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Guidance on the Use of Point-of-Care Testing of International Normalized Ratio for Patients on Oral Anticoagulant Therapy

Supporting Informed Decisions

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TABLE OF CONTENTS

ABBREVIATIONS

HTERP	Health Technology Expert Review Panel
INR	international normalized ratio
OAT	oral anticoagulation therapy
POC	point of care
PSM	patient self-management
PST	patient self-testing
QALY	quality-adjusted life-year
TTR	time in therapeutic range

1 GUIDANCE

1.1 Guidance in Brief

Patients with atrial fibrillation, prosthetic heart valves, or venous thromboembolism may be prescribed oral anticoagulation therapy (OAT) with warfarin or other vitamin K antagonists. When taking these drugs, a patient must be monitored for over-anticoagulation (possibly resulting in bleeding or hemorrhage) and under-anticoagulation (which could result in blood clots), typically by measuring the international normalized ratio (INR). The standard method for monitoring INR is laboratory testing of blood obtained by venipuncture. Point-of-care (POC) testing is another way to monitor INR. POC testing is defined as testing at or near where a patient is located. Possible benefits of POC testing are enhanced convenience; faster turnaround of test results to the health care provider, which potentially allows for faster clinical decision-making; improved clinical outcomes; and reduced health care resource use. There are three main ways in which POC INR testing can be implemented:

- patient self-management (PSM), in which the patient self-tests INR using a POC device and also self-adjusts the dose of the anticoagulant medication based on the results, using a pre-determined algorithm or protocol
- patient self-testing (PST), in which the patient self-tests INR using a POC device and a clinician adjusts the dose of anticoagulant medication based on the results
- clinic-based POC INR testing, in which POC testing is performed in a clinical setting such as a physician's office or anticoagulation clinic.

To assist decision-makers considering acquisition or optimal implementation of POC INR technology, CADTH conducted a review of the clinical evidence and performed a health economic analysis to compare POC INR testing with standard INR laboratory testing. Based on these assessments and clinical expertise, the Health Technology Expert Review Panel (HTERP) developed the following statements to provide guidance on the use of POC INR testing devices for patients on long-term (> 3 months) OAT with warfarin or other vitamin K antagonists.

1. **HTERP concluded that POC devices for INR measurement represent an accurate alternative to laboratory testing.**
2. **For patients who are willing and able to self-manage their OAT, HTERP recommends that PSM be offered.**
3. **For patients who are unwilling or unable to self-adjust their doses of oral anticoagulation therapy, HTERP:**
   - **does not recommend PSM**
   - **recommends PST only when there are significant barriers to accessing laboratory testing and patients are willing and able to self-test**
   - **recommends that the choice between laboratory INR testing and clinic-based POC INR testing requires careful consideration of setting-specific factors that may impact the relative costs for each strategy.**
4. **No recommendation can be made regarding a preferred POC INR device.**

More detailed information regarding this guidance, including reasons, implementation considerations, and key HTERP discussion points, is provided in Section 1.2.

1.2 Detailed Guidance

1. HTERP concluded that POC devices for INR measurement represent an accurate alternative to laboratory testing.

Reasons:

- POC INR methods are analytically valid. In the studies included in CADTH's systematic review, the diagnostic accuracy of POC INR testing was similar to laboratory testing of INR within the commonly targeted therapeutic range.

2. For patients who are willing and able to self-manage their OAT, HTERP recommends that PSM be offered.

Reasons:

- PSM is both clinically effective and cost-effective compared with laboratory testing for patients who are willing and able to self-manage OAT or have the social supports (such as a caregiver) to enable self-management.
- From the review of clinical effectiveness, PSM did not expose patients to additional risks as compared with laboratory testing of INR.
- Use of PSM may have other benefits not measured in the studies reviewed, such as enhanced patient engagement and autonomy.

Implementation Considerations:

- The majority of patients enrolled in studies of PSM had either atrial fibrillation or mechanical heart valves. The reviewed studies of PSM excluded patients for a variety of reasons (e.g., impaired cognition or dexterity, past stroke). Some of the included studies allowed enrolment of patients able to self-manage with the assistance of a caregiver, although there was no specific evidence regarding the safety and efficacy of PSM in patients requiring such assistance. HTERP considered PSM to be an appropriate option for patients unable to perform one or more PSM tasks without assistance, if adequate caregiver and psychosocial support is available.
- The included studies on the clinical effectiveness of PSM were based primarily on weekly or biweekly testing compared with monthly laboratory testing. Patients using PSM were instructed to initiate a professional consultation for extreme INR values (typically values < 1.5 or > 4.5). HTERP noted there may be differences between the testing algorithms used in clinical practice compared with those used in the reviewed studies, and that such differences may influence the clinical and cost effectiveness of PSM implementation in real-world practice.
- CADTH's economic analysis used a price of $499 per POC device, and $8.33 per test strip, thus devices that are considerably more costly to acquire or operate may not be cost-effective. PSM becomes a dominant strategy (i.e., more effective and less costly compared with laboratory testing) when the cost per test strip is $6.25 or lower. PSM remained a cost-effective option when various other costs and model inputs were changed (Appendix 2). Of

note, PSM was the least costly option (including in comparison to laboratory testing) if the payer reimburses patient costs associated with travel to a clinic or laboratory.

- Patients and/or caregivers must undergo adequate training and demonstrate the necessary competencies to manage their INR, including obtaining an adequate sample, operation of the instrument, interpretation of results, and performance of quality checks. Other components of PSM training programs described in the literature include: theoretical aspects of anticoagulation, including the influence of nutrition, alcohol, and other factors; recognition and handling of complications; and recognition of possible sources of error.[1-4] Ongoing demonstration of competency should be implemented. As well, POC INR results and changes in anticoagulant dose should be recorded in a reliable and accessible manner.
- HTERP considered that PSM may be advantageous in ensuring the safety and efficacy of anticoagulation therapy for patients in rural or remote settings or those who may be isolated for other reasons (e.g., elderly patients confined to their homes), particularly if laboratory services are not easily accessible or INR results cannot be obtained in a timely manner. However, there was no evidence available regarding the impact of PSM in these settings; therefore, further research is required.
- It is uncertain what proportion of patients on OAT can transfer to PSM; however, it is not appropriate for all patients. Hence, laboratory infrastructure and staffing to conduct INR will need to be maintained for those patients not performing PSM. Since per test laboratory costs for INR measurement are modest, the extent to which savings in laboratory-related expenditures or reductions in laboratory workload can be achieved by implementing PSM is uncertain.
- PSM requires the engagement and efforts of a multidisciplinary team. Planning activities for PSM implementation should identify and reflect these costs appropriately.
- The implementation of a quality assurance and quality control system for patient-operated POC INR devices that meets internationally accepted standards is essential for PSM to be safe and effective.

3. **For patients who are unwilling or unable to self-adjust their doses of OAT, HTERP:**
   - **does not recommend PSM**
   - **recommends PST only when there are significant barriers to accessing laboratory testing and patients are willing and able to self-test**
   - **recommends that the choice between laboratory INR testing and clinic-based POC INR testing requires careful consideration of setting-specific factors that may impact the relative costs for each strategy.**

Reasons:

- PST with a POC INR device without self-adjustment of anticoagulant doses was associated with similar or poorer clinical outcomes compared with PSM. PST was also more costly than PSM since patients using PST required a larger number of clinical interactions than those using PSM.
- Based on CADTH's economic analysis, PST was more costly compared with laboratory testing of INR and unlikely to be cost-effective. However, HTERP acknowledged that PST may enable safe and effective anticoagulation for patients who experience significant barriers in accessing laboratory testing, for example those who must travel long distances to reach the nearest laboratory.

- Due to a lower time in therapeutic range (TTR), clinic-based POC INR testing was more costly and associated with poorer clinical outcomes than PSM. CADTH's cost-effectiveness analysis showed that clinic-based POC INR testing was also more costly compared with laboratory testing of INR and unlikely to be cost-effective. However, HTERP considered that the cost-effectiveness of clinic-based POC INR testing may differ across settings due to variability in key cost drivers of the analysis.

Implementation Considerations:

- The majority of patients enrolled in studies of PST were receiving anticoagulation therapy due to atrial fibrillation or mechanical heart valves. No specific evidence was available regarding the safety and efficacy of PST in patients requiring assistance for self-testing. In situations where there are significant barriers to accessing laboratory testing, HTERP considered PST to be an appropriate option for patients unable to perform one or more PST tasks without assistance, if adequate caregiver and psychosocial support is available.
- Patients and/or caregivers must undergo adequate training and demonstrate the necessary competencies to perform PST, including obtaining an adequate sample, operation of the instrument, and performance of quality checks. Ongoing demonstration of competency should be implemented. As well, POC INR results should be recorded in a reliable and accessible manner.
- In the economic analysis, clinic-based POC INR testing became the most cost-effective strategy when PSM testing was assumed to occur 42 times per year or more, or when the annual cost of a five-minute physician consultation at each clinic visit was assumed to be $67 or less. Examples of other variables that may impact the real-world cost-effectiveness of clinic-based POC INR testing are patient case-load, the number and types of interactions between patients and clinicians with laboratory-based INR monitoring compared with clinic-based POC monitoring, and training requirements for staff.
- The advantages and disadvantages of clinic-based POC INR testing implementation are dependent on the context of the health setting (e.g., distance from clinic to laboratory, laboratory extramural programs). Advantages and disadvantages other than clinical and cost benefits may exist, such as patient convenience, or faster access to test results.
- Per test laboratory costs for INR monitoring are modest; therefore, the extent to which savings in laboratory-related expenditures or reductions in laboratory workload can be achieved by implementing clinic-based POC INR testing is uncertain.
- The implementation of a quality assurance and quality control system for clinic-based POC INR devices that meets internationally accepted standards is essential for POC INR testing to be safe and effective. Clinical and Laboratory Standards Institute guidelines[5] and Accreditation Canada standards[6] are examples of guidelines for reducing POC testing errors and ensuring the delivery of a high-quality POC testing program.

4. No recommendation can be made regarding a preferred POC INR device.

Reasons:

- There was limited evidence comparing POC devices; therefore, no recommendations could be made regarding superiority with respect to diagnostic accuracy or clinical effectiveness. In studies comparing POC INR to laboratory testing, the diagnostic accuracy and clinical effectiveness was found to be similar across devices for testing INR within the commonly targeted therapeutic range.

Implementation Considerations:

- While there was limited evidence comparing one POC INR device with another, comparisons with laboratory testing were available for CoaguChek XS, CoaguChek XS Plus, INRatio, i-STAT, and ProTime. Correlation coefficients between POC INR and laboratory testing were similar for all devices, ranging from 0.62 to 0.98. Most studies for each device reported a correlation coefficient > 0.9. Studies of PSM or PST used CoaguChek XS, ProTime, or INRatio. Studies of POC INR testing in anticoagulation clinics or hospital settings used these same devices as well as CoaguChek XS Plus and i-Stat.
- HTERP did not evaluate the user-friendliness, individual costs, and availability of devices and reagents, which may influence device preference.

1.3 Other Discussion Points for the Recommendations

- HTERP considered the possible utility of POC INR devices in long-term care facilities. However, there was no evidence identified regarding the use of POC INR testing in these settings.
- While the cost-effectiveness ratio for PSM versus laboratory testing was favourable, HTERP noted that quality-adjusted life-years (QALYs) likely do not encompass all potential benefits of PSM, such as patient empowerment and motivation. These benefits would make PSM an even more attractive option.
- POC devices that can integrate with the electronic clinical record of the patient, with due consideration to ethical and privacy concerns, may be beneficial in enhancing continuity of care.
- The use of POC INR testing might promote resilience to care when disasters/circumstances occur (e.g., flooding) that reduce hospital or clinic-based access to care.

2 BACKGROUND

Approximately 1% of Alberta and Ontario residents are prescribed OAT,[7,8] most commonly for atrial fibrillation, prosthetic heart valves, or venous thromboembolism. Extrapolating to all of Canada, this yields approximately 350,000 Canadians on OAT. Most patients prescribed OAT are taking warfarin, a vitamin K antagonist.[9] When taking these drugs, a patient must be monitored for over-anticoagulation (possibly resulting in bleeding or hemorrhage) and under-anticoagulation (which could result in blood clots), typically by measuring INR. Without anticoagulant use, INR ranges from 0.8 to 1.2. With anticoagulation, the typical target range for INR is 2 to 3, but may vary depending on the condition being treated.[7] INR monitoring typically occurs every three to five weeks in patients stabilized on anticoagulant therapy;[7] however, more frequent monitoring is required when starting therapy.

The standard method for monitoring INR is laboratory testing of blood obtained by venipuncture, in hospital or at an anticoagulation clinic. POC testing is another way to monitor INR. POC testing is sometimes referred to as bedside testing, but is more accurately defined as testing at or near where a patient is located. The aims of POC testing are to offer convenience for the patient; provide faster test results to the health care provider, thereby potentially allowing for faster clinical decision-making; improve clinical outcomes; and reduce health care resource use. As well, patients have reported a preference for capillary testing as compared with venous blood draw.[10]

The POC device used to measure a person's INR is called a coagulometer. There are nine POC coagulometers currently manufactured, available, or soon to be available, in Canada (Table 1).

POC testing for INR involves putting a sample of whole blood, usually capillary blood from a finger stick, onto a test strip. POC devices and test strips are not currently an insured benefit in most Canadian jurisdictions, although they may be available as part of hospital or clinic supply budgets. As of February 2014, CoaguChek XS test strips are covered as an exceptions item by the *Régie de l'assurance maladie du Québec.*

Table 1: POC Testing of INR Devices Available, or Soon to Be Available, in Canada

Manufacturer	Product
Roche	CoaguChek XS[a]
Roche	CoaguChek XS Plus[a]
Roche	CoaguChek XS Pro[a]
International Technidyne Corporation	ProTime[a]
Hemosense Inc.	INRatio[a]
Helena Laboratories	Cascade
Abbott Laboratories	CoaguSense
Abbott Laboratories	i-STAT[a]
Universal Biosensors	Mobius (not yet officially named)
iLine Microsystems	iLine device

INR = international normalized ratio; POC = point of care.
[a] Devices approved for use in Canada.

Given the increasing use of POC INR testing in the monitoring of patients on OAT, the availability of many POC INR devices, and the capital and operating costs of these devices, CADTH performed a review of the clinical evidence related to POC INR testing compared with standard INR laboratory testing, and conducted a health economic analysis.
To assist decision-makers considering acquisition of the technology or determining its optimal implementation, evidence-informed guidance on the use of POC testing for INR was developed by HTERP to address the following policy questions:

- **Question 1:** Is POC INR testing as effective as laboratory testing for determining whether INR is within the therapeutic range?

- **Question 2:** In what health care settings are there clinical and cost advantages or disadvantages for the use of POC INR testing as compared with laboratory testing?

- **Question 3:** In what health care settings are there advantages other than clinical and cost (for example, access to testing or convenience) for POC INR testing as compared with laboratory testing?

- **Question 4:** Is there one particular POC device that is superior to others in terms of clinical, cost, and other advantages?

The clinical and economic evidence used for developing this guidance was derived from the CADTH Optimal Use report: *Point-of-Care Testing of INR for Patients on Oral Anticoagulant Therapy*,[11] consisting of a systematic review of clinical evidence and a primary economic model.

HTERP considered the evidence and its limitations from a population-based perspective. The anticipated benefits, harms, and cost-effectiveness of POC INR testing were considered fundamental in the development of system-level guidance.

3 SUMMARY OF THE EVIDENCE

3.1 Clinical Evidence

The CADTH systematic review included 48 articles reporting on 47 unique studies, including 5 randomized controlled trials assessing the impact of POC INR testing on clinical outcomes.[11] Only studies evaluating POC coagulometers approved and available for purchase in Canada were eligible for inclusion.

The majority of diagnostic accuracy studies reported a short period of time between POC and laboratory tests, limiting the possibility that INR differences were due to changes in clinical condition, rather than differences in the tests themselves. However, the majority of diagnostic accuracy studies did not report study withdrawals or rates of uninterpretable results, both of which may influence accuracy findings. The studies on clinical outcomes were all randomized controlled trials, but may not have had sufficient sample sizes to detect differences in all outcomes of interest, particularly rare events such as hemorrhage or thromboembolism. The included populations may not have been representative of the general population that may require INR monitoring, as they were often selected on the basis of physical or mental competencies, and patients electing to enrol in a trial may be more engaged with their own care. Findings from the clinical review are described below.

Diagnostic accuracy
For INR values within the typical target therapeutic range (2 to 3.5), POC meters produced results comparable to those obtained with the use of standard laboratory methods for monitoring patients on OAT. The mean difference in INR values between the two measurement techniques was within 0.5 units the majority of the time, with a maximum average difference of 0.8 identified in one study.

The evidence shows a strong correlation between POC and laboratory INR values, with the overall correlation coefficient ranging from 0.62 to 0.98 across studies. However, the divergence in INR values between the two methods may increase at high INR values (≥ 3.5 units).

Time in therapeutic range
The use of POC coagulometers led to an average increase of 6.14% in time spent within the therapeutic range compared with laboratory testing, equivalent to approximately 25 days during the course of one year.

Clinical outcomes (adverse events)
The use of POC meters included in this review did not lead to a statistically significant change in the rate of major bleeding or in the rate of thromboembolic events or strokes compared with standard laboratory methods. However, the individual included studies may have lacked statistical power to detect differences in these outcomes, and other meta-analyses including a broader range of devices have reported statistically significant reductions in thromboembolic events, but not major bleeding events, with the use of POC INR meters.

Patient satisfaction and quality of life
Limited data on patient satisfaction suggest a preference for finger stick by POC meters as compared with venous collection by central laboratory methods.

Comparison of POC INR devices
Two studies directly compared the clinical agreement of POC INR devices. The mean difference in INR values between INRatio and CoaguChek XS was 13.9% in one study. The correlation between CoaguChek XS Plus and iSTAT was strong (correlation coefficient of 0.948). Evidence was identified comparing CoaguChek XS, CoaguChek XS Plus, INRatio, i-STAT, or ProTime to laboratory testing. The majority of studies available for each device had a correlation coefficient > 0.9.

3.2 Economic Evidence

HTERP considered the results of CADTH's cost-effectiveness analysis comparing laboratory testing, PSM, PST, and POC INR testing in a clinic setting in terms of incremental cost per quality-adjusted life-year (QALY) gained.[11] The cost-effectiveness analysis employed a Markov model adapted from a previously published model by the University of Alberta. The population cohort entering the model was comprised of 50-year-old patients on OAT for at least three months, relatively well managed INR, and good visual and cognitive ability. The direct costs for health care products and services allowed or reimbursed by a public payer were included in the base-case analysis. An expanded-payer perspective that included patient level costs associated with laboratory or clinic visits was also conducted to reflect scenarios in which patient travel costs are reimbursed by public payers. The effectiveness of various INR testing strategies was reflected by the TTR, which had an impact on the likelihood of experiencing hemorrhagic or thromboembolic events. A five-year time horizon approach was used in the model.

Key findings of the cost-effectiveness analysis were as follows:

- Using retail prices for POC devices ($499 per patient-grade POC and $2,056 for professional-grade POC), and $8.33 per test strip, laboratory testing was the least costly option in the base-case analysis, with a total cost of $7,033 per patient.
- PSM emerged as a cost-effective option at an incremental cost-effectiveness ratio of $13,028 per QALY gained compared with laboratory testing.
- PST and clinic-based POC were dominated by PSM as both were more costly and less effective in terms of total QALY gains.
- In probabilistic sensitivity analyses, laboratory testing had the highest probability (60%) of being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY gained. The strategy with the second highest probability of being cost-effective at the same threshold was PSM (30%). This result can be attributed to the lower total costs of laboratory testing compared with PSM and the uncertainty around the distributions assigned to the TTR values. The probabilities for clinic-based POC testing and PST were 15% and 6% respectively.
- When assuming equivalent effectiveness (i.e., no differences in TTR) for all strategies, laboratory testing remained the least costly testing strategy.
- When considering the expanded health care-payer perspective (i.e., inclusive of patient travel costs for clinic and laboratory visits), PSM was the least costly option, dominating the other three strategies (i.e., PST, clinic-based POC and laboratory testing). These results remained robust to variations in estimates of device costs, frequency of testing, health care provider costs in various settings, and patient travel time (such as rural versus urban settings). A threshold analysis revealed that patient travel costs would need to fall by approximately 90% in order for laboratory testing to be considered cost-effective (i.e., not dominated) over PSM in the expanded-payer perspective.

A summary of the results from key one-way sensitivity analyses is presented in Appendix 2.

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APPENDIX 1: HTERP

HTERP consists of up to seven core members appointed to serve for all topics under consideration during their term of office, and up to five expert members appointed to provide their expertise for a specific topic. For this project, four expert members were appointed; their expertise included hematology, clinical biochemistry, pathology, and nursing. The core members include health care practitioners and other individuals with expertise and experience in evidence-based medicine, critical appraisal, health technology assessment, bioethics, and health economics. One public member is also appointed to the core panel to represent the broad public interest.

HTERP is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system. Further information regarding HTERP is available at www.cadth.ca/en/advisory-bodies/health-technology-expert-review-panel.

HTERP Core Members

Dr. Stirling Bryan (Chair)
Leslie Anne Campbell
Anita Fineberg
Dr. Charlotte Moore
Dr. Lisa Schwartz

Expert Members

Dr. Ihssan Bouhtiauy
Dr. Michael O'Connor
Dr. Sam Schulman
Shari Glenn

Conflict of Interest

No members declared any conflicts of interest. *Conflict of Interest Guidelines* are posted on the CADTH website.

APPENDIX 2: IMPACT OF MODEL INPUTS ON COST EFFECTIVENESS RESULTS

Table 2: Model Inputs for Base Case and Selected Sensitivity Analyses			
	Base Estimate	**Range of Variation in Sensitivity Analyses**	**Key findings of Sensitivity Analysis**
Equipment/Device Cost			
Cost of lab test (per patient)	$2.00	$2.00 to $14.00	At ≥$6.50/test: PSM more effective and less costly than lab, Clinic POC, and PST
Cost of professional-grade device used in an INR clinic (per patient)	$4.11	$2.05 to $41.10	No substantive change in results
Cost of patient-grade device	$499	$499 to $1,100	At $1,100 per device: Clinic POC most cost effective, followed by PSM, and PST
Cost of testing strip	$8.33	$0 to $8.33	At ≤$6.25 per strip: PSM more effective and less costly than lab , Clinic POC, and PST
Frequency of Testing/Year			
Frequency of testing in PSM/year	26	12 to 52	At 12 times/year: PSM more effective and less costly than lab, Clinic POC, and PST At 42 times/year: Clinic POC most cost-effective, followed by PSM and PST
Frequency of PST/year	26	12 to 52	No changes in rank order of strategies, PSM remains cost effective
Frequency of clinic POC testing/year	23	12 to 52	No substantive change in results
Frequency of lab test/year	12	12 to 52	At 42 times/year: PSM more effective and less costly than lab, Clinic POC, and PST
Health Care Provider Costs			
Cost of one-time training for using home-based device (@$39.50/hr.)	$49.38	$29.63 to $49.38	No substantive change in results
Cost of one-time training for using home- based device and medication dose management (@$39.50/hr.)	$98.75	$59.26 to $98.75	No substantive change in results
Annual cost of a five-minute physician consult in each clinic visit (@ $16.95 per visit)	$203.40	$67.00 to $203.40	At $67; Clinic POC most cost-effective, followed by PSM and PST

Table 2: Model Inputs for Base Case and Selected Sensitivity Analyses			
	Base Estimate	**Range of Variation in Sensitivity Analyses**	**Key findings of Sensitivity Analysis**
Annual cost of nursing time for clinic visit (each visit for 15 min. @$39.50/hr.)	$118.50	$39.50 to $118.50	No substantive change in results
Annual cost of nursing time per lab visit (each visit for 13 min. @$39.50/hr.)	$102.70	$34.23 to $102.70	No substantive change in results
Cost of specialist consultation per year for lab patients	$42.18	$42.18 to $168.72	At ≥$127; PSM more effective and less costly than lab, Clinic POC, and PST