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Dear Professor Sansom,

Alere are writing to you in regards to your request for information on anticoagulation therapies in Atrial Fibrillation. Alere would like to provide you with a brief summary of our work in this area.

Alere has a long history in Australia for providing in *vitro* diagnostics in the fields of cardiovascular, infectious diseases, women's health, drugs of abuse and oncology. Alere support healthcare workers and patients by developing simple diagnostic equipment to ensure better quality in both inpatient and outpatient care. Alere's products range from over–the-counter tests to lab-based diagnostics to integrated home monitoring solutions. Alere is a market leader in health care management programs and services and offers comprehensive support for health care professionals and patients across the globe.

By supplying products that are accurate, effective, consistent and reliable for use in both the home and clinical environments, Alere is enabling doctors and patients to better connect with each other and provide the information necessary to make better healthcare decisions.

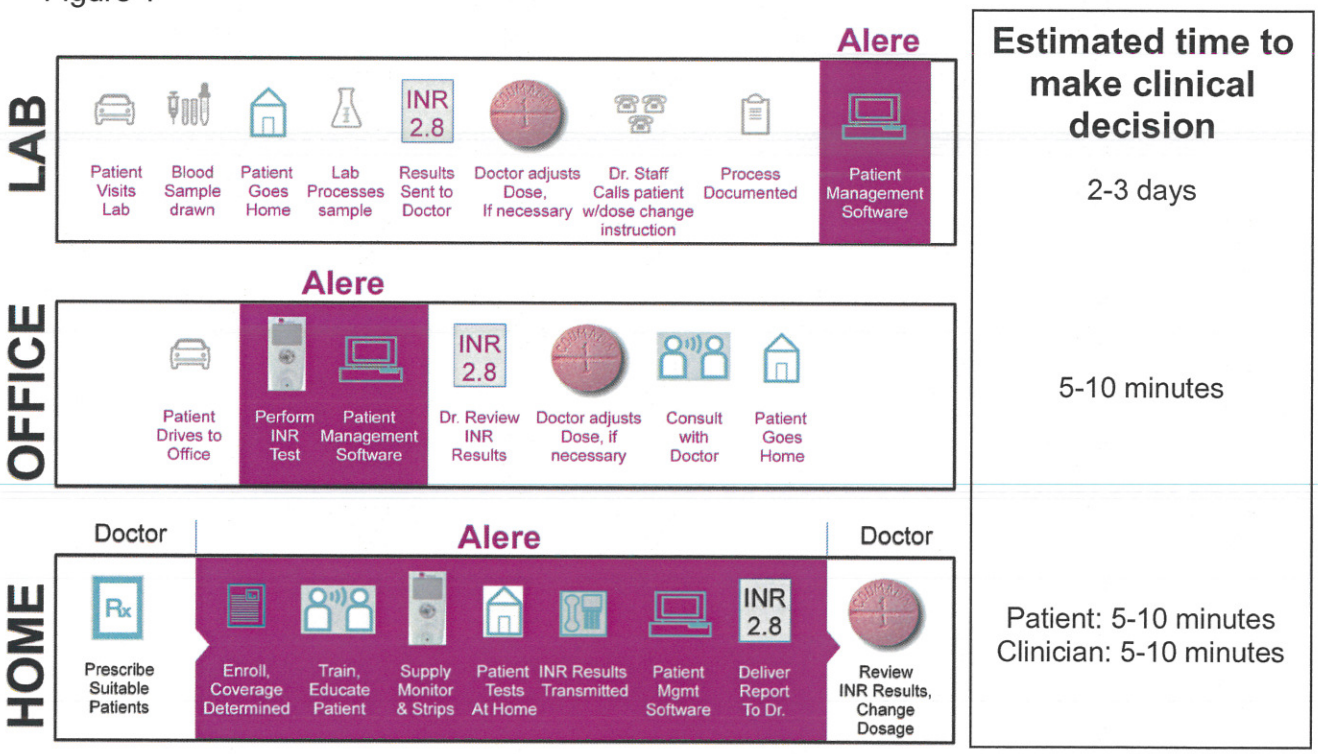
In the area of anticoagulation management, Alere has been providing patients, healthcare providers, and payers with reliable, comprehensive, and cost-effective anticoagulation management solutions for 14 years. Globally, Alere has provided solutions for 10,000 clinicians managing 450,000 patients and over 25 million INR tests. Alere are independent of any specific therapeutic modality or agent in the area of anticoagulation management.

Alere offers an integrated anticoagulation management system that is comprised of key modules that can positively influence the health and cost outcomes of anticoagulation therapy. The modules are comprised of:

1. A fingerstick INR monitor for professional use at the Point of Care or by patients at home to safely measure and monitor INR levels
2. Evidence based practice management decision support software to assist physicians in the management of patients on anticoagulation therapy
3. Patient home INR monitoring training, support, test result capture, and reporting services that enable patients to take a more active role in managing their anticoagulation therapy, while allowing physicians to maintain visibility and control in between office visits.

Figure 1 below illustrates each of the Alere anticoagulation key modules.

Figure 1



a. ***Current and future options for improving the health outcomes of patients with atrial fibrillation treated with oral anticoagulants.***

Current Options

Current options for management of patients with atrial fibrillation include treatment with oral anticoagulant drugs and routine monitoring of prothrombin time (PT) and international normalized ratio (INR). Monitoring of PT/INR can be performed by pathology laboratories and also at the point of care or patient home using one of the commercially available point of care PT/INR monitors. Alere is the manufacturer and Australian sponsor of the Alere INRatio®2 PT/INR monitoring system and providers of anticoagulation management services in the USA.

- Alere INRatio®2 product details can be found at www.alere.com/EN_US/products/alere-inratio-2-pt-inr-monitoring-system-poc-test/index.jsp
- Further information on Alere's anticoagulation management services is available at www.standingstoneinc.com/TakeaTour.aspx and a video tour is viewable following free registration to the website.

An example of Alere's work in anticoagulation therapy involves investigation of various testing and treatment methodologies, particularly in combination. A very successful combination is the concomitant use of Point of Care (POC) and computerized Decision Support Software (DSS) technologies. The peer-reviewed article by Rose outlines how this approach, when deployed in the USA, demonstrated statistically significant improvements in quality, economic, and clinical outcomes[1].

In Australia, point of care testing for PT/INR has been shown to be non-inferior to laboratory based testing for medication adherence and clinical outcomes whist being preferred by patients for reasons of general satisfaction and improved patient-doctor relationship[2,3].

The Australian Medical Association (AMA) supports calls for the introduction of point of care testing as an aid in chronic disease management, medication adherence and improving patient-GP relationships[4].

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Future Options

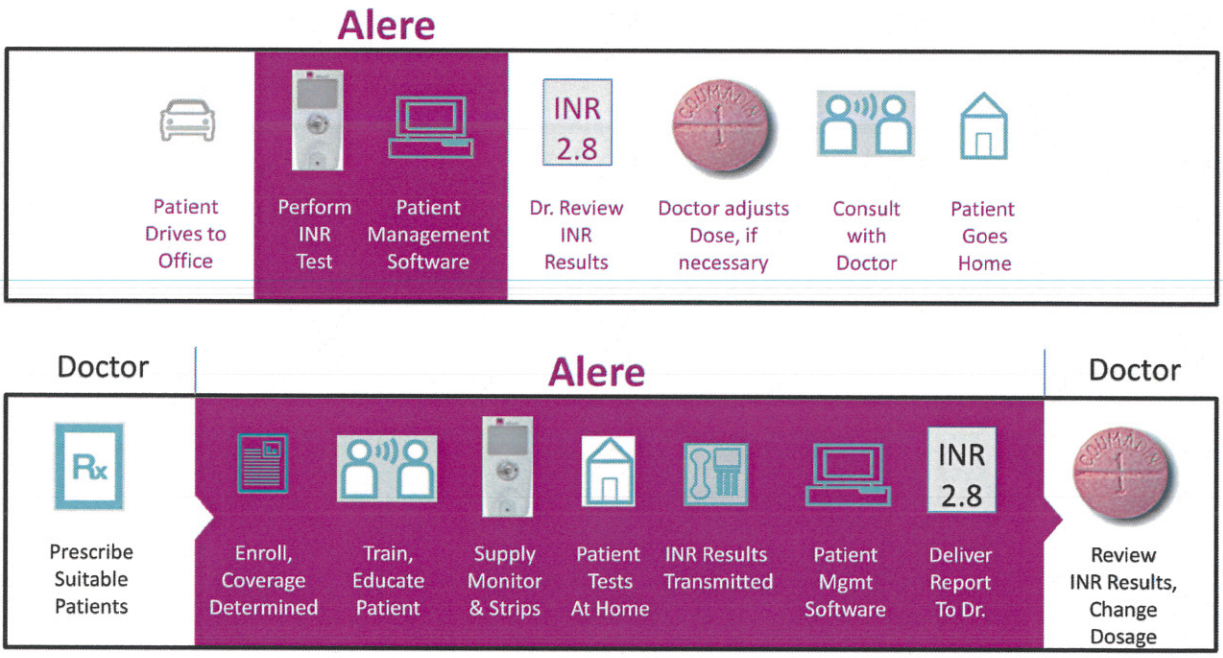
Alere is customising the anticoagulation patient management services currently offered in the USA for the Australian and New Zealand community. It is important to note that the Alere patient management software systems can be used in conjunction with any INR testing device independent of Alere.

Alere's anticoagulation management services include

- Decision Support Software
- Training and coaching for patient self monitoring
- Connectivity solutions for healthcare professionals to aid dose management
- Simple diagnostic devices for measuring INR
- Telephone support for patients

The modules can be deployed as a comprehensive system or independently, enabling providers to select the option to best suit their needs to communicate results and feedback with patients on a timely basis. Connectivity options such as software and devices which allow real time capture and reporting of data from the INR monitor and transmission to the health care professional are available. Figure 2 below illustrates how each of these modules can be adapted to different healthcare settings in Australia.

Figure 2



Alere's Decision Support Software, CoagClinic, is designed for clinicians to manage patients in their office or in the home setting. It incorporates

- Customisable dosing algorithms
- Ability to track INR compliance and time in therapeutic range
- Drug interaction alerts
- Patient tracking for follow up
- Integrated management of patient self monitoring results
- Quality assurance reporting
- Patient education resources
- Interfacing to point of care INR monitors from multiple manufacturers
- Tools to reduce chart pulls and improve patient flow

Extracts from the Decision Support Software (DSS) are shown in Figures 3, 4 and 5.

Figure 3: CoagClinic Welcome Screen

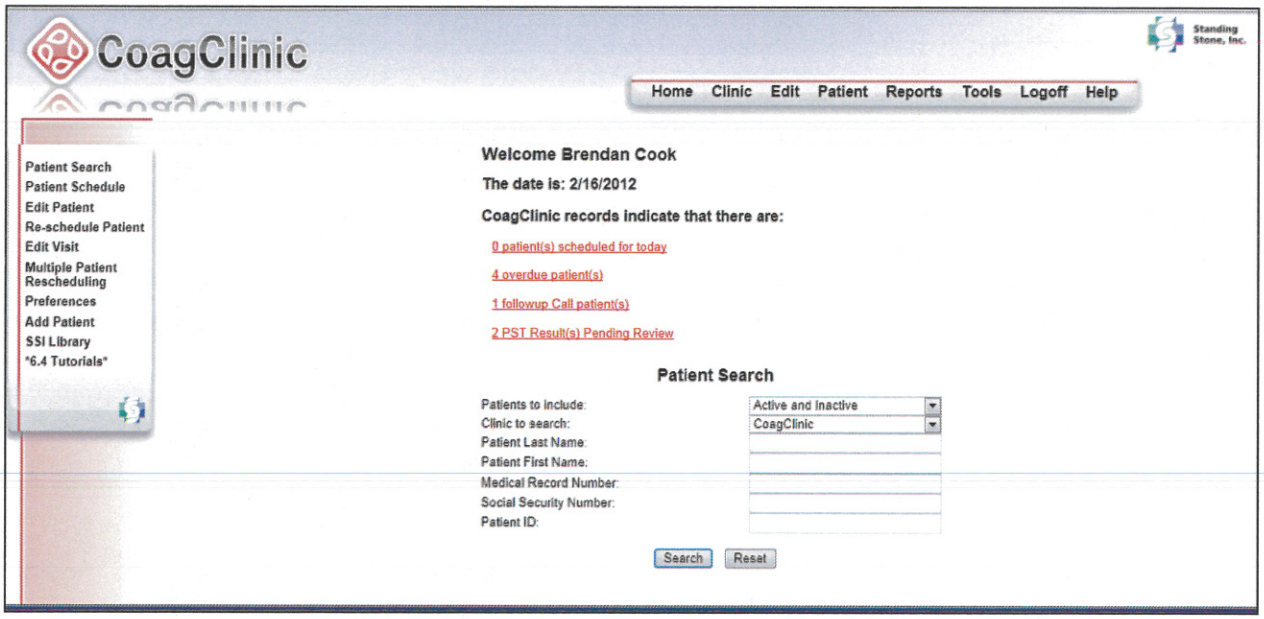


Figure 4: CoagClinic Quality Assurance Report Criteria

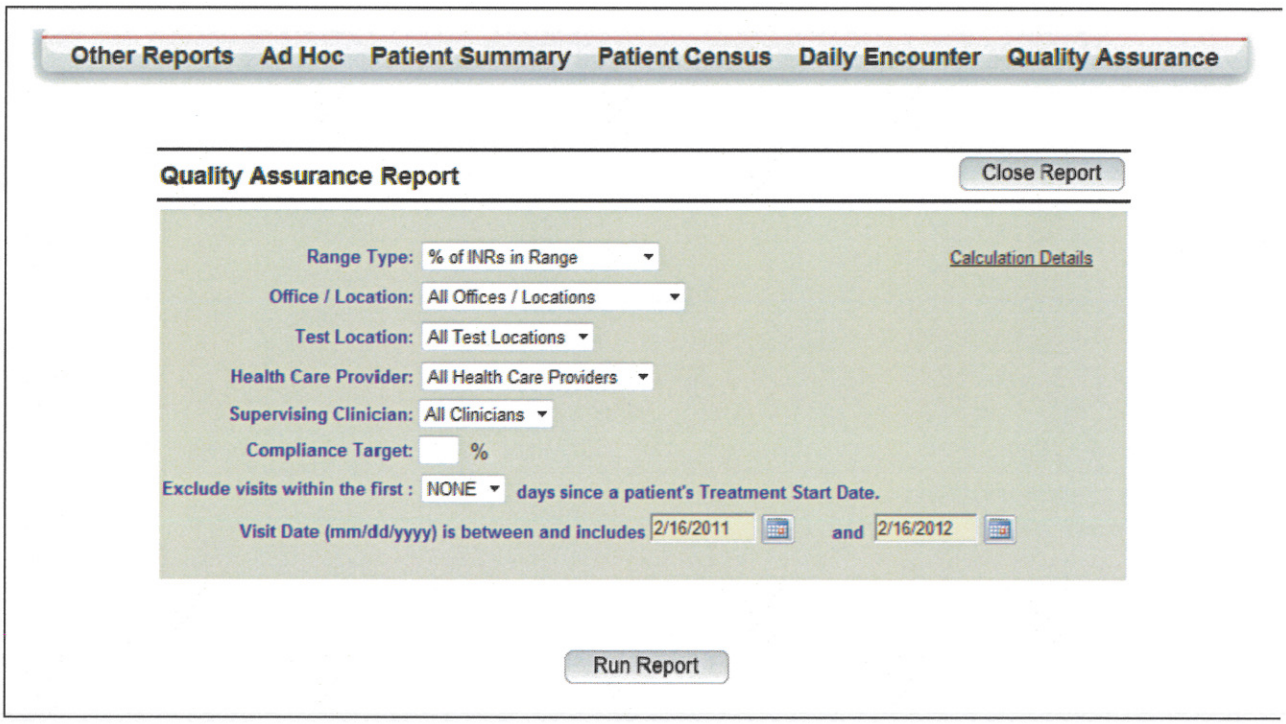
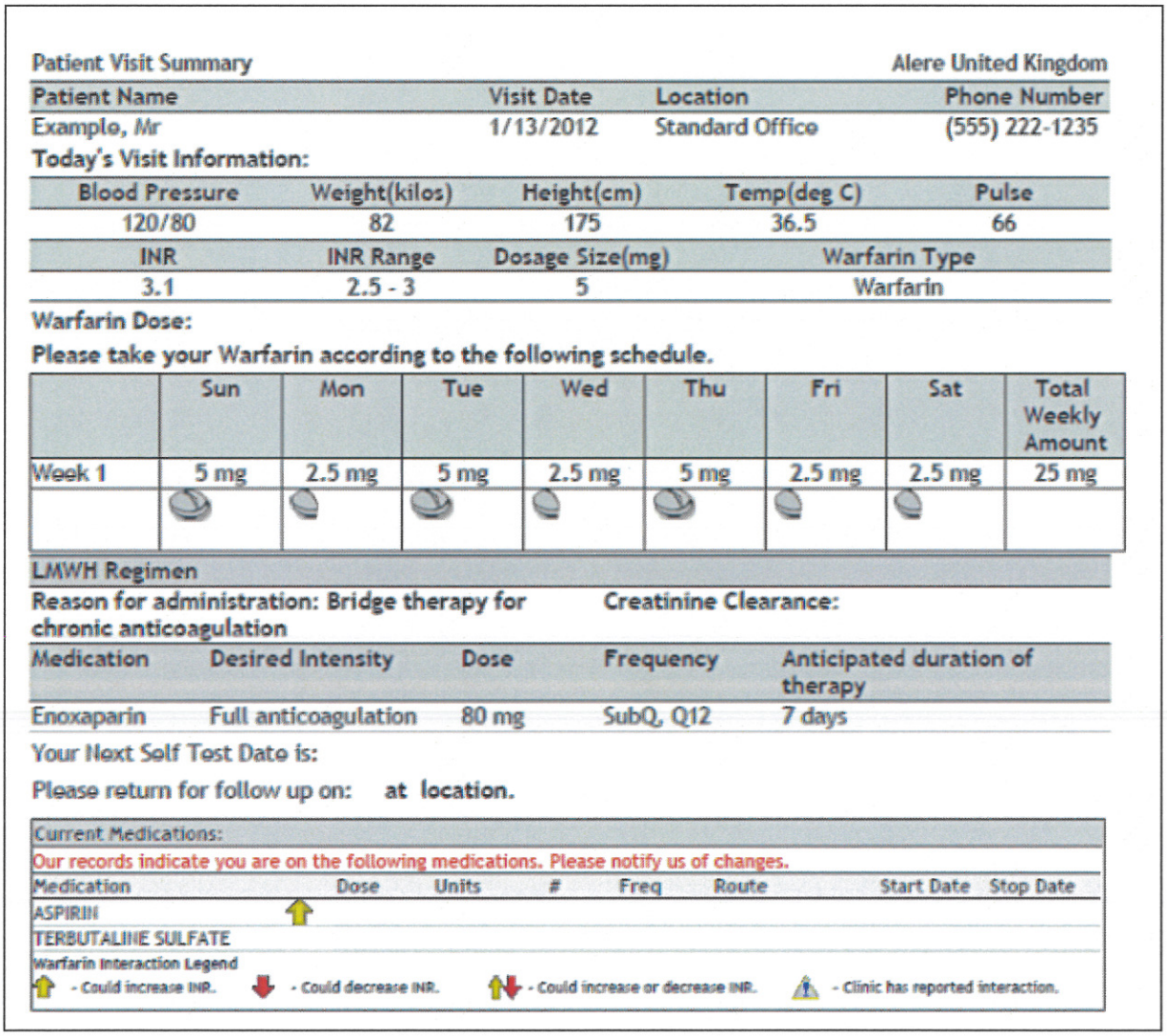


Figure 5: Example of Patient Visit Summary information provided to patients



Patient Visit Summary — **Alere United Kingdom**

Patient Name	Visit Date	Location	Phone Number
Example, Mr	1/13/2012	Standard Office	(555) 222-1235

Today's Visit Information:

Blood Pressure	Weight(kilos)	Height(cm)	Temp(deg C)	Pulse
120/80	82	175	36.5	66

INR	INR Range	Dosage Size(mg)	Warfarin Type
3.1	2.5 - 3	5	Warfarin

Warfarin Dose:

Please take your Warfarin according to the following schedule.

	Sun	Mon	Tue	Wed	Thu	Fri	Sat	Total Weekly Amount
Week 1	5 mg	2.5 mg	5 mg	2.5 mg	5 mg	2.5 mg	2.5 mg	25 mg

LMWH Regimen

Reason for administration: Bridge therapy for chronic anticoagulation **Creatinine Clearance:**

Medication	Desired Intensity	Dose	Frequency	Anticipated duration of therapy
Enoxaparin	Full anticoagulation	80 mg	SubQ, Q12	7 days

Your Next Self Test Date is:

Please return for follow up on: at location.

Current Medications:

Our records indicate you are on the following medications. Please notify us of changes.

Medication	Dose	Units	#	Freq	Route	Start Date	Stop Date
ASPIRIN							
TERBUTALINE SULFATE							

Warfarin Interaction Legend

- Could increase INR. - Could decrease INR. - Could increase or decrease INR. - Clinic has reported interaction.

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b. To report on modes of health system delivery which may be used to optimize the use of currently available anticoagulants.

Optimisation of currently available anticoagulants could have one or more of the following goals:

1. Improve adherence to therapy,
2. Increase time in therapeutic range for patients taking warfarin,
3. Greater patient and clinician satisfaction with the standard of care

Implementation and funding of point of care testing and patient self monitoring under clinical management can contribute to meeting each of these goals.

1. Improved adherence to therapy

Gialamas and colleagues have reported that the use of point of care testing for PT/INR is non-inferior to laboratory testing when evaluating adherence to anticoagulant therapy in an Australian patient population[3]. A contributing factor to medication adherence was the increased patient satisfaction as a result of point of care testing.

2. Increased time in therapeutic range

The paper by Wurster and Doran shows one example of an anticoagulation clinic that improved outcomes and reduced the cost of care through the implementation of point of care testing supported by decision support software[5].

- Time in therapeutic range increased from 34% to 67%
- Complications reduced in number by 90% and decreased in severity
- The cost of administration was approximately 25% of the usual care model
- The program recouped costs within one year of implementation

A decentralized approach, utilizing Decision Support Software (DSS) and point of care testing (POCT) can also involve Patient Self Testing (PST), also known as home INR monitoring. This approach allows a health care system to provide individualized care to each patient (even in geographically isolated areas) while consolidating business and patient support activities as needed to maximize administrative efficiency. Appendix 1 includes a recent study highlighting quality outcomes that can meet or exceed the US standard of care as measured by Time in Therapeutic Range (TTR) and related indicators.

Increased time in therapeutic range and improved health outcomes due to patient self monitoring is also supported by Ansell and Bloomfield[6, 7].

3. Greater patient and clinician satisfaction with the standard of care

The Australian government's Point of Care in General Practice trial showed that point of care testing could increase patient and clinical satisfaction with anticoagulation management[2]. General Practitioners in the intervention group:

- Were more satisfied with point of care testing than the control group
- Strongly agreed that point of care testing would help with disease management
- Strongly disagreed that point of care testing would interrupt patient flow

Patient satisfaction in the trial was reported by Laurence *et al*[8]. Patients in the trial:

- Were more motivated to look after their condition
- Felt that immediate test results was important
- Agreed that point of care testing strengthened their relationship with their GP
- Preferred finger prick to venipuncture for blood collection
- Liked the convenience of point of care testing

Systems to support delivery of point of care and patient self monitoring

An important component of point of care testing and patient self testing is operator training and patient education. The Australian consensus guidelines for warfarin therapy states that regular monitoring and educating patients can minimize bleeding[9]. Training and education can be delivered through a variety of methods. For example Alere offers:

- Clinical Support Specialist and Cert IV Trainer
  - Professional user training
  - Patient self testing training
  - Re-training and advice
- Customer and Technical Support
  - For healthcare professionals and patients
  - Provide operator training, field enquiries and resolve concerns
- Dedicated online training package for professional operators and patient self testing
  - http://www.alere.com/EN_US/products/alere-inratio-2-pt-inr-monitoring-system-poc-test/index.jsp
  - Separate Professional use and Patient Self Testing training
- With the Alere INRatio®2 monitor
  - User Guide and training program on CD ROM
  - Training Video on DVD
  - Quick Reference Guide (text and iconographic)

Additional training and educational resources

- Online patient education resources
  - www.PTINR.com and www.takingbloodthinner.com are patient education websites
  - Provide educational material regarding warfarin, dietary and other drug interactions, lifestyle factors that can effect INR and patient self monitoring
  - Health professionals information regarding continuing education and managing patient self testing
  - These sites are aimed at a USA audience and may be customised for Australia and New Zealand
- Continuing Professional Education
  - Additional training programs for PT/INR testing are available through the Australian Point of Care Practitioners network (www.appn.net)
  - Accreditation and education points available for members of Royal Australian College of General Practitioners (RACGP), Australian College of Rural and Remote Medicine (ACRRM) and Royal College of Nursing, Australia (RCNA)

c. ***To report to what extent optimization of the use of currently available anticoagulant treatments used in patients with atrial fibrillation would improve health outcomes and at what cost.***

A number of peer reviewed articles demonstrate that the use of point of care testing and patient self monitoring can improve health outcomes and reduce overall healthcare costs for patients with atrial fibrillation.

Evidence for improved Health Outcomes

- The review by Ansell shows that patient self monitoring/patient self testing programs can have greater time in therapeutic range for patients taking anticoagulant medications compared to usual care[6].
    - Several studes have shown improvements in quality of life and/or the quality of anticoagulation control as measured by time in therapeutic range or reduction in adverse events
    - Patient self monitoring can lead to significant cost savings and improvement in quality of life due to improved anticoagulation control
- Rose *et al* show the potential cost savings, in a USA setting, for various levels of improvement in time in therapeutic range[1].
    - A 20% increase in TTR could improve outcomes by
        - 14% reduction in Ischemic stroke
        - 29% reduction in major hemorrhages
        - 25% reduction in deaths
        - 23% reduction in total events
        - 2% increase in quality adjusted life years
        - 14% reduction in health care costs in this USA model
- Appendix 1 shows an example where real world point of care testing delivered time in therapeutic range results comparable to the gold standard lab testing used in published randomly controlled trials.
- In 2006-07 there were 45,600 hospitalisations in Australia due to atrial fibrillation[10].
- In 2008-09 PriceWaterhouseCoopers estimated the cost of atrial fibrillation to the Australian healthcare system at $435 Million, 48% of which was attributed to hospital services[10].
    - If a 14% cost reduction, as seen in the USA model, was observed in Australia this would equate to a saving of over $60 million

Australian Point of Care cost considerations

- The cost of a point of care test for PT/INR to general practice is approximately $4.80 to $5.20 per test. An INR monitor costs $600 - $700.
- The current MBS rebate for this test performed in a pathology laboratory, item 65120, is $13.80.
- 3,986,090 services were processed through Medicare in the 2011 financial year.
- Benefits of $46,393,113 were paid for item 65150 in the 2011 financial year.

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d. To examine the future role of newer anticoagulant therapies for atrial fibrillation.

Alere's goals in the arena of anticoagulation therapy are independent of any specific therapeutic modality or agent. We are most interested in optimizing use of each of the new agents as they are released. As an example, Alere are developing decision support modules for dabigatran, rivaroxaban, and apixaban that will allow clinicians to appropriately use these medications along with warfarin and heparin in the same clinical environment. In the USA Alere have a telephonic patient adherence and persistency program for individuals who are on high risk medications, including anticoagulation, to assist with prevention of complications and adherence to the medication prescription regime. Alere is currently developing is similar model for Australia and other countries.

Alere would welcome the opportunity to participate in any future forums on improving the health outcomes for Australian and New Zealand patients with anticoagulation therapy for atrial fibrillation.

Please don't hesitate to contact Alere for more information.

Yours sincerely,

Mr. Mark Volling
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References

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7) Bloomfield HE, Krause A, Greer N, Taylor BC, MacDonald R, Rutks I, Reddy P, Wilt, TJ. Meta-analysis: Effect of Patient Self-testing and Self-managemetn of Long-Term Anticoagulation on Major Clinical Outcomes. *Annals of Internal Medicine* 2011; 154(7); 472-482

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Appendix 1

Real-World Warfarin Patients Self-Testing Within a Comprehensive Support Service Represent a New Standard of Care, Attaining High Quality Anticoagulation Control

Abstract:

Background: Patient self-testing (PST) is a proven warfarin management tool, as demonstrated by randomized controlled trials (RCT), and supported by extensive clinical evidence. However, little is known about PST clinical outcomes outside of research settings. We report results from a retrospective analysis evaluating whether PST delivers high quality (HQ) anticoagulation control (AC) outside RCT.

Methods: We queried the Alere PST database (> 68,000 patients; 3.1 million results) consisting of patients enrolled in a comprehensive PST support service. Patients were referred from a variety of clinical settings, ranging from large organized clinics to small-sized usual care sites. Time in target range (TTR) was the surrogate end-point for outcomes, for comparison to published studies (THINRS RCT and Bloomfield's 22-study meta-analysis). In addition, adherence to weekly testing and frequency of critical values (International Normalized Ratios (INR) <1.5 or >5.0) were considered. We evaluated all patients with at least 9 months of PST between January 1, 2008 and June 30, 2011, excluding the first 3 month initiation period.

Results: Real-world PST (N=29,529) demonstrated a mean TTR of 69.6% (SD 0.33), exceeding TTR of published controlled trials including THINRS and Bloomfield's 22-study meta-analysis (TTR=66.1%). Adherence to weekly testing (83%, or 10/12 tests performed weekly) demonstrated a statistically significant higher mean TTR of 73.9% (SD 0.32; n=4,552) as compared to THINRS (weekly PST 66.2%, n=1,463; chi-square of 208.4, $p<0.001$). Importantly, frequent PST resulted in fewer incidences of critical value INR results: 47% reduction for weekly (2.33%) vs. variable testing frequency (4.61%).

Conclusions: PST within a comprehensive support service represents a new gold standard for HQAC that works for patients referred from any care setting, resulting in higher TTR than observed for PST in major RCTs, and in reduced critical value incidence.

Accepted for presentation at the American College of Cardiology, 61st annual scientific session to be held from March 24-27th 2012.