

***The use of INR
point-of-care
testing in general
practice***

May 2005

MSAC application 1071

Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Executive summary

Clinical problem

The international normalised ratio (INR) is used to monitor patients receiving warfarin therapy. Warfarin is used to prevent and treat thrombosis and embolism. However, the therapeutic range of warfarin is narrow. Therefore, monitoring of INR is conducted to avoid complications from both over- and under-dosage. Over-dosage increases the risk of haemorrhagic events while under-dosage may result in thromboembolic events. Specific indications for warfarin therapy include prophylaxis and treatment of thromboembolic events. Currently, patients monitored in general practice have their INR levels measured in the laboratory. INR point-of-care testing (POCT) has the potential advantage of obtaining an INR result in general practice, thus allowing direct discussion of the result and any indicated change in management at the same time as the INR testing.

The procedure

INR POCT is analysed using portable coagulometers. A drop of whole blood obtained by fingerstick is applied either to a disposable cartridge or a test strip. The cartridge/strip is then introduced into the coagulometer. The sample is mixed with a thromboplastin reagent which stimulates clot formation. Specific operating principles vary between devices. As an example, CoaguChek™ determines the time to clotting by measuring time to cessation of iron particle oscillation. A result is obtained within three minutes for all devices.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the New Zealand Health Technology Assessment (NZHTA) Research Unit, University of Otago was engaged to conduct a systematic review of literature on INR point-of-care testing in the general practice setting. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of INR POCT in general practice

MSAC was approached by Roche Diagnostics Australia Pty Ltd for Medicare funding for INR POCT by general practitioners using CoaguChek S Monitor™ for warfarin monitoring.

The Advisory Panel for this review developed the following research questions:

1. Does the replacement of INR laboratory-based testing with INR point-of-care testing in general practice improve patient outcome in people receiving warfarin?
2. What is the safety of INR point-of-care testing in general practice compared to INR laboratory-based testing in people receiving warfarin therapy?
3. What is the clinical need for INR point-of-care testing in general practice as a diagnostic test?
4. What is the cost-effectiveness of INR point-of-care testing in general practice compared to laboratory testing alone?

Clinical need

Laboratory-based INR testing is claimed under four Medicare codes and these codes are also used for other haematological tests. Expert opinion suggests approximately 90 per cent of the claims under these four codes would be for INR testing. On that basis, there were approximately 3.3 million claims for INR testing during 2003/4. It is estimated that between 2.7 and 3.1 million of these were performed from general practice. The number of claims has increased by approximately 9 per cent annually since 1999/2000.

Comparator

The comparator was selected based on the test used most frequently in current practice in Australia. This is laboratory-based INR testing in Australia.

Reference standard

The reference standard was either:

- A combined clinical endpoint consisting of thromboembolic and haemorrhagic events, or
- Laboratory-based INR result (inside or outside therapeutic range) in conjunction with a combined clinical endpoint, consisting of thromboembolic and haemorrhagic events.

Safety

No studies on the safety of INR POCT were available. The only risks/adverse reactions are those associated with obtaining the capillary sample, such as localised bleeding, bruising or a vaso-vagal episode. There is a risk of needlestick injury when obtaining the sample, which could potentially result in infection with a blood-borne virus to the operator. Advisory Panel opinion is that there are no excess safety concerns with capillary sampling when compared with venepuncture for laboratory-based INR testing.

Effectiveness

Two studies were identified that met the eligibility criteria for the assessment of diagnostic performance of INR POCT in general practice compared with INR laboratory-based testing. One was a randomised cross-over trial (level II evidence) and the other was a case series (level IV evidence). Overall, there was no significant difference in diagnostic performance between POCT and laboratory testing in the two studies. However, in the cross-over trial, at high INR levels, the POCT levels were higher than those obtained using laboratory testing. The key outcome measures were time in the therapeutic range in the cross-over trial and mean INR level in the case series. The cross-over trial was limited by a small sample size, resulting in low study power.

If a diagnostic test is to be effective it needs to be accurate, management needs to change as a result of the test, and that change in management needs to be effective. There was support for change in management in response to abnormal INR levels. When the INR level is low there is an increased risk of thromboembolism and when it is high there is an increased risk of bleeding. Given the use of time in the therapeutic range as an intermediate outcome measure in the cross-over trial, the results can be linked to the risk of haemorrhagic or clinical events. Patient management was changed in this trial according to specific INR levels. However, overall there was little data on the use of INR POCT in general practice, with only two studies identified that fulfilled the eligibility criteria, and there was uncertainty about the diagnostic performance of POCT at high INR levels. The POCT trial currently underway in Australia may help to resolve these uncertainties.

Cost-effectiveness

The economic analysis of INR POCT in general practice as a substitute for INR testing through laboratories in patients receiving warfarin therapy was limited to direct costs, due to the uncertainty surrounding the effectiveness of INR POCT in general practice. It was accepted that INR POCT would lead to an associated general practitioner consultation.

The limited analysis found that the incremental direct cost per test of INR POCT would be \$16.20. This estimate is based on the expert opinion of the MSAC Advisory Panel, which determined that the \$25 fee proposed by the applicant, combined with a short consultation fee and bulk-billing management fees, is likely to represent an accurate reflection of the true direct cost of using INR POCT in general practice on a widespread basis. This would result in an estimated total annual incremental direct cost of approximately \$44 million to the Australian health system, based on 2.7 million tests performed annually. The results of sensitivity analysis suggest that increasing the number of tests performed annually results in significantly higher costs to the Australian health system and to the Commonwealth.

If further studies demonstrate superior effectiveness for INR POCT in general practice, however, there may be potential for a favourable cost-effectiveness ratio when all direct, indirect and flow-on costs are considered.

Recommendation

After consideration of safety, effectiveness and cost-effectiveness, there is insufficient evidence to support the use of INR point-of-care testing in general practice at this stage.

- The Minister for Health and Ageing accepted this recommendation on 4 July 2005 -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of international normalised ratio (INR) point-of-care testing (POCT) in the general practice (GP) surgery. INR is a diagnostic test for the monitoring of people receiving warfarin therapy. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for INR POCT in general practice for people receiving warfarin.

More explicitly, the review addresses the following questions:

1. Does the replacement of INR laboratory-based testing with INR point-of-care testing in general practice improve patient outcome in people receiving warfarin?
2. What is the safety of INR point-of-care testing in general practice compared to INR laboratory-based testing in people receiving warfarin therapy?
3. What is the clinical need for INR point-of-care testing in general practice as a diagnostic test?
4. What is the cost-effectiveness of INR point-of-care testing in general practice compared to laboratory testing alone?

Background

Why do people need INR testing?

The INR is used to monitor patients receiving warfarin therapy. Warfarin is used to prevent and treat thrombosis and embolism. However, the therapeutic range of warfarin is narrow. Therefore, monitoring of INR is conducted to avoid complications from both over and under dosage. Over-dosage increases the risk of haemorrhagic events while under-dosage may result in thromboembolic events.

Specific indications for warfarin therapy include:

1. Patients with mechanical prosthetic heart valves
2. Prophylaxis of venous thrombosis
3. Treatment of venous thrombosis
4. Treatment of pulmonary embolism
5. Prevention of systemic embolism
6. Tissue heart valves (first three months)
7. Acute myocardial infarction (to prevent systemic embolism or recurrence)
8. Valvular heart disease
9. Atrial fibrillation.

INR is a measure developed by the World Health Organisation (WHO) in the early 1980s. It was designed to eliminate problems in oral anticoagulant therapy caused by variability in the sensitivity of different commercial sources and different lots of thromboplastin to blood coagulation factor VII. These variations resulted in variability in prothrombin time measurements. For example, there was wide variation in mean warfarin doses across countries, with a mean dose under 2-mg in Hong Kong compared with over 8-mg in North America (Fitzmaurice et al., 1996). The INR was developed to overcome these discrepancies. It was based on a comparison between the responsiveness of a thromboplastin to that of a reference thromboplastin from WHO. The relative responsiveness was called the international sensitivity index (ISI). The INR is calculated from:

$$\text{INR} = \text{prothrombin ratio}^{\text{ISI}}$$

However, variability still exists, with instrument variability being a particular issue. The INR is used by many laboratories worldwide and is routinely included in dosage planning for patients receiving warfarin. More latterly, INR POCT has developed and there is a growing body of literature on POCT in various settings, including patient self-testing and testing in pharmacy, nursing and general practice.

INR testing in general practice is the focus of this review. In the context of this review POCT is a pathology investigation by or on behalf of the treating medical practitioner on site, at the time of and for use during consultation.

The procedure

The portable coagulometers used in INR POCT require a drop of whole blood obtained by fingerstick, which is applied either to a disposable cartridge or a test strip. The cartridge/strip is then introduced into the coagulometer. The sample is mixed with a thromboplastin reagent, which stimulates clot formation. The sensitivity of the thromboplastin reagent may vary between devices and is reflected in the ISI. Specific operating principles vary between devices. As an example, CoaguChek™ determines the time to clotting by measuring time to cessation of iron particle oscillation. A result is obtained within three minutes for all devices (Douketis, 2001).

Issues in evaluation of INR point-of-care testing in general practice

The application

Various tests exist for INR POCT. This application was for the CoaguChek S Monitor™ but it was determined that any INR point-of-care device would be considered in the review. Specifically, the request was for the addition of INR POCT to the P9 section of the Medicare Benefits Schedule (MBS). The P9 section of the MBS includes tests performed in general practice and does not have any specific accreditation requirements associated with the performance of those tests. Most of the literature cited in the application related to self-management of INR testing rather than testing and management in general practice. The applicant suggested that the performance of INR POCT in general practice would be at least as good as that in the self-management setting. However, this disregards potential differences in the frequency of testing as self management offers the possibility of more frequent testing and therefore, better control.

Intended purpose of INR point-of-care testing in general practice

INR testing through laboratories has been occurring for some time in Australia. Typically, this involves venepuncture at regular intervals with the frequency of testing being determined by stability of INR levels and time since starting warfarin. This review examines INR POCT in general practice as a potential replacement for laboratory-based testing. Such an approach allows INR testing in general practice and direct discussion about the INR level, including the need for any change in management. It may also be advantageous in rural and remote settings as well as in paediatric populations due to improved access in the former group and increased ease of obtaining a sample in the latter group.

Laboratory testing may still be used, for example, to check some abnormal INR levels and as a check of concordance between POCT and laboratory testing after initiating warfarin therapy.

Potential advantages of the test

Potential advantages of INR POCT include:

- Availability of the INR level at the same time as the clinical consultation
- Improved compliance with warfarin as a result of seeing the INR analysis performed in front of the patient and having direct face-to-face guidance about suggested changes to warfarin rather than management changes suggested over the telephone
- Increased convenience for the patient, particularly if living some distance from phlebotomy services
- More appropriate use of warfarin in rural and remote areas that have limited access to laboratories for checking of INR levels
- Overcoming difficulties of frequent venepuncture, which is particularly advantageous in paediatric populations.

However, patients could attend laboratories for a check of INR levels before attending their GP so the INR result could be available at the time of the consultation. It is also unclear how many people have difficulties accessing laboratory services, given the availability of outreach services in Australia.

GP-based point-of-care testing trial in Australia

A POCT trial recently has been commissioned in general practice in Australia. INR testing is included in the trial. However, results will not be available until 2007 at the earliest.

Guidelines for INR point-of-care testing

Guidelines have been released in the UK for haematologic POCT, including coagulation testing. The scope of the guidelines included the principal philosophy for POCT, management issues, training needs, equipment standards, safety aspects, protocols for documentation of results, quality control and accreditation issues (Near Patient Testing Working Party, 1995).

The general philosophy expressed in the guideline is that POCT sites should work in conjunction with the central laboratory. Training protocols must be established and ongoing training needs should be addressed. An appropriate body should have evaluated the equipment selected. Protocols should be developed for safety aspects. There should be appropriate internal and external quality control assessment. Specific operational evaluation criteria are also documented in the guideline.

Clinical need/burden of disease

Laboratory-based INR testing is claimed under four Medicare codes: 65120, 65123, 65126 and 65129. Medicare code 65120 specifies: “Prothrombin time (including INR where appropriate), activated partial thromboplastin time, thrombin time (including test for the presence of heparin), test for factor XIII deficiency (qualitative), Echis test, Stypven test, reptilase time, fibrinogen, or one of fibrinogen degradation products, fibrin monomer or D-dimer – 1 test”. Items 65123, 65126 and 65129 are used for two tests, three tests and four tests described in item 65120 respectively. Expert opinion suggests 90 per cent of the claims under these codes would be for INR testing. The total number of claims for codes 65120, 65123, 65126 and 65129, by year, is shown in Figure 1.

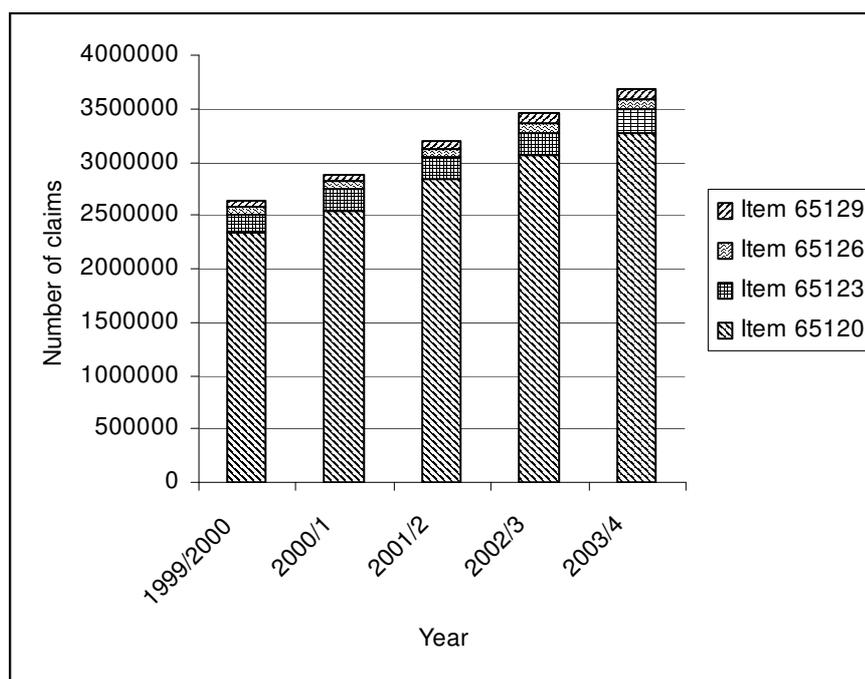


Figure 1 Number of claims for Medicare items 65120, 65123, 65126 and 65129 by year

Approximately 3.7 million claims were made in the 2003/4 time period under these codes. If 90 per cent of these claims represent INR testing, it suggests that approximately 3.3 million laboratory-based INR tests were performed during 2003/4. These claims are derived from both inpatient and outpatient sources. Based on total tests and benefits claimed in 2003/4, and using the different levels of benefit paid for inpatient and outpatient claims, it appears that approximately 99 per cent of the claims were for tests conducted in the non-hospital inpatient setting. The Advisory Panel suggested that between 85 and 95 per cent of the non-inpatient related INR tests were conducted in the general practice setting. Therefore, it is estimated that between 2.7 and 3.1 million laboratory INR tests were performed from the general practice setting during 2003/4. The number of tests being claimed increased by approximately nine per cent per year between 1999/2000 and 2003/4.

It is expected that some laboratory testing would continue if INR POCT was to be adopted in the GP surgery. However, it is unclear if there would be a change in the frequency of testing if INR POCT was adopted. If there is any change in frequency, it is likely to be an increase in testing frequency.

Relationship between INR level and event rates

Thromboembolic and haemorrhagic event rates are of primary interest in people receiving warfarin therapy. However, these outcomes are relatively uncommon. Therefore, studies using these event rates as the primary outcome measure need to be much larger than studies using INR levels as the primary outcome measure.

The proportion of INR values within the therapeutic range and the time in the therapeutic range (TTR) are potential surrogate measures for clinical event rates. The proportion of tests in the therapeutic range is biased because of the tendency for repeat testing in patients with a test outside the therapeutic range. This bias increases as the interval between tests increases.

The TTR is estimated by interpolating between observed test values in order to extrapolate data points on a daily basis, then defining the number of patient-days of follow-up that were within the therapeutic range divided by the total number of patient-days follow-up. Deficiencies of this process are:

- it is dependent on the width of the therapeutic range
- it does not differentiate between small and large departures from the therapeutic range.

Nevertheless, TTR is less biased than the proportion of in-range tests and also provides more information than the proportion measure (Samsa and Matchar, 2000).

TTR would be a useful surrogate measure, provided there is a strong association between TTR and clinical event rates. Such an association has been observed across a range of studies (Azar et al., 1996, Cannegieter et al., 1995, Chiquette et al., 1998, Connolly et al., 1991, European Atrial Fibrillation Trial Study Group, 1995, Palareti et al., 1996, Stroke Prevention in Atrial Fibrillation Investigators, 1996). As an example, Figure 2 shows the relationship between INR level and thromboembolic and haemorrhagic event rates in the study by Cannegieter et al, (1995).

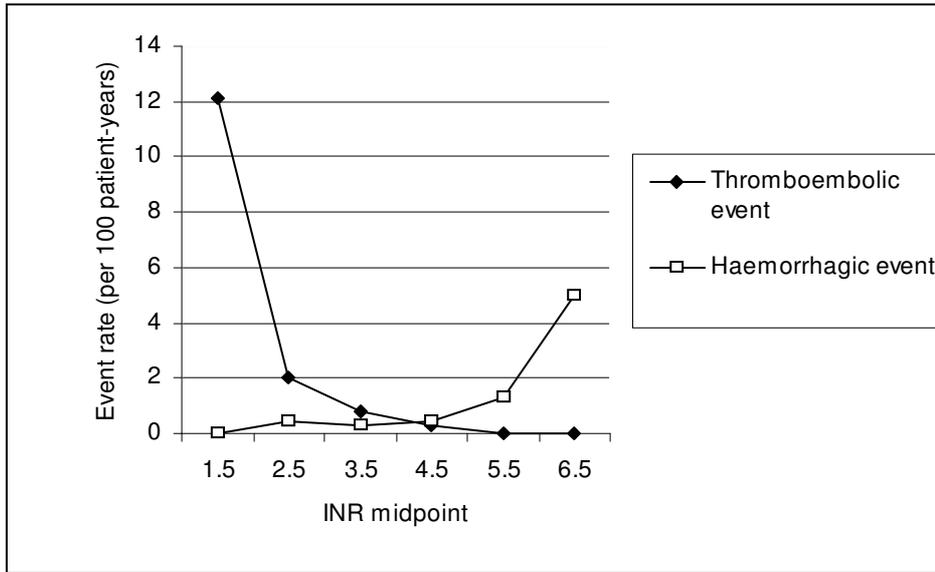


Figure 2 Relationship between INR level and clinical event rate

The need for a change in management when INR levels are outside the therapeutic range is illustrated in Figure 2. When the INR level is low, there is an increased risk of thromboembolic events, so an increase in the warfarin dose is indicated. When the INR level is high, there is an increased risk of haemorrhagic events. Therefore, at least a temporary reduction in the dose of warfarin is indicated. When the INR level is greater than 5.0, the risk of bleeding increases substantially. In cases with evidence of severe bleeding, intensive resuscitation may be needed. Intravenous fluids, controlling the source of bleeding, and fresh frozen plasma or vitamin K would be considered under those circumstances.

The therapeutic range varies by indication. The INR range for indications that are associated with a higher risk of thromboembolic events is typically 2.5 to 3.5. In “standard risk” indications the aim is to achieve INR levels in the range of 2.0 to 3.0. The main indication for the higher INR range is a mechanical prosthetic heart valve. However, alternative therapeutic ranges have been used in some centres. For example, some groups describe a therapeutic range of 3.0 to 4.5 (Daly et al., 2003, Fitzmaurice et al., 1998).

Factors associated with variation in INR level

Co-morbid conditions such as liver failure and congestive heart failure are associated with variation in INR level. A wide range of drugs is associated with variation in INR level. Examples are shown in Table 1. Age is also thought to be a determinant of INR variation. The dose of warfarin required to maintain a given INR level is lower in older than younger patients (Blann et al., 2003) although it is unclear if this association is due to co-morbid conditions alone (Ansell, 2003).

Table 1 Drug interactions with warfarin

Effect	Drug
Increased anticoagulation	Alcohol, allopurinol, analgesics (eg paracetamol), antidepressants (eg, selective serotonin re-uptake inhibitors), antidiabetics, antiplatelets, influenza vaccination, leukotriene antagonists, lipid regulating agents
Decreased anticoagulation	Oral contraceptives, retinoids, vitamin K
Variable effect	Antibiotics, antiepileptics, antifungals, cytotoxics.

Co-morbid conditions associated with an increased risk of bleeding in association with anticoagulation include (Ansell, 2003):

- history of bleeding, especially gastrointestinal bleeding
- history of stroke
- renal insufficiency
- anaemia
- hypertension
- cancer
- recent myocardial infarction.

Management of non-therapeutic INR levels

Approaches to managing high INR levels include stopping warfarin therapy, reducing the dose of warfarin or providing vitamin K₁, fresh frozen plasma or prothrombin concentrate. White et al (1995) estimated it took 65 hours for INR levels to drop from 2.6 to 1.6 after stopping warfarin. After vitamin K₁ the INR levels declined substantially within 24 hours. However, care must be taken as resistance to warfarin may occur for up to a week if the dose of vitamin K₁ is too high (Shetty et al., 1992). Weibert et al. (1997) evaluated the effectiveness of 2.5-mg of vitamin K₁ in 81 patients with an INR greater than 5.0. An INR less than 5.0 was achieved in 48 hours in 19 of 20 (95 per cent) patients with an initial INR less than 9.0 but the trial did not achieve this reduction in one of four (25 per cent) whose initial INR was greater than 9.0. In another study, patients with an INR level between 4.5 and 10.0 had the next dose of warfarin withheld and were given a 1-mg dose of vitamin K₁ (Crowther et al., 1998). After 16 hours, the INR level was lowered in 59 patients (95 per cent). No patients developed resistance to warfarin. The effect of vitamin K₁ on high INR levels has also been studied in Canada (Lewis and Wells, 2003). In episodes that were treated with 2.5 mg of vitamin K₁ in response to an INR level over 5.0, the mean INR fell from 6.8 (range 5.1 to 8.6) to 2.9 (range 1.4 to 5.9) 12 to 18 hours after taking vitamin K₁. In the six episodes where 5-mg of vitamin K₁ was taken in response to an INR level greater than 9.0, the mean INR fell from 11.3 (range 9.5 to 13.8) to 2.5 (range 1.8 to 3.9) 12 to 18 hours after taking vitamin K₁.

Lower INR level has been associated with a reduction in the risk of bleeding in at least four randomised controlled trials that compared high intensity with low intensity anticoagulant therapy (Altman et al., 1991, Hull et al., 1982, Saour et al., 1990, Turpie et al., 1988). These studies demonstrated a reduction in bleeding events when the INR was reduced from the 3.0-4.5 range to the 2.0-3.0 range.

The Australasian Society of Thrombosis and Haemostasis recently released a position statement that included guidelines for the management of an elevated INR. These are detailed in Table 2 (Baker et al., 2004).

Table 2 Guidelines for the management of an elevated INR released by the Australasian Society of Thrombosis and Haemostasis

Clinical setting	Action
INR higher than the therapeutic range but < 5.0; bleeding absent	<ul style="list-style-type: none"> - Lower the dose or omit the next dose of warfarin. Resume therapy at a lower dose when the INR approaches therapeutic range. - If the INR is only minimally above the therapeutic range (up to 10 per cent), dose reduction may not be necessary
INR 5.0-9.0; bleeding absent	<ul style="list-style-type: none"> - Cease warfarin therapy; consider reasons for elevated INR and patient-specific factors - If bleeding risk is high, give vitamin K₁ (1.0-2.0mg orally or 0.5-1.0mg intravenously) - Measure INR within 24 hours, resume warfarin at a reduced dose once INR is in therapeutic range.
INR > 9.0; bleeding absent	<ul style="list-style-type: none"> - Where there is a low risk of bleeding¹, cease warfarin therapy, give 2.5-5.0mg vitamin K₁ orally or 1.0mg intravenously. Measure INR in 6-12 hours, resume warfarin therapy at a reduced dose once INR<5.0 - Where there is high risk of bleeding, cease warfarin therapy, give 1.0mg vitamin K₁ intravenously. Consider Prothrombinex-HT (25-50 IU/kg) and fresh frozen plasma (150-300mL), measure INR in 6-12 hours, resume warfarin therapy at a reduced dose once INR<5.0.
Clinically significant bleeding where warfarin induced coagulopathy is considered a contributing factor	<ul style="list-style-type: none"> - Cease warfarin therapy, give 5.0-10.0mg vitamin K₁ intravenously, as well as Prothrombinex-HT (25-50 IU/kg) and fresh frozen plasma (150-300mL), assess patient continuously until INR<5.0, and bleeding stops². OR - If fresh frozen plasma is unavailable, cease warfarin therapy, give 5.0-10.0mg vitamin K₁ intravenously, and Prothrombinex-HT (25-50 IU/kg), assess patient continuously until INR<5.0, and bleeding stops². OR - If Prothrombinex-HT is unavailable, cease warfarin therapy, give 5.0-10.0mg vitamin K₁ intravenously, and 10-15 mL/kg of fresh frozen plasma, assess patient continuously until INR<5.0, and bleeding stops².

¹ Examples of patients in whom the bleeding risk would be expected to be high include those with active gastrointestinal disorders (such as peptic ulcer or inflammatory bowel disease), those receiving concomitant antiplatelet therapy, those who underwent a major surgical procedure within the preceding two weeks, and those with a low platelet count.

² In all situations carefully reassess the need for ongoing warfarin therapy.

Existing procedures

INR testing is currently included under MBS items 65120, 65123, 65126 and 65129. MBS item 65120 is the key code and covers “Prothrombin time (including INR where appropriate), activated partial thromboplastin time, thrombin time (including test for the presence of heparin), test for factor XIII deficiency (qualitative), Echis test, Stypven test, reptilase time, fibrinogen, or 1 of fibrinogen degradation products, fibrin monomer or D-dimer - 1 test”.

The remaining codes apply when two, three and four of the above tests are claimed. These codes are included in the Group P1 section of category six tests on the MBS. The tests must be conducted by or on behalf of an approved pathology practitioner in an accredited pathology laboratory. The proprietor of the laboratory where the test is performed must be an approved pathology authority.

Comparator

The comparator was selected based on the test used most frequently in current practice in Australia. This is laboratory-based INR testing in Australia.

Reference standard

The reference standard was either:

- A combined clinical endpoint, consisting of thromboembolic and haemorrhagic events, or
- Laboratory-based INR result (inside or outside therapeutic range), in conjunction with a combined clinical endpoint, consisting of thromboembolic and haemorrhagic events.

Accreditation

The Health Insurance Commission (HIC) administers the Australian pathology laboratory accreditation. In this function, HIC considers assessments performed by the National Association of Testing Authorities (NATA) and the Royal College of Pathologists of Australasia (RCPA), which assess compliance against standards developed by the National Pathology Accreditation Advisory Council (NPAAC), in determining accreditation status. Laboratories that are non-compliant can lose eligibility for Medicare benefits and are required to be accredited for eligibility to Medicare benefits, as set out in Section 16A(2) of the Health Insurance Act 1973. All laboratories are required to participate in external quality assurance programs (Commonwealth Department of Health & Ageing, 2002).

Under the Health Insurance Act, general practitioners are able to perform three categories of tests:

1. Basic tests with no regulatory requirements other than good clinical practice and for which there are no Medicare rebates. Glucose testing by glucometer is an example of this.
2. Relatively simple tests that are Medicare rebated in the P9 group of tests. These tests are available to all GPs without any approval process.
3. More complex tests that are available to GPs who have been accredited as a category M laboratory. These require participation in a quality assurance program.

In summary, INR laboratory-based testing will only draw a Medicare rebate if performed in an accredited laboratory. In contrast, an INR POCT, if included in the P9 group of tests on the MBS, would not require any approval process or ongoing quality assurance checks, other than medical registration of the GP performing the test. However, it should be noted that an external quality assurance program (QAP) has been established between Roche Diagnostics Australia and the RCPA-QAP Haematology Program for INR POCT.

Marketing status of the device

The Coaguchek S Monitor™ is currently listed on the Australian register of therapeutic goods. Before listing, sponsors are required to submit to the Therapeutic Goods Administration for assessment, information such as labelling, product literature and, for certain categories, evidence of quality systems compliance and test certificates.

Current reimbursement arrangement

Under current arrangements, a general practitioner would need to apply to become an Approved Pathology Practitioner, an Approved Pathology Authority and an Accredited Pathology Laboratory (Category M: Medical Practice) for INR POCT in general practice. Category M is allocated to laboratories that provide a specified range of tests for the patients of the medical practice at which the laboratory is situated. Once accredited, it would be possible to obtain reimbursement for INR point-of-care testing. A Category M laboratory is not able to provide tests on patients referred from other medical practices or other medical practitioners, other than those medical practitioners of the medical practice at which the laboratory is sited.

Laboratory-based INR testing is reimbursed under item number 65120 in the Medicare Benefits Schedule. The MBS fee is \$14.05.

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies and reviews for the period between 1966 and 2004. Searches were conducted using the databases shown in Table 3. Searches were not limited by language or date. Searching commenced in August 2004 and was updated in the first week of October 2004.

An Internet search of health technology assessment agency websites, clinical trials registers and selected relevant professional societies was undertaken. These are listed in Appendix C. No health technology assessments were identified.

Table 3 Electronic databases used in the search strategy

Primary databases	Period covered
Medline	1966-2004 October
Embase	1988-2004 October
Cochrane Controlled Trials Register	Up to 3rd Quarter 2004
Current Contents	1997-2004 October
Science Citation Index	1987-2004 October
Secondary databases	
Cochrane Database of Systematic Reviews	Up to 3rd Quarter 2004
Evidence-based reviews (<i>Evidence-based Medicine/ACP Journal Club</i>)	Up to August 2004
University of York databases (DARE, NHS EED, HTA)	Up to October 2004

Other sources included:

- Websites of relevant professional associations and research centres (see Appendix C)
- Websites and publications of HTA organisations (see Appendix C)
- Reference lists of retrieved papers

The Medline search strategy used to identify relevant papers is further outlined in Appendix D. This search was adapted for the other bibliographic databases. A simple search using major keywords only was used for the additional sources.

Eligibility criteria

The *a priori* criteria shown in Table 4 were developed to identify relevant literature for the review of diagnostic performance.

Table 4 Selection criteria for identification of effectiveness studies

Characteristic	Criteria
Inclusion criteria	
Publication type	Any clinical studies using human specimens that have tested the point-of-care sample at the time of sampling.
Patients	Patients receiving warfarin for one of the indications listed in the study scope.
Sample size	At least 15 human patients received INR point-of-care testing. If comparing POCT with laboratory-based INR testing, then at least 15 human patients received both POCT and laboratory-based testing.
Sample	Capillary blood used for INR point-of-care testing
Intervention/test	INR point-of-care testing conducted in the general practice setting
Comparator	Sampling for INR laboratory-based testing occurred within six hours of sampling for INR point-of-care testing in the studies included
Outcome	Outcomes identified in above sections will be included
Language	English language articles will be preferentially included. Any key foreign language articles will be included. ¹
Exclusion criteria	
Publication type	Non-systematic reviews, letters, editorials, expert opinion articles, conference proceedings, comments and articles published in abstract form.
Study setting	Studies involving point-of-care testing among hospital inpatients, hospital outpatients, pharmacy settings and self-management will be excluded unless results for patients tested in general practice can be clearly identified.

Two independent researchers selected the studies for inclusion in the review of diagnostic performance using a six phase process (see Figure 3).

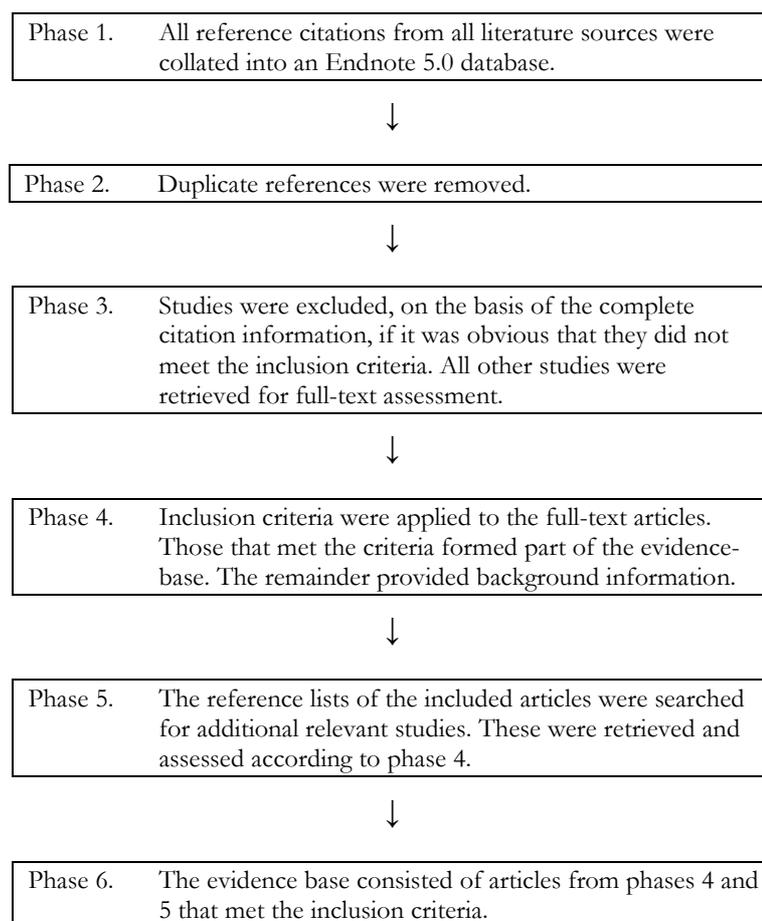


Figure 3 Six-phase study selection process

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (National Health and Medical Research Council, 2000).

These dimensions (Table 5) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

A quality review was undertaken to further assess the potential for bias in the results of the reviewed studies. The STEP protocol was adapted to help assess study quality (see Appendix E for the STEP tool).

The following additional questions were added to the appraisal of these diagnostic performance studies:

1. Was consecutive sampling used?
2. Have Bland-Altman curves been used to compare the point-of-care and laboratory-based measurements?
3. Has bias and imprecision been considered in the study measurements?

Table 5 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The <i>p</i> -value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the “null” value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 6

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 6.

Table 6 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from (National Health and Medical Research Council, 1999).

Additionally, a system for ranking all diagnostic studies was used in this review. This system is shown in Table 7.

Table 7 Grading system for the appraisal of diagnostic performance studies

Validity criteria	Description	Grading system
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy versus the comparator test strategy?	C1 direct comparison CX other comparison
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?	P1 applicable P2 limited P3 different population
Quality of study	Was the study designed to avoid bias? High quality = no potential for bias based on predefined key criteria Medium quality = some potential for bias in areas other than those pre-specified as key criteria Poor quality = potential for bias based on key pre-specified criteria	Q1 high quality Q2 medium quality Q3 poor quality or insufficient information

Classification of the applicable population criterion was based on the following *a priori* criteria:

- P1 Both representative subjects and setting
- P2 One of representative subjects and setting
- P3 Neither criterion satisfied.

In the context of this review the *a priori* criteria listed in Table 8 were determined to be the most discriminating and were used to compare the quality of the selected studies.

Table 8 Criteria and score assignment used to rank quality of selected studies

Level of Evidence	Criteria
I	Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard.
II	Independent, blind or objective comparison but in a set of non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard.
III	Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients.
IV	Any of: Reference standard was not applied blinded or not applied independently. No reference test applied (case series)

The quality of the study was scored using the level of evidence system outlined in Table 8. Using the system indicated, studies were classified as excellent quality if they fulfilled the criteria for level of evidence I, medium quality if level of evidence II or III and poor quality or insufficient information if level of evidence IV.

Assessment of test effectiveness

Three factors are considered necessary to determine the effectiveness of a diagnostic test:

- Accuracy of the test, ie, the diagnostic performance;
- Change in patient management as a consequence of the diagnostic test result;
- Effectiveness of the change in patient management.

Diagnostic test performance

In the context of this review, diagnostic performance represents the accuracy of test measurements. Usually it is examined by estimating the validity (sensitivity, specificity and positive and negative likelihood ratios) and reliability of the test. Alternative measures are appropriate in tests producing continuous, quantitative data.

Change in patient management

A test has therapeutic impact if the treatment decision is changed – ie, new therapy is added or the need for therapy is averted, or therapy may be modified as a result of the information provided by the test.

Patient health outcomes

The ultimate goal of diagnostic testing is to contribute to improvement in the health of patients. If a diagnostic test is to be beneficial, the diagnostic test performance needs to be satisfactory, the diagnostic test results should have an impact on therapy, and the therapy should be effective.

Diagnostic performance

The accuracy of a diagnostic test is primarily determined by its ability to identify the target disorder compared with the recognised reference test. Such performance is particularly relevant when the test under investigation and the reference standard are categorical variables or are normally converted into a categorical result (eg presence or absence of disease). When categorical data are used, measures of effect such as sensitivity, specificity, and positive and negative likelihood ratios can be calculated.

However, INR measurements produce continuous, quantitative data. Categorisation of these data results in some loss of information, although categorisation occurs when interpreting the need for a change in therapy. Specifically, a given INR level is determined to be within or outside the therapeutic range and management decisions are made that are determined substantially by how the INR level is categorised.

If available, the following data were extracted from the studies appraised to estimate the effectiveness of INR point-of-care testing in general practice:

- Proportion of tests in the therapeutic range
- Time in the therapeutic range
- Proportion of thromboembolic events
- Proportion of haemorrhagic events
- Mean INR level
- Measures of bias (including Bland-Altman curves)
- Measures of imprecision of the diagnostic test
- Measures of agreement between different testing strategies
- Frequency of testing
- Quality of life measures
- Measures of general treatment satisfaction
- Measures of patient satisfaction including satisfied to continue with current strategy
- Loss to follow up
- Compliance with recommended warfarin dose
- Dose changes made per unit time
- Percentage dose changes made per total tests performed.

When possible, the statistical significance of any differences in the above measures between INR POCT and laboratory testing was assessed.

Proportion of tests in the therapeutic range is estimated from the number of tests in the appropriate therapeutic range divided by the total number of tests. The appropriate therapeutic range may vary between patients but should be pre-specified for each patient.

Estimating the time in the therapeutic range requires interpolation between observed test values to extrapolate data points on a daily basis, then defining the number of patient-days of follow-up that were within the therapeutic range divided by the total number of patient-days follow-up.

Thromboembolic and haemorrhagic events were defined as stipulated in the individual studies selected for appraisal. The proportion of thromboembolic or haemorrhagic events was estimated using the total number of patients monitored, provided sufficient information was supplied in the selected papers.

Bland-Altman curves are plots of the difference between the index test and the comparator test on the y-axis and the average test result on the x-axis. The mean difference between methods represents systematic bias and the variation around the difference represents random fluctuation and is a measure of imprecision. The degree of bias may vary with differing levels of the index test. For example, the results shown in Figure 4 represent a positive bias in the INR POCT since the difference between INR POCT and laboratory results becomes greater as the average INR level increases. These results are used to illustrate the point; they do not represent any actual results identified in the course of this review.

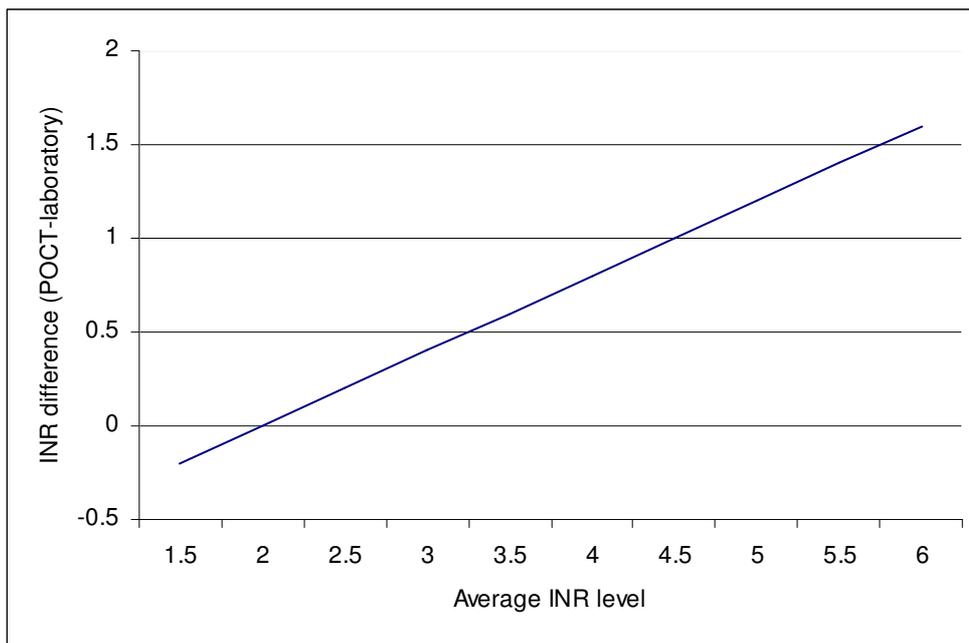


Figure 4 Illustrative Bland-Altman curve demonstrating positive bias in the index test

The other measures of effect listed were extracted and reported if the necessary information was supplied in the articles selected for appraisal.

If sufficient data had been included in the selected studies, sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios would have been estimated. However, this information was not provided in the selected studies so these measures of effect are not presented in the report. The use of these categorical measures would have resulted in loss of information resulting from the measurement of a continuous variable (INR level) so the measures of effectiveness presented in the individual papers were more appropriate than the use of categorical measurements.

Patient management and its effectiveness

The effectiveness of patient management, including the incidence of thromboembolic and haemorrhagic events was considered for different INR levels.

Expert advice

An Advisory Panel with expertise in INR POCT was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for Advisory Panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Research questions

The research questions for this assessment were:

1. Does the replacement of INR laboratory-based testing with INR point-of-care testing in general practice improve patient outcome in people receiving warfarin?
2. What is the safety of INR point-of-care testing in general practice compared to INR laboratory-based testing in people receiving warfarin therapy?
3. What is the clinical need for INR point-of-care testing in general practice as a diagnostic test?
4. What is the cost-effectiveness of INR point-of-care testing in general practice compared with laboratory testing alone?

Is it safe?

No studies on the safety of INR POCT were available. The only risks/adverse reactions are those associated with obtaining the capillary sample, such as localised bleeding, bruising or a vaso-vagal episode. There is a risk of needlestick injury when obtaining the sample, which could potentially result in infection with a blood-borne virus to the operator. Advisory Panel opinion is that there are no excess safety concerns with capillary sampling when compared with venepuncture for laboratory-based INR testing.

Is it effective?

Potential advantages of INR POCT compared with laboratory testing

Potential advantages of INR POCT include:

- Availability of the INR level at the same time as the clinical consultation
- Improved compliance with warfarin as a result of seeing the INR analysis performed in front of the patient and having direct face-to-face guidance about suggested changes to warfarin therapy, rather than management changes suggested over the telephone
- If INR levels are high, and especially if a haemorrhagic event is occurring, the immediate availability of INR testing may result in more appropriate management of the event.
- Increased convenience for the patient, particularly if living some distance from phlebotomy services

- More appropriate use of warfarin in rural and remote areas that have limited access to laboratories for checking of INR levels
- Overcoming difficulties of frequent venepuncture, which is particularly advantageous in paediatric populations.

Evidence to support these potential advantages was not identified. Availability of the INR level at the clinical consultation may improve compliance. It may also result in the possibility of more appropriate early action for the treatment of haemorrhagic events. However, the Advisory Panel felt that few GPs, particularly in the urban setting, in Australia would carry vitamin K for the immediate treatment of a haemorrhagic event related to high INR levels. The Advisory Panel also noted the potential role of POCT in rural and remote settings, given the potential time delays from these settings. One study identified (Daly et al., 2003) was conducted in nine practices that were between 15 and 120 miles from the nearest regional hospital. This study is described in fuller detail in Table 10, p.26. The proportion of POCT results in the therapeutic range was only 48 per cent in this study.

Papers selected for assessment of diagnostic performance

Articles that did not meet the selection criteria were excluded during an initial assessment of the abstracts. Ambiguous or unclear citations were included in the next assessment stage of examination in full text. Two reviewers independently examined each citation for inclusion. Discrepancies in selection were resolved by discussion and by re-examination of the relevant studies. A third reviewer was available in case of unresolved differences but third party arbitration was not needed. Only studies that successfully passed this process were included in this review.

The search strategies detailed in Appendix D, along with additional papers supplied by the applicant, resulted in the scanning of 645 references in the course of the search and the retrieval of 44 papers in full text. Two articles were identified that met the eligibility criteria for the review and these articles were critically appraised. Details of the selection process are shown in Figure 5.

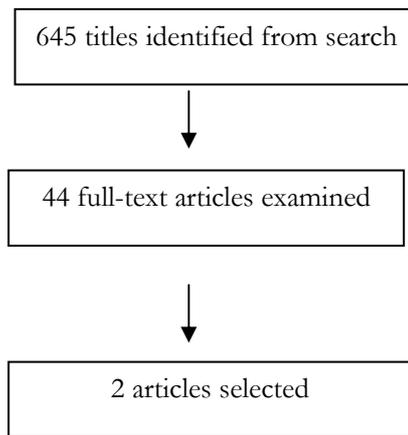


Figure 5 Study selection process for ESAT-6/CFP-10 papers

On the basis of their abstracts, articles were excluded from this initial literature database if they were duplicates, did not address the review question, or clearly did not meet the inclusion criteria. The reasons for exclusion of studies identified from the search are detailed in Table 9.

Table 9 Reasons for exclusion of studies of INR POCT diagnostic performance

Reason for exclusion	Number
Not GP setting	133 ¹
Not INR testing	311
Non-capillary sample	15
Not a relevant outcome	55
Non-human sample	4
Non-English language article	11
Inappropriate publication type	100
Results not interpretable for review questions	7
Sample size <15	2
Total	637

¹ Including six late papers supplied by the applicant

One of the two studies that were critically appraised used a randomised cross-over design (Level II evidence) and the other study was a case series (level IV evidence). The cross-over trial was classified as having an appropriate comparison but the population used had limited applicability (Shiach et al., 2002). Specific limitations of this study included uncertainty concerning the following quality factors:

- Use of an intermediate outcome measure instead of the combined clinical endpoint (thromboembolic and haemorrhagic events)
- whether the POCT was measured independently from clinical information.

The POCT and reference tests were measured independently of each other, and within four hours of each other.

The case series was classified as having an appropriate comparison but the population used had limited applicability using the *a priori* quality criteria set for this review (Daly et al., 2003). Specific limitations of this study included uncertainty concerning the following quality factors:

- demographic details of the study population resulting in uncertainty about the spectrum of patients
- use of an intermediate outcome measure instead of the combined clinical endpoint (thromboembolic and haemorrhagic events)
- whether the POCT was measured independently from clinical information.

The therapeutic range used in the study was broader than would typically be applied in the Australian setting.

The POCT and reference tests were measured independently of each other, and within four hours of each other. The design used was less robust in this study than the cross-over trial and a wider therapeutic range was used in this study than the cross-over trial, resulting in an increased likelihood of being in the therapeutic range than was the case in the cross-over trial.

Characteristics of the studies included are shown in Appendix F.

Studies of diagnostic performance of INR POCT in general practice

Two studies were identified that met the *a priori* eligibility criteria for this review. These studies are summarised in Table 10. In the cross-over trial there was no significant difference in the time in the therapeutic range between POCT and laboratory testing (Shiach et al., 2002). However, the difference between POCT and laboratory measurements increased as the average INR level increased, suggesting more uncertainty in the POCT estimate at higher INR levels. The cross-over design should control potential confounding. Specifically, participants were randomised to have their initial dosage based on the POCT result (group 1) versus having it based on the laboratory result (group 2). After six months, this order was reversed. During the first six months, group 1 participants had a laboratory result determined for comparison purposes and during the second six months the POCT result was determined for comparison purposes only. This order was reversed for group 2 participants. Limitations of the study are documented in Table 10. More significant issues included some vagueness in the eligibility criteria, arbitrary classification of what constitutes clinically relevant agreement and 15 per cent were withdrawn due to difficulties with venous access (9 per cent) or an insufficient number of tests taken (7 per cent).

In the prospective case series there was no significant difference in the mean INR level between the POCT and laboratory testing strategies (Daly et al., 2003). There were four minor haemorrhagic events in the POCT group. There were a number of limitations to this study (see Table 10).

Some of the more significant issues included:

- the use of more frequent laboratory testing than POCT testing
- high frequency of laboratory testing given the eligibility criteria would tend to select patients with more stable INR levels
- selection of study participants was left to the discretion of the individual practices
- only nine of 16 practices participated.

Table 10 Evidence table of studies selected for effectiveness component of INR POCT review

Reference	Sample characteristics	Grade ¹	Results	Comments
Study location (Shiach et al., 2002) United Kingdom	Prospective randomised cross-over trial comparing POCT with laboratory testing in a "community clinic" Warfarin indication unclear Target therapeutic range: 2.0-3.0, 2.5-3.5, 3.0-4.0 46 participants mean age: 65 years, age range 41-80 years 60% male. Receiving warfarin before enrolment in this study CoaguChek™ monitor used	NHMRC II C1 Q2 P2	TTR Period 1: 60.9% versus 59.3% (POCT v lab) Period 2: 64.3% versus 63.4% (POCT v lab) P=0.2 No significant difference in clinically relevant agreement Bland-Altman curve: evidence of positive bias (INR difference increased as average INR increased) Mean relative deviation less satisfactory when INR>4.0	<ul style="list-style-type: none"> • POCT and lab samples taken within four hours of each other • Limited description of procedures followed for POCT and lab testing although the study sites were requested to follow manufacturers' instructions in the testing procedures • Some vagueness in eligibility criteria: "had to live within reasonable travelling distance of the clinic" • No baseline comparison between the two groups • 85% follow up (withdrawals due to difficulty with venous access or insufficient number of tests) • Some arbitrary classification of results thus subject to measurement error • POCT performed less frequently than lab testing in period 2 – underestimating performance of POCT • Proportion agreeing to participate was not stated • Low study power

Table 10 Evidence table of studies selected for effectiveness component of INR POCT review (continued)

Reference Study location	Sample characteristics	Grade	Results	Comments
(Daly et al., 2003) Ireland	Prospective case series n=122 Warfarin for prosthetic heart valve, venous thrombosis, pulmonary embolism or atrial fibrillation Target therapeutic range unclear At least 93 had previously been monitored when enrolled in study Coaguchek MD™ monitor used for POCT (Roche Diagnostics) Organon Technika MDA 180™ used for laboratory testing	NHMRC IV C1 Q2 P2	POCT v lab testing Mean INR: 2.34 v 2.40 (p=0.53) Regression of mean of paired results on their difference r=0.00 (95% CI -0.38 to +0.38) POCT Haemorrhagic events: four minor 48% of tests in desired therapeutic range POCT frequency of testing: Mean 5.7 tests/patient (8 mths follow up) Range per practice: 1.3-9.0 tests/patient Laboratory frequency of testing (for verification of POCT): Mean 1.5 tests/patient (8 mths follow up)	<ul style="list-style-type: none"> • Each participating practice between 15 and 120 miles from the regional hospital • Blinding was used • Time between sampling for POCT and lab testing unclear • Unclear if spectrum of patients was appropriate • Limited description of procedures followed for POCT and lab testing although the study sites were requested to follow manufacturers' instructions in the testing procedures • POCT was independent of the reference standard • 185 of 692 (27 per cent) POCT verified by laboratory testing • Variation in mean tests/patient suggests patients effectively withdrew from the study and testing rate was particularly low in some practices • Inclusion left to the discretion of the practice • Unclear if GP or nurse ran the service (left to the discretion of each practice) • One sample/week was forwarded to the lab – this is more frequent than normal for stable patients • Nine of 16 practices participated • 7 per cent had a desired therapeutic range of 3.0-4.5 • Limited comparisons between POCT and lab testing • Patients considered more stable were more likely to be included in the study

¹ C1: Direct comparison; Q2: Medium quality; P2 population – limited applicability

Summary of results

Two studies were identified that met the eligibility criteria for this review. The best study used a cross-over design. There was no significant difference in the time in the therapeutic range between POCT and laboratory testing in this study. However, at higher INR levels, INR POCT read higher than INR laboratory testing. There was no significant difference in the mean INR level between POCT and laboratory testing in the

other study. Potential sources of bias existed in both studies and there was little research examining the use of INR POCT in general practice.

Conclusions on testing with INR POCT in general practice

Two studies were identified that met the *a priori* eligibility criteria for the assessment of diagnostic performance. The best study used a cross-over design and found no statistically significant difference in the time in the therapeutic range between the POCT arm and the laboratory testing arm. At higher INR levels POCT levels were higher than those obtained using laboratory testing in this study, casting some doubt on the accuracy of POCT at high INR levels. The lack of a statistically significant difference in the time in the therapeutic range may have been due to low study power given the small sample size of this study. The other study was a case series and there was no significant difference in the mean INR level using POCT and laboratory testing. The latter study was conducted in a rural setting but there was insufficient data to conclude there were any particular advantages for POCT compared with laboratory testing in a rural setting.

If a diagnostic test is to have an impact on health outcome it needs to be accurate, produce a change in management when appropriate and the change in management needs to be effective. INR testing is performed to check that the level of anticoagulation is appropriate to reduce the risk of thromboembolism and avoid haemorrhagic complications. The former is more likely when INR levels are too low and the latter is more likely when INR levels are too high (see Figure 2, p.7). If INR levels are too low, an increase in the dose of warfarin is indicated. When levels are too high, various management options are available and the choice depends on the INR level and whether bleeding is present. The Australasian Society of Thrombosis and Haemostasis has recently released a position statement that provides guidance for the management of high INR levels (Baker et al., 2004). These management options are recognised to reduce INR levels, resulting in a decreased risk of bleeding.

The purpose of this review was to evaluate whether INR POCT should replace INR laboratory testing in general practice. Given support that a change in management is effective in reducing the risk of thromboembolism and bleeding when INR levels are low and high respectively, adequate performance of POCT when compared with laboratory testing would produce support for the use of INR POCT in general practice. Diagnostic performance was assessed in two studies that examined the performance of INR POCT as a potential replacement for INR laboratory testing in general practice. While overall performance was similar between both strategies in these two studies, there were data to suggest POCT may be less accurate at higher INR levels. One of the studies was conducted in a rural setting and, while there are potential advantages to the use of POCT in this setting, only 48 per cent of the POCT measurements were within the desired therapeutic range in this study. Both studies also had a number of limitations that could have contributed to bias in the diagnostic performance.

What are the economic considerations?

Introduction

The purpose of an economic assessment of a new health technology is to determine its value for money, to identify and compare the direct, indirect, and flow-on costs of the technology and its comparator, and to balance these against the evidence of effectiveness.

Because a technology which is less effective than the comparator would not generally be considered for funding, even if a cost saving were possible, new technologies which cannot demonstrate a level of effectiveness which is at least equivalent to that of the comparator do not warrant a full cost-effectiveness analysis. Although the data presented in this review suggest that there may be potential for INR POCT in general practice to improve the monitoring of patients receiving warfarin therapy, there is at present insufficient evidence that INR POCT in general practice leads to an improved outcome for patients compared with INR testing through laboratories. There is, therefore, no justification for a full health economic analysis of INR POCT in general practice at present.

The specific objectives for the economic assessment were, therefore, to:

- identify and compare the direct costs of INR POCT in general practice and INR testing through laboratories
- identify the variables which may affect the indirect and flow-on costs of INR POCT in general practice compared with INR testing through laboratories
- identify any uncertain variables which may have a significant effect on the estimated cost of INR POCT in general practice

If further studies can demonstrate the superiority of INR POCT in general practice, the major benefits may imply improved quality of life for patients receiving warfarin therapy. There may also be potential for INR POCT in general practice to reduce the cost of INR testing and to overcome accessibility issues for remote areas. Ideally, to establish the cost differential between INR POCT in general practice and INR testing through laboratories, not only would the costs directly associated with the test be estimated but the flow-on costs, such as variations in management costs, would also be estimated. However, because there is uncertainty about the effectiveness of INR POCT in general practice, there is uncertainty about the magnitude of the associated indirect and flow-on costs.

Cost per patient of INR point-of-care testing

Direct Costs

The Medicare Benefits Schedule reimbursement fee for INR testing through laboratories is \$14.05 (MBS item number 65120). This fee is assumed to accurately reflect the direct cost of INR testing through laboratories. INR testing through laboratories also attracts a Patient Episode Initiation Fee of \$17.40 (MBS item number 73907).

Furthermore, a short consultation with a GP is required for every six INR tests through laboratories (one sixth of \$14.10 per INR test, MBS Level A number 3) and GPs may bulk-bill for these consultations, implying a bulk-billing management cost (one sixth of \$5.95, MBS bulk-billing management fee) for a total cost of \$34.80 (bulk-billing would take place in the majority of cases and a GP consultation would rarely follow INR testing, according to the expert opinion of the MSAC Advisory Panel).

There is currently no reimbursement of INR POCT in general practice unless accredited as an M laboratory. As a result, the cost of INR POCT in general practice has been estimated in order to allow for comparison with INR testing through laboratories.

There are three major components to the direct cost of INR POCT in general practice: The major capital cost (the portion of the cost that is attributable to the purchase price of the major capital equipment, which represents a fixed cost); the consumable equipment cost (the portion of the cost that is attributable to items which must be purchased each time a test is performed, which represents a variable cost); and the labour cost (the cost of labour required to perform the test and record results). In addition to these costs, a short consultation with the GP would be offered and bulk-billing of both the INR testing and also the GP consultations will result in bulk-billing management costs (bulk-billing would take place in the majority of cases, according to the expert opinion of the MSAC Advisory Panel).

If a single unit were purchased to perform all INR tests in Australia, the major capital cost per test would be very low. On the other hand, if every GP in Australia purchased a unit and, between them, performed all INR tests in Australia, the major capital cost per test would be significantly higher. The reality is likely to be somewhere between these two extremes, but the exact number of units which would be purchased is not known. As a result, two approaches, based on plausible but divergent scenarios, were used to reflect the uncertainty about the take-up of INR POCT in general practice and the capacity level at which the equipment is likely to be used. These approaches provided a plausible range for the major capital cost per test.

The first approach (the “high capacity” approach) estimates the major capital cost per test of INR POCT in general practice based on the applicant’s claim that some units run up to 20 tests per day. This approach implicitly assumes that only those GP practices which will run the units at this level will purchase the equipment.

The second approach (the “low capacity” approach) assumes the lowest plausible level of capacity use per unit, based on every GP practice in Australia purchasing the equipment. There are approximately 24,307 GPs in Australia (Department of Health and Ageing, 2001-2002 data) and a mean number of GPs per practice of five (personal communication from Jan Charles, project manager, BEACH, University of Sydney,

October 2004). This suggests that there are approximately 4,861 GP practices running 2.7 million tests in total annually.

Several assumptions regarding the equipment associated with INR POCT are common to both approaches:

- The major capital equipment used for INR POCT costs \$1,320 per unit (price supplied by the applicant);
- The expected lifetime of the major capital equipment used for INR POCT is three years (applicant's estimate);
- The major consumable equipment cost, the cost of reagents for the test, associated with INR POCT is approximately \$6 per test (cost supplied by the applicant);
- All other consumable equipment costs associated with INR POCT are insignificant (based on personal communication from the applicant); and,
- INR POCT in general practice would completely replace INR testing through laboratories that is currently requested from general practice.

According to the high capacity approach: If all units providing INR POCT in general practice run 20 tests per day, five days per week, for 50 weeks per year, each unit would run 5000 tests annually. With a capital cost of \$1,320 and an expected life of three years, each unit would run 15,000 tests at a major capital cost of approximately \$0.09 per test.

According to the low capacity approach: If all 4,861 general practices were to purchase the necessary capital equipment for INR POCT, the major capital equipment cost would be \$6,416,520. This value of equipment would be spread over three years worth of INR testing, resulting in approximately 8.1 million tests. Units would run on average 2.22 tests per day. The resulting major capital cost would be approximately \$0.79 per test.

These two different approaches to estimating the major capital cost of INR POCT in general practice, in the absence of take-up and capacity use data, suggest that, whatever the take-up and capacity use, the component of direct costs that is associated with the major capital equipment is likely to be insignificant.

Given that the consumable equipment cost associated with INR POCT is also low at \$5.90, albeit significantly higher than the major capital cost, the cost of labour is likely to be the main component of the total direct cost of INR POCT in general practice.

The applicant proposes a Medicare reimbursement fee of \$25. Deducting the major capital equipment and variable costs leaves approximately \$18 to \$19 to cover the labour costs associated with INR POCT in general practice. The resulting breakdown of cost components is shown in Table 11 below.

Table 11 Direct cost components of INR POCT

Cost component	Amount
Major capital equipment cost	\$0.09 - \$0.79
Consumable equipment cost	\$5.90
Fee proposed by applicant	\$25
Implied labour cost	\$18.31 - \$19.01

This amount, combined with a short consultation fee of \$14.10 and bulk-billing management fees totalling \$11.90, is expected to be enough to induce widespread use of INR POCT in general practice. If the proposed fee were paid for INR POCT in general practice, therefore, the total cost would amount to \$51. The incremental cost per test of INR POCT in general practice over INR testing through laboratories would be \$16.20. This is shown in Table 12 below.

Table 12 Total and incremental direct cost per test

	INR testing through laboratories	INR POCT
Fee	\$14.05	\$25.00
Patient episode initiation fee	\$17.40	n/a
Short consultation fee	\$2.35	\$14.10
Bulk-billing management fee	\$1.00	\$11.90
Total cost	\$34.80	\$51.00
Incremental cost		\$16.20

Direct cost to the Commonwealth

If the direct cost to the Commonwealth is considered, the estimates must take into account that benefits are paid by the Medicare system based on 85 per cent of the Medicare Benefits Schedule fees. As a result, both the direct cost to the Commonwealth of INR testing through laboratories and the direct cost to the Commonwealth of INR POCT in general practice are lower than the respective direct costs to the Australian health system. The direct costs to the Commonwealth are shown in Table 13 below.

Table 13 Total and incremental direct cost to the Commonwealth per test

	INR testing through laboratories	INR POCT
Benefit	\$11.95	\$21.25
Patient episode initiation benefit	\$14.80	n/a
Short consultation benefit	\$2.00	\$12.00
Bulk-billing management benefit	\$0.85	\$10.20
Total cost to the Commonwealth	\$29.60	\$43.45
Incremental cost to the Commonwealth		\$13.85

Indirect and flow-on costs

With a higher direct cost per patient, INR POCT would have to be associated with lower indirect and flow-on costs than INR testing through laboratories if any cost-savings were to be realised. If this is not the case, the total incremental cost per patient associated with the use of INR POCT in general practice would have to be weighed against any evidence of improved patient outcomes.

The indirect and flow-on costs associated with INR POCT in general practice and INR testing through laboratories include the costs associated with changes in the management of patients receiving warfarin therapy and the costs associated with adverse events of warfarin therapy.

However, without specific reliable estimates of the effectiveness of INR POCT in general practice it cannot be known whether a favourable cost-effectiveness ratio would be possible.

Total cost to the Australian Health System

Total annual cost

The total annual costs to the Australian health system were estimated for the approximately 2.7 million tests performed annually in Australia in general practice, based on the Medicare fee for INR testing through laboratories and the fee proposed by the applicant for INR POCT. These estimates represent the total annual direct cost if all laboratory-based INR testing ordered from general practice is replaced with INR POCT in general practice. It is likely, however, that due to the time that may be required to generate capacity among GPs, the number of INR POCT performed in the short term (and therefore the short-term annual direct cost of INR POCT in general practice) would be some fraction of this number.

The total long-term annual direct cost to the Australian health system for the approximately 2.7 million INR laboratory tests requested annually from general practice is estimated to be \$93,960,000. The total long-term annual direct cost to the Australian health system (for the approximately 2.7 million tests) of using INR POCT in general practice is estimated to be \$137,700,000. The use of INR POCT as a substitute for INR testing through laboratories for all INR testing in general practice is, therefore, expected to result in an annual increase in direct costs to the Australian health system of approximately \$43,740,000 annually.

The cost of replacing INR testing through laboratories with INR POCT in general practice represents a 47 per cent increase over the annual direct cost of INR testing through laboratories.

The Commonwealth share of these direct costs is expected to be \$79,920,000 for INR testing through laboratories and \$117,315,000 for INR POCT in general practice. The resulting incremental direct cost to the Commonwealth would be \$37,395,000.

These estimates are limited to the direct cost of testing and do not include flow-on costs, which are heavily dependent on the effectiveness of the test.

Sensitivity analysis

In order to test the sensitivity to the assumptions used of the estimates of direct cost per test and total annual direct cost, the following parameters are adjusted:

- The total number of tests performed in 2003-2004 is increased to 3.1 million (based on upper extreme of annual usage estimated for 2003-2004 in clinical need section, see p5);
- An annual growth rate of 9 per cent (as estimated in clinical need section, p5) is applied to the number of INR tests performed in 2003-2004 to generate estimates for 2004-2005 and 2005-2006; and,
- Higher numbers of tests are assumed as well as higher labour costs to generate the combined effect on costs.

The results of the sensitivity analysis are presented in Table 14 below.

Table 14 Estimated direct incremental costs* to the Australian health system under different assumptions

Assumption variation	Direct cost per test of INR Point-of-care Testing	Incremental cost per patient	Incremental annual cost to the Australian Health System
Base Case assumptions	\$51.00	\$16.20	\$43,740,000
3.1 million tests performed annually	\$51.00	\$16.20	\$50,220,000
2.7 million tests increase 9% to:			
- 2.943 million tests in 2004-2005	\$51.00	\$16.20	\$47,676,600
- 3.208 million tests in 2005-2006			\$51,969,600
3.1 million tests increase 9% to:			
- 3.379 million tests in 2004-2005	\$51.00	\$16.20	\$54,739,800
- 3.683 million tests in 2005-2006			\$59,664,600

* Incremental cost of INR POCT over INR testing through laboratories.

As shown in Table 14 above, the total incremental annual direct cost to the Australian health system is sensitive to assumptions regarding the number of tests performed, suggesting that even if the applicant's proposed fee is an accurate reflection of the true cost of widespread use of INR POCT in general practice, the incremental annual direct cost to the health system could be significantly greater than estimated in the base case: Changes in the assumptions regarding the number of tests performed annually and adjusting for growth in the total number of INR tests increased the incremental annual direct cost to the Australian health system to approximately \$60 million in 2005-2006 (based on 3.1 million tests in 2003-2004 and an annual growth rate of 9 per cent).

Applying the same variations in assumptions to the base-case estimates of costs to the Commonwealth generates similar results: By 2005-2006, the incremental direct cost to Commonwealth is estimated to be approximately \$51 million (based on 3.1 million tests performed annually in 2003-2004 and an annual growth rate of 9 per cent). These are shown in Table 15.

Table 15 Estimated direct incremental costs* to the Commonwealth under different assumptions

Assumption variation	Direct cost per test of INR point-of-care testing	Incremental cost per patient	Incremental annual cost to the Commonwealth
Base-case assumptions (with implied labour cost of approximately \$18-\$19)	\$43.45	\$13.85	\$37,395,000
3.1 million tests performed annually	\$43.45	\$13.85	\$42,935,000
2.7 million tests increase 9% to:			
- 2.943 million tests in 2004-2005	\$43.45	\$13.85	\$40,760,550
- 3.208 million tests in 2005-2006			\$44,430,800
3.1 million tests increase 9% to:			
- 3.379 million tests in 2004-2005	\$43.45	\$13.85	\$46,799,150
- 3.683 million tests in 2005-2006			\$51,009,550

* Incremental cost of INR POCT over INR testing through laboratories.

Summary

The limited economic analysis evaluating the use of INR POCT in general practice as a substitute for INR testing through laboratories in patients being monitored in general practice found that the incremental direct cost per test of INR POCT in general practice would be \$16.20. This estimate is based on the expert opinion of the MSAC Advisory Panel, which determined that the \$25 fee proposed by the applicant, combined with a short consultation fee and bulk-billing management fees, is likely to represent an accurate reflection of the true direct cost of using INR POCT in general practice on a widespread basis. For 2.7 million tests annually, this fee would result in an estimated total annual incremental direct cost of approximately \$43.7 million to the Australian health system. The corresponding incremental direct cost to the Commonwealth would be approximately \$37.4 million.

Sensitivity analysis was used to determine what the effect on costs would be if the true direct cost of INR POCT in general practice were higher than in the base case due to increased numbers of tests being performed. This revealed that increasing the number of tests to the higher end of the estimated range results in a significant increase in total annual costs.

The analysis was limited to direct costs due to the uncertainty surrounding the effectiveness of INR POCT in general practice. If further studies demonstrate superior effectiveness for INR POCT in general practice, there may be potential for a favourable cost-effectiveness ratio when all direct, indirect and flow-on costs are considered.

Conclusions

Safety

No studies on the safety of INR POCT were available. The only risks/adverse reactions are those associated with obtaining the capillary sample, such as localised bleeding, bruising or a vaso-vagal episode. There is a risk of needlestick injury when obtaining the sample, which could potentially result in infection with a blood-borne virus to the operator. Advisory Panel opinion is that there are no excess safety concerns with capillary sampling when compared with venepuncture for laboratory-based INR testing.

Effectiveness

Diagnostic performance of INR POCT in general practice compared with INR laboratory-based testing

Two studies were identified that examined the diagnostic performance of INR POCT in comparison with laboratory testing in general practice. One was a cross-over trial and the other a case series. There was no significant difference in the time in the therapeutic range between the POCT arm and the laboratory arm. However, at higher INR levels, the POCT INR levels were higher than the laboratory INR levels, resulting in doubt about diagnostic performance at high INR levels. In the case series, there was no significant difference in the mean INR level recorded using POCT and laboratory testing.

Conclusions on the impact of INR POCT in general practice

If a diagnostic test is to have an impact on patient outcome, the test needs to be accurate, it needs to be associated with change in management according to the results produced and the change in management needs to be effective. There was little data on the accuracy of INR POCT in general practice, with only two studies that met the eligibility criteria being identified. There was doubt about diagnostic performance at higher INR levels, in particular, and the study using the best design had a small number of participants. The lack of an overall difference in performance between POCT and laboratory testing in this study may have been due to the lack of study power in this small study. The key outcome measure used in this study was time in the therapeutic range. This measure is used as an intermediate measure for thromboembolic and haemorrhagic events. Results outside the therapeutic range are more likely to result in one of these two undesirable clinical events, with thromboembolic events being more likely when INR levels are low and haemorrhagic events occurring when levels are high. Therefore, it is possible to link time in the therapeutic range to patient outcome. Given the uncertainty about POCT performance at higher INR levels, there is currently uncertainty about the ability of INR POCT to detect an increased risk of haemorrhage with the same degree of accuracy as laboratory-based testing. The point-of-care testing trial that is currently ongoing in Australia will help resolve this uncertainty. Results for this trial are expected in 2007.

Cost-effectiveness

The limited economic analysis evaluating the use of INR POCT as a substitute for INR testing through laboratories in patients receiving warfarin therapy found that the incremental direct cost per test of INR POCT would be \$16.20 if the applicant's proposed \$25 fee is an accurate reflection of the direct cost of the widespread use of INR POCT in general practice. This would result in an estimated total annual incremental direct cost of approximately \$44 million to the Australian health system, based on 2.7 million tests performed annually.

The analysis was limited to direct costs due to the uncertainty surrounding the effectiveness of INR POCT in general practice. If further studies demonstrate superior effectiveness for INR POCT in general practice, there may be potential for a favourable cost-effectiveness ratio when all direct, indirect and flow-on costs are considered.

The results were sensitive to increases in the estimate of the number of tests performed annually and, in particular, to assumptions about the true cost of labour for INR POCT in general practice.

Recommendation

After consideration of safety, effectiveness and cost-effectiveness, there is insufficient evidence to support the use of INR point-of-care testing in general practice at this stage.

- The Minister for Health and Ageing accepted this recommendation on 4 July 2005 -

Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or Affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Associate Professor Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues

Ms Samantha Robertson
Professor Jeffrey Robinson
Professor Michael Solomon
Professor Ken Thomson
Dr Douglas Travis

Department of Health and Ageing representative
obstetrics and gynaecology
colorectal surgery, clinical epidemiology
radiology
urology

Appendix B Advisory Panel

Advisory Panel for MSAC application 1071: INR point-of-care testing in general practice

Professor Sydney Bell (Chair)

MBBS FRCPA MD

Area Director of Microbiology

South East Sydney Area Health Service, NSW

member of MSAC

Assoc. Prof. John Atherton

MBBS PhD FRACP

member of MSAC

Ms Karen Carey-Hazell

Consumers' Health Forum
of Australia nominee

Associate Professor Liz Farmer

BSc MBBS PhD FRACGP

Director PHC RED Program Flinders

University Department of General Practice

Royal Australasian College
of General Practitioners
nominee

Associate Professor Eng Gan

MBBS MBA FRCPA FRACP

Haematology Society of
Australia and New Zealand
nominee

Dr Mark Nelson

MBBS (Hons) MfamMed FRACGP FAFPHM

PhD

Member National Standing Committee –

Research, Royal Australian College of General
Practitioners

Royal Australasian College
of General Practitioners
nominee

Dr Beverley Rowbotham

MD FRACP FRCPA

Haematologist

Royal College of
Pathologists of Australasia
nominee

Appendix C Website sources of information

HTA Organisations	Website URL
Agence d'Evaluation des Technologies et des Modes d'Intervention (AETMIS)	http://www.aetmis.gouv.qc.ca/
Agencia de Evaluacion de Tecnologias Sanitarias (AETS)	http://www.isciii.es/unidad/aet/caet.html
Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA)	http://www.csalud.junta-andalucia.es/orgdep/AETSA/
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
Agency for Health Research Quality (AHRQ)	http://www.ahrq.gov
L'Agence nationale d'Accréditation et d'Evaluation en Santé	http://www.anaes.fr
L'Agence Nationale pour le Developpement de l'Evaluation Medicale (ANDEM)	http://www.upml.fr/andem/andem.htm
British Columbia Office of Health Technology Assessment (BCOHTA) publications	http://www.chspr.ubc.ca/cgi-bin/pub
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.aatm.es/
Canadian Coordinating Office for Health Technology Assessment (CCOHTA)	http://www.ccohta.ca
Centre for Clinical Effectiveness, Monash University	http://www.med.monash.edu.au/healthservices/cce/
Center for Medical Technology Assessment (CMT)	http://ghan.imt.liu.se/cmt/
College voor Zorgverzekeringen (CVZ)	http://www.cvz.nl
German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information (DIMDI)	http://www.dahta.dimdi.de/
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.dihta.dk/
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/
Unidad de Tecnologias de Salud (ETESA)	http://www.minisal.cl

EUROSCAN	http://www.euroscan.bham.ac.uk
Finnish Office for Health Care Technology Assessment (FinOHTA)	http://www.stakes.fi/finohta/
Health Technology Assessment International	http://www.htai.org/
Health Council of the Netherlands (GR)	http://www.gr.nl/
Minnesota Health Technology Advisory Committee (HTAC)	http://www.health.state.mn.us/htac/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Institute of Technology Assessment of the Austrian Academy of Science (ITA)	http://www.oeaw.ac.at/ita/hta/
International Network of Agencies for Health Technology Assessment (INAHTA)	http://www.inahta.org
Medical Technology Assessment Group (M-TAG)	http://www.m-tag.net/
Medical Technology and Practice Patterns Institute	http://www.mtppi.org/
National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.soton.ac.uk/~hta
National Horizon Scanning Centre (NHSC)	http://www.bham.ac.uk/PublicHealth/horizon
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
NHS Quality Improvement Scotland	http://www.nhsqis.org/
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.net/sanidad/
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se
Norwegian Centre for Health Technology Assessment (SMM)	http://www.oslo.sintef.no/smm/
Swiss Science Council/Technology Assessment (SWISS/TA)	http://www.ta-swiss.ch/
TNO Prevention and Health (TNO)	http://www.tno.nl/homepage.html
Veterans' Affairs Technology Assessment Program (VATAP)	http://www.va.gov/vatap/
WHO Devices and Clinical Technology	http://www.who.int/bct/Main_areas_of_work/DCT/Healthcare_Technology.htm

Other organisations

Australian Institute of Health & Welfare (AIHW)	http://www.aihw.gov.au
Australian National Health & Medical Research Council	http://www.health.gov.au/nhmrc/index.htm
Commonwealth Department of Health and Aged Care	http://www.health.gov.au
Centres for Medicare and Medicaid Services (US Health Care Financing Administration)	http://www.hcfa.gov
Health Economics Research Group (Brunel University)	http:// www.brunel.ac.uk/depts/herg
US Federal Drug Administration	http://www.fda.gov
Health Canada	http://www.hc-sc.gc.ca/
UK Department of Health publications	http://www.doh.gov.uk/publications/index.html
US Centers for Disease Control	http://www.cdc.gov

Professional Associations/Societies

American Heart Association	http://www.americanheart.org
American Society of Hematology	http://www.hematology.org
American College of Cardiology	http://www.acc.org
British Society for Haematology	http://www.b-s-h.org.uk
British Cardiac Society	http://www.bcs.com
Haematology Society of Australia & New Zealand	http://www.hsanz.org.au
Australasian Society of Haemostasis & Thrombosis	http://www.asth.org.au
Cardiac Society of Australia & New Zealand	http://www.asth.org.au
Royal Australian College of General Practitioners	http://www.racgp.org.au/
Royal New Zealand College of General Practitioners	http://www.rnzcgp.org.nz
Royal College of General Practitioners	http://www.rcgp.org.uk

Clinical Trials

Controlled Clinical Trials	http://www.controlled-trials.com/
Clinicaltrials.gov	http://www.clinicaltrials.gov

Appendix D Search strategy

- 1 international normalized ratio/
- 2 prothrombin time/
- 3 (inr or coagucheck or coaguchek or coagulometer).tw.
- 4 exp blood coagulation tests/
- 5 or/1-4
- 6 point of care systems
- 7 point of care.tw.
- 8 physicians' offices/
- 9 family practice/
- 10 (general practice or gp).tw.
- 11 primary health care/
- 12 office laboratory.mp.
- 13 physicians, family/
- 14 near patient.mp.
- 15 (primary care or primary health).tw.
- 16 or/6-15
- 17 warfarin/
- 18 (vitamin adj antagonist\$.mp.
- 19 exp vitamin k/
- 20 exp coumarins/
- 21 coumarin\$.tw.
- 22 exp anticoagulants/
- 23 (anticoagulant\$ or anti-coagulant\$.tw.
- 24 or/17-23
- 25 5 and 16
- 26 6 or 7 or 8 or 12 or 14
- 27 24 and 26

- 28 25 or 27
- 29 poct.mp.
- 30 pct.mp.
- 31 (near adj2 patient adj2 test\$.tw.
- 32 npt.tw.
- 33 (decentralised test\$ or decentralized test\$.tw.
- 34 (ancillary adj2 test\$.tw.
- 35 (alternat\$ adj2 site\$ adj2 test\$.tw.
- 36 (patient adj2 focus\$ adj2 test\$.tw.
- 37 (satellite adj2 test\$.tw.
- 38 (onsite adj2 test\$.tw.
- 39 (peripheral adj2 test\$.tw.
- 40 (extra adj2 laborator\$ adj2 test\$.tw.
- 41 (physician\$ adj2 office adj2 test\$.tw.
- 42 (office adj2 patholog\$.tw.
- 43 (office adj2 laborator\$.tw.
- 44 ((desktop or desk top) adj2 technolog\$.tw.
- 45 ((desktop or desk top) adj2 laborator\$.tw.
- 46 (rapid adj test\$.tw.
- 47 (set adj2 testing).tw.
- 48 (poc or (point adj2 care adj5 test\$.tw.
- 49 office visits/
50 or/29-49
- 51 5 and 50
- 52 24 and 50
- 53 51 or 52
- 54 53 or 28

Appendix E STEP tool for appraisal of diagnostic studies

Ask	Assess	Alert
Are the results of the study applicable to the systematic review?		
Is the research question appropriate to the review question?	Satisfies the PPICO criteria Satisfies the clinical algorithm, ie, the index test is used as a replacement/incremental or triage test as intended in the review	Justify study eligibility if not applicable
Is the target condition appropriate?	Yes/no/unclear	
Are these tests replicable in MSAC setting of interest?	Are the test specifications (including technology and protocol) appropriate? Is the test threshold explicit? Yes/no/unclear	Observer variability Instrument variability Threshold variation
Are the criteria for inclusion and exclusion appropriate?	Were the tests evaluated in an appropriate spectrum of patients? Consider demographic characteristics, co-morbidities, healthcare setting, referral history of the patients Yes/no/unclear	Spectrum variation - demographics - disease severity - disease prevalence Patient filtering bias
What is the quality of the study methods?		
Were eligible patients identified before the index test and standard were applied?	Prospective or retrospective study	Potential for selection bias if retrospective design
Is the reference standard likely to correctly classify the target condition?	Yes/no/unclear	Reference standard error bias
Were the tests independent (ie, not incorporated in) the reference standard?	Yes/no/unclear	Incorporation bias
Were the same clinical data available when test results were interpreted as would be available when the index test is used as intended in clinical practice?	Yes/no/unclear	Information bias
Were test results interpreted without knowledge of the results of other tests?	Yes/no/unclear	Test review bias/Diagnosis review bias
Did <i>all</i> patients (or a random selection) receive verification using a reference standard of diagnosis?	Per cent not verified	Partial verification bias
Did patients receive the <i>same</i> reference standard regardless of the test result?	Per cent verified using a different method eg, Pathology versus clinical follow-up	Differential verification bias
Was the time period between the index test and reference standard short enough to be reasonably sure that the target condition did not change between the two tests?	Yes/no/unclear	Detection bias
Were uninterpretable and/or indeterminate test results reported?	% index test results uninterpretable/intermediate %reference standard results uninterpretable/intermediate	Detection bias
Were withdrawals from the study explained?	% withdrawals	Attrition bias
Ask	Assess	Alert
If two or more tests are compared, were they assessed independently of each other on all patients (or in randomly allocated patients)?	Yes/no/unclear	Detection bias

Appendix F Studies included in review

Table F Characteristics of studies included in the review of diagnostic performance

Study Country	Study design	Eligibility criteria	Grade and quality ¹	n	Patient characteristics
(Daly et al., 2003) Ireland	Prospective case series	Receiving warfarin for prosthetic heart valve, venous thrombosis, pulmonary embolism or atrial fibrillation	NHMRC IV C1 Q3 P2	122	Demographic details not provided
(Shiach et al., 2002) United Kingdom	Randomised cross-over trial	Receiving warfarin	NHMRC II C1 Q2 P2	46	mean age 65 years age range 41-80 years 60% male

¹ C1: Direct comparison; Q2: Medium quality, Q3: Poor quality or insufficient information; P2 population – limited applicability

Abbreviations

AR-DRG	Australian Refined Diagnostic Related Groups
DARE	Database of Abstracts of Reviews of Effectiveness
DOR	diagnostic odds ratio
EED	Economic Evaluation Database
GP	General practitioner
HIC	Health Insurance Commission
HTA	Health Technology Assessment
INR	international normalised ratio
ISI	international sensitivity index
MBS	Medicare Benefits Schedule
MSAC	Medicare Services Advisory Committee
NATA	National Association of Testing Authorities
NHS	National Health Service
NPAAC	National Pathology Accreditation Advisory Council
OR	odds ratio
POCT	point-of-care testing
QAP	quality assurance program
RCPA	Royal College of Pathologists of Australasia
TTR	time in the therapeutic range
UK	United Kingdom
WHO	World Health Organisation

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