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A Proposed Model for an Internet-based Computerised Anticoagulant Monitoring System

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Abstract
Warfarin is an anticoagulant drug used to manage venous thrombosis, pulmonary embolus and several heart conditions. It has proved a valuable drug but there is a requirement for close monitoring of patients to whom it is administered to prevent overdose and bleeding. In New Zealand anticoagulant monitoring is not managed consistently and the "safe use of medicines" group has recognised the potential dangers of poor control. There are several elements to anticoagulant monitoring with accurate dose adjustment and consistent follow-up essential. However, many other procedural factors need to be in place to ensure patients are tested on time and to identify poor compliance and patients who do not attend for regular testing. All of these factors can be managed with the assistance of a computer system. Studies have shown that computer-based dosing for anticoagulant control can be as good as management by a clinician. In fact, in many countries patients are given the opportunity to manage their own warfarin and to test themselves using a home testing device. Self-testing is now available in New Zealand but patients who are self-testing have little access to clinical support. In this paper we propose a model of managing anticoagulant therapy using a web-based anticoagulant programme which is accessible to both general practitioners and patients performing self-testing.

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Introduction
Warfarin is the most widely used oral anticoagulant in New Zealand. It was introduced into clinical practice more than 40 years ago for the management of acute venous thrombosis and pulmonary embolus and still remains the drug of choice for the management of these life-threatening conditions. Warfarin also has a role as a prophylactic agent in preventing both venous and arterial thrombosis.[1] It is used to prevent thromboembolic complications associated with mechanical heart valves and has been used following heart attacks to reduce the risk of stroke and thromboembolism.[2] However, the use of oral anticoagulants has increased dramatically over the last 10 years since it was confirmed that warfarin can significantly reduce the risk of stroke in patients with an irregular heart rate due to atrial fibrillation.[3] The incidence of atrial fibrillation is 4.7 percent in people over 65 years of age, rising to 10 percent in men over 75 years of age. The result is that an increasing number of elderly patients are now taking warfarin on a long-term basis.

Warfarin has been a very successful drug but has limitations that complicate its use. The major disadvantage is that it has a narrow therapeutic range; if a patient does not have sufficient warfarin they are still at risk of thrombosis whereas if they have too much warfarin they are at risk of bleeding. Warfarin treatment therefore requires regular monitoring to achieve safe control.[4,5] Fortunately warfarin treatment can be monitored using a simple blood test based on a clotting test: the prothrombin time. A patient's prothrombin time is compared to the "normal" prothrombin time from a normal control and the result is expressed as a ratio of the two times. Internationally, it has been recognised that different reagents produce different results and, therefore, the ratio is corrected or "normalised" to reflect this variation. The final result is expressed as the International Normalised Ratio or INR.[6,7] A person not taking warfarin should have an INR of 1.0. The therapeutic range for most patients on warfarin is an INR of between 2.0 and 3.0, although some patients do require a higher therapeutic range. Many factors influence the INR and regular testing is necessary.

Bleeding is the most serious complication of warfarin therapy. Major bleeding has been reported at an incidence of 1.5 percent per year in patients on anticoagulant therapy for atrial fibrillation and at 2.5 percent in patients on warfarin for mechanical heart valve prophylaxis. The highest incidence of bleeding was 8.1 percent, reported in a series of patients receiving warfarin following stroke or transient ischaemic attacks.

Fatal intracranial haemorrhage is between 0.2 percent and 0.5 percent per annum, with a particularly high incidence in patients with a history of stroke (2.6 percent). Risk factors for bleeding include old age,[8] serious illness (cardiac, renal or liver disease), cerebrovascular or peripheral vascular disease, and unstable anticoagulant control.[9] Drug interactions and the effects of alcohol have some influence. Age alone is not a contraindication to warfarin therapy although one series showed that for each decade over the age of 40 years, the risk of major bleeding increased by almost 50 percent. The risk of bleeding is directly related to the INR value. In a 1996 study, the bleeding rate doubled as the INR increased from

2.0-2.9 to 3.0-4.4, quadrupled between 4.5-6.0, and was multiplied by five when the INR was above 7.0.[10] There is a consistent increase in major bleeding (including intracranial bleeding[11,12]) when the INR exceeds 4.0-5.5.[13-15].

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Managing Warfarin Treatment
Because of the high incidence of bleeding, warfarin treatment requires close supervision, preferably by a healthcare professional with some experience of controlling warfarin. A number of different approaches to anticoagulant control have been adopted with significant differences internationally. It is unclear which approach achieves the best control as there have been few audits comparing the various practices. There are advantages and disadvantages for each approach.[16,17]

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Anticoagulant Clinics
In the UK, dedicated anticoagulant clinics have been used to monitor patients on warfarin. The patient attends hospital for a blood test and is reviewed by a doctor. Dose adjustments are made as appropriate and the patient is advised when to attend for the next test. The advantage of this approach is very close medical supervision, which enables both patients with poor compliance and non-attenders to be identified and alerts the monitoring doctor to any changes to medication. The disadvantages are that such clinics are expensive to run and require a large amount of medical time and dedicated facilities. They are also inconvenient for patients, who have to attend a hospital clinic regularly. With the rapid increase in the number of patients taking warfarin this type of clinic has become impractical. In order to save on medical time, trained nursing or pharmacy staff have replaced the doctor in the clinic. Audits suggest that these personnel have achieved control to the same standard as a medical practitioner.

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Central Control with a Postal or Telephone System
In order to keep a warfarin patient out of hospital, a number of remote systems have been developed. Patients can have blood collected near home and the blood sample is then sent into a central laboratory for analysis. The results are reviewed by a doctor and dose adjustments made as necessary. The patient is either informed by post or phone about the details of any dose adjustment and the date of the next test. The advantage of this method is that it is cheaper than a clinic and patients do not need to attend hospital. Further, the dosing is supervised by a doctor with experience of warfarin treatment. The disadvantages are that there is loss of face-to-face contact between doctor and patient and it can be harder to identify non-attenders.

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Monitoring by General Practitioner
In this model, blood is collected at a remote site and sent to a central laboratory for processing. The INR result is sent to the patient's general practitioner (GP) who informs the patient of any dose change. The advantage of this system is that it is cheap and that the GP knows his or her own patients. The disadvantages are that the GP will have less experience of dosing as there may be only a small number of patients seen in their practice. It is also very difficult to identify non-attenders and testing may be carried out more frequently than necessary.

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Patient Self-Testing
There is a trend in Europe and the US to encourage patients to take on their own testing. Three portable testing devices have been approved for home testing by the US Food and Drug Administration (FDA). Initial studies showed rather poor correlation between results obtained by these devices and a laboratory-based test, but recent studies using the CoaguChek device (Roche Diagnostics) and improved reagents show comparable results with those of a reference laboratory.[18,19] The CoaguChek is a portable device that uses a finger prick sample to measure the INR. The feasibility and accuracy of patients self-testing was initially evaluated in two small studies with promising results.[20,21] More recently, Beyth and Landfield[22] randomly assigned 325 newly diagnosed patients to either conventional treatment by a personal physician, based on venous samples, or adjustment of dosage by a central investigator based on INR results from patient self-testing. Over a six-month period the rate of haemorrhage was 12 percent in members of the usual care group compared with 5.7 percent in the self-testing group. A large German study[23] showed that among 305 self-managed patients, INR values were more frequently in range - 78 percent compared with 61 percent in conventionally managed cases. Other reports have not shown such a significant difference between the two methods of testing, but no studies have shown that self-testing is worse than control by a physician . The disadvantage of self-testing is the loss of medical supervision and the uncertainty of the quality control of the device.

All of these systems can achieve good anticoagulant control in the well-motivated, reliable patient. However, the patients at most risk of bleeding are those with poor compliance, poor attendance at clinics or their GP's practice and frequent changes to other medication. It is, therefore, essential that an effective monitoring system be able to easily identify these high risk cases. None of the systems are designed to reliably identify non-attenders.

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Design of an Anticoagulant Monitoring System
The main priority for an anticoagulant system is to provide safe control. This can be achieved if the system has the following features:

1. Medical supervision. Provided by a trained nurse or pharmacist with overall supervision by a medical practitioner.
2. A reliable accurate method of dose adjustment.
3. A reliable method for recommending the time for the next test, based on the stability of the anticoagulant control.
4. Procedures to alert the supervisor to:
    - patients with an INR above a specified range;
    - patients who have altered their medication since their last visit;
    - patients who have had minor bleeding since their last visit;
    - patients who have failed to attend for a test on a specified date;
    - patients who remain overdue for a test;
    - patients who are due to discontinue their warfarin; or

    - patients with poor control.
5. A procedure to remind patients when testing is due.
6. Provide patients with adequate information about warfarin.
7. Provide patients with an emergency contact point in case of significant bleeding or injury.
8. Provide other health care professionals with information about specific patients in an emergency.
9. Auditing of results to ensure that all these procedures provide comprehensive safe management.

The management system described lends itself to a fully computer-based approach.

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Computer Based Anticoagulant Control
A number of computerised anticoagulant management programmes have been developed. These use different dose calculating algorithms either based on Bayesian forecasting[1] or proprietary mathematical equations.[25] In one randomised trial, the reliability of three established computerised dosage programmes was compared with warfarin dosing by experienced medical staff in an outpatient clinic.[26] Levels of control were similar for the computer-guided and the empirical dose adjustments in the INR range of 2.0 to 3.0, but the computer programs achieved significantly better control when more intensive therapy (INR 3.0 to 4.5) was required. In another randomised study of 101 chronically anticoagulated patients with prosthetic cardiac valves, computerised warfarin adjustments proved comparable to manual regulation in the percentage of INR values kept within the therapeutic range but required 50 percent fewer dose adjustments.[27] A multicentre randomised study of 285 patients found computer-assisted dose regulation more effective than traditional dosing at maintaining therapeutic INR values. Taken together, these data suggest that computer-guided warfarin dose adjustment is superior to traditional dose regulation, particularly when personnel are inexperienced.

The great advantage of a computerised system is the ability to automate a number of tasks, eg:

- Identifying potential interactions between other medication and warfarin.
- Alerting the supervisor to
    - Non-attenders.
    - Patients with poor control.
    - Patients with history of bleeding
- Automatically recommending a dose adjustment and the date for the next test. For stable patients, such a service could be fully automated so that the supervisor does not need to intervene. For less stable patients, the results could be reviewed by the supervisor and either accepted or modified as required. Details of all supervisor interventions could be recorded for future audit.
- Sending results electronically to the patient's GP.

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Patients with Internet Access or a Mobile Phone
For patients with Internet access or a mobile phone, the computer system could be extended to improve communication with the patient. A large number of patients on warfarin are elderly and may not routinely use email or mobile phones, but a significant number of patients do have access to these technologies and it is likely that the number will increase rapidly. Therefore, an efficient anticoagulant monitoring system should include the ability to:

1. Send an automatic reminder by email or text message to the patient the day before their next test is due.
2. Send results directly to the patient by email or text message together with a dose recommendation and the date of the next test.
3. Send a reminder to a patient who fails to attend.
4. Provide a website for patients which would allow patients to look up their own results and could provide information about warfarin and relevant medical conditions. It could also provide an email address to which patients could send messages asking for advice. A website would allow other health care professional to review a patient's anticoagulant control in an emergency if admitted to hospital.

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Proposed Model for an Internet Based Anticoagulant Monitoring System in New Zealand
We propose that a centralised, Internet-based, computerised anticoagulant monitoring system would improve anticoagulant control for New Zealand patients on warfarin therapy. A number of computerised, anticoagulant monitoring systems are available commercially, however these are all designed as stand-alone programs rather than web-based approaches. They are suitable for anticoagulant clinic based services but are less useful for a GP-based service and are not appropriate for self-testing by patients. We propose that a single system could be developed to manage all patients on warfarin in New Zealand. The system needs to be versatile to allow for both clinician based monitoring and patient self-testing.

The main program and database would be situated on a central secure server. The central client program would run the dosing algorithm based on a published dosing formula to predict a patient's dose and review the stability of results to recommend the date of their next test. INR results would be entered from a web-based browser or downloaded directly from laboratory computer systems. The relevant firewalls would be incorporated to ensure data security

Two models would be incorporated into the one system: clinician based management and patient self-testing.

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Clinician-Based Model
Figure 1 outlines the recommended procedure. The person managing anticoagulant treatment would be a GP, hospital clinician or nurse. To use the system, the manager would log onto the INR Manager website. The manager only has access to his or her own patients. The manager's home page at the INR website would show a list of all their patients due for an INR test and any patients for whom a test is overdue. A patient's INR result would be entered into the system either manually or downloaded from the laboratory system or the near-patient testing device. The computer system would then automatically provide advice on the warfarin dose and the date of the next test. The results would be reviewed by the manager and either accepted or modified as required. The patient would then be automatically added to a contact list. If the patient's anticoagulant control is stable and they have access to the internet or a mobile phone, a message stating the treatment dose and date of the next test would be sent to the patient. If the results show that anticoagulant control is unstable or the patient did not have an alternative form of contact, the manager would

contact them by phone. The manager would also be able to contact all non-attenders as required.

All patients with Internet access or a mobile phone would receive an email or text message reminder the day before their next test were due. They would continue to receive daily reminders until they attended for their next test.

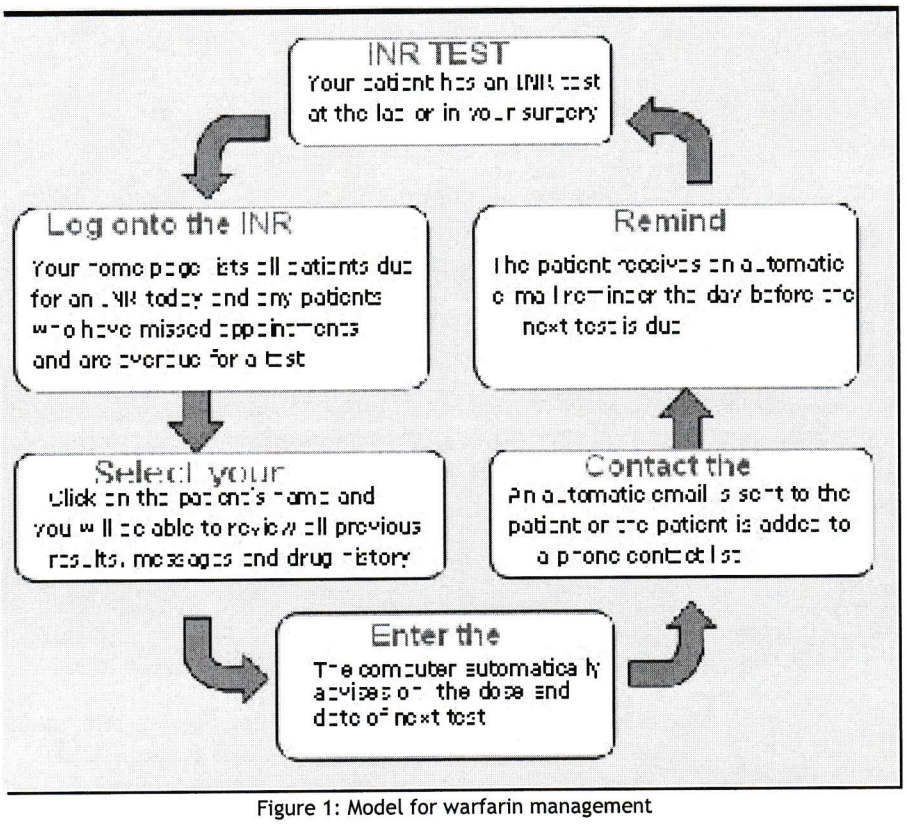

Figure 1: Model for warfarin management

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Self-Testing
The procedure for a patient performing self-testing is shown in figure 2. Patients using self-testing need to be well motivated and to have a clear understanding of their condition and the action of warfarin. The patient would be trained to use the near-patient testing device. The anticoagulant monitoring would be carried out via the internet site. The patient would only have access to his or her own results. In order to increase safety, a patient would be asked to confirm their present dose of treatment, to report any new medication and to report any bleeding problems since their last test before the INR result could be entered. If a patient's result indicates that their anticoagulant control is stable, their next dose and the date of the next test would be calculated immediately and displayed on the website. If a patient's INR is outside a specified range or the patient has indicated a change in medication or had problems with bleeding, their results would be stored to be reviewed by their manager later in the day. After review, the results would be emailed to the patient and would be available on the website. As a further safety measure, the patient would be advised to contact a supervising nurse if the INR were above 5.0.

The manager in these situations would most likely be the patient's GP. If the patient's results needed review, the manager would receive an email and the patient's name would appear on the review list on the manager's home page. The manager could then review the results and make adjustments as required.

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Safety Management
Additional features would be incorporated into this system to ensure safe management:

1. Details of all other medication for each patient would be stored on the system.
2. Known drug interactions would be identified automatically.
3. Advice on the management of warfarin overdose would be incorporated into the system; these would be based on the Australasian Guidelines for warfarin reversal.[28]
4. Patients who are self-testing would be asked to confirm their present treatment dose each time an INR result is entered.
5. Patients would be advised to contact their anticoagulant manager if they have any problems with bleeding.
6. The software would identify all patients requiring high doses of warfarin
7. The software would identify patients with poor anticoagulant control.
8. The software would identify patients with poor compliance.

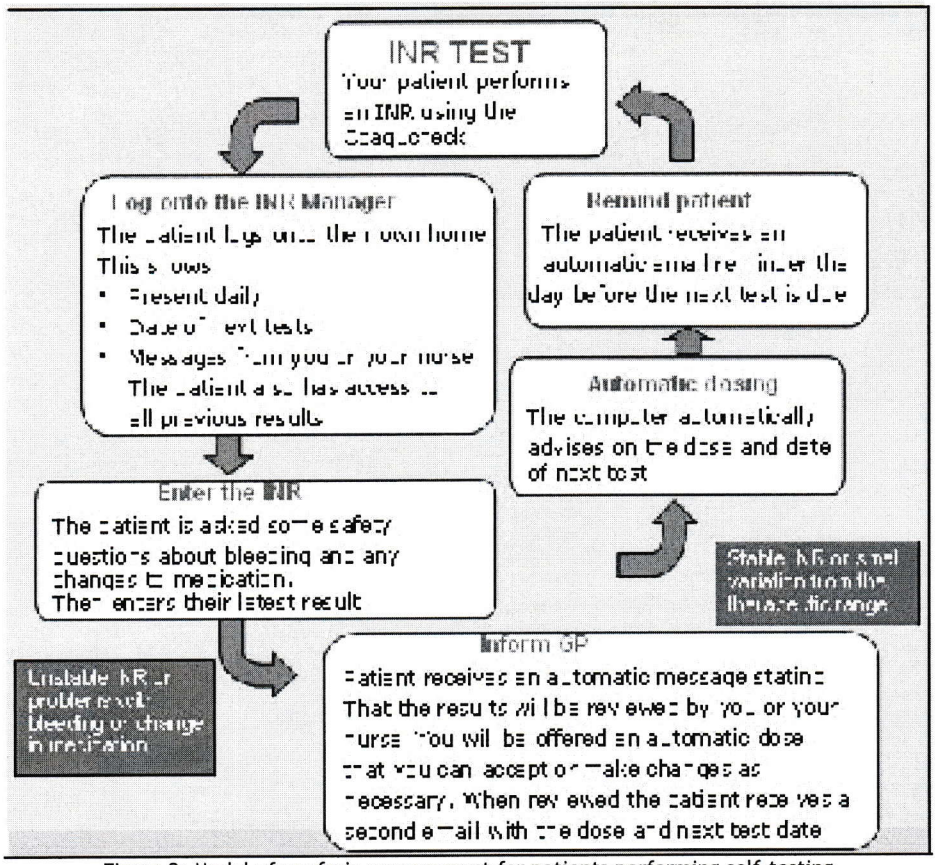

Figure 2: Model of warfarin management for patients performing self-testing

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Audit

The efficiency of the anticoagulant control would be measured by identifying the proportion of INR results that are within the therapeutic range. The INR measurements could also be used as a surrogate marker to estimate the risk of bleeding - by identifying the proportion of time that the INR measurement is above 5.0. These results would be compared with published audit data including our own results.[29]

We hypothesise that a computerised system would efficiently identify non-attenders and patients with poor compliance. The existing system has no reliable method of identifying these patients. Those patients the computerised system identified as poor attenders and non-compliant patients could be audited to ensure that the computer system had reliably identified these cases.

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Discussion

It is well recognised that warfarin is a potentially dangerous drug. This has recently been identified by the "safe use of medicines" group in New Zealand, which has recommended improvements to the anticoagulant control using warfarin in primary care. A computerised anticoagulant monitoring system should improve patient safety by reducing the risk of bleeding associated with anticoagulant therapy. This would be achieved by providing consistent dosing with close supervision by a trained nurse or clinician, automatic tracking of non-attenders and automatic reminders to ensure testing on time. Safety would also be improved by identifying potential drug interactions. The system would have significant advantages for patients as well, giving them more control of their treatment and easier access to help when needed. For patients who wanted to manage their own care with a near-patient testing device, the web-based system would give them confidence, knowing that their results were regularly reviewed by a health care professional. They would also know that they could receive advice if their anticoagulant control was outside the therapeutic range or appeared to have become unstable. Easy access to advice via email or a telephone help line would also reassure patients. The increased flexibility of being able to perform tests whenever and wherever they wanted would be particularly helpful for some patients on long-term treatment. Patients using a near-patient testing device could take the equipment with them anywhere in the world and still log-on to the website to check their results.

There would also be a number of advantages for clinicians managing these patients. Computerised systems have been validated in clinical studies and have been shown to achieve anticoagulant control as good as or better than medical staff working in traditional fashion. One of the benefits of the model we propose would be that a GP would remain responsible for their patient's anticoagulant control at all times. This is an important consideration as in some other models it is not always clear which doctor has responsibility for anticoagulant control. For example, in a laboratory-based model, dose adjustments would be made by a clinician who is not the patient's primary care physician and who, therefore, might not have access to all the clinical information necessary to make safe dose adjustments. The proposed model also has the advantage that patients performing self-testing remain supervised by their GP rather than becoming isolated with little clinical support. The model might also help to save time and resources. Where a computerised system such as that proposed is used, a practice nurse could largely manage a patient's anticoagulant monitoring with little input required from the GP. Financial savings achieved from using a computer system per se are less obvious, however, close monitoring may lead to a reduction in the frequency of INR testing. Our audit of GP practice in Auckland demonstrated that the majority of patients on warfarin, even those on long-term treatment, had blood tests weekly whereas international guidelines state that it is safe to leave testing for up to 4 weeks in stable patients.[29]

Storing information on one central database has wider management advantages as immediate access to a patient's anticoagulant history would be available and could assist in management of such patients admitted acutely to hospital. Data on a central server would also allow for regular on-going audits of all results to ensure safe management.

The final consideration is the cost of the system. As mentioned previously, commercial stand-alone programs are available, however, purchasing one

of these for a small practice with only a few patients on warfarin would not be not cost effective. Even in a large practice, the initial outlay and ongoing maintenance costs might not be worthwhile. However, a web-based system would mean that practices would not have to purchase software and that a small practice would have access to the same standard of monitoring as a larger one. Probably the most appropriate way to fund this service would be to charge a fee for each patient using the system. There might also be additional cost benefits in using such a computer system as improved control could reduce the incidence of complications and, in turn, reduce hospital admissions. Improved control could also reduce the need for frequent testing.

A pilot study to test this model is being developed and will be trialled at a GP practice in Auckland and on a small group of patients who manage their own warfarin using near-patient testing devices. If the results prove favourable, the process could be extended. It is envisaged that a computerised system could be used to monitor all patients on anticoagulant therapy in Auckland. This would require further investment to ensure that the software would be sufficiently robust to reliably manage several hundred patients on warfarin and ongoing software maintenance would be required. However, given sufficient investment, there would be the potential to manage all patients on warfarin in New Zealand via this system

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