practitioner or pharmacists and appropriate medical management would result;
2. Pharmacists received training to recognised the signs of adverse events (due to both sub-therapeutic or supra-therapeutic INR) and what to do if these occurred;
3. The protocol used in this study by pharmacists for making dose recommendations for consideration by the general practitioner has a clear procedure for dealing with low or high INR readings (Note: dose recommendations were only implemented once they have been approved by the patient's general practitioner);
4. Any adverse events related to the performance of the device would be reported via the TGA *IRIS Medical Device Incident Report Investigation Scheme.*

3.6 STUDY ENPOINTS and DATA ANALYSIS

A broad evaluation plan including clinical, humanistic and economic measures was developed. In the *Intervention* arm of the study these data were recorded in a prospective manner from pharmacy, pathology laboratory and physician records. These data were collected retrospectively for the *Control* phases of the study. Data collection sheets used in this study are presented in Appendix 8. The following sections describe these outcomes.

3.6.1 Clinical Outcomes

In the *intervention* study arm pharmacists recorded all relevant clinical data including INR results. In the *control* arm and *pre-intervention* period the clinical data, such as INR results, were obtained and recorded by pharmacists and general practitioners

after a direct approach from the study project officer. At no time was clinical data directly obtained from pathology providers or from patients by the research team.

(a) INR readings within the target range

The number of INR readings *within, below* and *above* the patient-specific INR target range (± 0.1) were counted and expressed as a percentage of the total number of INR measurements collected for each patient during the study periods. The INR data for individual patients in the *Intervention and Pre-intervention* periods or *Control* arm were included if the patient contributed data for at least 3 months or they has at least 4 INR readings recorded.

(b) Proportion of Time the INR is within target range

Since the control of INR has been shown to correlate with a reduction in complications [Samsa and Matchar, 2000], the measure of effectiveness used in this study was based on the proportion of time (expressed as a percent) a patient's INR was maintained within the target INR range. This was determined for each patient using their individual INR target range (± 0.1), INR observations and the time (expressed in days) that INR measurements were *within, below* and *above* the specified range. The calculation of time a patient's INR was within range was calculated using the linear interpolation method described by Rosendaal *et al* (1993). This approach assumes that the INR changes in a linear manner between each INR observation. The INR target range was specific for each patient and in these calculations was considered to as ± 0.1. For example, the INR readings of a patient with a target range of INR 2 to 3 was evaluated against the range 1.9 to 3.1.

(c) Episodes of adverse events including both haemorrhagic and thromboembolic events

These were recorded in patient interviews by the pharmacist and investigators (at the end of the study) and in medical records held by the general practitioner.

3.6.2 Humanistic Outcomes

(a) Patient satisfaction and experiences

The patient satisfaction with the pharmacy-general practitioner managed anticoagulant service was evaluated using a qualitative semi-structured interview with patients conducted by telephone. These were conducted by investigators (not the pharmacist) at the end of the project. The aim was to yield detailed information about the patient's experiences and the perceived benefits of the "pharmacy-general practitioner" versus "general practitioner – pathology lab" services.

(b) Quality of Life Assessment

A structured questionnaire (specific for patients receiving anticoagulants) was used to assess quality of life on entry to the study and on completion of *intervention* arm of the study and on 2 occasions for patients in the *Control* arm [Sawicki, 1999]. The questionnaire is validated and disease specific and covers 5 treatment related domains over 32 questions. The domains are "medical treatment satisfaction, self efficacy, general psychological distress, daily hassles and strained social network". The questionnaire uses a Likert-type scale for patients to respond with answers ranging from 'does not apply' to 'applies fully'. Each domain yields a score which is an average out of 6 since each patient is given 6 options on the scale. As the instrument is a self-completion questionnaire, this minimises potential bias from the pharmacist. This tool was developed and validated by Sawicki [1999] and has been successfully used by other researchers [Cromheecke *et al*, 2000]. A copy of this questionnaire is included in Appendix 9.

(c) Patient Warfarin Knowledge Assessment

A previously validated questionnaire was employed to evaluate patient knowledge and understanding of their warfarin therapy [Walters and Bajorek, 2005]. This was administered at the beginning and end of the *intervention* arm of the study. It was used as a tool to identify gaps in a patients knowledge which the pharmacist was

encouraged to discuss with their patient. A copy of the questionnaire is presented in Appendix 10.

(d) Pharmacist Experiences

The experiences of pharmacists in the study were evaluated at the end of the study using a written open ended feedback sheet.

3.6.3 Economic Outcomes

(a) Cost to Deliver the Service

A cost analysis was conducted to identify the estimated costs required to deliver the pharmacy-general practitioner managed anticoagulant service (as conducted in the *intervention*). This was compared to the cost of *usual care* of patients managed by their general practitioner assuming patients visit a pathology collection centre for blood collection as a Medicare subsidised patient. Indicative costs were calculated to determine the costs associated with delivering the intervention or usual care to 10 patients over the first and subsequent years of provision of this service. Acquisition costs for equipment were obtained from the Point-of-care Diagnostics Pty Ltd (valid for 2004). Pathology costs were obtained from the Royal Australian College of Pathologist website (section of the Medical Benefits Schedule for pathology) www.rcpamanual.edu.au/sections/mbsrestrictions.asp?#1. Pharmacist wages used in these calculations were set at two levels (i) award wage of a Pharmacist-in-Charge obtained from the Pharmacy Guild of Australia (11 June 2004) and (ii) set at $65 per hour recognising that anticoagulant services would be provided by pharmacists with considerable experience and training. In the cost analysis of *usual care* 4 general practitioner visits per year and in the pharmacist-managed anticoagulation service 2 GP visit per year were included. This is based on the patient's GP ordering 6 INR requests at a time. The cost associated with the general practitioner's time in evaluating dose recommendations was not included because this time is likely to be the same independent of the model of anticoagulant management.

(b) Medical Benefits Schedule Expenditure

In order to evaluate the health care costs related to warfarin management in the 6 months prior to entering the study ("*pre-intervention*") and up to 12 months in the study ("*intervention*") information was obtained from the Health Insurance Commission (HIC). Ethical clearance was obtained from the HIC and informed (signed) consent was obtained from patients who were willing to contribute Medicare data to the study. Details of patient-specific items and expenditure on the Medicare Benefit Schedule (MBS) were evaluated of the 6 month *pre-intervention* and 12 month *intervention* period was provided by the HIC. The data were analysed to allow three comparisons, which were the;

- Total MBS expenditure per patient per month;
- Expenditure on "anticoagulant management" per patient per month;
- Actual INR measurements, GP visits and Pathology collections per patient per month.

Items associated with INR measurement, pathology sample collection and general practitioner visits were identified using codes from the *Medicare Benefits Schedule* (MBS) (www7.health.gov.au/pubs/mbs/).

Statistical comparisons were made between the "*pre-intervention*" and "*intervention*" data. The frequency of INR measurements during the *pre-intervention* stage was also compared to the frequency of visits to the pharmacy for point-of-care INR testing. Both comparisons were made with a paired Student t-test. The number of INR readings per month was compared between the *pre-intervention* period with the frequency of INR measurements made by pharmacists during the *intervention* phase.

3.7 Data Management and Statistical Analyses of Endpoints

The data were collated and analysed using Excel (Microsoft) and SPSS (Version 11.5). In this study comparisons were made using patient clinical and humanistic data obtained from patients in the;

- ***Intervention*** – prospectively collected data from patients who received anticoagulant management by pharmacists in collaboration with general practitioners.
- ***Pre-intervention*** – retrospectively collected data from patients receiving *usual care* prior to the *intervention.*
- ***Control*** – retrospectively collected data from patients who received *usual care* over the same time frame as the separate groups of patients received the *intervention*.

Humanistic endpoints such as quality of life and warfarin knowledge were compared on entry into the study and at the completion of the study for patients in the *intervention* group and on 2 occasions for the *control* group.

A paired test with unequal variance (and Bonferroni correction) was employed to compare clinical and humanistic endpoints between the *intervention* and *pre-intervention* datasets. The quality of life questionnaire scores were not normally distributed and a before and after comparison was conducted using a Wilcoxon Signed Ranks test. Patient warfarin knowledge scores on entry and exit from the study were compared using repeated measures analysis of variance. All analyses were conducted at a significance level of 0.05.

3.8 Justification of patient numbers

The target number of patients in the original study was selected to allow this study to detect a 15% change in the proportion of INR measurements within the target range with 80% power (α=0.05). This calculation assumes at baseline that 20% of patients are likely to have INR measurements outside the range at baseline [Cromheecke *et al*, 2000] and assumes that at least 300 INR measurements will be compared during the

stages of this study (ie, at least 3 INR levels from each patient). Given the revised nature of the final study design the issue of study power is discussed later in this report (Section 5.7).

3.9 Ethical Clearance

This study was approved by the Human Research Ethics Committee of the University of Sydney (Protocol 6653). Patients could withdraw from the study at any time or the consent of the patient's general practitioner could be withdrawn at any time.

3.10 Deviations from Proposed to Actual Methodology

3.10.1 Randomisation

The original plan was to conduct a randomised control trial in which pharmacies were recruited and then randomly allocated to *intervention* or *control* arm. The plan was that pharmacists would then randomly recruit patients receiving warfarin from their practices. Due to very slow recruitment randomisation was not possible if the study was to be successful in recruiting adequate pharmacists and patients within the time frame of the funding agreement. The exact reason for the slow recruitment of pharmacists is unclear but factors affecting recruitment are described and discussed in the Sections 4.2 and 5.7 of this report.

3.10.2 Patient recruitment targets and study timeframes

The original study plan was to recruit 50 patients into each study arm and follow these patients for 12 months of the study representing a total of 100 patients recruited from 10 pharmacies. These targets were set based on the need to collected *adequate* INR observations over an *adequate* time frame to ensure meaningful assessment of clinical outcomes using the *apriori* assumptions. This study (despite a continuing and active recruitment process) did not achieve the patient target numbers. However, the number of INR readings and months of patient experience on warfarin did allow a meaningful assessment of patient outcome associated with the *intervention* arm of the study.

The combined data set contains data from 53 patients, 758 INR measurements and 537 pharmacist recommendations about anticoagulation. Collectively these data represented approximately 40 years of patient experience on warfarin.

3.10.3 Study group comparisons and data analysis

Despite continued efforts involving different strategies, slow recruitment was a major issue which affected the timeliness and size of the final study patient cohort. This led to a change in the study protocol (with the permission of the Pharmacy Guild of Australia) to allow three sets of clinical data to be collected. These are defined below;

- ***Intervention*** – prospectively collected data from patients who received INR management by pharmacists in collaboration with general practitioners.
- ***Pre-intervention*** – retrospectively collected data from patients prior to the *intervention*.
- ***Control*** – retrospectively collected data from patients who received usual care over the same time frame as the separate groups of patients received the *intervention*.

The aim of the *Control* arm was to capture clinical and humanistic data on patients who received usual care (ie anticoagulant management by general practitioners with INR monitoring by a pathology laboratory). The original purpose was to allow a parallel group comparison to data collected the intervention cohort. In the end, the issues of;

- Poor recruitment in the *control* arm of the study; and,
- The challenges of combining a mixture of retrospective and prospective data;

meant that a comprehensive comparison of the *control* and *intervention* cohort could not be justified.

However, in evaluating the utility of a pharmacist managed anticoagulant service conducted in close collaboration with general practitioner the limited data collected from the *control* arm of the study (combined with similar data from the literature) do

provide some basis for a limited assessment of patient outcome while receiving the *intervention*.

The descriptive statistics of the clinical endpoints for the available patients in each of the three data sets were presented and summarised.

Formal statistical comparisons were made between the clinical (portion of time INR readings are in range), humanistic and economic endpoint for selected patients in the *pre-intervention* and *intervention*. This revised statistical comparison only includes patients who provided *pre-intervention* INR data (up to 6 months) and *intervention* INR data. The focus of the statistical analysis related to a comparison of the primary clinical outcome "proportion of time that INR readings were within, above and below the target INR range for that patient". A paired *t-test* was employed to compare *pre-intervention* and *intervention* data.

Note: It was not possible to include retrospectively collected *pre-intervention* INR data for the exact same time period for each patient due to the naturalistic manner in which these data were collected. Patients who had *at least* 3 months or 4 INR readings before the intervention were included in this sub-group. INR readings beyond 6 months *pre-intervention* were not included in the analysis.

3.10.4 General Practitioners Experiences/Feedback

At the time of report writing no feedback from general practitioners had been received although this had been requested (and reminders sent) on at the completion of the study (February, 2005).

3.10.5 Economic Outcomes

The planned incremental cost effectiveness analysis was not performed. An assessment of the costs associated with delivering the pharmacist-general practitioner--managed service was estimated and compared to the cost of the general practitioner-pathology services. A comparison of the Medical Benefits Schedule Expenditure obtained through the Health Insurance Commission for selected patients during the *pre-intervention* and *intervention* periods was also presented (as outlined in Section 3.6.3 b).

4.0 RESULTS

The Results section will firstly describe the characteristics of the patients, pharmacists and general practitioner who participated in this study to provide an overview of the cohort that has been studied.

4.1 Patients and their data

This study followed the outcomes of pharmacist-general practitioner managed anticoagulation (*intervention* group) in 41 patients for an average of 8.2 ± 3.7 months (range; 1 –13 months) representing a cumulative patient experience of 27.3 patient years and 524 INR measurements. The *pre-intervention data* were obtained from 20 (of 41 *intervention* patients) with 142 INR observations collected over an average of 4.8 ± 3.7 months representing a cumulative experience of 8 patient years. The *control* data consisted of 92 INR readings collected from 6 (of the 12) patients who were followed for a period of 9.5 ± 3.7 months (cumulative experience of 4.7 patient years). The demographic data for the patients in this study are presented in Table 1. This patient cohort was elderly, predominantly male with atrial fibrillation and had been receiving maintenance warfarin therapy for an average of 4 years.

Appendices 11(a) and 11(b) describe the individual patient clinical and demographic characteristics and Appendix 12 provides a summary of patients recruited into the study and the data they contributed.

Table 1: Demographic and clinical characteristics of patients in the Intervention cohort

Characteristic*	**Intervention**	**Control**
Patient Number	44	12
Male/females	33 males / 11 females	8 males / 4 females
Age (years)	71.9 ± 1.6 (range; 54 to 85)	73.1 ± 3.7 (range: 51 to 87)
Duration of warfarin therapy (months)	39.4 ± 4.5 (range: 4 to 96)	79.5 ± 24.8 (range: 25 to 125)
Indication for warfarin	Atrial fibrillation 30 Cardiac Prosthetic Valve 5 Deep vein thrombosis 2 Cardiomyopathy 2 Post-myocardial infarction 1 Arterial Disease 1	Atrial Fibrillation 5 Cardiac Prosthetic Valve 6 Factor V Lieden 1 Bypass 2
Target INR range **2.0 to 3.0** **2.5 to 3.5**	 37 5	 7 5

*data presented as mean ± standard deviation with range shown in brackets

4.2 Pharmacists, General Practitioners and Patients

Intervention Arm – Pharmacist-general practitioner managed anticoagulation

In the *Intervention* arm of this study seven pharmacies contributed data from 41 patients who were in the care of a 27 general practitioners.

Initially, it was planned to recruit pharmacists into the *intervention* and *control* arms of the study by direct contact. QCPP accredited pharmacists from Sydney's north shore, inner west and northern suburbs region were approached. Fifty pharmacies were contacted via letter and telephone. Thirteen of these verbally agreed to participate. Also one of the investigators (AM) gave a presentation at a continuing

professional education lecture on anticoagulation run by the Pharmaceutical Society of Australia (NSW Branch) to provide an overview of the study and an invitation to participate. Two pharmacies showed interest in participating and 8 pharmacists showed interest in being involved in the education and training offered as part of the study but did not want to be directly involved.

Representatives from 8 of the 15 pharmacies who had been recruited to the study indicated their willingness to attend a purpose designed training programme on 16th November 2003. The training was attended by 14 pharmacists from 6 pharmacies. Two of these pharmacists were interested in the training however declined participation.

Of the 6 pharmacies, only 3 were able to successfully recruit patients, mainly due to lack of interest from the general practitioners in their area.

This prompted a second round of pharmacist recruitment. This group consisted of interested but previously untrained pharmacists from the initial contact round, pharmacists who had contacted us due to word of mouth, and a smaller group of 20 pharmacies outside the initial recruitment zone. This was equal to 25 pharmacies. Five pharmacists attended the second round of training. Of these only 4 were able to recruit patients.

The 7 pharmacies in the intervention arm of the study recruited 44 patients in collaboration with 27 general practitioners. Forty-one patients completed the study, with 3 withdrawing prior to commencement of data collection.

The *pre-intervention* data was obtained from 20 of the 44 patients initially recruited into the study prior to receiving the intervention. Of these patients, only 14 patients provided adequate clinical data for a rigorous comparison between INR control during the pre-intervention and intervention phases.

Control Arm

In the *Control* Arm, 5 pharmacies contributed retrospectively collected data from 15 patients. An initial contact was made with QCPP pharmacists from the greater Sydney region. This contact was for control pharmacists only after the study design was revisited in an attempt to improve patient recruitment. One hundred and three pharmacies were contacted but of those contacted only 9 consented to being involved in the control study. This involved 1 hour of in-house training on the data collection forms. However, only 5 of those pharmacies were able to recruit 15 of the required 50 patients. Two of the 15 were unable to complete the quality of life and warfarin knowledge assessments at end of the study due to cessation of warfarin prior to project finish date. This reflects the difficulty encountered in attempting to recruit pharmacies and patients into the control arm of the study.

4.3 CLINICAL OUTCOMES

Table 2 summarises the INR data and collection descriptive statistics for all of the patients in the study. The mean INR reading during both the *pre-intervention* and *intervention* stages of the study were in close agreement. The while the number of patients and INR measurements is different between the *pre-intervention* and *intervention* period there was no apparent difference in the frequency of INR testing (1.6 vs 1.7 INR tests per month, respectively). The *control* patients received, on average, slightly higher frequency of monitoring with 2.1 INR tests per month. These latter data should be viewed with caution given the limited sample size and the retrospective nature of the data included in the *control* arm of the study.

Figure 2 shows all of the INR versus time observations for *intervention* cohort of patients during the *pre-intervention* phase and during the trial.

4.3.1 Percent of INR readings within the target range

One measure of INR control is the number of readings for each patient that were maintained within the target range (± 0.1 INR unit). As discussed previously, poor control of INR is one of the main predictors of poor outcome for patients receiving anticoagulants. During the *intervention* the pharmacists in collaboration with general practitioner on average were able to maintain 73 % (range; 20 to 100%) of the INR readings per patient within the target range (Table 1). This is in agreement with *pre-intervention* data which showed that on average patients achieved 73 % (range; 33 to 100%) of INR readings were with range. The limited data from the *control* group indicated that 74 % (range; 52 to 94%) of INR observations were within the target INR range individual patients. Formal statistical comparisons were not appropriate given the different patient numbers and the combination of retrospective and prospective data.

These data were derived from 38 patients and 519 INR observations for *Intervention* and 14 patients and 126 INR observations for *Pre-intervention*. Only patients who contributed at least 5 INR observations or had been in the study for 3 months contributed data to the endpoints that compared the control of INR according to the target range (± 0.1). Including all patients would overly bias the results and not provide meaningful information about patient INR control. Figure 2 shows the data collected from patients in the *intervention* group. Data are presented from the *pre-intervention* period (before the study) and also during the pharmacist-general practitioner managed anticoagulation service. The characteristic variability in patient INR is evident from these data in both the *pre-intervention* and *intervention* periods of the study.

Figure 2: The relationship between INR and time for patients in the intervention group before (*pre-intervention*) and during (*intervention*) the study. Time zero represents the time that patients entered into the study. Dotted lines represent patients with INR target range of 2.5 to 3.5.

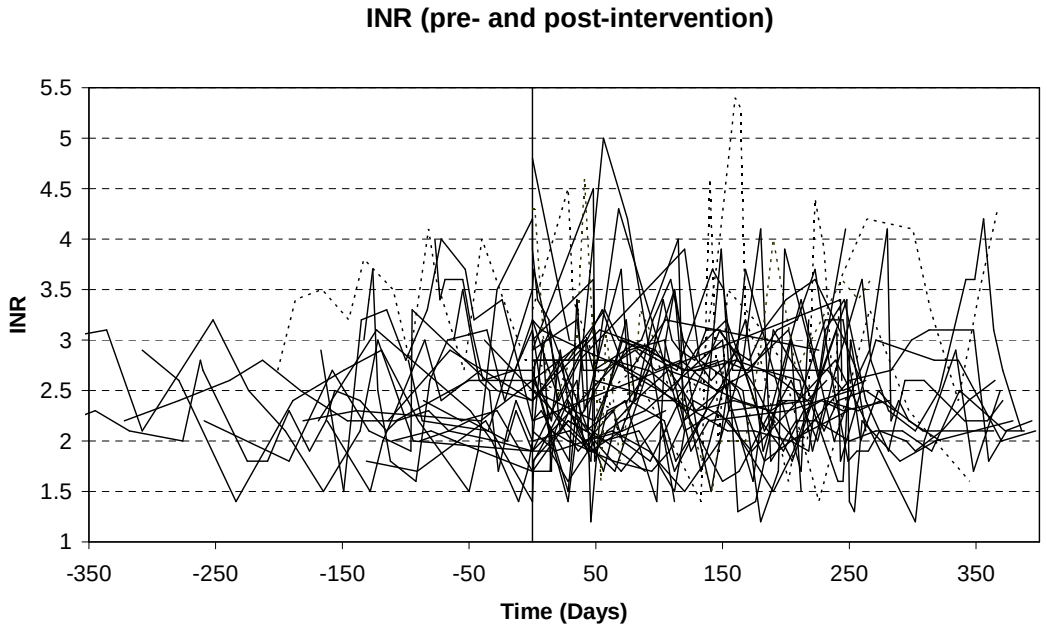


Table 2: Summary of the clinical outcomes for patients in the *control* and *intervention* group. *Pre-intervention* data were collected from the patients in the *intervention* cohort prior to entry into the study. Mean ± standard deviation is reported.

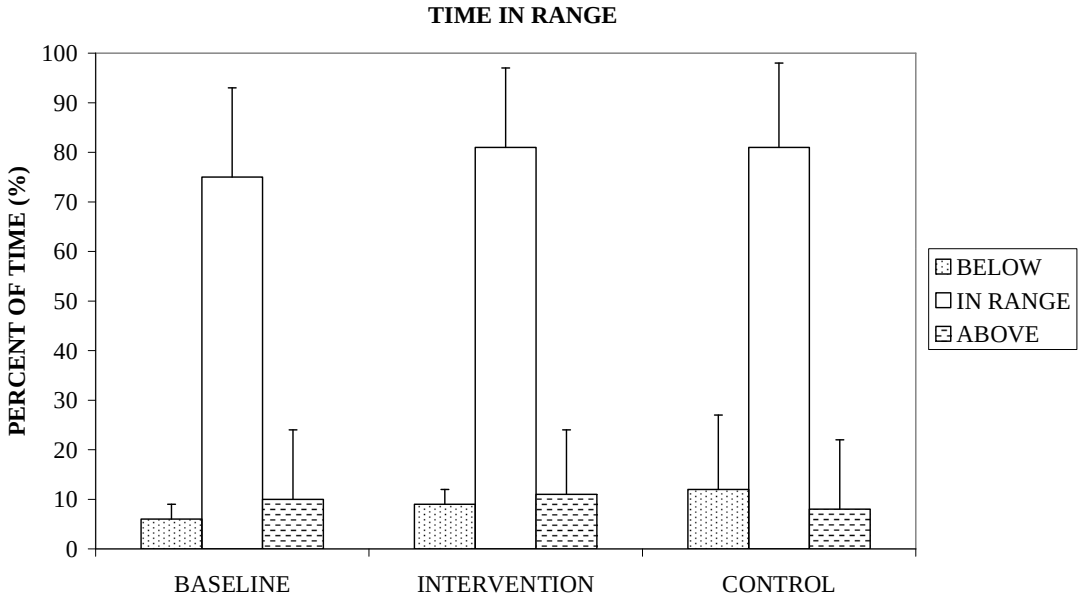
Parameter	**Control**	**Intervention**	
		Pre-intervention	**Intervention**
Patients	12[1]	20	41
INR results	92	142	524
INR results per patient	15 (6 – 33) [2]	7 (2 – 21) [2]	13 (1 – 28) [2]
Time in Study (months)	9.5 ± 5.8	4.8 ± 3.3	8.2 ± 3.7
Frequency of monitoring (readings per month)	2.1 ± 0.9 (1.2 -3.5)	1.7 ± 1.1 (0.6 – 5.0)	1.6 ± 0.7 (0.4 – 4.1)
INR (mean ± SD)	2.8 ± 0.7	2.5 ± 0.4	2.6 ± 0.6
Percent of INR readings WITHIN range (%)[3]	**74 ± 17 % (50 – 94)**	**73 ± 19 % (33 – 100)**	**73 ± 21 % (20 – 100)**
Percent of INR readings BELOW range (%)[3]	12 ± 15 % (0 – 36)	15 ± 18 % (0 – 67)	15 ± 14 % (0 – 46)
Percent of INR readings ABOVE range (%)[3]	14 ± 11 % (6 – 33)	11 ± 17 % (0 – 63)	13 ± 14 % (0 – 50)
Length of time INR readings were WITHIN range (%)[3]	**81 ± 17 % (52 – 95)**	**75 ± 18 % (35 – 100)**	**81 ± 16 % (45 – 100)**
Length of time INR readings were BELOW range (%)[3]	12 ± 15 % (0 – 32)	6 ± 3 % (2 – 12)	9 ± 3 % (2 – 13)
Length of time INR readings were ABOVE range (%)[3]	8 ± 4 % (3 – 15)	10 ± 14 % (0 – 46)	11 ± 13 % (0 – 44)

[1] INR data only available for 6 patients
[2] median and range (shown in brackets)
[3] Derived from data for 38 patients and 519 INR observations for *Intervention* and 14 patients and 126 INR observations for *Pre-intervention.*

4.3.2 Proportion of time the INR was within target range

Arguably the best predictor of patient outcome is actually the percent of time a patient's INR is within the target range because of the evidence linking this parameter to clinical outcomes [Samsa and Matchar, 2000]. This reflects not only the quality of monitoring but also dose recommendations and frequency of testing. In the *intervention* group pharmacists in collaboration with general practitioners were able to maintain patients INR within their target INR range for 81% (range; 45 to 100%) of the time (Table 2). This was in close agreement with the *pre-intervention* data which confirmed that patient INR was maintained in the target range for 77% (range; 35 to 100%) of the time and the separate control cohort of patients who were maintained within the target range 81% (52 to 94%) of the time. These data are summarised below in Figure 3. Statistical analyses were not conducted on these data because of different patient numbers and the combination of retrospective and prospective data.

Figure 3: A comparison of the average percent of time a patient's INR was below, in or above the target INR range for the *control* (n = 6) and *intervention* (n= 38) group. *Pre-intervention* (n=14) data was collected from the patients in the intervention cohort prior to entry into the study. Data are presented as mean and error bars represent standard deviation.



Fourteen patients provided adequate clinical data for a rigorous comparison between INR control during the *pre-intervention* and *intervention* phases. It was not possible to include retrospectively collected *pre-intervention* INR data for the exact same time period for each patient due to the naturalistic manner in which these data were collected. Patients who had *at least* 3 months or 4 INR readings before the intervention were included in this sub-group. INR readings beyond 6 months *pre-intervention* were not included in the analysis.

A summary of the individual and mean results for the 14 patients that contributed adequate *pre-intervention* and *intervention* INR data is summarised in Table 3.

Table 3: A comparison of the proportion of time INR was in the range for 14 patients in the *intervention* and *pre-intervention* groups. Mean ± standard deviation (and 95% confidence intervals) are reported.

Parameter	**Intervention**	
	Pre- *	**During***
Time in Study (months)	4.7 ± 1.6	8.8 ± 4.0
Proportion of time INR readings were WITHIN range (%)	75 ± 17 % (65 – 86)	78 ± 18 % (68 – 89)
Proportion of time INR readings were BELOW range (%)	15 ± 17 % (5 – 25)	8 ± 9 % (2 – 13)
Proportion of time INR readings were ABOVE range (%)	9 ± 14 % (1 – 18)	15 ± 16 % (5 – 25)

These results show that there was no statistically significant difference (p=0.66; paired 2-tailed t-test) between the proportion of time INR readings were <u>within</u> the target range for these 14 patients in the *pre-intervention* and *intervention* period. Furthermore, the proportions of time <u>above</u> and <u>below</u> the INR range were not statistically significant different (p=0.15 and p=0.07, respectively) for the *pre-intervention* and *intervention* periods.

4.3.3 Episodes of warfarin-related adverse events

There were no major (haemorrhagic and thromboembolic) or minor (episodes of bruising or bleeding) warfarin-related adverse events recorded during the trial. This was confirmed during semi-structured interviews with patients.

4.4 HUMANISTIC OUTCOMES

4.4.1 Patient satisfaction

At the completion of the study patients were contacted to conduct a semi-structured interview to record their level of satisfaction with the service and experiences within the study. A particular emphasis was put on the comparison to the usual care and whether or not they would consider paying for this service. The interview protocol and the transcribed responses are shown in Appendix 13.

The response rate was relatively low with only a quarter of the patients participating in this stage of the study. The majority of patients lost to follow-up were not available or could not be contacted. Of the patients who were contacted none declined to be interviewed. Although the response rate was low there was consistent agreement in the comments raised by the patients who participated in the study.

All patients who responded were either *satisfied* or *extremely satisfied* with this pharmacist-general practitioner managed anticoagulation service conducted using the point-of-care testing device. The overwhelming comment from patients was that the pharmacy service was more convenient than their usual care. The patients confirmed that each encounter in the pharmacy lasted about 15 min (ranging from 5 to 20 min) and many were attracted to the immediacy of the results. The point-of-care testing device was an attractive alternative for some patients who did not like "needles" and traditional blood sampling methods. Of those interviewed several patients perceived that they had better INR control during the study when compared to their usual care. At least one person found that being in the study improved their compliance with therapy.

Selected *verbatim* responses from interviewees illustrating positive aspects of the anticoagulant monitoring service (see Appendix 13)

Convenience:

"The convenience of going to the pharmacy in my local shops"

"The pharmacy service was very quick and provided me with reassurance and the factors that influence warfarin"

"Very flexible – we would chat about things as we went. The pharmacist did all the right precautionary stuff"

"It was quick and easy, no waiting and no booking"

"The immediacy of the results was a real advantage compared to queuing up at the pathology lab"

"No more convenient than the current GP and Hospital - I see my doctor regularly and am closely monitored – I have been on warfarin for 16 years"

Improved relationships with health care professionals:

"I like the close relationship with the pharmacist"

"Helpful advice offered"

"There was a three-way communication between me, the pharmacist and the doctor"

"The regular interaction with the pharmacist and the chance to ask questions was good"

Increased understanding:

"Being in the study helped me to remember to take the medicine"

"I like the opportunity to ask the pharmacists questions"

Point of Care testing:

"The finger prick was more acceptable to me as I do not like blood tests"

The majority of patients confirmed that they would continue to participate in an anticoagulant monitoring service that was managed in community pharmacy and would either pay for such a service or suggested that it should be a subsidised as an alternative (not replacement) to the current pathology testing approach for anticoagulant management. Of those who indicated a willingness to pay, the suggested fee ranged from $10 to $20 per visit.

Selected *verbatim* responses from interviewees illustrating willingness-to-pay for the anticoagulant monitoring service (see Appendix 13)

"The fee should recognise the pharmacist time and maybe subsidised by Medicare"
"As a DVA patient I would not expect to pay for this service but it should be subsidised"
"A reasonable payment would be $20 per visit"
"No, I have a pension. I could not put a price on this but I think it should be available and subsidised by Medicare"

A range of other valuable comments were contributed by the patients in the study. These included insights into the pharmacist-patient relationship and also a number of patients expressed an interest in self-monitoring using the point of care testing device. One patient indicated that his local general practitioner now has a point of care testing device since the study ended. The only criticisms of the service were about the time it took for general practitioner and pharmacist communication about dosing.

4.4.2 Quality of Life Assessment

The patient's quality of life was evaluated before and after the *intervention* arm and on two occasions in the *control* arm using a 32-item assessment tool [Sawicki, 1999]. The instrument was designed to assess aspects of the quality of life relevant to anticoagulation under 5 main categories. These are outlined in Table 4 which shows the quality of life data for the *Intervention* and *Control* patients in the study.

Table 4: Quality of life of patients in the *Intervention* and *Control* groups assessed using the validated 32-item instrument of Sawicki (1999). Each score is presented as a mean ± standard deviation within a range of 1 (minimum) to 6 (maximum).

	Intervention (n=26)		**Control (n=12)**	
Treatment related domain	**Before** Mean ± SD	**After** Mean ± SD	**Entry** Mean ± SD	**Exit** Mean ± SD
Medical Treatment Satisfaction	4.67 ± 1.17	5.03 ± 0.92	5.07 ± 1.02	4.98 ± 1.10
Self Efficacy	4.49 ± 1.14	4.90 ± 1.30	5.00 ± 1.44	4.94 ± 1.44
General Psychological Distress	2.09 ± 0.85	1.84 ± 0.76*	2.62 ± 0.98	2.60 ± 1.02
Daily Hassles	2.25 ± 2.12	2.10 ± 0.61	2.25 ± 0.85	2.21 ± 0.89
Strained Social Network	1.64 ± 0.80	1.65 ± 0.64	1.95 ± 1.04	2.08 ± 1.10

Score range from 1 (minimum) to 6 (maximum).

* Significant decrease in distress after the intervention (Wilcoxon Signed Rank test, p= 0.025)

All other statistical comparisons were not significantly different.

These data show that on entry into the study patients in both the *intervention* and *control* groups had high levels of *medical treatment satisfaction* and *self-efficacy*. While there was a trend towards an increase in these categories at the end of the *intervention* arm of the study there was no statistically significant difference (p = 0.102). Both patient groups had relatively low levels of *distress, daily hassles* and *strained social network*. However, patients in the *intervention* group who received pharmacist-general practitioner managed anticoagulation showed a further and statistically significant decrease (p=0.038) in *distress* as measured using this tool.

4.4.3 Patient Warfarin Knowledge Assessment

An important part of this study was the provision and evaluation of patient education using targeted counselling and written information. Table 5 provides a summary of the impact of this education on patient knowledge about warfarin .

Table 5: Comparison of the pre- and post performance in the Warfarin Knowledge assessment

Parameter	**Entry (Pre)**	**Exit (Post)**	**Percent Change (Post – Pre)**
Intervention (n=26)	67 ± 12 %	82 ± 10 %	14.7 % (8.3 - 21.2 %)*
Control (n=12)	69 ± 15 %	76 ± 15 %	6.9 % (1.7 – 12.2)#

Data shown as mean ± standard deviation with 95% confidence interval shown in brackets

* Not significantly different (Repeated measures analysis of variance, p = 0.062)

The results show a trend towards improvement in the warfarin knowledge in both the *intervention* and *control* patients as measured using the questionnaire (Table 5) but this did not reach statistical significance (probably due to the relatively low sample size). Both groups of patients had reasonable knowledge of warfarin on entry into the study (67% vs 69%) but the 95% confidence interval for the change in knowledge scores showed that the patients in the intervention group displayed a larger increase during the study. This supports the observation that pharmacists used the warfarin knowledge questionnaire to identify gaps in patient knowledge and used specific counselling to address these gaps or misconceptions.

These data were consistent with data from the semi-structure interviews with patients. Many patients indicated that the "*Warfarin Medication Information Booklet For Patients and their Carers*" [Bajorek, 2002; Appendix 5] and education provided by the pharmacist during the trial reinforced their knowledge of warfarin therapy and that

it gave them a better understanding of what influences their INR and why they needed dose changes from time to time.

Selected *verbatim* responses from interviewees illustrating the impact of pharmacist education activities delivered as part of the anticoagulant management service (see Appendix 13)

"By being in regular contact with the pharmacist and doctor I could ask questions – it gave me a greater understanding of INR and what influenced it for me.
I had good feedback on diet. It was a motivator"

"The pharmacist and the booklet gave me more information than I had previously. This reaffirmed what I know and reminded me what was important"

"Discussing things that influenced my warfarin or why my dose was adjusted was great. You can't always talk to the doctor about why (changes are made) especially when he has many patients. (The pharmacist) had a more personal approach"

"I don't remember being given any booklets. Talking to the pharmacist did reinforce what I knew about warfarin"

"Talking to the pharmacist reinforced what I already new and addressed some of the "folklore" about warfarin"

"I think I have a better understanding of INR and the dose changes through talking to the pharmacist"

4.4.4 Pharmacist Recommendations and General Practitioner Responses

An important aspect of this study was the role that pharmacists played in optimizing anticoagulant therapy in collaboration with general practitioners. Pharmacists received training and used a dosing protocol to make recommendations for consideration by general practitioners. In the *intervention* arm of this study pharmacists made a total of 537 recommendations about warfarin management (with 20% of these involving an alteration to therapy), in response to 524 INR measurements. These are summarised in Table 6.

Table 6: Summary of pharmacist recommendations and general practitioner responses

Recommendation	Pharmacist Recommendations	General Practitioner Agreement	Rate of implementation of pharmacist's recommendation
Continue with this dose and monitor as recommended	427	419	98%
Decrease dose	53	48	91%
Increase dose	48	42	88%
Miss a dose	9	8	89%
Overall	**537**	**517**	**96%**

General practitioners actioned 96% of the 537 recommendations made by pharmacists in response to dosing and anticoagulant management suggestions.

4.4.5 Pharmacists Experiences

At the end of the study pharmacists involved in the *intervention* arm of the study were surveyed to determine their experiences, opinions and perception of the utility of the pharmacy-general practitioner managed anticoagulant service. Half of the pharmacists returned surveys. The quantitative responses are summarised in Table 7 and the transcribed open-ended responses are presented in Appendix 14.

These data address some of the important logistical aspects of delivering a pharmacy managed anticoagulant service. The responses emphasise the importance of training and support for pharmacists implementing such a service. All pharmacists referred to the professional rewards involved in delivering the service and the benefits in further developing pharmacy practice and even business opportunities. Pharmacists also highlighted how their involvement lead to their own professional development related to skills, knowledge and confidence.

A very positive aspect of the pharmacist feedback centred on the effect such a service had on developing the pharmacist-patient relationship reinforcing the perception of improved care and trust. There were mixed responses to the questions related to inter-

professional relationships between pharmacists and general practitioners. Some pharmacists identified the positive aspect of building professional collaborations and trust with general practitioners whereas others identified concerns over general practitioner resistance to engage in the trial with pharmacists. These findings reinforce the need to ensure that any future pharmacy based anticoagulant management service must be developed in close collaboration and consultation with general practitioners. This latter point cannot be underestimated.

It is noteworthy that pharmacists agreed that they would offer such a service in the future.

Table 7: Pharmacists experiences in the study

Question	**Response**
The training provided to me was adequate to enable me to deliver the anticoagulant management service	4.0 ± 0.8
Pharmacy was too busy to deliver this service	3.0 ± 1.4
Customers were very keen to participate in this service	4.0 ± 0.8
More support from the researchers was needed to implement and deliver this service	2.8 ± 1.7
Changes in personal circumstances during the course of this study affect my ability to participate in the study	2.5 ± 1.0
Local GPs were supportive of this service	3.3 ± 1.2
Patients were reluctant to participate due to concerns about the changes to their anticoagulant management	3.3 ± 1.2
Pharmacy is currently involved in other studies/projects, making it difficult to be involved in this study	1.7 ± 0.6
Too much time was spent on administration in this study	2.3 ± 0.6
Anticoagulant management is a priority area in my pharmacy	4.3 ± 0.6
Patients appeared confident in the pharmacists ability to effectively manage their anticoagulation	4.0 ± ND
Local GPs were resistant to pharmacist involvement in anticoagulant management	2.7 ± 1.5
It was difficult to recruit patients into this study	4.0 ± ND
It was difficult to approach local GPs regarding this study	2.7 ± 1.2
I would be happy to offer this anticoagulant management service in the future	4.3 ± 1.2

Likert scale from to 1 = Strongly Disagree, 3 = Neutral, 5 = Strong Agree.
Responses recorded as mean ± standard deviation (n = 3 or 4).
ND – not determined (n = 2)

4.5 ECONOMIC OUTCOMES

(a) Cost to deliver the service

A key finding of this study was that the clinical outcome of patients (based on INR control) in the pharmacist-general practitioner managed anticoagulant service and those receiving usual care were similar (see Table 2 and 3). The cost of delivering the service to 10 patients for a period of 12 months was estimated. This is presented as a per patient per year cost and the cost per INR test (Tables 8 to 10). The costs were considered for the first year (Year 1) the service is established and then subsequent years (Year 2) of the service.

Table 8: Estimated cost involved in delivering pharmacist-general practitioner managed anticoagulant service in collaboration using of point-of-care testing based on a pharmacist-in-charge earning **$21.75** per hour (Option A).

Aspect of Service	**Year 1**	**Year 2**
INRatio Point-of-care testing device	$1,200.00	
Quality control program (per year)	$500.00	$500.00
Cost per *INRatio* test (including disposables)	$6.27	$6.27
Pharmacist's time ($21.75 per h) 0.5 h	$10.88	$10.88
GP consultations (2 visits per year; based on MBS fees)	$30.85	$30.85
Cost to deliver pharmacy managed anticoagulant service to 10 patients (20 INR tests per year) for 1 year	**$5,746.17**	**$4,546.00**
Cost per patient per year	**$574.62**	**$454.60**
Cost to deliver each INR test	**$28.73**	**$22.73**

Table 9: Estimated cost involved in delivering pharmacist-general practitioner managed anticoagulant service in collaboration using of point-of-care testing on a pharmacist earning **$65.00** per hour (Option B).

Aspect of Service	**Year 1**	**Year 2**
INRatio Point-of-care testing device	$1,200.00	
Quality control program (per year)	$500.00	$500.00
Cost per *INRatio* test (including disposables)	$6.27	$6.27
Pharmacist's time ($65.00 per h) 0.5 h	$32.50	$32.50
GP consultations (2 visits per year; based on MBS fees)	$30.85	$30.85
Cost to deliver pharmacy managed anticoagulant service to 10 patients (20 INR tests per year) for 1 year	**$10,071.17**	**$8,871.00**
Cost per patient per year	**$1,007.12**	**$887.10**
Cost to deliver each INR test	**$50.36**	**$44.36**

These results utilise information from the present study including the average time spent by the pharmacist (15 min testing and counselling patients per visit and approximately 15 min recording and communicating recommendations with the general practitioner and patient). In total 30 min per test was allotted to the pharmacists time and this has been costed at two levels – lower award level for *pharmacist-in-charge* and a higher remuneration level of $65 for a pharmacist who has experience and undergone training. These calculations are based on the assumption of approximately 20 INR tests per year. Only two general practitioner visits (related to warfarin management) per year are included in the cost analysis which is half that expected for usual care. This was selected in light of expectations that the close collaboration between pharmacists and general practitioner in patient management will lead to the need for less general practitioner visits related to warfarin management. These estimated costs do not include the cost for the time of the general practitioner to review and communicate their management option for the patients in light of the pharmacist recommendation. This was not included as the time is expected to be the same whether this is a pharmacy-general practitioner managed service or the patients usual care where they are tested at by a laboratory service and seen by the general practitioner.

Table 10: Estimated cost involved in delivering the anticoagulant services by the general practitioner and the pathology provider from the perspective of the Government.

Aspect of Service	**Year 1 or 2**
Collection Centre (MBS)	$17.40
INR pathology (MBS)	$14.05
GP consultations (4 per year; 6 INR requests per visit) (MBS)	$30.85
Cost to deliver this service to 10 patients for 1 year (20 INR tests per year)	**$7,524.00**
Cost per patient per year	**$752.40**
Cost to deliver each INR test	**$37.62**

The calculations in Table 10 assume that patients visit their general practitioner at least 4 times per year and visit a pathology collection centre to provide a blood test which is communicated to the general practitioner who later contacts the patient to advice of dose adjustments or management advice.

A direct comparison of the costs, suggests that the cost of delivering the pharmacist-general practitioner managed service using of point-of-care testing is comparable to the costs associated with usual care. The findings suggest that in the first year of delivery the community pharmacist-general practitioner managed anticoagulant service was considerably more expensive to deliver (reflecting the need for set up costs and training) but in subsequent years the pharmacy based service offered considerable cost savings.

(b) Medicare Benefits Schedule Expenditure

Seventeen patients in the *intervention* arm of the study provided consent for their MBS expenditure data to be analysis for the 6 months prior (*pre-intervention*) to entering the study (intervention). The results of the MBS data are summarised in Tables 11, 12 and 13.

Table 11: Actual Medical Benefits Schedule (all items) expenditure for 17 patients in the *pre-intervention* and *intervention* phase. Data presented as mean ± standard deviation (and 95% confidence intervals; CI).

	Pre-intervention			**Intervention**		
	Months	**Total**	**$ per month**	**Months**	**Total**	**$ per month**
Total	122	$21,807		159	$34,819	
Mean	7.2 ± 2.3	$1,283 ± $1,023	$172 ± $106	9.3 ± 2.8	$2,048 ± $1,413	$208 ± $140
95% CI		$726 - $1,838	$115 - $230		$1,280 - $2,817	$132- $284

Table 12: Frequency of utilisation of Medical Benefits Schedule items related to anticoagulant management for 17 patients in the *pre-intervention* and *intervention* phase. Data presented as mean ± standard deviation (and 95% confidence intervals; CI) of items utilised per month.

	Pre-intervention			**Intervention**		
	Pathology [1] Collections	**INR [2] Tests**	**GP visits[3]**	**Pathology Collections [1]**	**INR [2] Tests**	**GP visits[3]**
Mean	1.51 ± 0.60	1.38 ± 0.73	1.18 ± 0.81	1.00 ± 0.77	0.76 ± 0.76	1.11 ± 0.76
95% CI	1.19 - 1.84	0.98- 1.77	0.74 - 1.62	0.58 -1.42	0.35-1.18	0.70- 1.53

[1] Comparison of *Pre-intervention* and during *intervention*, p=0.004 (Paired t-test)
[2] Comparison of *Pre-intervention* and during *intervention*, p=0.005 (Paired t-test)
[3] Comparison of *Pre-intervention* and during *intervention*, p=0.6283 (Paired t-test)

Table 13: Actual expenditure of Medical Benefits Schedule items related to anticoagulant management for 17 patients in the *pre-intervention* and *intervention* phase. Data presented as mean ± standard deviation (and 95% confidence intervals; CI) of total expenditure and expenditure per month (n=17).

	Pre-intervention		**During intervention**	
	Total	*Per month*	*Total*	*Per month*
TOTAL	$9, 743		$10,077	
Mean ± SD	$ 573 ± $457	$ 73 ± $ 43	$ 593 ± $ 448	$ 63 ± $ 50
95% CI	325 - 822	50 - 96	349 - 836	36 - 90

The data in Table 11 show that the total MBS expenditure was not different in the month prior to and drug the study. It should be noted that data for only 17 patients make it difficult to detect subtle differences in expenditure given that this is a elderly population with multiple conditions and expenditure is likely to be variable over time.

As expected the data in Table 12 show that the number of pathology visits and INR tests utilised by these 17 patients significantly decreased during the *intervention* phase (p=0.004 and p=0.005, respectively) of the study compared to the frequency of MBS tests in the *pre-intervention* period. This is expected as patients were receiving the pharmacist-general practitioner anticoagulant service at this time. The number of visits to the general practitioner did not significantly change (p=0.63). However, this analysis of MBS data provide by the HIC did not discriminate the reasons for the general practitioner visit. A comparison between the number of INR tests conducted per month under the MBS prior to the study (*pre-intervention*) and the number of INR measurements made per month by pharmacists (1.51 ± 0.44 INR tests per month) in the study were not significantly different (p=0.53, paired t-test, n=17). The MBS expenditure on anticoagulant management (based on the costs attributed to relevant MBS items) was not significantly different in these 17 patients (Table 13), although the trend was towards lower expenditure during the intervention. The inability to observe a different may be associated with the relatively low patient numbers and significant variability.

4.6 Quality Control Data for the *INRatio* device

In this study the quality control of the INR results provided by the *INRatio* point-of-care testing device were collected over the last 3 to 4 months of the trial. The QC prothrombin time results (recorded by the trained pharmacists using the device) were compared against known low and high quality control (QC) samples. The mean prothrombin times for the QC1 [low control] and QC2 [high control] was 11.8 sec and 20.5 sec, respectively. The cumulative data for the low and high QC data provided by National Serology Reference Laboratory are presented in Figures 10 and 11.

In this study the INRatio device when used by the trained pharmacists showed a high level of internal accuracy and precision was also shown for both the variability compared with the 5% variability shown by the low control. However both the high and low controls were well within the expected 8% error acceptable for INR testing in Australia. The high level of inter-pharmacy conformity for both high and low controls is shown in Figure 12 and 13 for QC1 (low control) and QC2 (high control), respectively.

Figure 10: Low QC results versus time. Different coloured lines represent different pharmacies.

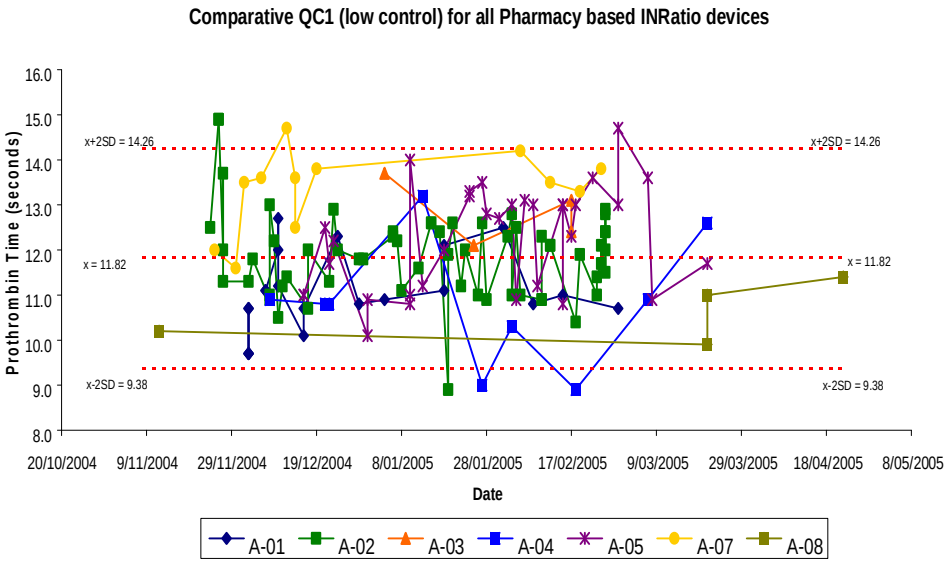


Figure 11: High QC results versus time. Different coloured lines represent different pharmacies.

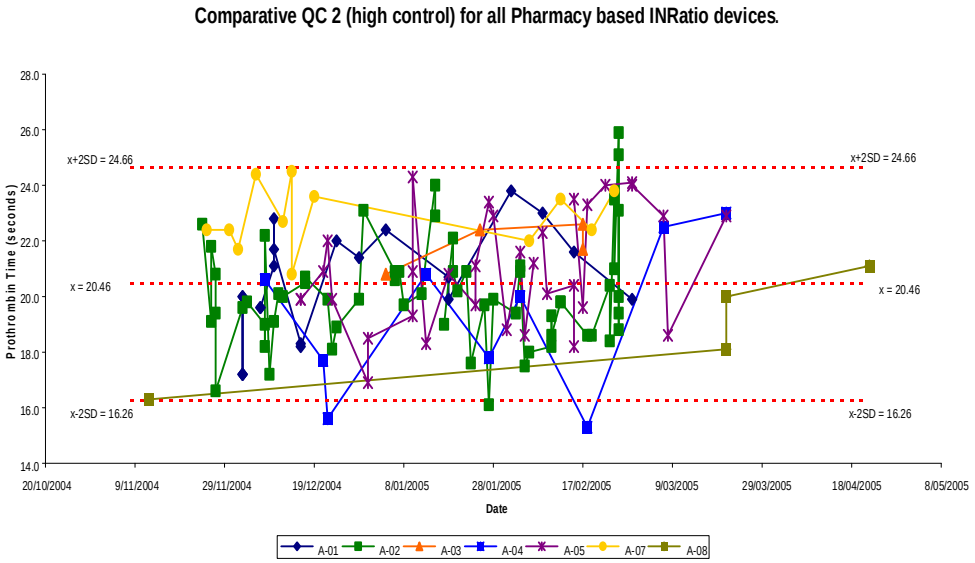


Figure 12: Low QC results compared between pharmacies.

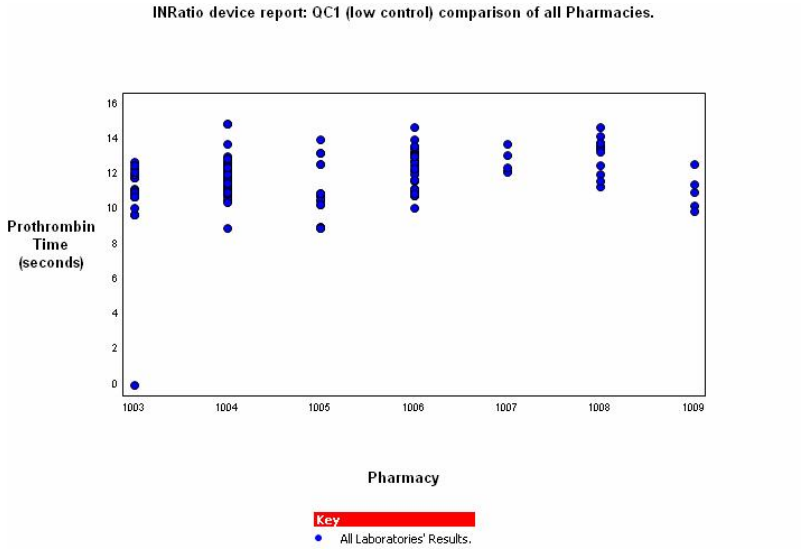
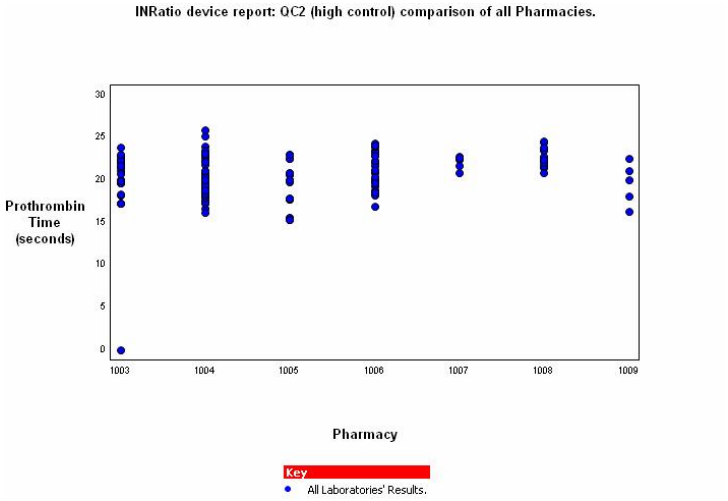


Figure 13: Low QC results compared between pharmacies.



The results of the quality control section of this study show that pharmacists are able to use the *INRatio* point-of-care device in an appropriate manner to produce reliable results. This also demonstrates a high level of precision and accuracy has been applied to the INR results gained through the pharmacists' use of the *INRatio* point-of-care device. However, it is acknowledged that an external proficiency testing procedure would be ideal for the evaluation of the *INRatio* device in future investigations or services involving point-of-care testing.

5.0 DISCUSSION

5.1 Achievements against the study objections

5.1.1 *Improve INR control and optimise clinical outcomes of patients receiving warfarin*

In designing this study the original aim was to investigate if a community pharmacist managed anticoagulant service, conducted in close collaboration with general practitioners, point-of-care testing and patients education, could improve the outcomes of patients receiving warfarin. The time frame of this study meant that assessing outcomes using major clinical endpoints, such as episodes of bleeding, hospitalisation and thrombosis or death, was not likely to be feasible. However, there is compelling evidence that the proportion of time a patient's INR is within the target INR range is a good predictor of clinical outcome [Samsa and Matchar, 2000]. This was the primary outcome evaluated in this study and it was shown that a community pharmacist-general practitioner managed anticoagulant service was as effective in the control of INR as usual care i.e., a general practitioner-pathology service. A pharmacist-general practitioner managed service was not superior to *usual care* with respect to patient outcomes but provided the same control of INR and the associated benefits and risks to patients receiving warfarin.

5.1.2 *Cost effectiveness compared to usual care*

This *apriori* objective was evaluated using a comparison of the cost of delivering the community pharmacist managed anticoagulant service compared to the associate costs of providing usual care. This approach was selected based on the observations that patient INR control (and therefore outcomes) was similar across the three data cohorts evaluated in this study. Furthermore, over the total of 40 patient years experience on warfarin collected in the three data cohorts of this study there were no major bleeds or hospitalisations recorded. On the assumption that the pharmacist-general practitioner managed anticoagulant service was not inferior to *usual care* and that the monthly frequency of INR testing was similar, a cost comparison was conducted. The findings

suggest that in the first year of delivery the community pharmacist managed anticoagulant service was considerably more expensive to deliver (reflecting the need for set up costs and training) but in subsequent years the pharmacy based service offered considerable cost savings.

The Medical Benefits Schedule data clearly indicated that many general practitioners continued to have patients monitored using the usual care model during the *intervention*. Hence, while there was a trend towards lower MBS expenditure on anticoagulant monitoring a difference between the *pre-intervention* and *intervention* expenditure was not observed. The frequency of INR monitoring by general practitioners during the *pre-intervention* and by pharmacists and general practitioner in the *intervention* were not significantly different. This was an important finding given that the convenience of point-of-care testing of INR may have lead to more frequent monitoring of patients which would not reflect typical practice or clinical need.

5.1.3 *Professional links between community pharmacists and general practitioners in providing patient care*

The community pharmacist-general practitioner managed anticoagulant service investigated in this study relied heavily on the close collaboration between pharmacists, general practitioners and their patients. The findings from the pharmacists' experiences in the study reflect in both qualitative and quantitative terms evidence of improved collaboration with general partitioners. The response from one patient in the study reflected this with the comment "*There was a three-way communication between me, the pharmacist and the doctor*". However, the qualitative data on pharmacist experiences also point to the fact that some barriers remain between pharmacist and general practitioners and that this will be an important issue for the future implementation of such as service.

5.2 Justification for study design

The proposed study design brings together key elements explored in other research studies involving pharmacy-based service provision, previous published studies involving pharmacists in the provision of anticoagulant services and addresses outcomes widely used by other researchers in the field. This provided the opportunity to assess meaningful changes in the main clinical, economic and humanistic endpoints between the *intervention* and *pre-intervention*. The clinical outcomes for this study were selected to allow a rigorous assessment of the clinical significance that this pharmacist-general practitioner anticoagulant service may provide. Studies have clearly linked INR control to patient outcome [Samsa and Matchar, 2000; Cromheecke *et al*, 2000] which was recently confirmed in a systematic review conducted by Fitzmaurice *et al*, [2003] who indicated that at least 2 different clinical outcome measure should be employed. As expected there were no haemorrhagic and thromboembolic events within the time frame of this study so this study relied on INR control parameters as the primary clinical endpoints. Jones *et al* [2005] have demonstrated, using a record linkage study combining the data from over 2000 patients, that INR readings outside the target range increase the rate of hospitalisation. Their work shows that a 10% increase in the time a patient spends outside the INR target range is associated with a 29% increase in the likelihood of death and a 12% increase in the risk of thromboembolic events.

5.3 Impact on Quality of Life

In this study a validated 32 item question was employed to evaluate aspects of quality of life and the impact of warfarin therapy. A before and after comparison was made between the *intervention* and *control* groups. There was a clear trend towards an improvement in quality of life for the patients who received the community pharmacist-general practitioner managed anticoagulant service. This was supported by patient feedback data which strongly highlighted the convenience aspect and acceptability of the pharmacy-general practitioner managed anticoagulation model evaluated in this study (Section 4.4.1). It was clear from the quality of life assessment that the general treatment satisfaction was already high being 4.7 ± 1.2 and 5.1 ± 1.0

(on a 6 point scale) in the *intervention* and *control* groups, respectively. Gadisseur *et al* [2004] also used a 32-item questionnaire and showed similar *pre-intervention* observations and benefits on the quality of life of patients when they considered the impact of patient education (about anticoagulation) and the self-monitoring monitoring. Cromheecke *et al* [2000] compared the anticoagulant control and impact on quality of life for patients who were trained in self-management compared to those who received usual care. This study demonstrated a significant improvement in each of the 5 treatment related domains during self-management highlighting the possible improvements that different management strategies can achieve in patients quality of life when compared to usual care.

The present study showed that community pharmacy managed anticoagulation service could significantly reduce patient distress and this observation was supported by feedback from patients in the semi-structured interviews used to evaluate this service (Appendix 13).

5.4 Reliability of Point-of-Care INR testing using the *INRatio* device

The reproducibility and reliability of the INRatio device is central to this proposal. While the manufacturer provides an exhaustive list of literature supporting the use of the *INRatio* device, a recent independent study assessed the precision and accuracy of the *INRatio* device compared to laboratory based INR results. Taborski *et al* [2004] evaluated INR readings collected using the *INRatio* and Coaguchek S devices from 82 people in two centres who received warfarin. Readings from point-of-care INR testing devices were compared to laboratory based measurements. Both point-of-care testing devices provided accurate INR readings within 7 to 9% over the INR range of 1 to 5. The precision of INR readings was approximately 8% which demonstrated that in the hands of appropriately trained professionals these devices provide reliable results (see also comments in Section 2.4).

In the latter part of this study an internal QC program (that was externally managed) was implemented to assess the reliability of the *INRatio* device performance. Due to

the lack of an available external QC sample, which is equivalent to capillary blood sample, we utilised an identical batch of the *INRatio* test strips and recorded the prothrombin time readings for the high and low QC samples which are run each time a patient's INR sample is analysed. These results, at the very least, confirm the reproducibility of INR measurements and can identify any errors related to systematic, device or operator errors. The internal QC data collected in this study confirm the (internal) reproducibility of INR results generated as part of this study.

5.5 Patient Knowledge of warfarin therapy

An important feature of the community pharmacy-general practitioner based anticoagulant service investigated in this study was the inclusion of warfarin education provision and knowledge assessment. This targeted approach to "filling in the gaps" in patient knowledge about warfarin lead to improvements in patient understanding (although this did not reach statistical significance due to a limited sample size). Interestingly, the patients in the *control* group also demonstrated an increase in their warfarin knowledge (although to a lesser extent than patients in the *intervention* arm of the study). Khan *et al* [2004] have demonstrated the important link between patient education and improvements in patient outcome on warfarin. These researchers allocated 125 patients receiving warfarin to usual care or to receive an education intervention. The patients (n=85) that received the education intervention were further allocated to receive either usual care or were trained in self-monitoring. For those patients that received education alone, the percentage time their INR readings were within the therapeutic range increased from 61 ± 15 % prior to the study to 70 % ± 24% at the end of the study. This highlights the importance of combing anticoagulant monitoring strategies with supportive measures such as education to ensure optimal anticoagulation management.

5.6 Comparison with published studies

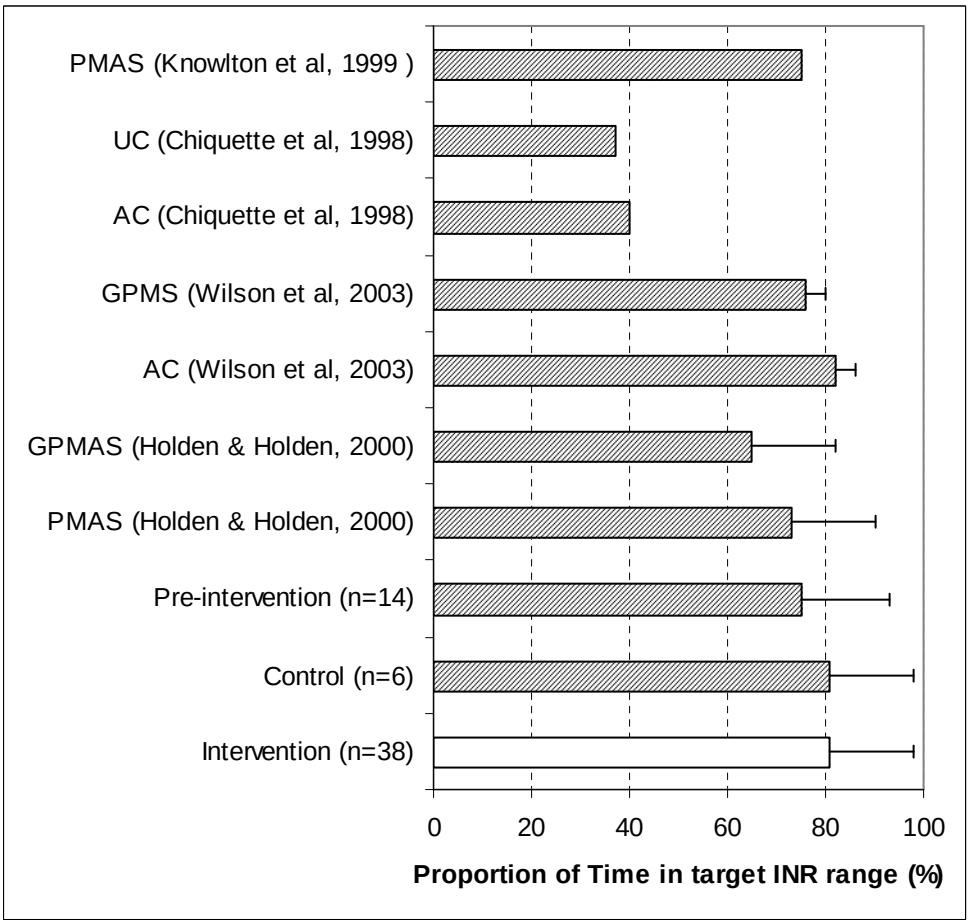
There is a comprehensive literature related to evaluating the clinical, humanistic and economic outcome of patients receiving anticoagulant management under different models (see Section 2.2 and 2.3). Figure 13 provides a graphical summary of the

mean time that INR readings are within the target range for this study compared to different anticoagulant management options from selected studies. The studies selected for comparison were;

- Knowlton *et al* [1999] who studied INR control using a prospective observational study in a convenience sample of 26 patients using the pharmacist-managed anticoagulant service (PMAS) employing point-of-care INR testing;
- Chiquette *et al* [1998] who compared INR control in an anticoagulant clinic (AC) involving 183 patients and 145 patients receiving usual care (UC);
- Wilson *et al* [2003] conducted a prospective study comparing INR control for 221 patients who received management by a pharmacist in an anticoagulant clinic (AC) and a general practitioner-managed anticoagulant service (GPMS);
- Holden and Holden [2000] used a sequential study design and retrospective analysis to compare INR control in 51 patients who received anticoagulant management by either a pharmacist (PMAS) or a general practitioner (GPMAS).

This comparison shows that the control of INR varies from study to study. The difference between these studies reflects a number of factors including the study design and the nature of the patient population. The INR control achieved in this study is comparable to results obtained from other published studies. Any conclusion about the possible superiority of the collaborative pharmacist-general practitioner model evaluated in this study needs to be cautiously interpreted in light of the factors described above (See Section 5.7).

Figure 13: Compares the mean proportion of time INR readings are within the range for this study and previously published studies which utilise different anticoagulant management approaches. Abbreviations are presented in the text.



5.7 Limitations of this study

Despite the use a multiple recruitment strategies, this community pharmacy based study was not able to enrol adequate numbers of patients into the *control* arm to allow appropriate comparisons of key endpoints. This was overcome in a limited way by the use of *pre-intervention* data collected from patients in the *intervention* group. However, combining retrospective and prospective data is not optimal because of the inherent difficulties in maintaining data integrity and completeness. Furthermore, the temporal aspects related to patient care mean that direct comparisons of retrospective and prospective data should be done with caution. Due to the same recruitment issues the randomised nature of the original design was revised (with the permission of the Pharmacy Guild of Australia) to include a convenience sample of pharmacists who then invited patients within their practices to participate in the study. The impact of these changes in the design and the nature of pharmacist and patient recruitment should be carefully considered when interpreting the results of the present study and may limit the generalisability of the findings. Although, the original plan to conduct a controlled trial of anticoagulation monitoring could not be achieved due to the lack of a suitable control data set or comprehensive *pre-intervention* data, the data from the patients in the *intervention* arm of study do provide important information about the control of INR and changes in quality of life and patient knowledge over the time of the study. Based on historical comparisons, with previously published research, the clinical endpoint data from the present study are in general agreement with other models of anticoagulant management from different populations. The fact that time within the INR range appears to better in the *intervention* group of the present study cannot be considered a significant finding given that the patients recruited into this study were not randomly selected and likely to be "uncomplicated" patients (reflecting possible *selection bias* in the present study). This recruitment issue is likely to bias the results in favour of the intervention. This observation is supported by the lack of major bleeds or thromboembolic events observed in the *intervention* cohort of patients despite examining a total of 27 years of patient experience data. Finally, it is important to note that these data were collected during warfarin maintenance therapy and cannot be extrapolated to warfarin initiation.

The final statistical analysis of INR data obtained during the *pre-intervention* and *intervention* phases of the study only included data from 14 patients. Although the inter-patient variability observed in the key endpoint, proportion of time INR was within the target range, was relatively small (approximately 23%) it is unlikely that this relatively low number of patients provides adequate power to detect the size of the difference in INR control planned prior to the study (see Section 3.8) with adequate power.

Pharmacists in this study were trained to use the *INRatio* point-of-care INR testing device. One of the limitations of using this device in this study was the lack of an available external quality control program to monitor the reliability of the INR measurements. The reasons for this are discussed above but an important recommendation from this study is that both an internal and external proficiency testing programs are essential if the uptake of this approach to anticoagulant monitoring is to be successful and safe. In this study no haemorrhagic or thromboembolic events were observed across the 40 patient years of experience analysed. Patients remained in the care of their general practitioner and pharmacists were trained to recognise (and subsequently educated patients about) the warning signs of serious unwanted effects related to warfarin. Furthermore, the dosing recommendation chart used by pharmacists had clear guidelines about when patients should be retested or referred to their general practitioner. These latter measures provided confidence that clinically significant problems could be identified and appropriately managed if and when they occurred. However, an external proficiency testing program would have reinforced the reliability and reproducibility of the INR measurements obtained from the *INRatio* device – a point raised by both pharmacists and general practitioner's in this study.

A significant challenge to the successful implementation of this study was the lack of engagement of pharmacists and general practitioners in patient recruitment and clinical data collection. It is important to reflect on these challenges because it is likely that the same issues are likely to influence the broader implementation of a community pharmacist-general practitioner anticoagulant management service. The willingness of practitioners to engage with this study (and this model of anticoagulant

management) are likely to be multifactorial and are influenced by the following factors which were identified through discussion with pharmacists involved or invested to participate in this study;

- **Practitioner's patient mix** (pharmacists and general practitioners need to have a relatively large number of patients receiving warfarin in their practice. A number of pharmacists declined to enter the study as they did not have the patient mix to support recruiting patients into the study);
- **Organisation of practice** (some pharmacies did not have the staff profile or space requirements to readily offer the anticoagulant management service);
- **Level of remuneration** (the level of remuneration for pharmacist and general practitioners was only a token amount– due to budget restrictions and did not reflect the time and effort required by pharmacists and general practitioners. The lack of "reasonable" financial incentives, especially amidst the numerous financial imperatives in a practice setting is a critical factor);
- **Motivation for change** (this is a novel service and requires a change in practice for both general practitioners and pharmacists);
- **Relationship between health care practitioners** (the successful implementation of the service relies on close collaboration between pharmacists and general practitioners. In this study some pharmacists indicated that general practitioners in their area were not willing to refer patients to the study).

Consideration of these factors will be essential is subsequent studies and during the implementation of a pharmacist-general practitioner managed anticoagulant service.

6.0 CONCLUSIONS

A community pharmacist-general practitioner managed anticoagulant service using point-of-care INR testing can;

- maintain the control of patient INR within the target range to help achieve optimal anticoagulation outcomes;
- improve patient knowledge which, in turn, has been linked to reduced risk of warfarin-related complications;
- improve patient quality of life by reducing treatment related distress;
- foster timely and appropriate inter-professional collaboration between pharmacists and general practitioners;
- be delivered in a manner which is comparable to the cost of existing pathology services.

Furthermore, this study demonstrated that the community pharmacist-general practitioner managed anticoagulant service was acceptable to patients and pharmacists involved in the study. Trained and supported pharmacists were able to make credible management recommendations about anticoagulation that were accepted by general practitioners.

Taken together the results of this study demonstrate that a community pharmacist-general practitioner managed anticoagulant service is feasible and an alternative option for some patients receiving warfarin.

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Appendices

1. Pharmacist Study Information and Consent forms
2. General Practitioner Study Information and Consent forms
3. Patient Study Information and Consent forms
4. Educational training session for pharmacists – including copies of slides and educational protocols
5. Patient Education Booklet
6. (a) Study flow chart
   (b) Pharmacy Specific Dosing Protocol (adapted from Foss *et al*, 1999).
7. Pharmacist Recommendation Fax form for Communication to General Practitioners
8. Data collection sheets used in this study
9. Quality of Life Assessment tool (adapted from Sawicki, 1999)
10. Warfarin Knowledge Assessment Questionnaire
11. Individual patient clinical and demographic characteristics
12. Summary of patients recruited into the study and the data they contributed
13. Patient Responses to Semi-structured interview on experiences in the study
14. Pharmacists Responses to questionnaire on experiences in the study