Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH OPTIMAL USE REPORT

July 2014
Volume 3, Issue 1B

Point-of-Care Testing of International Normalized Ratio for Patients on Oral Anticoagulant Therapy: Systematic Review and Economic Analysis

Supporting Informed Decisions

Cite as: Canadian Agency for Drugs and Technologies in Health. Point-of-Care Testing of International Normalized Ratio for Patients on Oral Anticoagulant Therapy: Systematic Review and Economic Analysis [Internet]. Ottawa: The Agency; 2014 Jul. (CADTH Optimal Use Report; vol.3 no.1b). [cited *yyyy mmm dd*]. Available from: http://www.cadth.ca/media/pdf/OP0515_POC%20INR_Science_Report.pdf

Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward Island, Saskatchewan, and Yukon.

ISSN: 1927-0127

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Context and Policy Issues

Approximately 1% of Alberta and Ontario residents are prescribed oral anticoagulation therapy (OAT),[1,2] most commonly because of atrial fibrillation, prosthetic heart valves, or venous thromboembolism. Extrapolating to all of Canada, this yields approximately 350,000 Canadians on OAT. A significant proportion of these patients are older than 70 years of age. Most patients prescribed OAT are taking warfarin, a vitamin K antagonist.[3] When taking these drugs, patients must be monitored for over-anticoagulation (which could result in bleeding or hemorrhage) and under-anticoagulation (which could result in blood clots), which is typically measured by the international normalized ratio (INR). Without anticoagulant use, the INR ranges from 0.8 to 1.2. With anticoagulation, the typical target range for the INR is 2 to 3, but may vary depending on the condition being treated.[1] INR monitoring typically occurs every three to five weeks in patients stabilized on anticoagulant therapy;[1] however, more frequent monitoring is required when starting therapy.

The standard method for monitoring the INR is laboratory testing of blood obtained by venipuncture in a hospital or anticoagulation clinic. Point-of-care (POC) testing is another way to test the 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 convenience for the patient, faster test results to the health care provider, and potentially more timely clinical decision-making — all of which improve clinical outcomes and reduce health care resource use. The results from POC testing are available within approximately three minutes, compared with laboratory testing that ranges from 1 hour (best-case scenario in an emergency department) to 24 hours. This time frame may not include the transit time required, especially in remote settings, where samples may need to be flown to lab facilities.[1] In northern settings, the transport of samples introduces additional risks to the specimens, including inaccurate results caused by the deterioration of clotting factors as a result of inadequate freezing. Additional POC testing benefits may include improved patient compliance, reduction in patient travel time, reduction in the number of appointments needed to manage treatment, fewer adverse events than with venipuncture, and implementation of more frequent testing (more than one test per month, if required).[1] For the purposes of this report, POC testing can extend beyond health care professional testing to include patient self-testing (PST), and can occur in a variety of locations as long as the technology is in close proximity to the patient: in a hospital, a doctor's office, a pharmacy, the patient's home, a community clinic, or an anticoagulation clinic.

The POC device used to measure a person's INR is called a coagulometer. There are 10 POC coagulometers being manufactured that are available, or soon to be available, in Canada. 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.*

From a payer's perspective, the economic implications of POC INR testing can be quite complex and context-specific. The payer would have to consider resource utilization associated with different settings such as lab, clinic, or home. 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, a review of the evidence related to cost-effectiveness of POC INR compared with standard INR lab testing is needed to assist decision-makers who are

considering the acquisition of the technology or determining its optimal implementation. Comparisons to inform choices between different POC INR devices are also needed.

The objectives of this health technology assessment were to evaluate the accuracy, and clinical and cost-effectiveness of POC INR devices compared with standard lab testing, and between POC INR devices. A systematic review was performed to evaluate the accuracy and clinical effectiveness of POC INR. We also performed a primary economic analysis of the cost-effectiveness of POC INR from a Canadian perspective, as well as a review of the health services impact in Canada.

Research Questions

POC tests for INR compared with laboratory methods for testing INR:

1. What is the diagnostic test accuracy of POC test methods compared with central laboratory methods for measuring the INR in patients taking warfarin or other vitamin K antagonists?
2. What is the comparative clinical effectiveness of POC tests for measuring INR compared with laboratory methods of measuring the INR in patients taking warfarin or other vitamin K antagonists?
3. What is the comparative cost-effectiveness of patient self-management, patient-self-testing, clinic-based POC INR testing, and laboratory measurement of INR in patients taking warfarin or other vitamin K antagonists?

POC tests for INR compared with other POC tests for INR:

4. What is the diagnostic test accuracy of POC test methods compared with other POC test methods for measuring INR in patients taking warfarin or other vitamin K antagonists?
5. What is the comparative clinical effectiveness of POC tests compared with other POC tests for measuring INR in patients taking warfarin or other vitamin K antagonists?

Additional Considerations:

6. What are the environmental, ethical, legal, and social issues associated with POC INR testing?
7. What factors related to implementation may be relevant when considering POC INR?

Methods

A literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with In-Process records & daily updates through Ovid; Embase (1974-) through Ovid; CINAHL through EBSCO; The Cochrane Library through Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were point-of-care testing and INR. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year, but was limited to the English language. Conference abstracts were excluded from the search results.

The initial search was completed on February 25, 2013. Regular alerts were established to update the search until the publication of the final report, and regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters). Google and other Internet search engines were used to search for additional web-based materials.

These searches were supplemented by reviewing the bibliographies of key papers, and through contacts with appropriate experts and industry members.

Studies were selected for inclusion if they included patients treated with vitamin K antagonist therapy for at least three months, compared a POC INR test available in Canada with either laboratory testing or another POC INR test, and reported outcomes related to diagnostic test accuracy or clinical effectiveness (e.g., time in therapeutic range [TTR], thromboembolic events, bleeding events). Only randomized controlled trials and studies evaluating diagnostic accuracy were eligible for inclusion. Meta-analyses was performed where feasible, otherwise study findings were summarized narratively.

Supplemental searches were conducted to identify contextual issues and implementation considerations for POC INR. The information from these searches was not systematically reviewed, but was described narratively.

For the assessment of cost-effectiveness, a Markov model was adapted from a previously published model by the University of Alberta in which standard of care (lab testing) was compared with clinic-based testing (clinic POC), patient self-testing (PST), and patient self-management (PSM) options. PST refers to a testing strategy in which the patient self-tests INR using a POC device, and dose adjustments to anticoagulant therapy are made by a health care provider. PSM refers to a strategy in which the patient both self-tests and makes dose adjustments to anticoagulant therapy based on a predefined algorithm. The analysis population included patients who were 50 years or older and were on OAT for a period of three months or longer. The target population was limited to patients whose INR was relatively well-managed, and those who had the visual and cognitive ability to comprehend INR values displayed by home-based devices. The analysis assumed a payer's perspective. A five-year time horizon and a 5% discount rate were used for the economic analysis. The effectiveness of various INR strategies was reflected in the TTR, which refers to the percentage of time spent within the target INR range; the TTR had an impact on the likelihood of a patient experiencing hemorrhagic or thromboembolic events. Estimates of TTR were obtained primarily from the clinical systematic review, as well as from published literature when needed. The analysis considered the cost of lab testing, POC devices, physician and nurse time, and the cost of treating adverse events and complications. A cost-effectiveness analysis was conducted in which costs were measured in dollars and the outcome was measured in quality-adjusted life-years (QALYs).

Summary of Findings

For INR values within the target therapeutic range, POC meters produced results comparable to those obtained with the use of standard laboratory methods in monitoring patients on anticoagulant therapy; the meters also provided a shorter time from blood withdrawal to INR results. However, differences greater than 15% between POC INR values and standard laboratory values, sufficient to result in changes to clinical management, occurred in a number of patients. This varied across studies and according to the type of POC meter used. The use of POC meters led to a statistically significant increase of 6.14% in the time the tests were within the TTR, as compared with the use of standard laboratory methods, with CoaguChek XS providing the largest increase. According to our review, the use of POC meters 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 the use of standard laboratory methods. Data on all-cause mortality from the included trials in our systematic review were scarce and could not be pooled.

The difference in INR values between POC and lab-based methods may increase at higher INR values (≥ 3.5). The observed decrease in POC meter sensitivity at high INR values may contribute to this difference.

Results of the economic analysis suggest that lab testing was the least costly option while PSM led to the greatest gain in QALYs; the incremental cost-effectiveness ratio (ICER) of PSM as compared with lab testing was $13,028 per QALY gained. Clinic POC and PST were dominated by PSM (i.e., PSM was less costly and was associated with greater QALYs). Differences between strategies with respect to QALY gains were small, and driven by the impact of differences in TTR on clinical complications (i.e., thromboembolic events/stroke, bleeding). Several sensitivity analyses were conducted on variables related to cost of testing, frequency of testing, provider costs, patient costs, risk of adverse events, and quality of life. For most one-way sensitivity analyses, the overall results of the base-case analysis did not change. Probabilistic sensitivity analyses (PSAs) showed that, at willingness-to-pay thresholds ranging from $0 to $100,000 per QALY, lab testing had the highest probability of being the most cost-effective option followed by PSM. Based on a scenario analysis that included patient costs (travel time and lost wages), PSM dominated PST, clinic POC and lab (i.e., PSM was the least costly strategy and was associated with the most QALYs).

Conclusions and Implications for Decision or Policy-Making

The available evidence indicates that POC INR technologies are generally precise and accurate when INR values are in the commonly targeted therapeutic range. They can improve anticoagulation control by increasing the time INR values are within the TTR; however, discordances in INR values of a magnitude that would alter clinical management occur in some patients. Our review did not demonstrate a significant difference in the risk of hemorrhagic or thromboembolic events between POC and standard laboratory testing methods; however, previous reviews have shown statistically significant differences favouring POC INR testing on these outcomes, as well as on mortality. There was a lack of evidence on the comparative effectiveness between different POC INR technologies, and for PST versus PSM. Evidence for the use of POC INR technologies in Canadian rural and remote areas was lacking.

Although lab testing was the least costly strategy in the base-case analysis, the results of the economic analysis support the use of POC devices for PSM in the management of INR for select patients on OAT. PSM remained a cost-effective option even when resource utilization and costs were varied in order to model potential differences in these parameters across various settings. While evidence for the use of POC INR technologies in Canadian rural and remote areas was lacking, self-testing strategies, particularly PSM, may be an even more cost-effective option in areas where lab testing is difficult to access. Resource utilization and costs for each POC strategy and lab testing are likely to vary in diverse health care settings; hence, the use of setting-specific inputs and costs may better inform decision-making within each setting.

ACRONYMS AND ABBREVIATIONS

AHTDP	Alberta Health Technologies Decision Process
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	confidence interval
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
INR	international normalized ratio
NHS	National Health Service (UK)
OAT	oral anticoagulation therapy
OHTAC	Ontario Health Technology Advisory Committee
POC	point of care
PSA	probabilistic sensitivity analysis
PSM	patient self-management
PST	patient self-testing
PT	prothrombin time
QALY	quality-adjusted life-year
RCT	randomized controlled trial
TE	thromboembolism
TTR	time in therapeutic range
WTP	willingness to pay

1 INTRODUCTION

1.1 Background

Approximately 1% of Alberta and Ontario residents are prescribed oral anticoagulation therapy (OAT),[1,2] most commonly because of atrial fibrillation, prosthetic heart valves, or venous thromboembolism. Extrapolating to all of Canada, this yields approximately 350,000 Canadians on OAT. A large proportion of these patients are more than 70 years of age. Most patients prescribed OAT are taking warfarin, a vitamin K antagonist.[4] 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). Prothrombin time (PT) is a measure of the effectiveness of anticoagulants. Measurements of PT are susceptible to variations according to the type of analytical system employed. The international normalized ratio (INR), a mathematically adjusted prothrombin time, was devised to standardize PT results, and is used to monitor and optimize OAT with warfarin or other vitamin K antagonists. Without anticoagulant use, the INR ranges from 0.8 to 1.2. With anticoagulation, the typical target range for the INR is 2 to 3.[1] There are some indications, such as coronary artery disease when OAT is administered alone, or for patients with a mechanical heart valve, where the desired target range for INR is 2.5 to 3.5.[1] INR monitoring typically occurs every three to five weeks in patients stabilized on anticoagulant therapy;[1] however, implementation of more frequent monitoring is required when starting therapy. The recent practice guidelines on the management of anticoagulant therapy suggests an INR testing frequency of up to 12 weeks rather than 4 weeks for patients taking vitamin K anticoagulant therapy, with consistently stable INRs, but this frequency may not be applicable to patient self-testing (PST) with point-of-care (POC) INR.[4] INR monitoring keeps the health care provider informed as to whether dose adjustments are required to keep the patient within the optimal therapeutic window. INR testing may also occur in an emergency situation.

The standard method for monitoring INR is laboratory testing of blood obtained by venipuncture, in a hospital or at an anticoagulation clinic. Point-of-care (POC) testing is another way to test the INR. POC testing differs markedly from the conventional delivery model of centralized laboratories, and is rapidly evolving in analytical scope and clinical applications. Some clinical settings are considering POC INR for the first time, while others are determining how best to use POC INR testing in their settings. Evidence-based information to guide the introduction and ongoing use of this technology would be beneficial.

1.2 Overview of Technology

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 convenience for the patient, faster test results to the health care provider, and potentially more timely clinical decision-making — all of which improve clinical outcomes and reduce health care resource use. For the purposes of this report, POC testing can extend beyond health care professional testing to include PST, and the site of POC is not restricted to the bedside, but can occur in a variety of locations, as long as the technology is in close proximity to the patient: in a hospital, a doctor's office, a pharmacy, the patient's home, a community clinic, or an anticoagulation clinic. A POC device may be hand-held and portable, or it can be a small bench analyzer or another type of fixed equipment.

The POC device used to measure a person's INR is called a coagulometer. POC testing for INR involves putting a sample of whole blood, usually capillary blood from a finger stick, onto a test

strip. The coagulometer adds thromboplastin to activate the coagulation system and then measures the time until a clot is formed.[5] The time from the point that the thromboplastin is mixed to the time of clot detection is referred to as the PT. This can then be converted to an INR (which is the ratio of a patient's PT to a control sample, raised to the power of the international sensitivity index value for the analytical system used).

There are 10 POC coagulometers being manufactured that are available, or soon to be available, in Canada (Table 1).

Table 1: Point-of-Care INR Devices Available, or Soon to be Available, in Canada

Manufacturer	Product	MSRP
Roche	CoaguChek XS[a]	$499
Roche	CoaguChek XS Plus[a]	$2,056 (Phase out 2015/16)
Roche	CoaguChek XS Pro[a]	$2,982
International Technidyne Corporation	ProTime	NA
Alere Inc.	INRatio	$1,100
Helena Laboratories	Cascade	NA
Abbott Laboratories	CoaguSense	NA
Abbott Laboratories	i-STAT	NA
Universal Biosensors	Mobius (not yet officially named)	$660 to $890
iLine Microsystems	iLine device	NA

[a]Devices approved for use in Canada.
INR = international normalized ratio; MSRP = manufacturer-suggested retail price; NA = not available (price not provided by manufacturer).

POC INR testing can occur in different scenarios, or models.[5] The three most common scenarios are:

- At home — the patient tests the INR and adjusts the dose of the OAT accordingly (based upon provided reference material); can be referred to as self-management.
- At home — the patient tests the INR and reports the results to a health care provider (e.g., physician or pharmacist), and is then advised on how to adjust the dose; can be referred to as self-testing.
- At hospital or clinic — the POC test is administered and interpreted by a health care provider; the type of health care provider may vary (e.g., nurse, pharmacist, primary care physician).

2 ISSUES

POC devices and test strips are not currently an insured benefit in Canadian jurisdictions, although they may be available as part of hospital or clinic supply budgets. The results from POC testing are available within approximately three minutes, compared with laboratory testing that ranges from 1 hour (best-case scenario in an emergency department) to 24 hours. This time frame may not include the transit time required, especially in remote settings, where samples may need to be flown to lab facilities.[1] In northern settings, the transport of samples introduces additional risks to the specimens, including inaccurate results caused by the deterioration of clotting factors as a result of inadequate freezing and hemolysis. The significant number of different physicians dosing patients on OAT, and the lack of means of communication

between laboratories and patients are also added concerns. Additional POC testing benefits may include improved patient compliance, reduction in patient travel time, reduction in the number of appointments needed to manage the treatment, fewer adverse events than with venipuncture (required by laboratory testing), and implementation of more frequent testing (more than one test per month, if required).[1]

From a payer's perspective, the economic implications of POC INR testing can be quite complex and context-specific. The payer would have to consider resource utilization associated with different settings such as lab, clinic, or home. This would include health care provider time, patient time, and lost wages (if reimbursed by the payer), in addition to fixed and recurring costs associated with each type of testing method. Given the increasing use of POC INR in the monitoring of patients on OAT, the availability of many POC INR devices, and the capital and operating costs of these devices, a review of the evidence related to accuracy, and clinical and cost-effectiveness of POC INR compared with standard INR lab testing, is needed to assist decision-makers that are considering the acquisition of the technology or determining its optimal implementation. Comparisons to inform choices between different POC INR devices are also needed.

3 OBJECTIVES

The objectives of this health technology assessment (HTA) are to evaluate the accuracy and clinical and cost-effectiveness of POC INR devices compared with standard lab testing, as well as to compare between POC INR devices. A systematic review was performed to evaluate the accuracy and clinical effectiveness of POC INR. We performed a primary economic analysis of the cost-effectiveness of POC INR from a Canadian perspective, as well as a review of the health services impact in Canada. The report addresses the following questions:

3.1 POC Tests for INR Compared With Laboratory Methods for Testing INR

1. What is the diagnostic test accuracy of POC test methods compared with central laboratory methods for measuring INR in patients taking warfarin or other vitamin K antagonists?
2. What is the comparative clinical effectiveness of POC tests for measuring INR compared with laboratory methods of measuring INR in patients taking warfarin or other vitamin K antagonists?
3. What is the comparative cost-effectiveness of patient self-management, patient-self-testing, clinic-based POC INR testing and laboratory measurement of INR in patients taking warfarin or other vitamin K antagonists?

3.2 POC Tests for INR Compared With Other POC Tests for INR

4. What is the diagnostic test accuracy of POC test methods compared with other POC test methods for measuring INR in patients taking warfarin or other vitamin K antagonists?
5. What is the comparative clinical effectiveness of POC tests compared with other POC tests for measuring INR in patients taking warfarin or other vitamin K antagonists?

3.3 Additional Considerations

6. What are the environmental, ethical, legal, and social issues associated with POC INR testing?
7. What factors related to implementation may be relevant when considering POC INR?

Subgroup analyses were conducted a priori, if possible, based on criteria such as patient group, users, clinical settings (such as hospital, anticoagulation clinics, home), and urban/rural/remote/isolated settings, to determine how these factors may have affected the clinical and cost-effectiveness of POC testing.

4 CLINICAL REVIEW

4.1 Methods

4.1.1 Literature search

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with In-Process records & daily updates through Ovid; Embase (1974-) through Ovid; CINAHL through EBSCO; The Cochrane Library through Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were point-of-care testing and INR. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year, but was limited to English language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on February 25, 2013. Regular alerts were established to update the search until the publication of the final report, and regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters), which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 1 for more information on the grey literature search strategy.

Supplemental searches were conducted to identify issues and implementation considerations for POC INR testing. The information from these searches was not systematically reviewed, but was described narratively.

4.1.2 Selection criteria

The following criteria were established a priori for the selection of studies for inclusion.

Table 2: Selection Criteria	
Population	• Patients taking warfarin or other vitamin K antagonists, for atrial fibrillation or other indications where POC would be used. • Any age group. • For clinical outcomes, only patients on long-term therapy (> 3 months) were considered; no therapy duration criteria were applied for accuracy outcomes.
Intervention	POC test methods for measuring INR, approved in Canada
Comparator	• POC tests approved by Health Canada • Central laboratory methods.
Outcomes	*Diagnostic test accuracy:* • Agreement between POC INR and comparator test (a result difference of a priori defined 15% between the POC INR test and the comparator test would alter the clinical management). • Sensitivity and specificity, AUROC, and positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, interferences, linearity, carry-over (if applicable), correlation between POC and central lab, precision of the POC (same time, over time). *Clinical effectiveness:* Achievement of therapeutic range, TTR, thromboembolic event, hemorrhagic event, mortality, quality of life, bleeding (minor and major), impact on clinical management, non-health benefits, other safety concerns.
Study design	• RCTs • Diagnostic accuracy evaluation studies.

AUROC = area under the receiver operator curve; INR = international normalized ratio; POC = point of care; RCT = randomized controlled trial; TTR = time in therapeutic range.

4.1.3 Selection method

Two reviewers independently screened the titles and abstracts of all citations retrieved from the literature search and, based on the selection criteria (Table 2), ordered the full text of any articles that appeared to meet those criteria. The reviewers independently reviewed the full text of the selected articles, and compared the independently chosen included/excluded studies. Disagreements were resolved through discussion until consensus was reached. Duplicate publications of the same trial were excluded unless they provided additional outcome information of interest.

Studies were excluded if they did not meet the selection criteria or if they presented preliminary results in abstract form. Duplicate publications, narrative reviews, and editorials were also excluded.

The PRISMA flow chart detailing the selection process is provided in Appendix 2, and lists of included and excluded studies are provided in Appendix 3.

4.1.4 Data extraction strategy

A data extraction form for the clinical review was designed a priori to document and tabulate relevant study characteristics (e.g., study design, inclusion criteria, patient characteristics, setting) and measures of test accuracy and clinical effectiveness (as outlined previously) in the

selected studies. Data were extracted independently by two reviewers, and any disagreements were resolved through discussion until consensus was reached. A draft of the data extraction form for the clinical review is provided in Appendix 4.

4.1.5 Strategy for quality assessment

The validity of the included clinical trials on accuracy and clinical effectiveness was assessed using the QUADAS checklist,[6] and Downs and Black checklist,[7] respectively. Disagreements were resolved through consensus.

4.1.6 Data analysis methods

A systematic review was performed for studies that fulfilled the selection criteria. A review that included a narrative synthesis and summary of study findings was conducted, if meta-analysis was not feasible due to the nature of the data. Meta-analyses were performed using Review Manager Version 4.2. The I^2 test was used to assess heterogeneity between studies, with $I^2 \geq 75\%$ indicating high heterogeneity across trials. If heterogeneity was identified, a random effects model was applied. Forest plots are presented for all evidence syntheses to supplement reported estimates. The measures of effect for dichotomous data such as adverse event rates are expressed as an odds ratio with 95% confidence intervals (CIs). The measures of effect for continuous data such as time within target therapeutic range are expressed as weighted mean difference with 95% CI. Findings are reported as “not statistically significant” if the 95% CI of the overall estimate included unity for dichotomous data or included zero for continuous data.

When sufficient data were available, subgroup analysis was employed to increase the robustness of the findings. Stratification factors for subgroup analysis included study quality, patient characteristics (e.g., race, gender, age group, pre-existing disease, etc.), delivery model (self-testing alone or self-testing plus self-management), type of health care providers, location (rural/remote), outlying data points, and other factors such as funded source (private versus public). If required measures of variance were found to be missing from a relevant article, the study’s authors were contacted to determine if the measure could be provided for the purposes of this investigation. If relevant data were not available, variances were imputed, if possible.

4.2 Results

4.2.1 Quantity of research available

The literature search identified 895 studies, and the alerts identified an additional 22 studies. From this search, 700 articles were excluded based on the screening of title and abstract, and 217 studies were ordered for further examination. Upon full-text review, 171 studies were excluded; two studies were added from an additional search. Forty-eight articles describing 47 studies were included in the report. The PRISMA flow chart (Appendix 2) shows the selection process in detail.

4.2.2 Study and patient characteristics

Details of the characteristics of the included studies and patients are summarized in Appendices 5 and 6, respectively.

a) Study design

A total of 48 articles describing 47 studies were included in the systematic review. Six studies were randomized controlled trials (RCTs),[8-13] and 41 were accuracy evaluation studies.[14-54]

b) Population

All trials included patients on oral anticoagulants, with five involving pediatric populations only.[17,25,35,49,54] Mean ages of the study populations ranged from 18 months[17] to 78 years.[39] The majority of trials included patients attending anticoagulation clinics. Of the trials, 4 involved patients presenting at emergency departments,[23,38,39,52] 14 trials used PST,[8-13,15,17,18,35,43,46,47,53] and 5 of the trials also used patient self-management (PSM).[11,13,43,47,53] Many of the studies did not specify the patient indications for taking OAT. Of the trials, 5 indicated that the study populations consisted of patients with heart valve replacement,[9,12,16,46,53] 2 studies included patients with atrial fibrillation,[9,53] and 5 studies included patients with other cardiac conditions.[16,24,28,41,45,49,54]

c) Interventions and comparators

CoaguChek XS was the POC meter used in 23 trials,[8,10,13,16-18,21,24-26,30,34,35,38-40,47-51,53,54] CoaguChek XS Plus in two trials,[27,31] INRatio in three trials,[12,44,46] i-STAT in four trials,[20,23,36,52] and ProTime in 11 trials (12 articles).[9,11,14,15,19,28,32,37,42,43,45,55] Common comparators were different standard laboratory methods. One study compared CoaguChek XS and INRatio with standard laboratory methods, and compared CoaguChek XS with INRatio;[41] one compared i-STAT and CoaguChek XS Plus with standard laboratory methods, and compared i-STAT with CoaguChek XS Plus;[22] one compared CoaguChek XS and i-STAT with standard laboratory methods;[29] and one compared ProTime and INRatio with standard laboratory methods.[33] Patient or home self-test was performed in 15 studies,[8-15,17,18,35,43,46,47,53] and 4 of these studies also incorporated PSM.[11,13,43,53]

d) Outcomes

All included studies except four[8,9,12,13] evaluated POC test accuracy. The outcomes reported were accuracy (average INR unit difference between POC and lab methods; correlation coefficient, sensitivity, specificity), clinical agreement rate, and precision. Five studies reported clinical outcomes associated with each testing method.[8,9,11-13] Clinical outcomes reported were major bleeding rates and thromboembolism (TE)/stroke rates, time from blood withdrawal to INR results, and time in the therapeutic range (TTR).

e) Funding status

Twenty-six trials were partially or totally funded by industry, or used POC meters supplied by industry.[9-11,13-15,18,20,21,23-25,28,30-34,36,37,41,43,44,48,56,57] Fifteen studies did not report the funding source.[12,17,19,27,29,35,40,42,45-47,50-52,54]

4.2.3 Quality appraisal

Details of the quality appraisal of individual studies are summarized in Appendix 7.

The majority of included studies on accuracy had good validity. A short period of time (within the same day) between the tests was reported in the studies, with the exception of four studies[16,51,52,58] in which the interval between index (POC INR) and reference (standard laboratory method) tests was unclear. A short period of time between tests limits the possibility that the clinical condition of the patient has changed during the between-test interval. In the majority of studies (25 of 42) the results of the index test was interpreted without knowledge of

the results of the reference standard and vice versa. Blinding to the results of the index and reference tests minimizes the potential risk of bias in interpretation. This potential source of bias is also reduced given that the reference and index tests provide a numerical output, which is less subject to clinical judgment and interpretation. In all studies, selection criteria were clearly described and the results were representative of the patients who would receive the test in practice. Withdrawals from the studies and rates of uninterpretable results were not commonly described (33 of 42 studies on diagnostic accuracy did not include this information). A large number of studies (17 of 42) also failed to describe the execution of index and reference tests in sufficient detail to permit replication.

Studies on clinical outcomes were all RCTs, with method of patient selection, patient characteristics, and patient withdrawals clearly described. However, the included patient populations may not have been representative of the general population that would require INR monitoring: they were often selected based on physical and mental competencies, as well as other factors such as education or perceived reliability regarding medication adherence and compliance with physician orders. Patients electing to enrol in a trial of self-testing or self-management may be more engaged with their own care than the broader population on OAT. An HTA produced by Connock et al. for the National Health Service (NHS) HTA program[59] found that, on average, 33% of eligible participants agree to participate in trials, highlighting the potential for self-selection. None of the studies reported blinding of patients or outcome assessors, though this may not have been feasible given the nature of the interventions. One limitation common to two studies[11,12] was a lack of estimates of random variability or actual probability values for clinical outcomes. All studies reported power calculations, and all were adequately powered to detect a clinically important effect; however, one study was not sufficiently powered for all outcomes of interest.[13] Four studies were powered to detect differences in TTR,[8,11] percentage of tests in the therapeutic range,[12] or certain quality of life outcomes,[13] and therefore may not have had sufficient sample sizes to detect differences in rates of more rare events such as hemorrhage or TE. The included studies that reported on TTR did not provide estimates for the proportion of tests above or below the target range.

4.2.4 Data analysis and synthesis

a) Precision, accuracy, and clinical agreement of POC INR compared with lab methods

Details from individual studies of precision, accuracy, and clinical agreement of various POC INR devices versus laboratory methods are summarized in Appendix 8. Because of the heterogeneity in terms of methods and comparators across trials reporting outcomes on precision, accuracy, and clinical agreement of POC INR compared with lab methods, a narrative summary was performed.

In general, findings showed that POC INR testing is precise and accurate in monitoring patients on anticoagulant therapy compared with standard laboratory methods.

Precision (the consistency of measurements when performed many times, as measured by coefficient of variation): the coefficient of variation ranged from 2.3% for CoaguChek XS to 8.6% for INRatio.

Accuracy (the average INR units' difference between POC and laboratory methods; the linear relationship between POC and laboratory methods, as measured by correlation coefficient r): the mean difference in INR values almost always within 0.5 units. The correlation coefficient r between POC meters and conventional lab methods showed strong correlation (r close to 1)

between the two methods. Bland-Altman analyses, in general, showed an increased scatter at mean INR values of greater than or equal to 3.5 units, reflecting an increase in INR value differences between the two methods at higher INR values.

Clinical agreement (the mean deviation of POC INR relative to laboratory methods, with 15% as a predetermined threshold that would have altered clinical management): 2% to 45% of patients had POC INR values and standard laboratory INR values that differed by more than 15%.

The following are the comparative accuracy and clinical agreement data for different types of POC INR meters.

When comparing CoaguChek XS to standard laboratory methods,[10,17,18,21,24-26,29,30,34,35,38-41,47,48,50,51,53,54] the difference in INR values between the two methods ranged from –0.4 units to +0.25 units (correlation coefficient ranging from 0.81 to 0.98). A range of 5.1% to 43% of patients had a difference in CoaguChek XS INR values and laboratory values that would have altered clinical management (Appendix 8, Table A5).

For CoaguChek XS Plus,[22,27,31] the difference in INR values between POC and laboratory methods ranged from –0.13 units to +0.27 units (correlation coefficient ranging from 0.75 to 0.96). A range of 16.4% to 17.8% of patients had a difference in CoaguChek XS Plus INR values and laboratory values that would have altered clinical management (Appendix 8, Table A6).

In studies comparing INRatio[12,33,41,44,46] to standard laboratory methods, the difference in INR values between the two methods ranged from 0.00 units to +0.09 units (correlation coefficient ranging from 0.79 to 0.93). The percentage of patients who had a difference in INRatio values and laboratory values that would have altered clinical management was not available (Appendix 8, Table A7).

For i-STAT,[20,22,23,29,36,52] the difference in INR values between the POC and laboratory methods ranged from –0.1 units to +0.51 units (correlation coefficient ranging from 0.83 to 0.96). The percentage of patients who had a difference in i-STAT values and laboratory values that would have altered clinical management was not available (Appendix 8, Table A8).

For ProTime,[9,11,14,15,19,28,32,33,37,42,43,45,55] the difference in INR values between the two methods ranged from +0.02 units to +0.80 units (correlation coefficient ranging from 0.62 to 0.96); 2% to 45% of patients had a difference in ProTime INR values and laboratory values that would have altered clinical management (Appendix 8, Table A9).

Sensitivity, specificity, and predictive values of POC INR meters were reported in one study using CoaguChek XS.[51] Using lab testing as the reference test, it was reported that the CoaguChek XS coagulometer had a sensitivity of 65.5%, specificity of 67.6%, positive predictive value of 76%, and negative predictive value of 56%. Low predictive values of CoaguChek XS may affect the accuracy on the time within target range that this POC device provided.

b) Precision, accuracy, and clinical agreement of POC INR compared with another POC INR

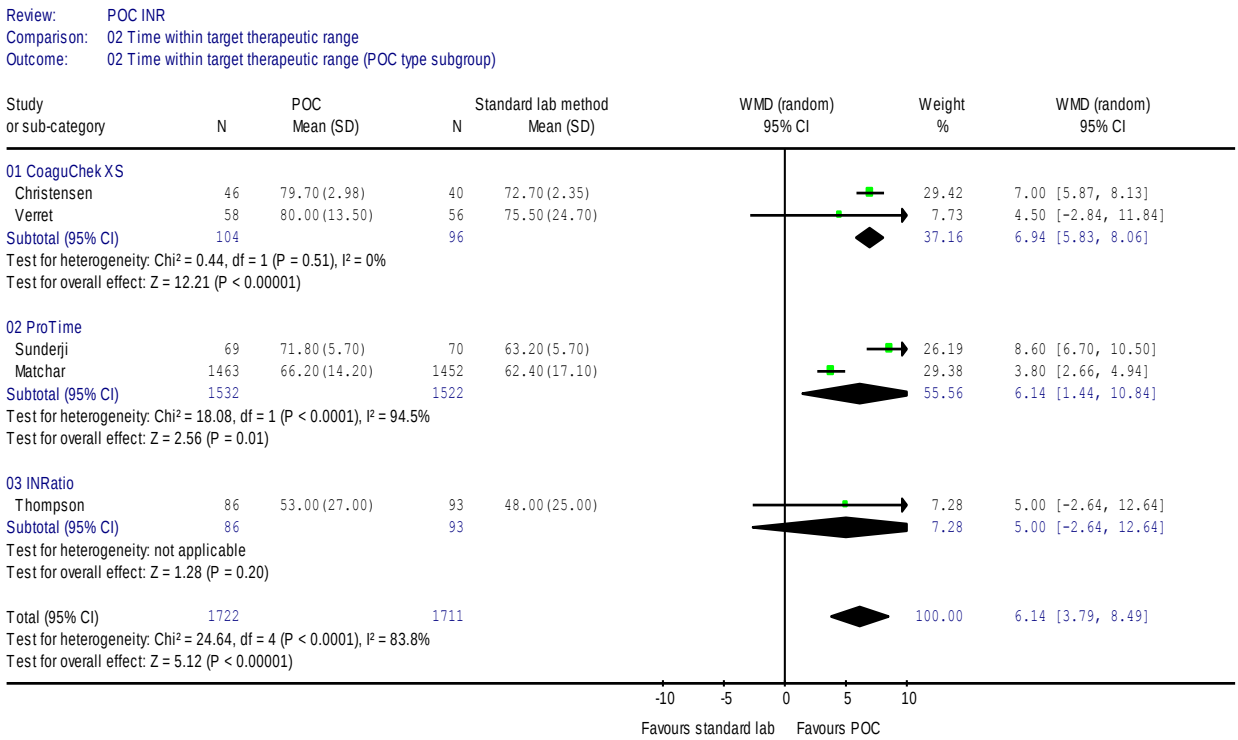
The mean difference in INR values between INRatio and CoaguChek XS was 13.9% in one study.[41] The correlation between CoaguChek XS Plus and i-STAT was strong (correlation coefficient
r = 0.948), and INR values were within 0.4 units 69% of cases in one study.[22]

c) Time within target range using POC INR compared with laboratory method

Five RCTs compared the time that INR values stayed within the therapeutic target range between POC INR meters and conventional laboratory methods.[8,9,11-13] The trials included 3,433 outpatients on anticoagulant therapy, in which 1,722 self-tested INR using POC meters once a week, and 1,711 patients used standard procedures once a month at an anticoagulation clinic. Two trials used CoaguChek XS,[8,13] two used ProTime,[9,11] and one used INRatio.[12] All five trials showed weighted mean differences that favoured the use of POC INR meters. The pooled estimate from this limited number of trials showed that the use of POC meters leads to a statistically significant increase of 6.14% (95% CI, 3.79 to 8.49) in the time INR values remained within the therapeutic target range. The I^2 test showed heterogeneity across trials (Figure 1).

Subgroup analysis based on the type of POC meters showed that the use of CoaguChek XS or ProTime lead to a statistically significant increase in the time the INR values stayed within the therapeutic target range. The increase in time within the therapeutic target range was smallest with INRatio (5%) and was not statistically significant ($P \geq 0.05$). The small number of included trials rendered subgroup analyses based on self-testing versus self-management, trial quality, and funding status findings inconclusive.

Figure 1: Time Within Target Therapeutic Range



CI = confidence interval; INR = international normalized ratio; POC = point of care; SD = standard deviation; WMD = weighted mean difference.

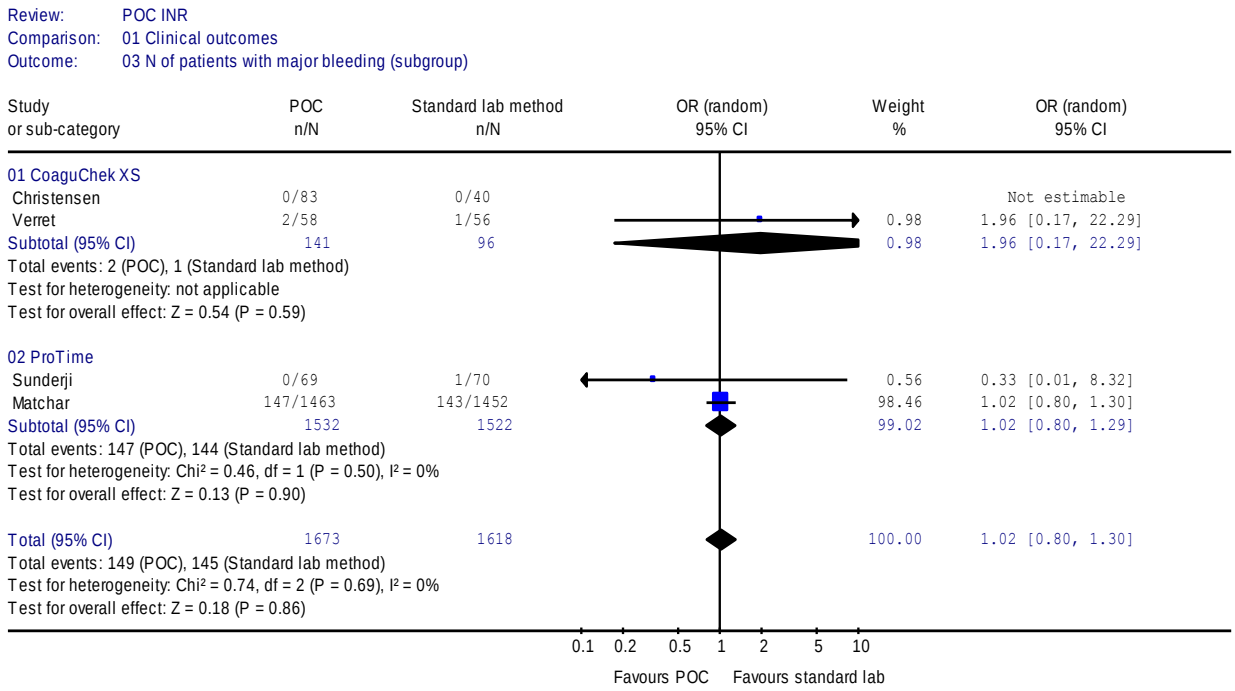
d) Clinical outcomes using POC INR compared with laboratory methods

Major bleeding rates

Four RCTs compared the rates of major bleeding between the use of POC INR meters and the use of conventional laboratory methods.[8,9,11,13] The trials included 3,291 outpatients on anticoagulant therapy, in which 1,673 self-tested INR using POC meters once or twice a week, and 1,618 patients used standard laboratory testing procedures once a month at an

anticoagulation clinic. Two trials used CoaguChek XS,[8,13] and two used ProTime.[9,11] The pooled estimate from this limited number of trials showed that the use of POC meters did not lead to a statistically significant change in the rate of major bleeding (odds ratio 1.02; 95% CI, 0.80 to 1.30). The I^2 test did not suggest the presence of heterogeneity across trials. (Figure 2)
The small number of included trials rendered subgroup analyses based on self-testing alone or self-testing together with self-management, trial quality, or funding status inconclusive.

Figure 2: Major Bleeding



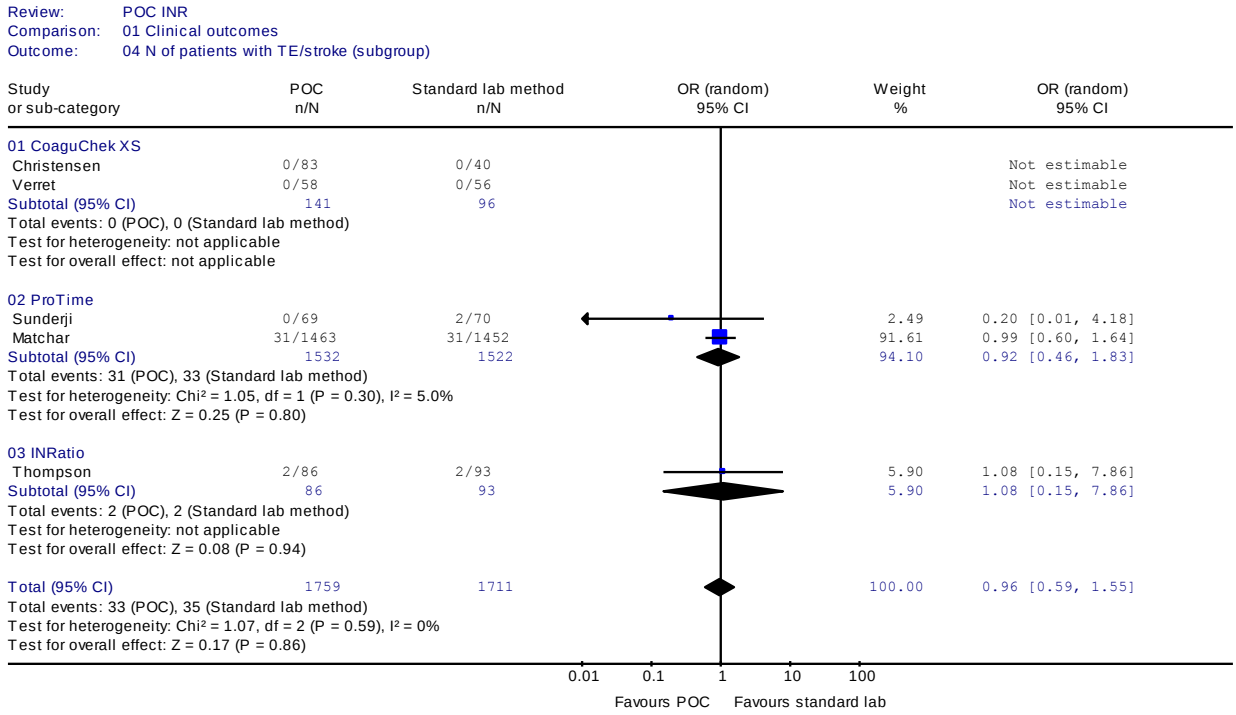
CI = confidence interval; INR = international normalized ratio; OR = odds ratio; POC = point of care.

e) Thromboembolism or stroke rates

Five RCTs compared the rates of thromboembolic events or strokes between the use of POC INR devices and the use of conventional laboratory methods.[8,9,11-13] The trials included 3,470 outpatients on anticoagulant therapy, in which 1,759 self-tested INR using POC meters once or twice a week, and 1,711 patients used standard lab procedures once a month at an anticoagulation clinic. Two trials used CoaguChek XS,[8,13] two used ProTime,[9,11] and one used INRatio.[12] The pooled estimate from this limited number of trials showed that the use of POC meters did not lead to a statistically significant change in the rate of thromboembolic events or strokes (odds ratio 0.96; 95% CI, 0.59 to 1.55). The I^2 test did not suggest heterogeneity across trials ($P = 0.59$) (Figure 3). In addtion to the primary endpoint of stroke, reported in Figure 3, Matchar et al.[9] also reported secondary endpoints of non-stroke thrombotic events and found no statistically significant difference in the number of participants experiencing at least one event of the total number of secondary events.

The small number of included trials rendered subgroup analyses based on self-testing alone or self-testing together with self-management, trial quality, or funding status inconclusive.

Figure 3: Thromboembolism or Stroke



CI = confidence interval; INR = international normalized ratio; OR = odds ratio; POC = point of care; TE = thromboembolism.

f) Mortality

Four studies, with follow-up times of less than one year (from 4 months[12] to 11 months[8]), reported no mortality (n = 624),[8,11-13] and one study, with a follow-up time of 2.0 to 4.75 years, reported an annual mortality rate of 3.4% for POC users and 3.7% for patients using standard laboratory methods (*P* = 0.41) (n = 2,922).[9]

g) Effects on time to results and time to reversal

One study compared time from blood drawn to time of INR results between CoaguChek XS and standard laboratory methods in a hospital emergency setting (n = 10).[38] For POC INR using CoaguChek XS, the mean time was 1.8 minutes, while standard laboratory methods took 52 minutes. In patients with acute subdural hemorrhage, the median total time for emergency INR reversal (the time from blood drawn to the time the anticoagulatory effects of oral anticoagulants were reversed) was 27 minutes with POC and 70 minutes with standard laboratory procedures.

h) Satisfaction and quality of life with POC INR meters

In one study, 17 patients who used CoaguChek XS gave a median score of 7.5 out of 10 when evaluating the ease of use of the POC meter. On the degree of confidence in meter accuracy, 15 patients gave a median score of 9 out of 10 and 16 doctors gave a score of 8.2 out of 10.[18] Eighty-one per cent (81%) of 82 patients who used ProTime INR meters reported ease of use; 85% reported ability to use at home; and 90% in clinics reported preference for finger stick by POC meters over venous collection by central laboratory methods.[15] Eighty-six per cent (86%) of 50 patients found INR monitoring using INRatio easier than laboratory procedures, and 80% preferred self-testing to standard laboratory methods.[46]

Improvement in quality of life after four months of treatment compared with baseline values in 56 patients randomized to CoaguChek XS was better than in the 53 patients who were randomized to standard laboratory methods ($P < 0.001$).[13] General treatment satisfaction increased; daily hassles, psychological stress, and strained social network significantly decreased in the POC group compared with the standard laboratory methods group ($P < 0.05$). Self-efficacy (the ability to cope with a variety of difficult demands in life) was not statistically significantly different between the two groups.

5 PRIMARY ECONOMIC EVALUATION

5.1 Methods

5.1.1 Type of economic evaluation

A cost-utility analysis was conducted using costs and resource utilization related to various INR testing strategies and effectiveness measured in quality-adjusted life-years (QALYs).

5.1.2 Target population

The target population was selected based on a set of criteria that would describe a typical patient eligible for home-based INR testing. It included patients aged 50 years or older, who were on OAT for a period of three months or longer. In addition, the target population was limited to patients whose INR was relatively well-managed, and those who had the visual and cognitive ability to comprehend INR values displayed by home-based devices. The analysis excluded patients with extreme INR values, who may be best managed through lab testing due to concerns of precision of the POC devices at extreme INR values.

5.1.3 Strategies

For this analysis, the following strategies were considered:

- Laboratory testing: INR testing in the laboratory, using a blood sample obtained through venipuncture.
- Clinic-based testing (Clinic POC): the patient is tested in a physician's office using a professional-grade POC device following an OAT protocol.
- PST: the patient records INR values using a home-based POC device, and a health care provider adjusts the medication dosage following an OAT protocol.
- PSM: the patient tests INR values using a home-based POC device and also adjusts the medication dosage following an OAT protocol.

5.1.4 Perspective

The analysis assumed the perspective of a Canadian ministry of health. The payer perspective incorporated only direct costs for health care products and services allowed or reimbursed by the payer, which does not normally include patient costs. Through consultation with clinical experts and stakeholders, it was revealed that some Canadian public payers reimburse patient costs (e.g., travel costs and lost wages). Hence, an additional scenario using an expanded health care-payer perspective that includes the reimbursement of patient costs was included to reflect these payers.

5.1.5 Efficacy and adverse events

The effectiveness of various INR strategies can be reflected by the TTR, which refers to the percentage of time spent within (or out of) target INR ranges. Estimates of TTR were obtained from our systematic review of the primary literature. Five RCTs compared the time the INR values stayed within the therapeutic target range when patients used POC INR meters or when they used conventional laboratory testing.[9,13,53,55] The pooled estimates from these trials favoured the use of POC INR meters because patients spent more time within the target range with these devices, as compared with lab. Effectiveness of each of the model strategies was either obtained from the clinical systematic review or from published literature, where applicable.[11,59,68] The majority of included studies in the systematic review reported patients' INR control as either being within or outside the therapeutic range. These results did not distinguish between values that were outside of the range; for example, patients would be at higher risk of bleeding with an INR of 6 than with an INR of 3.5, but the studies simply reported both values as being outside the therapeutic range. One study by Sunderji et al.[11] evaluated self-management and physician management of warfarin therapy in patients with atrial fibrillation, a mechanical heart valve, or venous TE; INR results were reported as time spent below, in, or above therapeutic range. Based on expert opinion, it is recognized that the clinical management and implications of thromboembolic events differ from those for hemorrhagic events; hence, the economic model used in this analysis applied the three-tier classification system as per the Sunderji study[11] in order to appropriately capture these different costs and implications. The results from our systematic review were used to populate the "within therapeutic range" values (i.e., TTR). The values for "below" and "above" the therapeutic range were estimated based on our review and the results reported by Connock et al.[59] The report by Connock et al.[59] is a UK systematic review that examined the clinical and cost-effectiveness of self-testing and self-management of OAT compared with clinic-based monitoring based on published evidence up to 2005. The Connock systematic review[59] examined 16 randomized and 8 non-randomized trials. It reported that PST and/or self-management of OAT was more effective than poor-quality usual

care provided by family doctors in maintaining the quality of anticoagulation therapy, and as effective as good-quality specialized anticoagulation clinics. Recently published studies (included in the clinical review) had not presented the INR control as above, in, or below therapeutic range; however, the values incorporated into the economic model were deemed appropriate by an expert panel. Estimates of the percentage of time spent within, below, and above target range for each of the testing strategies are shown in Table 3.

Table 3: Time in Therapeutic Range (%) With Various Strategies for INR Testing

	Lab	Clinic POC[a]	PST	PSM
Below TR	20.93[b]	17[a]	18.20[b]	11.91[b]
In TR	62.32[c]	68[a]	65.75[c]	77.76[c]
Above TR	16.75[b]	15[a]	16.05[b]	10.33[b]

INR = international normalized ratio; POC = point of care; PSM = patient self-management; PST = patient self-testing; TR = therapeutic range.

[a]Data from Connock et al. study.[59]
[b]Estimated based on clinical systematic review and Connock et al. study.[59,69]
[c]Clinical systematic review.

The TTR predicts the likelihood of adverse events, which can be broadly categorized as major hemorrhagic events, minor hemorrhagic events, or major thromboembolic events. Our clinical review synthesized data from four RCTs that compared the rates of major hemorrhagic events and concluded that the use of POC INR devices was not associated with any significant change in the rates of these events.[9,13,53,55] Data from five RCTs were pooled to estimate the risk of thromboembolic (stroke) events among users of POC INR devices and lab testing.[9,12,13,53,55] Again, no significant difference was observed. Therefore, the rate of adverse events (either hemorrhagic or thromboembolic) did not differ based on a particular type of INR testing.

The economic model therefore assumed that rates of adverse events were solely dependent upon TTR and not on the type of testing strategy used by the patient. While each of the strategies had different TTR estimates, there was no additional risk or benefit by virtue of utilizing a particular testing method. Estimates for risk of adverse events were obtained from previous CADTH work,[69] published literature, and expert opinion. It was assumed that clinical estimates would be fairly uniform across settings and could provide adequate inputs for the model. Estimates used for the risk of adverse events in the economic model are shown in Table 4.

Table 4: Risk of Adverse Events Among Patients on Oral Anticoagulation Therapy		
Clinical Estimate	**Value**	**Source**
Thromboembolic (Clotting) Events		
Probability of major event when INR is above normal	0.004	Connock et al.[59]
Probability of major event when INR is below normal	0.0136	Connock et al.[59]
Probability of major event when INR is normal	0.0036	Connock et al.[59]
Probability of venous thromboembolism in a thromboembolic event	0.34	Expert opinion/author assumption
Hemorrhagic (Bleeding) Events		
Probability of major event when INR is above normal	0.0337	Connock et al.[59]
Probability of major event when INR is below normal	0.0117	Connock et al.[59]
Probability of major event when INR is normal	0.0092	Connock et al.[59]
Probability of minor event when INR is above normal	0.1129	Connock et al.[59]
Probability of minor event when INR is below normal	0.061	Connock et al.[59]
Probability of minor event when INR is normal	0.0475	Connock et al.[59]
Probability of not requiring medical attention after a minor hemorrhagic event	0.85	Expert opinion/author assumption
Disability		
Probability of permanent disability in hemorrhagic event	0.1	CADTH 2007[69]
Probability of permanent disability in thromboembolic event	0.6	CADTH 2007[69]

INR = international normalized ratio.

5.1.6 Discounting and time horizon

For the primary analysis, a time horizon of five years and a discount rate of 5% were used. An annual cycle length was assumed. A time horizon of 5 years was applied, as most INR POC devices have a limited warranty and may need to be replaced after 5 years. However, there are emerging data with longer-term follow-up (10 years) on the impact of using POC devices in patients on oral anticoagulants.[70]

5.1.7 Modelling

a) Strategies

The model started with a typical patient who would be a good candidate for home-based INR monitoring. The patient had a choice of four options: lab, clinic, PST, and PSM.

b) Time spent in therapeutic range

Choice of setting for INR monitoring was associated with the likelihood of being within the therapeutic range. States reflecting time spent in TTR were:

- Above therapeutic range: patients had the risk of major or minor hemorrhagic event, major thromboembolic event, or no event.
- Below therapeutic range: patients had the risk of major or minor hemorrhagic event, major thromboembolic event, or no event.
- Within therapeutic range: patients had the risk of major or minor hemorrhagic event, major thromboembolic event, or no event.
- Permanent disability due to a thromboembolic event.

- Permanent disability due to a hemorrhagic event.
- Death.

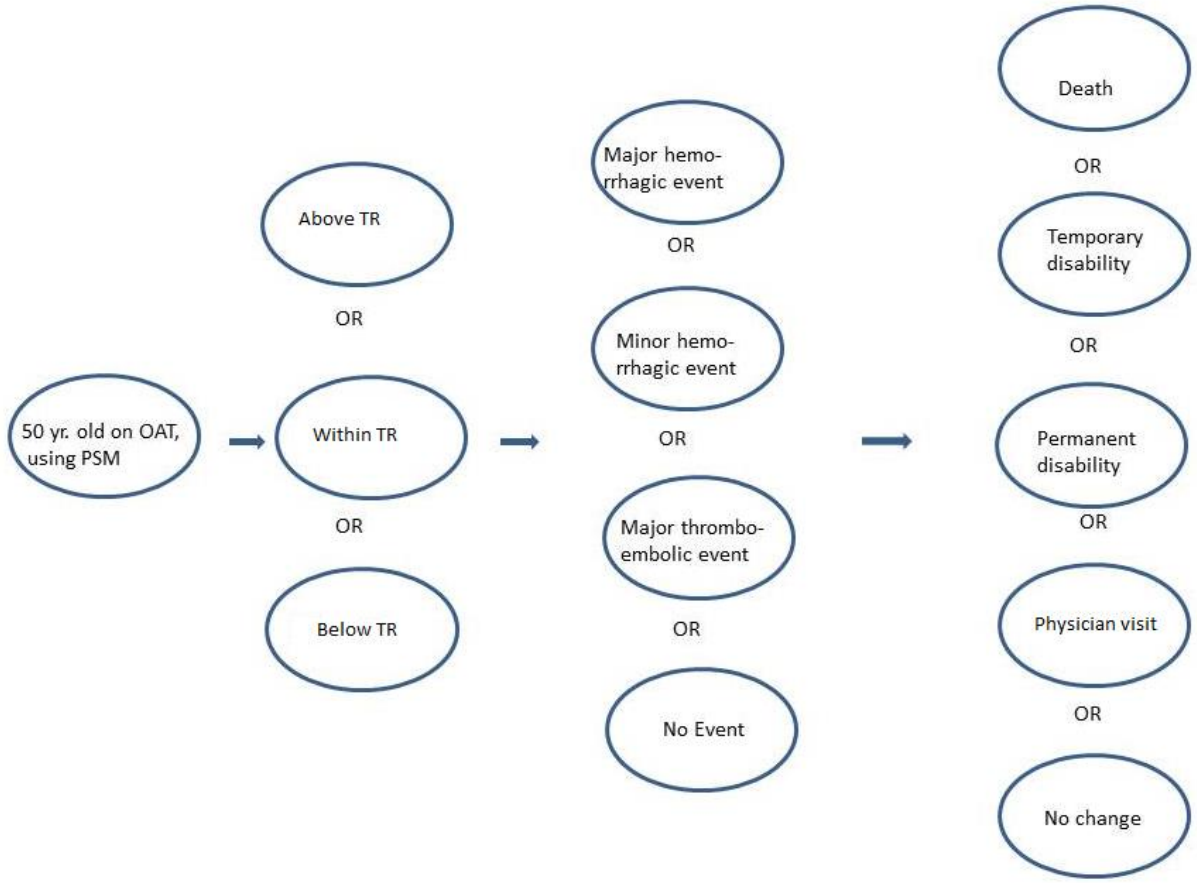
c) Adverse events

The time spent outside therapeutic range predicted the likelihood of adverse events, as follows:

- Major hemorrhagic event: A major hemorrhagic event was associated with a specific cost related to hospitalization. This was followed by one of the following three states: permanent disability, temporary disability, or death. There were specific costs for permanent disability, temporary disability, and hospital death. Both permanent and temporary disabilities were associated with reduced QALYs, while death had zero QALYs. Specific costs were also allocated to a hospital death due to a major hemorrhagic event. These branches were terminal and determined the state in which the patient would start the next model cycle.
- Minor hemorrhagic event: A minor hemorrhagic event required a physician's attention. The majority of patients did not need additional care, while some required another visit to the physician. The end result of either of these options was a return to normal INR.
- No event: This state represented status quo, where the patient started the next cycle in the same state as the previous one.
- Major thromboembolic event: A major thromboembolic event resulted in specific costs related to hospitalization. Patients could have a deep vein thrombosis or pulmonary embolism. The model assumed no deaths for deep vein thrombosis and some deaths for pulmonary embolism (as per discussion with the clinical experts). Specific costs were also allocated to a hospital death due to a major thromboembolic event. However, the absorbing state "death" had zero costs. The next cycle could be started in one of the states for therapeutic range, or as a disabled patient, or could end in the absorbing state of death.

A model schematic is provided in Figure 4.

Figure 4: Model Schematic



OAT: oral anticoagulation therapy; PSM: patient self-management; TR: therapeutic range.

5.1.8 Valuing outcomes

The primary outcome measure in the analysis was the QALY. Patients on OAT without any complications were assumed to have QALY estimates comparable to the general population. Significant reductions in QALYs were assumed for acute hemorrhagic or thromboembolic events. Patients could suffer temporary or permanent disability as a consequence of one of these acute events. If they suffered temporary disability (assumed to last 30 days) or permanent disability due to one of the adverse events, their QALY estimates were assumed to be lower for the duration of their disability. Table 5 shows the utility estimates used in the model. There was limited data on the utility estimates related to the use of different testing strategies or those related to living in different settings; therefore, these aspects were not included in the utility estimates. Outcomes were discounted at a rate of 5% and a half-cycle correction was used for the first and the last year in the model.

Table 5: Utility Estimates		
State	**Utility Value**	**Source**
General population	0.93	Mittmann et al. 1999[71]
Major hemorrhagic event, acute stage	0.72	Regier et al. 2006[68]
Major thromboembolic event, acute stage	0.70	Regier et al. 2006[68]
Temporary disability due to hemorrhage or thromboembolism	0.70	Assumed
Permanent disability due to hemorrhage or thromboembolism	0.5	Brown et al. 2007 (CADTH report)[69]

5.1.9 Cost estimates and resource utilization

a) Costs

Cost estimates for POC devices and testing materials were obtained from the manufacturer or provincial reimbursement data. The manufacturer-suggested retail price for the CoaguChek XS system (Roche Diagnostics, Canada) was applied in the model as it was the least costly alternative among the devices for which cost data were available. Costs of individual POC devices and related consumables are provided in . Cost estimates of physician and nurse time, patient driving costs, lost wages, hospitalization, medications, and ongoing therapy were obtained from the literature, Statistics Canada, and Schedule of Medical Benefits from Alberta, Ontario, British Columbia, Manitoba, and Saskatchewan.[72-77] For the base-case analysis, Alberta-specific costs were used. The scenario analysis using the expanded-payer perspective also included patient-level costs of driving to the lab and an estimate of opportunity cost (lost wages) of each visit for lab and clinic POC, where travel was required by the patient. Costs included in each strategy are outlined, as follows (Table 7):

- Lab: This strategy included cost of lab testing, cost of nursing/physician time, and the cost of warfarin therapy.
- Clinic POC: This strategy included the one-time cost of a professional testing device, recurring cost of testing strips and lancets, cost of nursing/physician time, and the cost of warfarin therapy. As one professional-grade device in a clinic can be used by multiple patients (assumed at 500 patients annually), device cost was adjusted accordingly to reflect per-patient cost. Costs of device maintenance, training, and accreditation were not available for incorporation at this time.
- PST: This strategy included the cost of a patient-grade INR testing device, test strips and lancets, cost of one-time nurse training for using the home-based device, cost of anticoagulation supervision, and the cost of warfarin therapy.
- PSM: This strategy included the cost of a patient-grade INR testing device, test strips and lancets, cost of specialist visit, cost of patient training, and the cost of warfarin therapy.

Table 6: Costs of POC Devices and Consumables available in Canada			
Product	**MSRP**	**Test Strips**	**Lancets**
Roche CoaguChek XS[a]	$499	$402 (2 x 24 strips) $201 (24 strips) $50 (6 strips)	$7-8 (Softclix lancets, 50 per box)
Roche CoaguChek XS Plus[ab]	$2,056	$402 (2 x 24 strips) $201 (24 strips) $50 (6 strips)	$47 (Safe-T-Pro PLUS lancing device, 200 per box)
Roche CoaguChek XS Pro[a]	$2,982	$402 (2 x 24 strips) $201 (24 strips) $50 (6 strips)	$47 (Safe-T-Pro PLUS lancing device, 200 per box)
International Technidyne Corporation ProTime	NA		
Alere Inc. INRatio	$1,100	$115 (12 strips) $384 (48 strips)	$100 (200 per box, not specific to INRatio)
Helena Laboratories Cascade	NA		
Abbott Laboratories CoaguSense	NA		
Abbott Laboratories i-STAT	NA		
Universal Biosensors Mobius (not yet officially named)	$660 to $890	$4.25 to $4.90 per strip	NA
iLine Microsystems iLine device	NA		

[a]Devices approved for use in Canada. [b]Being phased out 2015/16.
MSRP = manufacturer-suggested retail price; NA = not available (price not provided by manufacturer upon request).

b) Resource utilization

Each of the strategies in the model included specific estimates of resource utilization; i.e., physician and nursing time.

- Lab: The lab testing option included nurse consultation during each lab visit and an annual consultation with a specialist. Based on expert opinion, it was assumed that patients would get tested in the lab on a monthly basis.
- Clinic POC: The clinic POC testing option included nurse consultation and the cost of a brief consultation with the general physician in each visit. It was assumed that patients would get tested in the clinic on a monthly basis.
- PST: The PST option included the time spent by a nurse for a one-time training session on using the home-base device. Based on expert opinion, patients using the PST option would also require anticoagulation supervision by a physician, where the physician would provide a brief consultation on adjusting the medication dose and managing the INR values. Experts also suggested that, on average, patients use home-based testing every two weeks.
- PSM: The PSM option included the time spent by a nurse for a one-time training session on using the home-based device. Experts suggested that, while patients using the PSM option managed their own medication to stay within the optimal INR range, they would still require an annual visit with a specialist to discuss their condition and to make any necessary adjustments to their treatment plan. Similar to the frequency of testing on PST, it was assumed that patients would use home-based testing every two weeks.

c) Adjustment of costs

Whenever possible, the most current cost estimates were used. All cost estimates older than 2013 were adjusted to 2013 Canadian dollars, using the consumer price index inflation calculator from the Bank of Canada.[78]

Table 7: Cost Estimates and Resource Utilization

Costs (2013 C$)	Estimate	Source
Lab		
Cost of lab equipment (per patient)	$1.00	Expert opinion 2013
Cost per lab test	$2.00	Expert opinion 2013
Annual frequency of testing in lab	12	Expert opinion 2013
Annual cost of nursing time per lab visit (each visit for 13 minutes @$39.50/hour)	$102.70[a]	Lafata et al.[79]; Alberta Health Services 2013[73]
Clinic POC		
Cost per patient of professional-grade device used in an INR clinic ($2,056/500 to calculate per patient cost)	$4.11	Roche medical devices 2013
Professional-grade lancet	$0.23	Retail list price — Roche medical devices 2013
Cost of test strip	$8.33	Retail list price — Roche medical devices 2013
Annual frequency of testing in clinic	12	Expert opinion 2013
Annual cost of physician consultation during clinic visits (@ $16.95/visit)	$203.40[a]	Schedule of medical benefits in Alberta 2013[73]
Annual cost of nursing time for clinic visit (each visit for 15 minutes @$39.50/hour)	$118.50[a]	Lafata et al.[79]; Alberta Health Services 2013[73]
PST		
Cost of patient-grade device	$499	Retail list price — Roche medical devices 2013
Cost of patient-grade lancet	$0.16	Retail list price — Roche medical devices 2013
Cost of test strip	$8.33	Retail list price — Roche medical devices 2013
Annual frequency of testing in PST	26	Expert opinion 2013
Cost of one-time training for using home-based device (75 minutes of nursing time @$39.50/hour)	$49.38[a]	Lafata et al.[79]; Alberta Health Services 2013[73]
Annual cost of anticoagulation supervision	$144	Expert opinion 2013
PSM		
Cost of patient-grade device	$499	Retail list price — Roche medical devices 2013
Cost of patient-grade lancet	0.16	Retail list price — Roche medical devices 2013
Cost of test strip	$8.33	Retail list price — Roche medical devices 2013
Annual frequency of testing in PSM	26	Expert opinion 2013
Cost of one-time training for using home-based device (150 minutes of nursing time @$39.50/hour)	$98.76[a]	Lafata et al.[79]; Expert opinion 2013, Alberta Health Services 2013[73]
Cost of annual specialist visit	$42.18[a]	Schedule of medical benefits in Alberta 2013[73]

Table 8: Cost Estimates and Resource Utilization		
Costs (2013 C$)	**Estimate**	**Source**
Treatment Costs		
Cost per physician visit	$25.63[a]	Schedule of medical benefits in Alberta 2013[73]
Annual cost of warfarin	$87.53[b]	OHTAC 2009,[2,80] adjusted to 2013
Annual cost of Omeprazole after a GI bleed	$803.00[b]	OHTAC 2009,[2,80] adjusted to 2013
Cost of a major hemorrhagic event	$15,876.33	OHTAC 2009,[2,80] adjusted to 2013
Cost of major thromboembolism	$19,738.98	OHTAC 2009,[2,80] adjusted to 2013
Cost of minor hemorrhagic event	$3,654.61	U of C AHTDP analysis, adjusted to 2013
Cost of a fatal hemorrhagic hospitalization	$7,424.97	OHTAC 2009,[2,80] adjusted to 2013
Cost of fatal thromboembolic hospitalization	$3,440.14	OHTAC 2009,[2,80] adjusted to 2013
Cost per day of temporary disability	$612.32	OHTAC 2009,[2,80] adjusted to 2013
Cost per day of permanent disability	$143.43	OHTAC 2009,[2,80] adjusted to 2013
Patient-Level Costs (*included in additional scenario using expanded-payer perspective*)		
Cost of specialist consultation per year for lab patients	$42.18[a]	Schedule of medical benefits in Alberta 2013[73]
Cost of patient driving time and lost wages per lab visit	$42.43	Lafata et al.[79]; Statistics Canada 2013[72]
Cost of patient driving time and lost wages per clinic visit	$21.21	Lafata et al.[79]; Statistics Canada 2013[72]

AHTDP = Alberta Health Technologies Decision Process; C$ = Canadian dollars; GI = gastrointestinal; OHTAC = Ontario Health Technology Advisory Committee; U of C = University of Calgary.
[a]Alberta-specific costs.
[b]Pharmacy mark-up and dispensing fees included.

5.1.10 Variability and uncertainty

One of the objectives of this study was to assess the model results given the variability surrounding diverse testing scenarios. Therefore, one-way sensitivity analyses were conducted around key variables related to device costs, frequency of testing, health care resource utilization costs, and measures of quality of life. As the base-case analysis incorporated retail list prices for the POC devices and the required accessories (strips and lancets), a scenario analysis was conducted using wholesale prices for the POC patient-grade devices, as well as the required accessories, to reflect possible purchasing by public health plans of the devices at wholesale costs prior to their issuance to patients and caregivers. A scenario analysis was also conducted assuming no differences between POC devices and labs in terms of clinical events based on the lack of evidence showing statistical significance between POC and lab (standard of care).

Several factors, such as model structure and assumptions may lead to model uncertainty. This was handled by conducting a probabilistic sensitivity analysis (PSA) on the same set of variables, which allowed for an understanding of the potential impact of uncertainty on the overall results of the model. Triangular distributions were applied as only point estimates were available for the majority of the variables. The PSA was conducted using 10,000 iterations of the expected range of values for each of the variables. A cost-effectiveness acceptability curve was

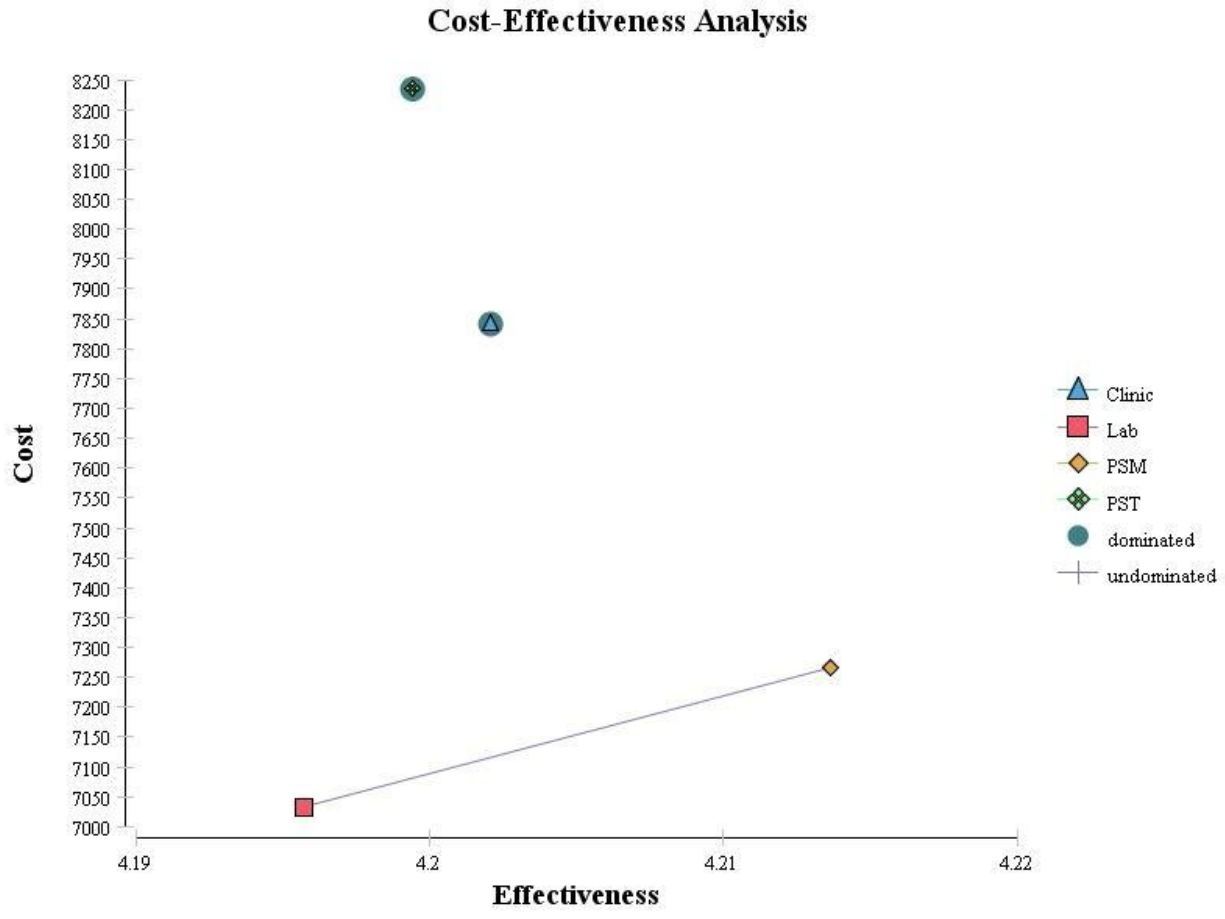
generated in which willingness to pay (WTP) was plotted against the likelihood of being cost-effective for each of the strategies.

5.2 Results

5.2.1 Base-case analysis

The base-case analysis compared lab, clinic POC, PST, and PSM strategies. A graphic representation (Figure 5) of the base-case cost-effectiveness analysis shows that lab is the least costly option and that PSM is the option leading to the greatest number of QALYs (Table 9). Lab was associated with an estimated total cost of $7,033 and 4.1957 QALYs per patient; whereas, PSM resulted in additional costs of $233 more and marginally more QALYs per patient (4.2136) than lab, leading to an incremental cost-effectiveness ratio (ICER) of $13,028 per QALY gained for PSM compared with lab. The remaining strategies, clinic POC and PST, were dominated by PSM. Clinic POC was associated with total incremental costs of $575 more per patient and with fewer QALY gains (4.2021) compared with PSM. Finally, PST resulted in $968 more per patient and 0.014 QALYs less per patient than PSM.

Figure 5: Cost-Effectiveness Analysis: Base Case



PSM = patient self-management; PST = patient self-testing.

Table 9: Results of the Base-Case Analysis Using Alberta-Specific Costs				
Strategy	**Cost ($)**	**Effectiveness (QALY)**	**ICER ($/QALY) (compared with most cost-effective strategy)**	**Sequential ICER ($/QALY)**
Lab	$7,033	4.1957		
PSM	$7,266	4.2136	13,028	13,028
Clinic POC	$7,841	4.2021	127,315	Dominated
PST	$8,234	4.1994	325,283	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; POC = point of care; PSM = patient self-management; PST = patient self-testing.

5.2.2 One-way sensitivity analyses

a) Cost of testing devices, number of patients per clinic, and frequency of testing

The base-case analysis included manufacturer costs for professional-grade and patient-grade devices. It was assumed that the average per patient cost of lab equipment is $1.00. This estimate was varied between $0.50 and $5.00. For professional-grade devices, which are typically used in POC testing in clinics, it was assumed that each device would serve up to 500 patients. Therefore, the cost per patient was adjusted accordingly. Device costs were available from two Canadian manufacturers. The costs of both professional-grade and patient-grade devices were varied based on manufacturer estimates. The estimated number of patients served by each professional-grade device was also varied from 50 to 1,000. Overall model results were robust to variations in the cost of lab equipment and cost of professional- or patient-grade devices.

There was considerable uncertainty surrounding the cost per lab test for INR; hence, a threshold analysis was conducted for this parameter. The range used in the threshold analysis covered the base-case estimate (which was supported by the opinion of experts in laboratory medicine), up to the per test cost listed in the schedule of benefits in Alberta.[73] The results of this analysis revealed that at a cost of approximately $6.50 and above per lab test, PSM became the dominant option over lab, PST and clinic POC. Uncertainty surrounding cost per test strips in POC testing was examined using a range of cost per test strip from $0 dollars up to the base-case estimate of $8.33. The results of this analysis revealed that at a cost per test strip below and up to $6.25 per strip, PSM became the dominating option over lab, PST, and clinic POC. The frequency of testing in each of the settings (i.e., PSM, PST, clinic POC, and lab) was also varied, from 12 tests per year to 52 tests per year, which translates into testing on a quarterly, biweekly, or weekly basis. Model results were robust to most one-way sensitivity analysis for these scenarios, except when total costs for PSM and lab increased. A summary of the results of the one-way sensitivity analyses using variations in cost of devices and frequency of testing are shown in Table 10.

Table 10: Results of One-Way Sensitivity Analyses for Device Cost and Frequency of Testing				
	Base Estimate	**Range**	**Source**	**Change in Rank Order for ICERs of Strategies Referencing Lab[a]**
Equipment/Device Cost				
Cost of lab test (per patient)	$2.00	$2.00 to $14.00	Expert opinion	At $6.50/test: PSM dominates all strategies
Cost of lab testing equipment (per patient)	$1.00	$0.50 to $5.00	Expert opinion	No change
Cost of professional-grade device used in an INR clinic (per patient)	$4.11	$2.05 to $41.1	Manufacturer estimate	No change
Cost of patient-grade device	$499	$499 to $1,100	Manufacturer estimate	At $1,100 per device: Clinic POC most effective, followed by PSM, and PST
Cost of POC testing strip	$8.33	$0 to $8.33	Expert opinion	At a cost between $0 to $6.25/test strip: PSM dominates all strategies
Frequency of Testing /Year				
Frequency of testing in PSM/year	26	12 to 52	Expert opinion	At 12 times/year: PSM dominates all other strategies At 42 times/year: Clinic POC most cost-effective, followed by PSM and PST
Frequency of PST/year	26	12 to 52	Expert opinion	No change
Frequency of clinic POC testing/year	23	12 to 52	Expert opinion	No change
Frequency of lab test/year	12	12 to 52	Expert opinion	At 42 times/year: PSM dominates lab, Clinic POC and PST

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; POC = point of care; PSM = patient self-management; PST = patient self-testing.
[a]Full results for the one-way sensitivity analyses are available in Appendix 9.

b) Health care provider costs in various settings

One-way sensitivity analyses were conducted for physician and nursing time in clinic, lab, and home-based settings. For the clinic-based testing, the base model assumed that patients visit the clinic every month, and are offered a brief nursing consultation and a very short (five minutes) consultation with the physician. Scenarios were conducted where physician or nursing consultations were offered every month, every two months, or every three months in a clinic-based testing environment. In each of the scenarios, the overall model results remained unchanged.

For lab-based testing, the base model assumed a monthly nursing consultation (at each of the visits) and an annual specialist consultation. The one-way sensitivity analyses considered scenarios in which nursing consultations were offered every month, every two months, or every

three months. A more frequent specialist consultation schedule was also considered where the patient would meet with the specialist up to four times a year. None of the variations had any significant impact on the overall model results.

The base model assumed a one-time nursing cost associated with a 75-minute home-based training session for PST and a 150-minute training session for PSM options. This estimate was varied in the one-way sensitivity analysis. Overall model results remained unchanged in response to these variations (summary results are presented in Table 11).

Table 11: Results of One-Way Sensitivity Analyses for Health Care Provider Costs

Health Care Provider Cost	Strategy to Be Affected	Base Estimate	Range	Source	Change in Rank Order for ICERs of Strategies Referencing Lab[a]
Cost of one-time training for using home-based device (@$39.50/hour)	PST	$49.38	$29.63 to $49.38	Assuming a range of 45 minutes to 75 minutes per session	No change
Cost of one-time training for using home- based device and medication dose management (@$39.50/hour)	PSM	$98.75	$59.26 to $98.75	Assuming a range of 90 minutes to 150 minutes per session	No change
Annual cost of a five-minute physician consult in each clinic visit (@ $16.95 per visit)	Clinic POC	$203.40	$67.00 to $203.40	Assuming a frequency of monthly to quarterly consultation	At $67; Clinic POC most cost-effective, followed by PSM and PST
Annual cost of nursing time for clinic visit (each visit for 15 minutes @$39.50/hour)	Clinic POC	$118.50	$39.50 to $118.50	Assuming a frequency of monthly to quarterly consultation	No change
Annual cost of nursing time per lab visit (each visit for 13 minutes @$39.50/hour)	Lab	$102.70	$34.23 to $102.70	Assuming a frequency of monthly to quarterly consultation	No change
Cost of specialist consultation per year for lab patients	Lab	$42.18	$42.18 to $168.72	Assuming a frequency of 1 to 4 consultations per year	At $127; PSM dominates lab, clinic POC and PST

ICER = incremental cost-effectiveness ratio; POC = point of care; PSM = patient self-management; PST = patient self-testing.
[a]Full results for the one-way sensitivity analyses are available in Appendix 10.

c) Risk of adverse events

The estimates for major and minor hemorrhagic events, as well as the risk of major thromboembolic events, were varied. The overall ICER of the model remained unchanged when one-way sensitivity analyses were performed for each of these variations. The results of one-way sensitivity analyses of the risk of various adverse events are shown in Table 12.

Table 12: Results of One-Way Sensitivity Analyses for Risk of Adverse Events

Risk of Adverse Events		Strategy to Be Affected	Base Estimate	Range	Source	Change in Rank Order for ICERs of Strategies Referencing PSM[a]
Major hemorrhagic event, if INR value is:	above target range	All	0.0337	0.03 to 0.037	Assumed around base estimate	No change
	within target range	All	0.0092	0.005 to 0.013	Assumed around base estimate	No change
	below target range	All	0.0117	0.008 to 0.015	Assumed around base estimate	No change
Minor hemorrhagic event, if INR value is:	above target range	All	0.1129	0.06 to 0.17	Assumed around base estimate	No change
	within target range	All	0.0475	0.02 to 0.08	Assumed around base estimate	No change
	below target range	All	0.0610	0.04 to 0.10	Assumed around base estimate	No change
Major thromboembolic event, if INR value is:	above target range	All	0.004	0.002 to 0.008	Assumed around base estimate	No change
	within target range	All	0.0036	0.001 to 0.007	Assumed around base estimate	If risk is at 0.001; PSM dominates lab, clinic POC, and PST.
	below target range	All	0.0136	0.006 to 0.018	Assumed around base estimate	No change

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; POC = point of care; PSM = patient self-management; PST = patient self-testing.
[a]Full results for the one-way sensitivity analysis can be found in Appendix 12.

d) Utility estimates

Utility estimates of the general population were varied between 0.837 QALYs and 1.0 QALYs. Estimates of an acute hemorrhagic or thromboembolic event were varied around the base estimate of 0.72 QALYs. Similarly, variations in estimates for the utility of being temporarily disabled or permanently disabled were assumed around the base estimates; between 0.63 QALYs to 0.77 QALYs and 0.45 QALYs to 0.55 QALYs, respectively. The variations around the utility estimates was adapted from the study by Regier et al.[68] that examined the cost-effectiveness of self-managed versus physician-managed OAT in Canada. Each of the sensitivity analyses on utility estimates resulted in changes in the overall ICER as shown in Table 13. However, none of these changes affected the overall direction of the model results.

Table 13: Results of One-Way Sensitivity Analyses for Utility Estimates

Utility	Strategy to Be Affected	Base Estimate	Range	Source	Change in Rank Order for ICERs of Strategies Referencing PSM[a]
General population	All	0.93	0.837 to 1.0	Adapted from Regier et al., 2006[68]; assumed a range of +/- 10% around base estimate	No change
Acute hemorrhagic event	All	0.72	0.648 to 0.792	Adapted from Regier et al., 2006[68]; assumed a range of +/- 10% around base estimate	No change
Acute thrombo-embolic event	All	0.70	0.63 to 0.77	Adapted from Regier et al., 2006[68]; assumed a range of +/- 10% around base estimate	No change
Temporary disability	All	0.70	0.63 to 0.77	Adapted from Regier et al., 2006[68]; assumed a range of +/- 10% around base estimate	No change
Permanent disability	All	0.5	0.45 to 0.55	Adapted from Regier et al., 2006[68]; assumed a range of +/- 10% around base estimate	No change

ICER = incremental cost-effectiveness ratio; PSM = patient self-management.
[a]Full results for the one-way sensitivity analysis can be found in Appendix 13.

5.2.3 Scenario analyses

a) Scenario analysis: use of wholesale prices for POC devices and accessories

The base-case analysis incorporated the retail list prices for the POC devices (professional and patient grades) and the required accessories (lancets and strips). To reflect a scenario in which public health plans would purchase the devices from the manufacturers and then issue them to patients and caregivers, a scenario analysis was conducted using wholesale prices. The results (Table 14) showed that PSM became the least costly and most effective option.

Table 14: Results of the Base-Case Analysis Using Wholesale Prices for POC Devices				
Strategy	**Cost ($)**	**Effectiveness (QALY)**	**ICER ($/QALY) (compared with most cost-effective strategy)**	**Sequential ICER ($/QALY)**
PSM	$6,921	4.2136		
Lab	$7,033	4.1957	Dominated	Dominated
Clinic POC	$7,729	4.2021	Dominated	Dominated
PST	$7,890	4.1994	Dominated	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; POC = point of care; PSM = patient self-management; PST = patient self-testing.

b) Scenario analysis: similar clinical benefits (cost-minimization analysis)

Given that there was no evidence from our clinical systematic review that POC represents an improvement over lab in clinical outcomes (i.e., hemorrhage or thromboembolic events), a scenario analysis was conducted which assumed no differences in clinical outcomes between the various strategies (i.e., TTR is similar). The times spent above, below, and within target therapeutic range for PSM were applied for remaining strategies (PST, clinic POC, and lab). Results of this cost-minimization analysis (Table 15) showed that lab is the least costly option.

Table 15: Results of the Base-Case Analysis Assuming Similar Clinical Outcomes		
Strategy	**Cost ($)**	**Cost Difference (from least costly strategy)**
Lab	$6,261	-
PSM	$7,266	$1,005
Clinic POC	$7,375	$1,114
PST	$7,659	$1,398

POC = point of care; PSM = patient self-management; PST = patient self-testing.

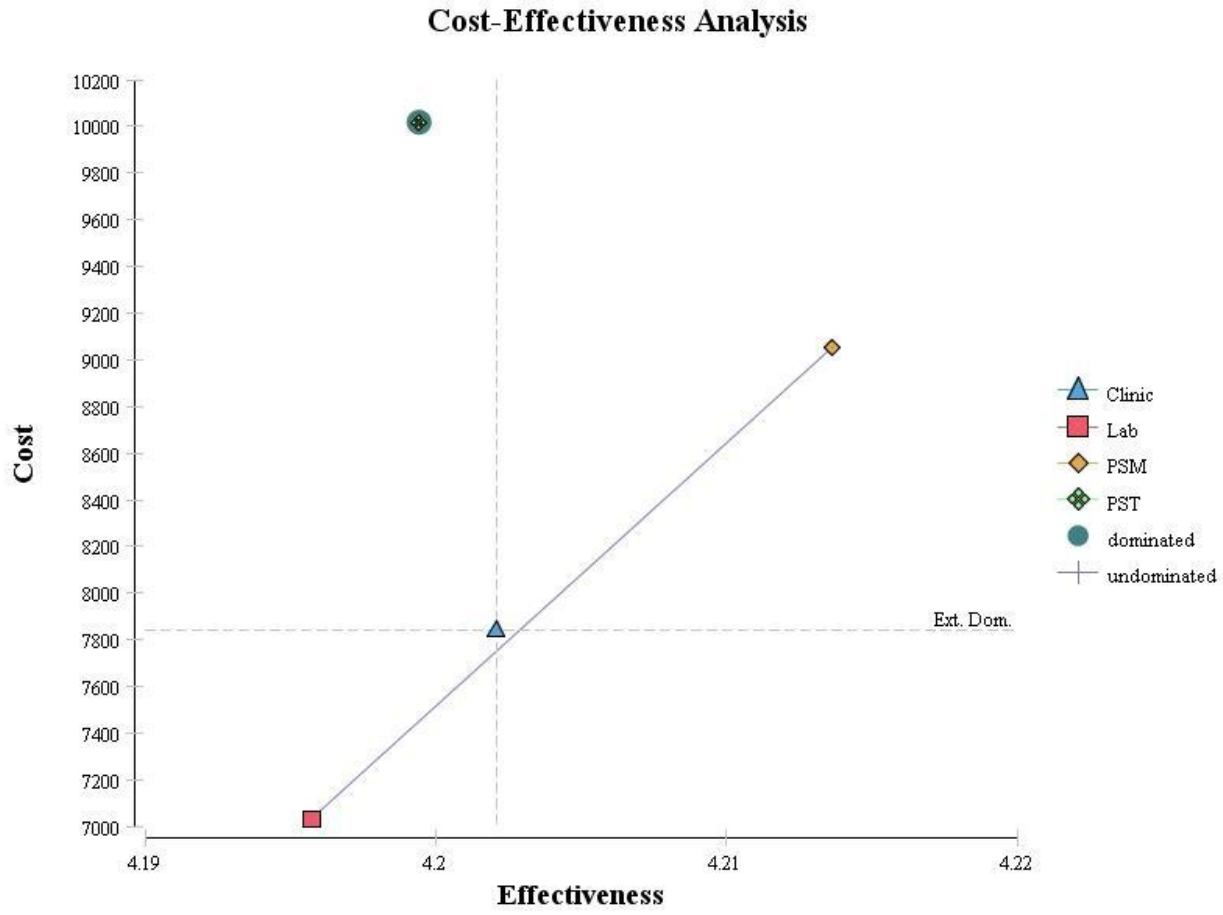
c) Scenario analysis: POC testing provided by home-care nurses

In this scenario, it was assumed that a home-care nurse facilitated POC testing for patients with mobility issues unable to travel to lab or clinic. It was assumed that the overall health status of this hypothetical cohort was comparable to the target population of this analysis. It was further assumed that it takes an hour of the nurse's time for such a visit (including driving time). The cost of driving for a round trip to the patient's home was also included. The frequency of such home visits was estimated at once a month, which is lower than the frequency of PST in PSM or PST. In this scenario, the results of the cost-effectiveness analysis showed that lab testing was the least costly option, followed by clinic POC and PSM. Clinic POC was extendedly dominated by PSM while PST was dominated by PSM (being more costly than clinic POC, while producing less QALYs) (Table 16, Figure 6).

Table 16: Results of Scenario Analysis: POC Testing Provided by Home-Care Nurses				
Strategy	**Cost ($)**	**Effectiveness (QALY)**	**ICER ($/QALY) (Compared with Most Cost-Effective Strategy)**	**Sequential ICER ($/QALY)**
Lab	$7,033	4.1957		
Clinic POC	$7,841	4.2021	127,356	Extendedly dominated
PSM	$9,055	4.2136	112,964	112,964
PST	$10,018	4.1994	808,160	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; POC = point of care; PSM = patient self-management; PST = patient self-testing.

Figure 6: Cost-Effectiveness Analysis Scenario: POC Testing Provided by Home-Care Nursing Staff

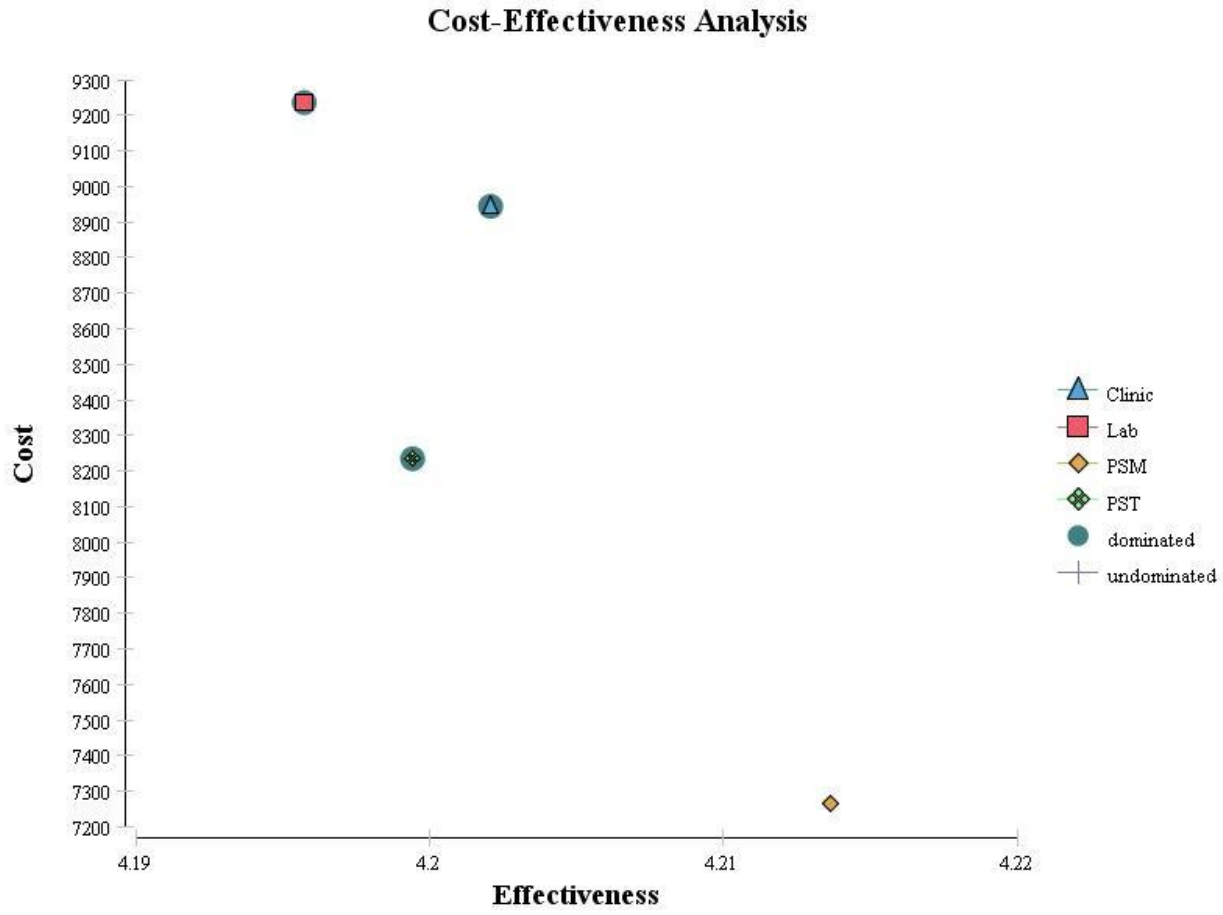


POC = point of care; PSM = patient self-management; PST = patient self-testing.

5.2.4 Scenario analysis: Expanded-payer perspective (includes patient costs)

The base-case analysis assumed that the payer would not cover patient costs of travel to clinic or lab, or lost wages as a consequence of the visit. However, this may not be applicable to all situations. A scenario analysis with an expanded-payer perspective was conducted in which it was assumed that the payer would cover any patient-level costs. Results of this scenario analysis showed that PSM dominated the other strategies (Figure 7, Table 17).

Figure 7: Cost-Effectiveness Analysis Scenario: Patient Costs Covered by Payer



PSM = patient self-management; PST = patient self-testing.

Table 17: Results of Scenario Analysis: Patient Costs Covered by Payer				
Strategy	**Cost ($)**	**Effectiveness (QALY)**	**ICER ($/QALY) (Compared with Most Cost-Effective Strategy)**	**Sequential ICER ($/QALY)**
PSM	$7,266	4.2136	-	-
PST	$8,234	4.1994	Dominated	Dominated
Clinic POC	$8,944	4.2021	Dominated	Dominated
Lab	$9,236	4.1957	Dominated	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; POC = point of care; PSM = patient self-management; PST = patient self-testing.

a) Scenario analysis on expanded-payer perspective

Canadian estimates were available for patient driving time and lost wages for clinic visits.[72] Both of these factors were used in calculating an *overall cost* of patient time. It was assumed that a visit to the lab would be double the distance to the clinic, as the number of labs tends to be fewer than that of clinics. The base model assumed an approximate driving distance of 20.8 km for a round trip to the clinic. This was varied from 10 km to 30 km per round trip in the one-way sensitivity analysis. Corresponding driving distances for a round trip to the lab were varied between approximately 20 km and 60 km. Model results remained robust to these changes (detailed results are presented in Table 18).

Table 18: Results of One-Way Sensitivity Analyses Patient Costs					
Patient Cost	**Strategy to Be Affected**	**Base Estimate**	**Range**	**Source**	**Change in Rank Order for ICERs of Strategies Referencing PSM**
Cost of patient driving time and lost wages per clinic visit	Clinic POC	$21.21	$10.61 to $31.82	Statistics Canada 2013[72]	No change
Cost of patient driving time and lost wages per lab visit	Lab	$42.43	$21.22 to $63.65	Statistics Canada 2013[72]	No change

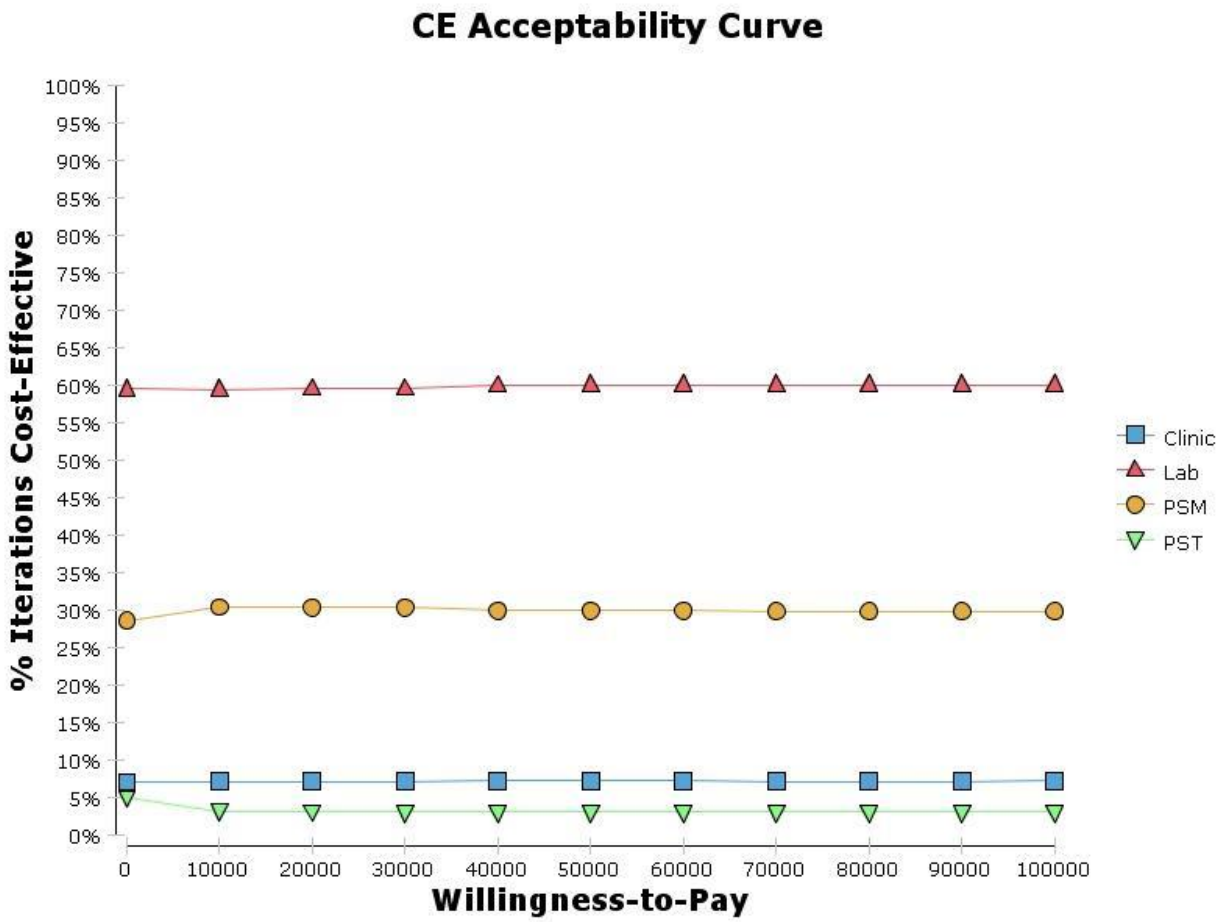
ICER = incremental cost-effectiveness ratio; POC = point of care; PSM = patient self-management.

Full results for the one-way sensitivity analysis can be found in Appendix 11.

5.2.5 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted to evaluate the impact of uncertainty on the model results. Figure 8 shows the cost-effectiveness acceptability curve for all four strategies (i.e., lab, clinic POC, PST, and PSM), when WTP is varied from $0 to $100,000. The results of the PSA showed that lab had the highest probability of being cost-effective with 60% at a WTP of $50,000 per QALY. The second most probable strategy was PSM with 30% at a WTP of $50,000 per QALY. The probability of lab being the most cost-effective option can be attributed to the lower total costs of lab compared with PSM and the uncertainty around the distributions assigned to the TTR values. For Clinic POC and PST the probabilities of being cost-effective at $50,000 per QALY were 15% and 6% respectively.

Figure 8: Cost-Effectiveness Acceptability Curve



CE = cost-effectiveness; POC = point of care; PSM = patient self-management; PST = patient self-testing.

6 DISCUSSION

6.1 Findings From the Clinical Review

For INR values within the target therapeutic range, POC meters produced results comparable to those obtained with the use of standard laboratory methods in monitoring patients on anticoagulant therapy, while providing a shorter time from blood withdrawal to INR results. Despite this, differences greater than 15% between POC INR values and standard laboratory values that would have changed the clinical management occurred in a number of patients, which varied across studies and according to the type of POC meters used. However, it remains unclear which method showed the more correct result, as errors can occur with either technique.

The use of POC meters led to a statistically significant increase of 6.14% in the time the tests were within the therapeutic target range as compared with the use of standard laboratory methods, with CoaguChek XS providing the largest increase.

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 the use of standard laboratory methods.

Limited data on patient satisfaction reported preference for finger stick and POC meters over venous collection by central laboratory methods, with the majority of patients preferring self-testing to standard laboratory methods. A greater improvement in quality of life after four months of treatment compared with baseline values was also observed in patients using POC meters.

Under the assumption that standard laboratory methods represent the standard reference for assessing the diagnostic accuracy of POC INR, evidence shows a strong correlation between POC INR values and lab INR values. Values in the commonly targeted therapeutic range of 2.0 to 3.5[81] were comparable between the two methods. However, the difference between INR values between the two methods may increase at high INR values, as Bland-Altman analyses in general showed an increased scatter at mean INR values of greater than or equal to 3.5 units. The decrease in POC meter sensitivity at high INR values may contribute to this difference. This review may point to the need for reconfirmation of INR values with standard laboratory methods when POC INR values are greater than or equal to 3.5 units.

While patient selection and characteristics were clearly described in the included RCTs, patient populations may not have been representative of the general population that would require INR monitoring. Patients in the included studies were often selected based on physical and mental competencies, as well as other factors such as education or perceived reliability in medication adherence and compliance with physician orders. Patients electing to enrol in a trial of self-testing or self-management may be more engaged with their own care than the broader population on OAT. An HTA produced by Connock et al. for the NHS HTA program[59] found that, on average, 33% of eligible participants agree to participate in trials, highlighting this potential self-selection. Given that TTR is often used as a proxy for risk of bleeding or thromboembolic event, information on whether out-of-range tests lie above or below the target range could provide additional clinical context. The HTA by Connock et al.[59] found that out-of-range tests are not uniformly distributed above and below the target range. While time or number of tests in a range is a surrogate for a decreased risk of negative clinical outcomes, they neither reflect the actual rate of clinical events, nor do they reflect the degree to which a measurement is outside

the range, with large deviations from the therapeutic range potentially representing a greater risk than small variations.

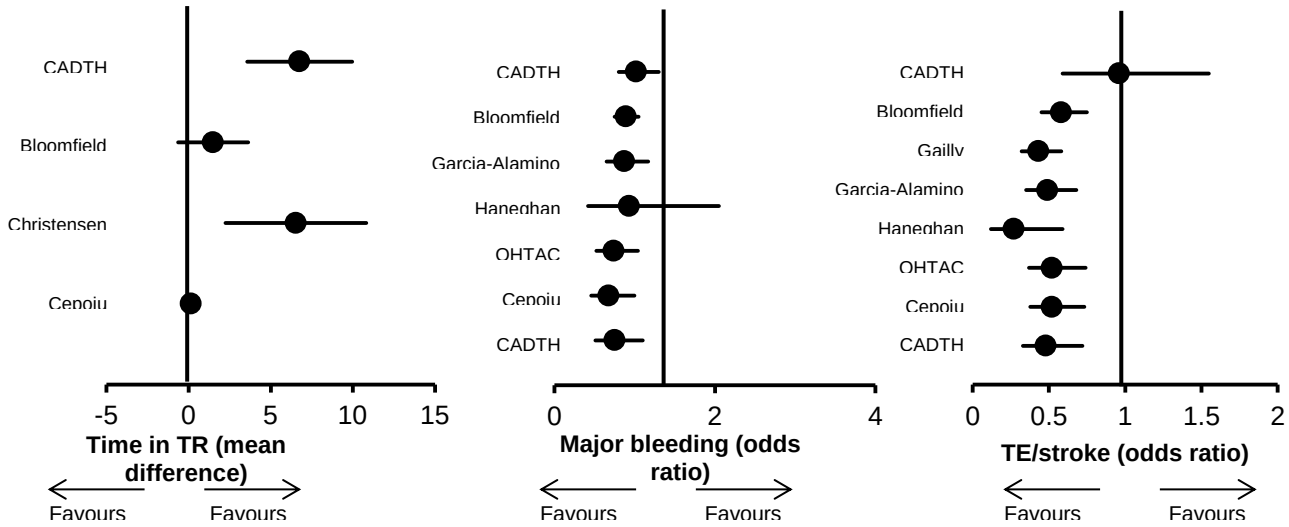
Despite the strong correlation between POC INR values and standard laboratory values, and the shorter turnaround time with POC, an important clinical consideration is the frequency of differences in INR values between the two methods large enough to alter clinical management. This review showed that patients from many studies had POC INR values that deviated more than 15% from laboratory measurements, and would have altered clinical management. This may have impacted the quality of treatment. However, this must be weighed with the statistically significant increase in the time patients' INR values stayed within the therapeutic target range when POC meters were used instead of conventional laboratory methods. The 6.14% increase means that, if the patient was under coagulation treatment for one year, monitoring the INR values by POC meters instead of conventional laboratory methods would have increased the time that INR values stayed within the target range by an average of approximately 25 days. Increased TTR is a potential advantage but did not statistically change the major bleeding rates and the thromboembolic/stroke rates compared with the use of conventional laboratory methods in this review, although most studies were not of adequate duration or size to reliably determine differences in these outcomes.

This systematic review adds to nine other systematic reviews that compared major clinical outcomes and time within target range between INR self-testing, or self-testing plus self-management, to usual care at anticoagulation clinics.[1,59,69,80,82-86] While the scope of our review is limited to POC meters that are currently in use in Canada *and* that are still being manufactured (resulting in the inclusion of five POC meters: CoaguChek XS, CoaguChek XS Plus, INRatio, i-STAT, and ProTime), the other systematic reviews did not limit the type of POC meters analyzed, In particular, CoaguChek S, which is no longer manufactured, was studied in a large number of trials included in past reviews. As a consequence, our review included fewer RCTs than the other reviews. Figure 9 shows outcomes of different systematic reviews when appropriate data were available. As shown, findings from our review are mostly in concordance with those from the other systematic reviews, in particular on time within target range and major bleeding rates. Our review and the systematic reviews by Christensen et al.[83] and Connock et al.[59] found the use of POC meters was associated with a statistically significant increase in time within target range, while the increases found in systematic reviews by Bloomfield et al. and Cepoiu et al.[1,82] were not statistically significant (Figure 9, Graph A). The inconsistent finding on this outcome may derive from variability across studies in the definitions of the therapeutic target range; a wider target range such as 1.8 to 4.0 would tend to yield a higher time the INR values stayed within the range than would a smaller range such as 2.0 to 3.5.

Our review and all the other systematic reviews agreed that there was no significant change in major bleeding rates between the two methods (Figure 9, Graph B). Regarding the rate of TE or stroke, there was disagreement between our review and the other systematic reviews (Figure 9, Graph C). While our review did not find a change in TE/stroke with the use of POC meters as compared with the use of standard laboratory methods, all the other systematic reviews found a statistically significant reduction in the risk of TE/stroke with POC meters. The reason behind this discrepancy may be due to the higher number of published trials on PST with POC *plus* PSM than the number of trials on PST alone that these systematic reviews included. Since subgroup analyses by these systematic reviews found that PST plus PSM statistically reduced the risks of TE /strokes while PST alone did not, the pooled estimates across all trials were deviated in favour of POC. The reduced risk of TE/stroke is expected, due to more frequent monitoring and dose adjusting, resulting in the increase in time in target range that POC was shown to provide. Had the number of trials on PST plus PSM included in our review[11,13] been

greater, a statistically significant difference in TE/strokes in favour of POC meters may have been found. Additionally, the trials included in our systematic review were primarily powered to detect differences in TTR and not clinical events. Therefore, real differences in the rates of potentially rare events may not be detected. Data on the all-cause mortality rate from the included trials in our systematic review were scarce and could not be pooled, but most systematic reviews showed pooled estimates that are statistically significant in favour of POC compared with laboratory-based methods. However, the NHS[59] found that a reduction in complications or deaths was not consistently associated with an improvement in anticoagulation control, and may be due to alternative explanations such as patient education and empowerment.

Figure 9: Review of Reviews



Graph A Graph B Graph C

CADTH = Canadian Agency for Drugs and Technologies in Health; OHTAC = Ontario Health Technology Advisory Committee; TE = thromboembolism; TR = therapeutic range.

The limited number of included trials in our review provides a Canadian focus to the report because it included only devices that are currently on the Canadian market. Limiting only to those devices currently being sold and manufactured (and therefore potentially more recently introduced devices) may also account for concurrent advances in laboratory testing technology or other aspects of anticoagulation management that may have changed since the introduction of POC devices. However, the small number of included trials made analyses of some outcomes such as mortality rate difficult, and limited subgroup analyses that would have provided information on outcomes based on trial quality, trial funding status, patients' underlying conditions, coagulopathy status, and settings (e.g., emergency room, hospital ward, anticoagulation clinic, home, PST alone, and PST plus PSM). These subgroup analyses could have helped to explain the heterogeneity across the included trials that need to be considered when interpretations of results are made. Findings on quality of life and patient satisfaction were drawn from scarce data using subjective and non-comparable parameters.

In general, the clinical review indicated that POC meters are reliable and comparable to standard laboratory methods in measuring INR values in the usual therapeutic target range. INR values above this range may need to be reconfirmed with standard laboratory methods. Compared with standard laboratory use, the use of POC INR meters may increase the time that INR values are within the target range but does not seem to change the risk of major bleeding. Despite other systematic reviews indicating that the use of POC INR lead to a statistically significant reduction in the risk of TE/stroke, the trials included in this review did not support that finding. The results of the meta-analysis must be interpreted with careful consideration given the significant level of heterogeneity across the studies.

6.2 Findings From the Economic Analysis

The results of the economic analysis suggest that lab is the least costly option and that PSM is a cost-effective option, with an ICER of approximately $13,000 per QALY gained. Clinic POC and PST continued to be dominated by PSM as they were associated with increased costs and fewer QALY gains than PSM. These results were primarily driven by small differences in QALYs across strategies, hence they should be considered alongside the disaggregated costs and QALYs.

Costs of patient-grade and professional-grade testing were varied based on the estimates provided by Canadian manufacturers. Most of these variations did not change the direction of the results from the cost-effectiveness analysis except when the cost of the patient-grade device was increased from $499 to $1100; this resulted in clinic POC emerging as the most cost-effective option compared with lab. The cost of lab tests for INR is also likely to vary across jurisdictions due to factors such as test volumes, staffing, and equipment. Based on the opinion of specialists in laboratory medicine, per test costs reported in benefits schedules were considered to be much higher than actual costs. Hence, the per-test cost was assumed to be $2.00 in the reference case analysis. To examine the impact of variance in this parameter, a threshold analyses was conducted using a range of $2 to $14 dollars per lab test. The results of this analysis revealed that at a cost of approximately $6.50 and above per lab test, PSM became the dominant option over lab, PST and clinic POC. Sensitivity analyses on variables pertaining to frequency of testing (varied between weekly testing to monthly testing) showed that PSM dominates when its testing frequency is reduced to 12 times a year, resulting in lower total costs than lab testing. In contrast, increasing the PSM testing frequency to 42 times a year or more leads to clinic POC becoming the most cost-effective option compared with lab as a result of the increased total costs of PSM due to increased testing. Variations in the utility estimates did not influence the overall results. As the patient population simulated in the economic model was relatively healthy, with POC INR values within a well-managed range, it is likely that a similar analysis with a cohort of patients who were less well-managed (and therefore with increased clinical events resulting in lower quality of life estimates) would produce differing results.

Another scenario analysis assuming that home-care nurses would provide INR testing using a home-based device at the patient's residence showed that such a strategy would be more expensive than lab testing. The average wages for nurses are higher than that of the general population, and therefore time spent by a home-care nurse on INR testing would result in higher expenses.

Based on the findings of our clinical systematic review, there is no evidence showing POC to be superior to lab testing in improving overall clinical outcomes. Because of this conclusion, a cost-

minimization analysis was conducted using the TTR values of PSM across all strategies (PST, clinic POC, and lab). The results provide an estimate of the overall costs of each strategy, with lab being the least costly option.

When a scenario analysis using an expanded-payer perspective was conducted assuming that patient costs (travel and lost wages) would be covered by the payer, the results of the analysis changed. PSM became the dominant strategy, being the least costly option with the most QALYs. However, the second least costly option was lab testing in this scenario, although it was also dominated by PSM. Both clinic POC and PST became dominated (more costly and less effective) in comparison with PSM. Results of this scenario analysis may be attributed to the differential costs associated with PST, causing it to become less cost-effective compared with lab testing. In addition to the device cost, PST also requires the annual expense of anticoagulation supervision by a physician, which is more expensive compared with the single annual specialist consultation needed for the PSM and lab strategies. Further, when patient travel costs are not covered by the payer for the lab-testing strategy, it becomes a more attractive option relative to a clinic or PST.

This study adds to the existing knowledge on the cost-effectiveness of POC INR devices, particularly from a decision-maker perspective. A systematic review was used to inform the effectiveness of various testing strategies in this model. While the review showed significant differences in TTR for each of the strategies, no discernible benefit was observed with respect to the risk for adverse events that could be attributed to the use of a specific testing strategy. Possible reasons for TTR differences not resulting in clinical benefits can be attributed to studies not being powered to detect differences in clinical outcomes. For the purposes of this analysis, benefit in health outcomes was assumed to be gained by remaining in the therapeutic range longer in the case of testing through POC INR devices, as compared with lab testing. Conversely, adverse events were directly related to the likelihood of being above or below the therapeutic range. The costs for testing devices were obtained from Canadian manufacturers, most health service provision costs were obtained from the provincial Schedule of Medical Benefits, and all estimates of wages were from Canadian data. These aspects render the results relevant to the Canadian context. The scenario analysis using an expanded-payer perspective that included patient-level costs (i.e., travel time and lost wages) helped elucidate the cost differences pertaining to various settings, such as home versus clinic or lab, or rural versus urban. These details are also relevant to the objectives of this analysis and provide additional information to decision-makers.

Despite its strengths, this analysis also had a number of limitations. The model assumed that the target population would include patients who had relatively well-managed INR, and had the visual and cognitive ability to understand the INR results presented by portable devices. Therefore, the results may not be generalizable to other patient populations on OAT, such as patients with extreme INR values or patients with limited vision, comprehension, or dexterity. While estimates on the cost of patient-grade or professional-grade devices were available through Canadian manufacturers, corresponding information on the upfront cost of lab-testing equipment was not included, primarily because the cost of lab equipment would be considered as a capital investment. Further, the equipment used in labs is likely utilized for a variety of other tests as well, and the isolated cost of capital investment attributable to INR testing would be difficult to discern. There was limited data that directly compared patient outcomes for the range of different brands of testing devices. Therefore, it was assumed different brands of devices within each category were equally effective. Furthermore, the model was based on broad estimates of variability in resource utilization and patient time. If more detailed data on these

estimates becomes available, the implications of this analysis may change. Results can also vary across provinces based on patient reimbursement policies. The analysis was based on the attributes of a relatively healthy patient population. The QALY estimates reflect this assumption. If the analysis were to include a broader spectrum of the underlying disease, these estimates may no longer be applicable. In addition, there was limited evidence available on the impact of quality of life when a patient uses a home-based testing device versus being tested in the clinic or lab. While it is likely that the patient's family also experiences stress and loss in quality of life owing to the patient's illness, it was beyond the scope of this model to include such subjective measures. It is important to point out that the introduction of POC would not likely translate into proportional decreases in expenditures, as POC is unlikely to entirely replace existing laboratory capacity for INR measurement; hence, many of the fixed costs such as equipment, personnel, etc., will need to be maintained regardless of whether POC is implemented for selected patients.

Another limitation was the inability of the proposed model to incorporate some of the other findings of our systematic review, such as the apparent reduction in sensitivity of POC devices compared with laboratory testing when INR is greater than 3.5, and the finding in some studies of a relatively high rate of clinically relevant discordance between POC and lab testing.

The health status of rural and remote area patients continues to fall behind that of city-dwelling Canadians, with residents in remote and rural areas experiencing higher rates of morbidity, mortality, and risk factors for ill health.[87,88] Regarding access to health services, people in rural and remote areas may be disadvantaged because of distance, time, cost, and availability of transport, as well as shortages and uneven distributions of health services and professionals. Appropriate allocation of resources and professionals is recognized as a requirement for the provision of high-quality health care that reflects best practice and is evidence-based. Rural and remote health practice, particularly in a country as large and geographically and culturally diverse Canada, presents different contexts that need to be carefully considered when implementing initiatives to assist practitioners to use evidence. However, we found a paucity of empirical literature on the clinical or cost impacts of implementing POC INR technology in rural and remote settings.

Lab testing of INR in remote and rural settings may be associated with higher costs than assumed in our analysis due to factors such as shipping costs, sample loss (such as due to freezing), or increased travel time and lost wages. As well, higher turnaround times for lab test results in remote and rural areas, or inaccurate results caused by sample deterioration (such as due to inadequate freezing), may compromise TTR, potentially leading to increased rates of clinical events such as thromboembolism, stroke, and hemorrhage. Hence, self-testing strategies generally, and PSM in particular, could be even more attractive from a cost-effectiveness perspective versus lab testing in remote/rural areas than was observed in the base-case analysis. The availability of self-testing strategies for INR in areas where lab testing is difficult to access could also enable initiation of OAT for a greater proportion of patients who are candidates for such therapy, which could have further clinical and cost benefits.

7 CONCLUSIONS

The available evidence indicates that POC INR technologies are generally precise and accurate when INR values are in the commonly targeted therapeutic range. They can improve anticoagulation control by increasing the time INR values are within the therapeutic target range; however, discordances in INR values of a magnitude that would alter clinical management occur in a number of patients. While improved anticoagulation control, as indicated by increased TTR, may be associated with a decreased risk of major bleeding or thromboembolic events, our review did not demonstrate a significant difference in the risk of hemorrhagic or thromboembolic events between POC and standard laboratory testing methods. Limited evidence showed that POC INR devices can be used efficiently following patient training. There was a lack of evidence on the comparative effectiveness between different POC INR technologies, and for PST versus PSM.

Although lab testing was the least costly strategy in the base-case analysis, the results of the economic analysis support the use of POC devices for PSM in the management of INR among select patients on OAT. PSM remained a cost-effective option even when resource utilization and costs were varied in order to model potential differences in these parameters across various settings. While evidence for the use of POC INR technologies in Canadian rural and remote areas was lacking, self-testing strategies, particularly PSM, may be even more cost-effective options in areas where lab testing is difficult to access. Resource utilization and costs for each POC strategy and lab testing are likely to vary in diverse health care settings; hence, the use of setting-specific inputs and costs may better inform decision-making within each setting.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

OVERVIEW	
Date of Search:	February 25, 2013
Interface:	Ovid
Databases:	• Embase 1974 to 2013 (with daily update) • MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to Present **Note:** Subject headings will be customized for each database. Duplicates between databases will be removed in Ovid.
Study Types:	No filters were applied to limit the retrieval by study type. Conference abstracts, comments, editorials, and letters were removed.
Limits:	English Humans No date limits were applied.
Alerts:	Monthly search updates began March 2013 and ran until May 2014.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
Exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type
.dm	Device manufacturer (in Embase)
.dv	Device trade name (in Embase)
use oemezd	Limit search line to Embase database only
use pmez	Limit search line to MEDLINE database only

MULTI-DATABASE STRATEGY	
#	**Strategy**
1	Point of Care Systems/ use pmez
2	point of care testing/ use oemezd
3	(point of care or POC or POCT or self-test* or self-monitor* or self-manag* or near patient or bedside or bed-side or portable or hand-held or handheld or mobile or ambulatory or rapid test* or rapid screen* or remote test* or rapid diagnos*).ti,ab.
4	(iSTAT or i-STAT).ti,ab,dm,dv.
5	or/1-4
6	International Normalized Ratio/
7	Prothrombin Time/
8	(international normalised ratio* or international normalized ratio* or INR or prothrombin time* or prothrombin ratio* or rapid coagulation or "PT/INR" or PT-INR or PT ratio* or protime or protrombin time* or protrombin ratio* or prothrombine time* or prothrombine ratio*).ti,ab.
9	or/6-8
10	5 and 9
11	(CoaguChek or CoaguCheck or INRatio or CoaguSense or Coag-Sense).ti,ab,dm,dv.
12	10 or 11
13	exp animals/
14	exp animal experimentation/ or exp animal experiment/
15	exp models animal/
16	nonhuman/
17	exp vertebrate/ or exp vertebrates/
18	animal.po.
19	or/13-18
20	exp humans/
21	exp human experimentation/ or exp human experiment/
22	human.po.
23	or/20-22
24	19 not 23
25	12 not 24
26	25 not Conference abstract.pt.
27	26 not (comment or newspaper article or editorial or letter or note).pt.
28	limit 27 to English language
29	remove duplicates from 28
	Filters for economic subset only: SR, MA, HTA, and economic publications
30	meta-analysis.pt.
31	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
32	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.

MULTI-DATABASE STRATEGY	
#	**Strategy**
33	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
34	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
35	(data synthes* or data extraction* or data abstraction*).ti,ab.
36	(handsearch* or hand search*).ti,ab.
37	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
38	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
39	(meta regression* or metaregression*).ti,ab.
40	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
41	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
42	(cochrane or (health adj2 technology assessment) or evidence report).jw.
43	(meta-analysis or systematic review).md.
44	(comparative adj3 (efficacy or effectiveness)).ti,ab.
45	(outcomes research or relative effectiveness).ti,ab.
46	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
47	or/30-46
48	29 AND 47
49	(economic adj2 model*).mp.
50	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
51	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit).ti.
52	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
53	(cost or costs or economic*).ti. and (costs or cost-effectiveness or markov).ab.
54	or/49-53
55	29 AND 54

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
CINAHL through EBSCO	Same keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used and MeSH translated to CINAHL headings.
HEED through EBSCO	Same keywords and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for HEED.
Cochrane Library through Wiley	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

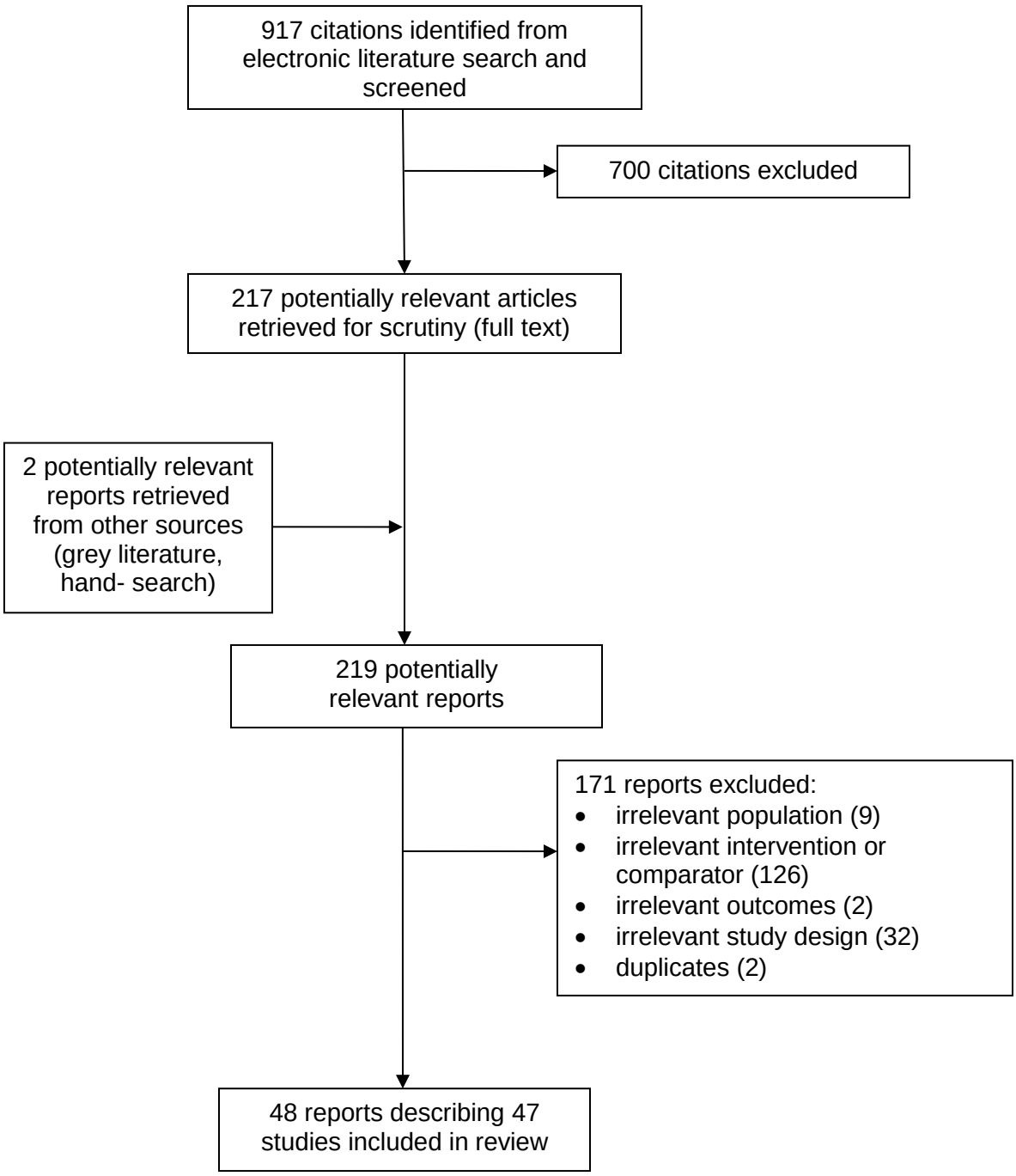
Grey Literature

Keywords:	Will include terms for point-of-care testing (POCT) and INR
Limits:	No date limits

The following sections of the CADTH grey literature checklist, *Grey matters: a practical deep web-based tool for evidence-based medicine* (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

APPENDIX 2: SELECTION OF INCLUDED STUDIES



APPENDIX 3: INCLUDED AND EXCLUDED STUDIES

Included Studies

Adkinson CL, Pettus JD, Chirico MJ, Taylor JR. Assessment of international normalized ratio using coaguchek xs and coaguchek s as compared with central laboratory testing. Point Care. 2009;8(3):126-30.

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Population not of Interest

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APPENDIX 4: DATA EXTRACTION FORM FOR ACCURACY AND CLINICAL EFFECTIVENESS REVIEW

Reviewer		
RefID		
Author, date		
Country of origin		
Industry funding (partial or total)		
Study design		
Study duration		
Eligibility criteria		
Patient group:	**Intervention**	**Control**
Number enrolled		
Number completing study		
Age, gender (female/male)		
Other		
Intervention name:		
Intervention type:	POC INR	Comparator
Accuracy outcomes:	**Precision**: coefficient of variance (CV) **Analytical accuracy (**Average difference between POC and Lab; predetermined < 0.5 units as acceptable agreement): Bland-Altman 95% limits of agreement: **Diagnostic accuracy (**Median deviation of POC INR relative to lab INR; predetermined ≤ 15% as acceptable accuracy) **Time in therapeutic range** (quality of OAT)	
Clinical effectiveness outcomes	**Adverse events**	
Study Limitations		
Other		
Notes		

POC =point of care; INR = international normalized ratio; OAT = oral anticoagulation therapy.

APPENDIX 5: STUDY CHARACTERISTICS

Table A1: Study Characteristics

First Author, Year; Study Design	Study Setting; Industry Funding (Yes/No)	Comparison Groups	POC Technique	No. of Patients/ No. of Comparison Measurements
Adkinson et al., 2009;[51] prospective observational	University outpatient anticoagulation clinic; NR	CoaguChek XS; laboratory instrument NR	Finger stick by HCW	95/95
Andrew et al., 2001;[14] prospective observational	Multi-hospital outpatient anticoagulation clinics; Yes	ProTime; Electra 900 (reference lab)	Patient self-test	386/NR
Andrews et al., 2001;[15] prospective observational	Hospital outpatient anticoagulation clinic; Yes	ProTime; Electra 900 (reference lab)	Home self-test	82/NR
Bardakci et al., 2013;[16] prospective observational	Hospital; cardiovascular surgery clinic; No	CoaguChek XS; CA-7000 (Sysmex)	Finger stick by HCW	105/NR
Bauman et al., 2008;[17] prospective observational	Children's hospital outpatient anticoagulation clinic; NR	CoaguChek XS; Hemoliance	Home self-test	62/NR
Bereznicki et al., 2007;[18] prospective observational	Home self-test; Yes	CoaguChek XS; CA1500 (Sysmex)	Home self-test	22/59
Biasiolo et al., 2000;[19] prospective observational	University outpatient anticoagulation clinic; NR	ProTime; Electra 1400 system	Finger stick by HCW	150/180
Boehlen, 2005;[20] prospective observational	Hospital outpatient anticoagulation clinic; Yes	i-STAT; BCS analyzer	Finger stick by HCW	35/35
Christensen et al., 2009;[53] case series	Outpatient anticoagulation clinic; No	CoaguChek XS; STAR Evolution	Home self-test and self-management	
Christensen et al., 2011;[8] RCT	Hospital outpatient anticoagulation clinic; No	CoaguChek XS; STAGO STAR Evolution	Home self-test	140/NR
Colella et al., 2012;[21] prospective observational	Hematology centre outpatient anticoagulation clinic; Yes	CoaguChek XS; AMAX Destiny	Finger stick (NR if patient or HCW)	170/200

Table A1: Study Characteristics				
First Author, Year; Study Design	**Study Setting; Industry Funding (Yes/No)**	**Comparison Groups**	**POC Technique**	**No. of Patients/ No. of Comparison Measurements**
Donaldson et al., 2010;[22] prospective observational	Hospital outpatient anticoagulation clinic; NR	i-STAT; CoaguChek XS Plus; STAGO system (reference lab)	Finger stick by HCW	52/52
Drescher et al., 2011;[23] prospective observational	Hospital emergency room; Yes	i-STAT; BCS	Venous blood by HCW	32/28
Giles et al., 2010;[24] prospective observational	Hospital cardiac wards; Yes	CoaguChek XS; Sysmex CA-7000	Finger stick by HCW	50/117
Greenway et al., 2009;[25] prospective observational	Children's hospital anticoagulation service; Yes	CoaguChek XS; STA Compact or STAR Evolution	Finger stick by HCW	31/31
Hashimoto et al., 2012;[26] prospective observational	University anticoagulation clinic; No	CoaguChek XS; BCS XP	Finger stick by HCW	124/148
Hur et al., 2013;[27] prospective observational	Medical centre outpatient anticoagulation clinic; NR	CoaguChek XS Plus; STAR system	Venous blood by HCW	118/118
Joshi et al., 2008;[28] prospective observational	Hospital surgical unit; Yes	ProTime; laboratory instrument NR	Finger stick by HCW	4/41
Karon et al., 2008;[29] prospective observational	Medical centre outpatient anticoagulation clinics; NR	CoaguChek XS; i-STAT; MDA 180	Finger stick by HCW	98/NR
Kong et al., 2008;[30] prospective observational	Outpatient anticoagulation clinic; Yes	CoaguChek XS; STart 4	Finger stick by HCW	250/253
Lakshmy et al., 2010;[50] prospective observational	Cardiothoracic centre outpatient anticoagulation clinic and inpatients; NR	CoaguChek XS; Diagnostica STAGO	Finger stick by HCW	42/42
Lawrie et al., 2012;[31] prospective observational	Hospital outpatient anticoagulation clinic; Yes	CoaguChek XS Plus; CA-7000 or CA-1500 analyzer	Finger stick (NR if patient or HCW)	168/168

Table A1: Study Characteristics				
First Author, Year; Study Design	**Study Setting; Industry Funding (Yes/No)**	**Comparison Groups**	**POC Technique**	**No. of Patients/ No. of Comparison Measurements**
Matchar et al., 2010;[9] RCT	Veterans Affairs medical centres anticoagulation clinics; Yes	ProTime; laboratory instrument NR	Patient self-test	2922/NR
McBane et al., 2005;[32] prospective observational	Medical clinic anticoagulation clinic; Yes	ProTime; MDA 180	Finger stick by HCW	94/94
Moon et al., 2010;[54] Case series	Medical centre; NR	CoaguChek XS; STAR Evolution	Finger stick by HCW	43/120
Moore et al., 2007;[33] prospective observational	Hospital outpatient anticoagulation clinic; Yes	ProTime; INRatio; Sysmex CA1500	Finger stick by HCW	186/50 ProTime; 96 INRatio
Nam et al., 2008;[34] prospective observational	Hospital outpatient cardiac clinic; Yes	CoaguChek XS; ACL 9000	Finger stick (NR if patient or HCW)	93/NR
Nanduri et al., 2012;[52] retrospective observational cohort	Hospital emergency room; NR	i-STAT; Diagnostica STAGO Neoplastine C1 plus prospective observational	Finger stick by HCW	637/637
Paioni et al., 2009;[35] prospective observational	Children's hospital outpatient anticoagulation clinic; NR	CoaguChek XS; STA Compact	Home self-test	35/27 (using CoaguChek XS)
Pena et al., 2012;[36]pProspective observational	Hospital outpatient anticoagulation clinic; Yes	i-STAT; MDAII	Finger stick by HCW	50/50
Reed and Rickman, 1999;[37] prospective observational	Veterans Affairs medical centre; Yes	ProTime; Electra 1600C	Finger stick by HCW	93/93
Rizos et al., 2010;[38] prospective observational	Hospital neurological emergency room; No	CoaguChek XS; laboratory instrument NR	Venous blood by HCW	10/NR
Rizos et al., 2009;[39] prospective observational	Hospital neurological emergency room; No	CoaguChek XS; laboratory instrument NR	NR	161/NR
Ryan et al., 2010;[10] RCT crossover	Hospital outpatient anticoagulation clinic; Yes	CoaguChek XS; Sysmex CA-7000 or CA-1500	Home self-test	162/673

Table A1: Study Characteristics				
First Author, Year; Study Design	**Study Setting; Industry Funding (Yes/No)**	**Comparison Groups**	**POC Technique**	**No. of Patients/ No. of Comparison Measurements**
Sobieraj-Teague et al., 2009;[40] prospective observational	At-home health service; NR	CoaguChek XS; ACL Futura Plus	Finger stick by HCW	98/337
Solvik et al., 2010;[41] prospective observational	Hospital outpatient anticoagulation clinic; Yes	CoaguChek XS; INRatio; STA Compact	Finger stick by HCW	36/136
Stoysich et al., 2001;[42] prospective observational	Hospital inpatients; NR	ProTime; Sysmex CA6000	Finger stick by HCW	30/51
Sunderji et al., 2004/2005;[11,55] RCT	Hospital outpatient anticoagulation clinic and home-based management; Yes	ProTime; BCS Coagulometer	Patient self-test and self-management	170/91
Sunderji et al., 1999;[43] prospective observational	Home-based management; Yes	ProTime; laboratory instrument NR	Patient self-test and self-management	10/16
Taborski et al., 2004;[44] prospective observational	NR (possibly anticoagulation clinic); Yes	INRatio; STA Compact	Finger stick (NR if taken by patient or HCW)	82/82
Tay et al., 2002;[45] prospective observational	Hospital outpatient anticoagulation clinic; NR	ProTime; MCL2	Finger stick by HCW`	50/50
Thompson et al., 2008;[46] prospective observational	Hospital outpatient anticoagulation clinic; NR	INRatio; laboratory instrument NR	Home self-testing	50/NR
Thompson et al., 2012;[12] RCT	Hospital outpatient anticoagulation clinic; NR	INRatio; laboratory instrument NR	Home self-testing	200/NR
Torreiro et al., 2009;[47] prospective observational	Hospital outpatient anticoagulation clinic; NR	CoaguChek XS; Sysmex CA1500	Home self-testing	41/218
Verret et al., 2012;[13] RCT	Heart institute outpatient anticoagulation clinic; Yes	CoaguChek XS; laboratory instrument NR	Home self-testing and self-management	114/NR

Table A1: Study Characteristics				
First Author, Year; Study Design	**Study Setting; Industry Funding (Yes/No)**	**Comparison Groups**	**POC Technique**	**No. of Patients/ No. of Comparison Measurements**
Wieloch et al., 2009;[48] prospective observational	Hospital outpatient anticoagulation clinic; Yes	CoaguChek XS; BCS XP	Finger stick by HCW	397/NR
Williams and Griffiths, 2007;[49] prospective observational	Hospital; No	CoaguChek XS; STA Compact	Finger stick by HCW	38/97

HCW = health care worker; NR = not reported; RCT = randomized controlled trial.

APPENDIX 6: PATIENT CHARACTERISTICS

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Adkinson et al., 2009[51]	CoaguChek XS	Include: adult patients on warfarin therapy Exclude: none	n = 95; Sex: 45/50 (47/53%); Age: 59 ± SD 15	No
Andrew et al., 2001[14]	ProTime	Include: patients attending anticoagulation clinics Exclude: none	n = 386; Sex: 212/174 (54.9/45.1%); Age: 45 (range 1 to 85)	No
Andrews et al., 2001[15]	ProTime	Include: adult patients (≥ 18 years) attending anticoagulation clinics Exclude: physically or mentally unsuitable for self-testing	n = 82; Sex: 32/50 (39/61%); Age: 55 (range 18 to 81)	Self-test
Bardakci et al., 2013[16]	CoaguChek XS	Include: patients undergoing open-heart surgery for mechanical valve replacement Exclude: patients on warfarin for another reason, emergency operations, heart valve redo procedures, diabetes, hypertension	n = 105; Sex NR; Age: 56.4 ± 12.9 (range 27 to 82	No
Bauman et al., 2008[17]	CoaguChek XS	Include: children < 18 years old, requiring more than 3 months of warfarin therapy Exclude: NR	n = 62; Sex NR; Age: < 18 years (range 18 months to 17 years)	Self-test
Bereznicki et al., 2007[18]	CoaguChek XS	Include: patients involved in a pilot trial of warfarin home-monitoring; Internet accessibility Exclude: NR	n = 22; Sex: 5/15; Median age: 73 years	Self-test
Biasiolo et al., 2000[19]	ProTime	Include: patients attending anticoagulation clinic; stable OAT; ≥ 3 preceding INRs in	n = 150; Sex NR; Age NR	No

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
		therapeutic range Exclude: NR		
Boehlen et al., 2005[20]	i-STAT	Include: patients on oral anticoagulation therapy (vitamin K antagonists) attending outpatient clinic; age ≥18 years Exclude: concomitant therapy with heparin	n = 35; Sex NR Age NR	No
Christensen et al., 2009[53]	CoaguChek XS	Include: >18 years old; warfarin therapy for mechanical aortic valve or atrial fibrillation; stable OAT; therapeutic target range 2 to 3 INR Exclude: major complications after onset of OAT; major bleeding event; other indication of OAT except mechanical aortic valve or atrial fibrillation; other antithrombotic medicine other than warfarin or Aspirin	n = 24; Sex: 6/18; Age: 61.5 ± 7.7	Self-test; self-management
Christensen et al., 2011[8]	CoaguChek XS	Include: patients on lifelong therapy and treated ≥ 6 months; Internet accessibility Exclude: NR	n = 140; Sex: 245/424 (37/63%); Age: 66.9 (range 19 to 93)	Self-test
Colella et al., 2012[21]	CoaguChek XS	Include: adult patients of an anticoagulation clinic Exclude: NR	n = 170; Sex NR; Age: 50 (range 18 to 84)	No
Donaldson et al., 2010[22]	i-STAT; CoaguChek XS Plus	Include: patients aged ≥18 years attending an anticoagulation clinic; receiving warfarin for at least 7 days Exclude: NR	n = 52; Sex: 22/30 Age: 71.2 ± SD 10.9	No
Drescher et al., 2011[23]	i-STAT	Include: adult patients in the emergency department; taking warfarin Exclude: NR	n = 32; Sex NR; Age: range 19 to 92	No

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Giles et al., 2010[24]	CoaguChek XS	Include: adult patients in cardiac/cardiovascular wards and cardiac catheter laboratory Exclude: NR	n = 50; Sex: 17/33 (34/66%); Median age 70 (range 29 to 99)	No
Greenway et al., 2009[25]	CoaguChek XS	Include: pediatric patients <16 years old, managed by hospital anticoagulation unit Exclude: NR	n = 31; Sex: 15/16; Age range: 0.5 to 16 years	No
Hashimoto et al., 2012[26]	CoaguChek XS	Include: patients of a university anticoagulation clinic; INR >3.5 Exclude: NR	n = 124; Sex NR; Age: 49 (range 13 to 78)	No
Hur et al., 2013[27]	CoaguChek XS Plus	Include: patients attending an anticoagulation clinic; receiving OAT Exclude: NR	n = 118; Sex: 48/70 Age: median 68 (range 5 to 87)	No
Joshi et al., 2008[28]	ProTime	Include: cardiac assist patients > 18 years old, with cardiac assist device implant; on warfarin; good cognition levels Exclude: NR	n = 4; Sex: 0/4 (0/100%); Age: 52 ± SD1.3	No
Karon et al., 2008[29]	CoaguChek XS; i-STAT	Include: patients of 2 anticoagulation clinics; long-term anticoagulation; stable INRs with warfarin therapy for >1 month Exclude: patients receiving heparin; new patients	n = 98; Sex NR; Age NR	No
Kong et al., 2008[30]	CoaguChek XS	Include: patients of an anticoagulation clinic Exclude: NR	n = 250; Sex: 103/123 (44/56%); Age: 58.4 (range 17 to 90)	No
Lakshmy et al., 2010[50]	CoaguChek XS	Include: patients attending anticoagulation clinic plus inpatients Exclude: NR	n = 24; Sex: NR Age: NR	No

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Lawrie et al., 2012[31]	CoaguChek XS Plus	Include: patients attending anticoagulation clinic; INR 4.5 to 8.0 Exclude: NR	n = 168; Sex: 86/82 Age: 66 (range 24 to 91)	No

Matchar et al., 2010[9]	ProTime	Include: patients of Veterans Affairs anticoagulation clinics; atrial fibrillation, mechanical heart valve, or both; requiring long-term warfarin therapy for an indeterminate period; competent to perform self-test (with or without caregiver assistance)
		Exclude: NR
			n = 2,922;
			Intervention:
			n = 1,465;
			Sex: 25/1440 (2/98%);
			Age: 66.6 ± SD 9.7
			
			Control:
			n = 1,457;
			Sex: 26/1431 (2/98%);
			Age: 67.4 ± SD 9.4
				Self-test (intervention group only)

McBane et al., 2005[32]	ProTime	Include: Patients with acute thrombotic disorders on long-term anticoagulation Exclude: NR	n = 94; Sex: 34/66% Age: 59 years ± SD 17 (range 27 to 84)	No
Moon et al., 2010[54]	CoaguChek XS	Include: pediatric patients < 16 years attending a cardiac and vascular medical centre; hematocrit 23% to 54% Exclude: NR	n = 43; Sex: 20/23; Age: 7.4 (range 2.7 to15.0)	No
Moore et al., 2007[33]	ProTime; INRatio	Include: patients attending an anticoagulation clinic Exclude: none	n = 186; Sex NR Age NR *ProTime:* n = 50 *INRatio*: n = 96	No
Nam et al., 2008[34]	CoaguChek XS	Include: adult patients with atrial fibrillation attending an anticoagulation clinic; taking warfarin Exclude: NR	n = 93; Sex: 28/65; Age: 62 (range 43 to 83)	No

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Nanduri et al., 2012[52]	i-STAT	Include: patients presenting to the emergency department; acute cerebrovascular disease; age ≥ 18 years; using a POC INR instrument < 30 months Exclude: taking unfractionated or LMW heparin	n = 637; Sex: 50/50% Age: 73.6 ± SD 14.1	No
Paioni et al., 2009[35]	CoaguChek XS	Include: pediatric patients on long-term OAT with phenprocoumon willing to perform home self-testing Exclude: none	n = 35; Sex: 12/23; Age: 9.2 (range 0.4 to 18.5)	Self-test
Pena et al., 2012[36]	i-STAT	Include: anticoagulation clinic adult patients receiving Coumadin; target INR of 2.0 to 3.0; plus 20 healthy volunteers not receiving anticoagulation therapy to determine in-house normal ranges Exclude: patients receiving other anticoagulation medications or heparin; those diagnosed with lupus	n = 50; Sex: 14/36 Age: median 66.5 (range 27 to 92)	No

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Reed and Rickman, 1999[37]	ProTime	Include: adult patients attending a warfarin clinic or homebound patients receiving warfarin; additional 20 control patients not receiving warfarin Exclude: none	n = 93; *Clinic:* n = 61 Sex: 1/60 (2/98%) Age: 65 (range 49 to 84) *Homebound:* n = 10 Sex: 0/10 (0/100%) Age: 74 (64 to 82) *Control:* n = 22 Sex: 3/19 (14/86%) Age: 60 (38 to 76)	No
Rizos et al., 2010[38]	CoaguChek XS	Include: patients receiving phenprocoumon and admitted to the neurological emergency room with acute nontraumatic subdural hemorrhage Exclude: traumatic subdural hemorrhage; chronic subdural hemorrhage	n = 10; Sex: 5/5 (50/50%); Median age: 77	No
Rizos et al., 2009[39]	CoaguChek XS	Include: *phase 1:* patients on OAC in an emergency-room setting*; phase 2:* OAC stroke patients in an emergency-room setting Exclude: NR	n = 161; *Phase 1:* n = 113; Sex: 51/62; Age: 76 ± SD 11 (range 28 to 95) *Phase 2:* n = 48; Sex: 26/22; Age: 78 ± SD 10 (range 34 to 96)	No
Ryan et al., 2010[10]	CoaguChek XS	Include: patients on long-term OAT attending an anticoagulation management service Exclude: NR	n = 162; Sex: 57/93 (38/62%); Age: 59.5 ± SD 14 (range 19 to 91)	Self-test

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Sobieraj-Teague et al., 2009[40]	CoaguChek XS	Include: adult patients (>18 years) in home health care service with new warfarin treatment Exclude: patients not receiving concurrent enoxaparin; those with established warfarin treatment with subtherapeutic INR levels; warfarin treatment that was interrupted, or surgery, or other procedure	n = 98; Sex: 44/54; Age: 66 (range 20 to 92)	No
Solvik et al., 2010[41]	CoaguChek XS; INRatio	Include: adult outpatients; on OAT for >1 month Exclude: none	n = 36; Sex: 16/20 Age: median 67.5 (range 41 to 92)	No
Stoysich et al., 2001[42]	ProTime	Include: hospital inpatients ≥ 18 years old, receiving warfarin; additional 7 untreated healthy volunteers Exclude: NR	n = 30; *Warfarin:* n = 23 Sex: 17/6 (74/26%) Age: 66 (range 34-8) *Untreated:* n = 7 Sex: 6/1 (86/14%) Age: 42 (range 30 to 58)	No
Sunderji et al., 2004/2005[11,55]	ProTime	Include: patients age ≥ 18 years; on warfarin for at least 1 month before enrolment, with planned anticoagulation of at least 1 year; and target INR of 2.0 to 3.0 or 2.5 to 3.5 Exclude: patients with known hypercoagulable disorders, mental incompetence, or a language barrier	n = 139; *Intervention:* n = 69 Sex: 25/44 (36/64%) Age: 57.6 (range 20 to 79) *Control:* n = 70 Sex: 16/54 (23/77%) Age: 62.3 (range 24 to 85)	Self-test/self-management for intervention

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Sunderji et al., 1999[43]	ProTime	Include: patients on warfarin for at least 1 month previous to enrolment, with intended target of INR 2.0 to 3.0 or 2.5 to 3.5; age > 18 years Exclude: patients with history of major bleeding, hypercoagulable disorder, liver disease, renal failure, malignancy, psychiatric illness, alcohol abuse, stroke, or concomitant therapy with NSAIDs	n = 10; Sex: 2/8 (20/80%) Age: 55 years (range 42 to 74)	Self-test/self-management
Taborski et al., 2004[44]	INRatio	Include: patients on anticoagulation therapy plus 5 non-anticoagulated healthy subjects Exclude: NR	n = 82; Sex NR; Age NR	No
Tay et al., 2002[45]	ProTime	Include: unselected group of cardiac patients receiving warfarin, attending an anticoagulation clinic Exclude: none	n = 50; Sex: 7/43 (14/86%) Age: 55 ± SD 12 (range 26 to 80)	No
Thompson et al., 2008[46]	INRatio	Include: adult patients undergoing mechanical heart valve implant Exclude: patients with disabilities or poor English language skills that would interfere with instruction for self-testing	n = 50; Sex: 17/33 (34/66%) Age: median 54 (18 to 88)	Self-test

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Thompson et al., 2012[12]	INRatio	Include: adult patients with mechanical heart valve implant; on warfarin therapy Exclude: patients with disabilities or poor English language skills that would interfere with instruction for self-testing	n = 200; *Intervention:* n = 86 Sex: 40/60 Age: median 55 *Control:* n = 93 Sex: 33/67 Age: median 53	Self-test (intervention group)
Torreiro et al., 2009[47]	CoaguChek XS	Include: adult patients (age 18 to 70), with indication for long-term OAT Exclude: patients with lupus anticoagulant or relevant physical or psychological difficulties	n = 41; Sex: 15/26 (37/63%); Age: 52.1 ± SD 7.8(range 36 to 68)	Self-test/self-management

Verret et al., 2012[13]	CoaguChek XS	Include: adult patients (18 to 75 years) of an anticoagulation clinic; receiving warfarin ≥ 6 months; expected to continue warfarin ≥ 4 months; last 2 INRs 1.5 to 4.0 (target of 2.0 to 3.0) or 2.0 to 4.0 (target of 2.5 to 3.5)
		Exclude: patients with hypercoagulable condition including active cancer, active or recent major bleeding event in last 3 months, recent cardiovascular event or surgery, limited comprehension or motor skills
			n = 114;
			Intervention:
			n = 58;
			Sex: 19/39 (23/67%);
			Age: 58.4 ± SD 10.1
			
			Control:
			n = 56;
			Sex: 17/39 (30/70%);
			Age: 57.0 ± SD 10.9
				Self-test/self-management (intervention group only)

Wieloch et al., 2009[48]	CoaguChek XS	Include: adult patients attending an anticoagulation clinic; stable on warfarin; INR 2 to 3 for ≥ 3 months Exclude: NR	n = 397; Sex: 135 /262 (34/66%); Median age: 69.0 (range 50 to 88)	No

Table A2: Patient characteristics				
First Author, Year	**POC Instrument(s)**	**Inclusion/ Exclusion Criteria**	**No. of Patients (n); Sex: F/M (total percentage); Mean Age (Years)**	**Patient Self-Test/ Self-Management**
Williams and Griffiths, 2007[49]	CoaguChek XS	Include: cardiac pediatric patients on lifelong anticoagulation Exclude: none	n = 38; Sex: NR Age: < 18	No

INR = international normalized ratio; LMW = low-molecular weight; NR = not reported; NSAIDs = non-steroidal anti-inflammatory drugs; OAT= oral anticoagulation therapy; SD = standard deviation.

APPENDIX 7: SUMMARY OF CRITICAL APPRAISAL OF INCLUDED STUDIES

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
Adkinson et al., 2009[51]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the time period between reference standard and index test not mentioned; the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Andrew et al., 2001[14]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Andrews et al., 2001[15]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test)	Reporting: withdrawals from the study not mentioned

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	
Bardakci et al., 2013[16]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the time period between reference standard and index test not mentioned; the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Bauman et al., 2008[17]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Bereznicki et al., 2007[18]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in	

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
	practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	
Biasiolo et al., 2000[19]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Boehlen et al., 2005[20]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Christensen et al., 2009[53]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
Colella et al., 2012[21]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the time period between reference standard and index test not mentioned; the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Donaldson et al., 2010[22]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Drescher et al., 2011[23]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
Giles et al., 2010[24]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Greenway et al., 2009[25]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Hashimoto et al., 2012[26]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Hur et al., 2013[27]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the	Reporting: withdrawals from the study not mentioned

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
	execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	
Joshi et al., 2008[28]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Karon et al., 2008[29]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Kong et al., 2008[30]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication)

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
		Reporting: withdrawals from the study not mentioned
Lakshmy et al., 2010[50]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Lawrie et al., 2012[31]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	
McBane et al., 2005[32]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Moon et al., 2010[54]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that	Reporting: withdrawals from the study not

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
	the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	mentioned
Moore et al., 2007[33]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Nam et al., 2008[34]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Nanduri et al., 2012[52]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the time period between reference standard and index test not mentioned; the execution of the index test not described in sufficient detail to permit

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
		replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Paioni et al., 2009[35]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Pena et al., 2012[36]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Reed et al., 1999[37]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication)
Rizos et al., 2010[38]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in	Validity: unclear (the execution of the index

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
	practice; selection criteria clearly described)	test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Rizos et al., 2009[39]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Ryan et al., 2010[10]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	
Sobieraj-Teague et al., 2009[40]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
		described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Solvik et al., 2010[41]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Stoysich et al., 2001[42]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Sunderji et al., 1999[43]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication)
Taborski et al., 2004[44]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in	Validity: unclear (the execution of the index

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
	practice; selection criteria clearly described)	test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned
Tay et al., 2002[45]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Reporting: withdrawals from the study not mentioned
Thompson et al., 2008[46]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication)
Torreiro et al., 2009[47]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described) Reporting: withdrawals from the study mentioned	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication)
Wieloch et al., 2009[48]	Validity: yes (the time period between reference standard and index test short enough to be reasonably sure that	Reporting: withdrawals from the study not

Table A3: Critical Appraisal of Studies Included for Accuracy (QUADAS[6])		
First Author, Publication Year	**Strengths**	**Limitations**
	the target condition did not change between the two tests; the execution of the index test described in sufficient detail to permit replication of the test; the execution of the reference standard described in sufficient detail to permit its replication; the index test results interpreted without knowledge of the results of the reference standard; the reference standard results interpreted without knowledge of the results of the index test) Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	mentioned
Williams and Griffiths, 2007[49]	Generalizability of results: yes (spectrum of patients representative of the patients who will receive the test in practice; selection criteria clearly described)	Validity: unclear (the execution of the index test not described in sufficient detail to permit replication of the test; the execution of the reference standard not described in sufficient detail to permit its replication) Reporting: withdrawals from the study not mentioned

Table A4: Critical Appraisal of Studies Included for Clinical Outcomes (Downs and Black[7])		
First Author, Publication Year	**Strengths**	**Limitations**
Christensen et al.,[8] 2011	• Randomized controlled trial • Hypothesis clearly described • Method of selection from source population and representation described • Study had sufficient power to detect a clinically important effect • Main outcomes, interventions, patient characteristics, and main findings clearly described • Estimates of random variability and actual probability values provided • Losses to follow-up described	• Characteristics of patients lost to follow-up were not described
Matchar et al.,[9] 2010	• Randomized controlled trial • Hypothesis clearly described • Method of selection from source population and representation described • Study had sufficient power to detect a clinically important effect • Main outcomes, interventions, patient characteristics, and main findings clearly described • Estimates of random variability and actual probability values provided • Losses to follow-up described • Characteristics of patients lost to follow-up were described	
Sunderji et al.,[11] 2004	• Randomized controlled trial • Hypothesis clearly described • Method of selection from source population and representation described • Study had sufficient power to detect a clinically important effect • Main outcomes, interventions, patient characteristics, and main findings clearly described • Losses to follow-up described • Characteristics of patients lost to follow-up were described	• Estimates of random variability and actual probability values for clinical outcomes not provided
Thompson et al.,[12] 2012	• Randomized controlled trial • Hypothesis clearly described • Method of selection from source population and representation described • Study had sufficient power to detect a clinically important effect • Main outcomes, interventions, patient characteristics, and main findings clearly described	• Estimates of random variability and actual probability values for clinical outcomes not provided

Table A4: Critical Appraisal of Studies Included for Clinical Outcomes (Downs and Black[7])		
First Author, Publication Year	**Strengths**	**Limitations**
	• Losses to follow-up described • Characteristics of patients lost to follow-up were described	
Verret et al.,[13] 2012	• Randomized controlled trial • Hypothesis clearly described • Method of selection from source population and representation described • Study had sufficient power to detect a clinically important effect • Main outcomes, interventions, patient characteristics, and main findings clearly described • Estimates of random variability and actual probability values provided • No loss to follow-up	

APPENDIX 8: ACCURACY AND CLINICAL AGREEMENT OF POC DEVICES VERSUS LABORATORY

Table A5: Accuracy and Clinical Agreement of CoaguChek XS Versus Laboratory

First Author, Year	Accuracy (Average INR Units Difference Between POC and Lab); Correlation Coefficient (*r*)	Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)	Precision (CV %)	POC Sensitivity, Specificity, PPV, NPV
Adkinson et al., 2010[51]	*r* = 0.927 (*P* < 0.001)	22% differed by > 0.5 units	NR	Sensitivity: 65.5% Specificity: 67.6% PPV: 76% NPV: 56%
Bauman et al., 2008[17]	−0.11 units	5.7% (99% CI, 2.4 to 9.1)	5%	NR
Bereznicki et al., 2007[18]	−0.07 units; *r* = 0.91 (*P* = 0.01)	5.1% differed by > 15%	NR	NR
Christensen et al., 2011[8]	NR	NR	NR	NR
Christensen et al., 2009[53]	−0.4 units	43% differed by > 15%	2.3%	NR
Colella et al., 2012[21]	−0.08 units; *r* = 0.91 (*P* < 0.0001)	15% differed by > 15%	NR	NR
Giles et al., 2010[24]	0.2 units; *r* = 0.95 *(P* < 0.0001)	NR	NR	NR
Greenway et al., 2009[25]	0.22 units; *r* = 0.81	20% differed by > 15%	NR	NR
Hashimoto et al., 2012[26]	−0.005 units; *r* = 0.86	3.7% gave INR results of >3.5 units when lab result was within therapeutic limits	NR	NR
Karon et al., 2008[29]	0 units	NR	NR	NR
Kong et al., 2008[30]	−0.03 units *r* = 0.94 (*P* < 0.05)	Approximately 10% differed by > 0.5 units at results up to 3.5 units	NR	NR
Lakshmy et al., 2010[50]	*r* = 0.94 *(P* = 0.29*)*	NR	NR	NR
Moon et al., 2010[54]	−0.08 units ± 0.04 (*P* = 0.63); *r* = 0.97 (*P* < 0.01)	NR	NR	NR
Nam et al., 2008[34]	−0.07 units; *r* = 0.96	NR	NR	NR

Table A5: Accuracy and Clinical Agreement of CoaguChek XS Versus Laboratory				
First Author, Year	**Accuracy (Average INR Units Difference Between POC and Lab); Correlation Coefficient (*r*)**	**Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)**	**Precision (CV %)**	**POC Sensitivity, Specificity, PPV, NPV**
Paioni et al., 2009[35]	−0.13 units; *r* = 0.95	NR	NR	NR
Rizos et al., 2010[38a]	0.013 units (SD 0.32)	NR	NR	NR
Rizos et al., 2009[39a]	0.02 units (SD 0.27); *r* = 0.98 (P < 0.01)	NR	NR	NR
Ryan et al., 2010[10]	0.25 units; *r* = 0.91	3/150 patients stopped POC because of differences between 2 methods > 0.5 units on at least 2 occasions	NR	NR
Sobieraj-Teague et al., 2009[40]	−0.09 units; *r* = 0.95	NR	NR	NR
Solvik et al., 2010[41]	−0.01 units	NR	3.8% (3.4 to 4.3)	NR
Torreiro et al., 2009[47]	0.1 units (SD 0.291); *r* = 0.94	NR	NR	NR
Verret et al., 2012[13]	NR	NR	NR	NR
Wieloch et al., 2009[48]	−0.02 units; *r* = 0.94 (*P* < 0.001)	NR	NR	NR
Williams and Griffiths, 2007[49]	NR	13% of paired tests differed by >0.5 units	NR	NR

CI = confidence interval; CV = coefficient of variation; INR = international normalized ratio; NPV = negative predictive value; NR = not reported; POC = point of care; PPV = positive predictive value; SD = standard deviation.
[a] Venous blood used for POC samples.

Table A6: Accuracy and Precision of CoaguChek XS Plus Versus Laboratory				
First Author, Year	**Accuracy (Average INR Units Difference Between POC and Lab); Correlation Coefficient (*r*)**	**Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)**	**Precision (CV %)**	**POC Sensitivity, Specificity, PPV, NPV**
Donaldson et al., 2010[22]	0.27 units (SD ± 0.31); $r = 0.95$ ($P < 0.0001$)	33% of paired tests differed by 0.4 units	NR	NR
Hur et al., 2013[27a]	−0.13 units; $r = 0.964$ ($P < 0.0001$)	17.8% of paired tests produced results that would result in dosing differences	NR	NR
Lawrie et al., 2012[31]	−0.001 units; compared with CA-7000 analyzer, $r = 0.87$; compared with CA-1500 analyzer, $r = 0.75$; results within ≤ 0.5 INR units in 98/154 (63.6%) patients	NR	NR	NR

CV = coefficient of variation; INR = international normalized ratio; NPV = negative predictive value; NR = not reported; POC = point of care; PPV = positive predictive value; SD = standard deviation.
[a] Venous blood used for POC samples.

Table A7: Accuracy and Precision of INRatio Versus Laboratory				
First Author, Year	**Accuracy (Average INR Units Difference Between POC and Lab); Correlation coefficient (*r*)**	**Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)**	**Precision (CV %)**	**POC Sensitivity, Specificity, PPV, NPV**
Moore et al., 2007[33]	No. of paired results within 0.5 INR units: 52/96 (54.2%); $r = 0.80$ ($P < 0.001$)	No. of POC results out of therapeutic range, while lab method indicated in range: 11 (11.5%)	NR	NR
Solvik et al. 2010[41]	0.14 units		8.6%	NR
Taborski et al., 2004[44]	Concordance in 81% of measurements (n = 62); $r = 0.95$	CV = 7.8% (SD 0.09) for INR in the normal range of 1.1; CV = 5.4% (SD 0.21) for INR in the high therapeutic range of 3.9; CV = 8.4% (SD 0.44) for INR in the high range of 5.3	NR	NR
Thompson et al., 2012[12]	NR	NR	NR	NR
Thompson et al., 2008[46]	0.09 units; $r = 0.79$, ($P < 0.001$)	NR	NR	NR

CV = coefficient of variation; INR = international normalized ratio; NPV = negative predictive value; NR = not reported; POC = point of care; PPV = positive predictive value; SD = standard deviation.
Of Note: Venous blood used for POC samples.

Table A8: Accuracy and Precision of i-STAT Versus Laboratory				
First Author, Year	**Accuracy (Average INR Units Difference Between POC and Lab); Correlation Coefficient (*r*)**	**Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)**	**Precision (CV %)**	**POC Sensitivity, Specificity, PPV, NPV**
Boehlen et al., 2005[20]	0.2 units (95% CI, 0.02 to 0.39); $r = 0.95$	NR	*Using 2 control samples:* 5% for INR levels of 1.60 units (95% CI, 3.4 to 9.1); 3% for INR level of 2.75 units (95% CI, 2.1 to 5.5)	NR
Donaldson et al., 2010[22]	0.51 units (SD ± 0.44); $r = 0.91$ ($P < 0.0001$)	NR	NR	NR
Drescher et al., 2011[23a]	0.27 units; $r = 0.96$	NR	NR	At INR of 2.1 units: sensitivity of lab INR being higher than 1.7 was 100% (CI, 62.9 to 100.0%), specificity 90.5 (CI, 69.6 to 98.5). At INR of 1.8 units: sensitivity of lab INR being lower than 1.7 was 62.5% (CI, 24.7 to 91.0%), specificity 100% (CI, 83.7 to 100%) Area under curve: 0.979 (95% CI, 0.843 to 0.991)
Karon et al., 2008[29]	–0.1 units	NR	NR	NR
Nanduri et al., 2012[52]	0.24 units (SD 0.69); 137 patients (21.5%) had discrepancy between POC and lab of greater than ± 0.25 units; 69 POC results < lab; 68 POC results > lab result	NR	NR	NR

Table A8: Accuracy and Precision of i-STAT Versus Laboratory				
First Author, Year	**Accuracy (Average INR Units Difference Between POC and Lab); Correlation Coefficient (*r*)**	**Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)**	**Precision (CV %)**	**POC Sensitivity, Specificity, PPV, NPV**
Pena et al., 2012[36]	49/50 pairs (98%) showed acceptable clinical agreement or concordance (≤ 0.4 units); *r* = 0.90	NR	Performed 10 times each on normal and abnormal plasma controls provided by manufacturer, on 2 i-STAT devices: *Device 1 Normal control*: Mean INR = 1.13 (range 1.1, 1.2), SD = 0.05, CV = 4.3% *Device 2 Normal control*: Mean INR = 1.1 (range 1.1, 1.1), SD = 0, CV = 0% *Device 1 Abnormal control*: Mean INR = 3.07 (range 3, 3.2), SD = 0.07, CV = 2.2% *Device 2 Abnormal control*: Mean INR = 3.1 (range 3, 3.1), SD = 0.05, CV = 1.7%	NR

CV = coefficient of variation; INR = international normalized ratio; NPV = negative predictive value; NR = not reported; POC = point of care; PPV = positive predictive value; SD = standard deviation.
Of Note: Venous blood used for POC samples.

Table A9: Accuracy and Precision of ProTime Versus Laboratory

First Author, Year	Accuracy (Average INR Units Difference Between POC and Lab); Correlation Coefficient (*r*)	Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)	Precision (CV %)	POC Sensitivity, Specificity, PPV, NPV

Andrew et al., 2001[14]	Approximately 80% of results were within 0.4 units of difference;
	Finger stick performed by HCW:
	r = 0.90;
	Systematic error at 2 INR= −0.11, at 3 INR= −0.29, at 4 INR= −0.29
	
	Finger stick performed by patient:
	r = 0.92;
	Systemic error at 2 INR= 0, at 3 INR= −0.05, at 4 INR= −0.1
		NR	NR	NR

Andrews et al., 2001[15]	*Finger stick performed by HCW:* 0.03 units; r = 0.92; Systematic error = 0.04 at 3.0 INR *Finger stick performed by patient:* 0.23 units; r = 0.86 Systematic error = 0.23 at 2.5 INR, 0.22 at 3.0 INR, 0.20 at 4.0 INR	68% of POC by HCW and 66% of POC self-tested matched the therapeutic range of lab values	NR	NR
Biasiolo et al., 2000[19]	0.02 units;	5/180 samples (2.77%) had differences of > 1.0, with 4 of these being clinically relevant	NR	NR

Table A9: Accuracy and Precision of ProTime Versus Laboratory				
First Author, Year	**Accuracy (Average INR Units Difference Between POC and Lab); Correlation Coefficient (*r*)**	**Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)**	**Precision (CV %)**	**POC Sensitivity, Specificity, PPV, NPV**
Joshi et al., 2008[28]	0.11 units; *r* = 0.96 (*P* < 0.0001) Average difference between 3 ProTime devices and lab device: 0.11 ± 0.28 (95%CI, 0.03 to 0.19) Absolute mean: 0.23 ± 0.19 (95%CI, 0.18 to 0.28)	NR	NR	NR
Matchar et al., 2010[9]	NR	NR	NR	NR
McBane et al., 2005[32]	0.8 units (SD 0.68); INR agreed with lab within ± 0.2 INR 21% of the time; within 0.4 INR 39% of the time; 25% of values were different by 1.0 INR units or more; *r* = 0.73	NR	NR	NR
Moore et al., 2007[33]	No. of paired results within 0.5 INR units: 46/50 (92%) No. of paired results within 0.5 to 1.0 INR units: 4/50 (8%) No. of paired results within >1.0 INR units: 0 (0%); *r* = 0.96 (*P* < 0.001)	No. of POC results out of therapeutic range, while lab method indicated in range: 1 (2.0%); No. of Lab results out of therapeutic range, while POC method indicated in range: 2 (4.0%)	NR	NR
Reed and Rickman, 1999[37]	0.46 units (SD 0.38); *r* = 0.934 INRs between POC and lab differed by > 0.5 INR units: 28 patients (39%);	45% of warfarin patients had a clinically important difference between POC and lab INRs (which may lead to different dosage adjustment)	NR	NR
Stoysich et al.,	0.3 units;	NR	NR	NR

Table A9: Accuracy and Precision of ProTime Versus Laboratory				
First Author, Year	**Accuracy (Average INR Units Difference Between POC and Lab); Correlation Coefficient (*r*)**	**Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)**	**Precision (CV %)**	**POC Sensitivity, Specificity, PPV, NPV**
2001[42]	*r* = 0.953 (P < 0.001) Mean difference of paired tests: 0.32 ± 0.285 (*P* = 0.419)			
Sunderji et al., 2004/ 2005[11,55]	0.44 units (SD 0.61); *r* = 0.62 INR values within 0.5 units: 69/91(76%) INR values within 0.7 units: 78/91 (86%)	NR	NR	NR
Sunderji et al., 1999[43]	0.33 units; 2/16 measurements differed by > 0.5. ProTime values consistently higher than lab by mean of 0.26		NR	NR
Tay et al., 2002[45]	0.123 units; *r* = 0.940 (*P* = 0.061)	*Results < 2.0 INR units:* Lab:12/50 (24%) POC: 21/50 (42%) *Results > 3.0 INR units:* Lab: 8/50 (16%) POC: 5/50 (10%) 77.8% of POC results matched therapeutic range classification (INR 2 to 3) of the lab result	NR	NR

CV = coefficient of variation; INR = international normalized ratio; NPV = negative predictive value; NR = not reported; POC = point of care; PPV = positive predictive value; SD = standard deviation.

Table A10: Accuracy and precision of POC versus POC				
First Author, Year	**Accuracy (Average INR Units Difference Between Instruments); Correlation Coefficient (*r*)**	**Diagnostic Accuracy (Median Deviation of POC INR Relative to Lab INR)**	**Precision (CV %)**	**POC Sensitivity and Specificity**
CoaguChek XS Plus versus i-STAT				
Donaldson et al., 2010[22]	Range of INR values = 1.5 to 5.7; *r* = 0.948 (95% CI, 0.9107 to 0.9700); Mean absolute difference = 0.23 (SD ± 0.33), *P* < 0.0001; INR results were within 0.4 units of each other 69% of the time	NA	NR	NR
CoaguChek XS versus INRatio				
Solvik et al. 2010[41]		13.9%	6.4% (5.7% to 7.3%)	NR

CV = coefficient of variation; INR = international normalized ratio; NR = not reported; POC = point of care; SD = standard deviation.

APPENDIX 9: RESULTS OF ONE-WAY SENSITIVITY ANALYSES FOR DEVICE COST AND FREQUENCY OF TESTING

Cost of lab test

Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness ($/QALY)	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
2	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.19944	1,961	968	-0.0142	-68,144[a]
5	Lab	7,189	4.1957	1,713	-	-	-
	PSM	7,266	4.2136	1,724	77	0.0179	4,328
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
8	PSM	7,266	4.2136	1,724	-	-	-
	Lab	7,345	4.1957	1,750	78	-0.0179	-4,372[a]
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
11	PSM	7,266	4.2136	1,724	-	-	-
	Lab	7,500	4.1957	1,788	234	-0.0179	-13,073[a]
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
14	PSM	7,266	4.2136	1,724	-	-	-
	Lab	7,656	4.1957	1,825	390	-0.0179	-21,773[a]
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Cost of lab equipment

Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness ($/QALY)	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.5	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,042
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
1.625	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,011
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
2.75	Lab	7,034	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	232	0.0179	12,979
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
3.875	Lab	7,035	4.1957	1,677	-	-	-
	PSM	7,266	4.2136	1,724	232	0.0179	12,948
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
5	Lab	7,035	4.1957	1,677	-	-	-
	PSM	7,266	4.2136	1,724	231	0.0179	12,917
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Cost of professional-grade device

Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
2.05	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,839	4.2021	1,866	573	-0.0116	-49,569[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
11.8125	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,849	4.2021	1,868	582	-0.0116	-50,414[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
21.575	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,859	4.2021	1,870	592	-0.0116	-51,259[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
31.3375	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,868	4.2021	1,872	602	-0.0116	-52,104[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
41.1	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,878	4.2021	1,875	612	-0.0116	-52,949[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Cost of patient-grade device

Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
499	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
649.25	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,417	4.2136	1,760	383	0.0179	21,422
	Clinic	7,841	4.2021	1,866	425	-0.0116	-36,743[a]
	PST	8,385	4.1994	1,997	968	-0.0142	-68,144[a]
799.5	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,567	4.2136	1,796	534	0.0179	29,816
	Clinic	7,841	4.2021	1,866	274	-0.0116	-23,739[a]
	PST	8,535	4.1994	2,032	968	-0.0142	-68,144[a]
949.75	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,717	4.2136	1,831	684	0.0179	38,209
	Clinic	7,841	4.2021	1,866	124	-0.0116	-10,735[a]
	PST	8,685	4.1994	2,068	968	-0.0142	-68,144[a]
1,100	Lab	7,033	4.1957	1,676	-	-	-
	Clinic	7,841	4.2021	1,866	808	0.0064	127,315
	PSM	7,867	4.2136	1,867	26	0.0116	2,270
	PST	8,835	4.1994	2,104	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-years; PSM = patient self-management; PST = patient self-testing.
* Dominated.

Cost of POC Test Strips

Cost Per Strip ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0	PSM	6,326	4.2136	1,501	-	-	-
	Lab	7,033	4.1957	1,676	707	-0.0179	-39,501[a]
	PST	7,297	4.1994	1,738	971	-0.0142	-68,318[a]
	Clinic	7,408	4.2021	1,763	1,082	-0.0116	-93,649[a]
2.08	PSM	6,561	4.2136	1,557	-	-	-
	Lab	7,033	4.1957	1,676	472	-0.0179	-26,368[a]
	Clinic	7,516	4.2021	1,789	955	-0.0116	-82,674[a]
	PST	7,531	4.1994	1,793	970	-0.0142	-68,275[a]
4.17	PSM	6,796	4.2136	1,613	-	-	-
	Lab	7,033	4.1957	1,676	237	-0.0179	-13,236[a]
	Clinic	7,625	4.2021	1,814	828	-0.0116	-71,698[a]
	PST	7,766	4.1994	1,849	969	-0.0142	-68,231[a]
6.25	PSM	7,031	4.2136	1,669	-	-	-
	Lab	7,033	4.1957	1,676	2	-0.0179	-104[a]
	Clinic	7,733	4.2021	1,840	702	-0.0116	-60,723[a]
	PST	8,000	4.1994	1,905	969	-0.0142	-68,187[a]
8.33	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Frequency of testing in PSM

Frequency Per Year	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
12	PSM	6,750	4.2136	1,602	-	-	-
	Lab	7,033	4.1957	1,676	283	-0.0179	-15,800[a]
	Clinic	7,841	4.2021	1,866	1,091	-0.0116	-94,410[a]
	PST	8,234	4.1994	1,961	1,484	-0.0142	-104,466[a]
22	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,119	4.2136	1,689	86	0.0179	4,792
	Clinic	7,841	4.2021	1,866	722	-0.0116	-62,508[a]
	PST	8,234	4.1994	1,961	1,116	-0.0142	-78,521[a]
32	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,487	4.2136	1,777	454	0.0179	25,383
	Clinic	7,841	4.2021	1,866	354	-0.0116	-30,606[a]
	PST	8,234	4.1994	1,961	747	-0.0142	-52,577[a]
42	Lab	7,033	4.1957	1,676	-	-	-
	Clinic	7,841	4.2021	1,866	808	0.0064	127,315
	PSM	7,856	4.2136	1,864	15	0.0116	1,296
	PST	8,234	4.1994	1,961	378	-0.0142	-26,633[a]
52	Lab	7,033	4.1957	1,676	-	-	-
	Clinic	7,841	4.2021	1,866	808	0.0064	127,315
	PSM	8,225	4.2136	1,952	384	0.0116	33,198
	PST	8,234	4.1994	1,961	10	-0.0142	-688[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Frequency of testing in PST

Frequency Per Year	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
12	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	PST	7,720	4.1994	1,838	453	-0.0142	-31,917[a]
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
22	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,087	4.1994	1,926	821	-0.0142	-57,793[a]
32	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,455	4.1994	2,013	1,189	-0.0142	-83,669[a]
42	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,823	4.1994	2,101	1,556	-0.0142	-109,545[a]
52	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	9,190	4.1994	2,188	1,924	-0.0142	-135,421[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Frequency of testing in clinic

Frequency Per Year	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
12	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
22	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	8,212	4.2021	1,954	946	-0.0116	-81,844[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
32	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
	Clinic	8,583	4.2021	2,043	1,316	-0.0116	-113,940[a]
42	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
	Clinic	8,954	4.2021	2,131	1,687	-0.0116	-146,036[a]
52	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
	Clinic	9,324	4.2021	2,219	2,058	-0.0116	-178,132[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Frequency of testing in lab

Frequency Per Year	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
12	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
22	Lab	7,120	4.1957	1,697	-	-	-
	PSM	7,266	4.2136	1,724	147	0.0179	8,195
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
32	Lab	7,206	4.1957	1,717	-	-	-
	PSM	7,266	4.2136	1,724	60	0.0179	3,361
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
42	PSM	7,266	4.2136	1,724	-	-	-
	Lab	7,293	4.1957	1,738	26	-0.0179	-1,472
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
52	PSM	7,266	4.2136	1,724	-	-	-
	Lab	7,379	4.1957	1,759	113	-0.0179	-6,306[a]
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

APPENDIX 10: ONE-WAY SENSITIVITY ANALYSES FOR HEALTH CARE PROVIDER COSTS

Cost of one-time training for using home-based device (@$39.50/hour)

Estimated Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
29.63	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,215	4.1994	1,956	948	-0.0142	-66,753[a]
36.21333	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,221	4.1994	1,958	955	-0.0142	-67,217[a]
42.79667	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,228	4.1994	1,959	962	-0.0142	-67,680[a]
49.38	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Cost of one-time training for using home-based device and medication dose management (@$39.50/hour)

Estimated Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
59.26	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,227	4.2136	1,715	194	0.0179	10,822
	Clinic	7,841	4.2021	1,866	614	-0.0116	-53,165[a]
	PST	8,234	4.1994	1,961	1,008	-0.0142	-70,923[a]
69.1325	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,237	4.2136	1,717	204	0.0179	11,374
	Clinic	7,841	4.2021	1,866	604	-0.0116	-52,311[a]
	PST	8,234	4.1994	1,961	998	-0.0142	-70,228[a]
79.005	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,247	4.2136	1,720	213	0.0179	11,925
	Clinic	7,841	4.2021	1,866	595	-0.0116	-51,456[a]
	PST	8,234	4.1994	1,961	988	-0.0142	-69,533[a]
88.8775	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,256	4.2136	1,722	223	0.0179	12,477
	Clinic	7,841	4.2021	1,866	585	-0.0116	-50,602[a]
	PST	8,234	4.1994	1,961	978	-0.0142	-68,839[a]
98.75	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Annual cost of a five-minute physician consult in each clinic visit (@ $16.95 per visit)

Estimated Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
67	Lab	7,033	4.1957	1,676	-	-	-
	Clinic	7,250	4.2021	1,725	217	0.0064	34,204
	PSM	7,266	4.2136	1,724	16	0.0116	1,397
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
112.4667	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,447	4.2021	1,772	181	-0.0116	-15,651[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
157.9333	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,644	4.2021	1,819	378	-0.0116	-32,699[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
203.4	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Annual cost of nursing time for clinic visit (each visit for 15 minutes @$39.50/hour)

Estimated Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
39.5	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,499	4.2021	1,785	233	-0.0116	-20,126[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
59.25	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,584	4.2021	1,805	318	-0.0116	-27,531[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
79	Lab	7,033	4.195	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,670	4.2021	1,825	404	-0.0116	-34,937[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
98.75	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,756	4.2021	1,846	489	-0.0116	-42,342[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
118.5	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Annual cost of nursing time per lab visit (each visit for 13 minutes @$39.50/hour)

Estimated Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
34.23	Lab	6,737	4.1957	1,606	-	-	-
	PSM	7,266	4.2136	1,724	529	0.0179	29,576
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
57.05333	Lab	6,836	4.1957	1,629	-	-	-
	PSM	7,266	4.2136	1,724	431	0.0179	24,060
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
79.87667	Lab	6,934	4.1957	1,653	-	-	-
	PSM	7,266	4.2136	1,724	332	0.0179	18,544
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
102.7	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Cost of specialist consultation per year for lab patients

Estimated Cost ($)	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
42.18	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
84.36	Lab	7,216	4.1957	1,720	-	-	-
	PSM	7,266	4.2136	1,724	51	0.0179	2,834
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
126.54	PSM	7,266	4.2136	1,724	-	-	-
	Lab	7,398	4.1957	1,763	132	-0.0179	-7,360[a]
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
168.72	PSM	7,266	4.2136	1,724	-	-	-
	Lab	7,581	4.1957	1,807	314	-0.0179	-17,554[a]
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

APPENDIX 12: RESULTS OF ONE-WAY SENSITIVITY ANALYSES FOR RISK OF ADVERSE EVENTS

Major hemorrhagic event, if INR value is above target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.03	Lab	6,962	4.1962	1,659	-	-	-
	PSM	7,223	4.2139	1,714	260	0.0177	14,700
	Clinic	7,778	4.2025	1,851	555	-0.0114	-48,604[a]
	PST	8,167	4.1999	1,945	944	-0.0141	-67,208[a]
0.0335	Lab	7,029	4.1958	1,675	-	-	-
	PSM	7,264	4.2136	1,724	235	0.0179	13,117
	Clinic	7,838	4.2021	1,865	574	-0.0116	-49,687[a]
	PST	8,231	4.1994	1,960	967	-0.0142	-68,094[a]
0.037	Lab	7,096	4.1953	1,691	-	-	-
	PSM	7,305	4.2133	1,734	209	0.0181	11,583
	Clinic	7,897	4.2017	1,879	592	-0.0117	-50,727[a]
	PST	8,294	4.1990	1,975	989	-0.0144	-68,943[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Major hemorrhagic event, if INR value is within target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.0092	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
0.0111	Lab	7,238	4.1945	1,726	-	-	-
	PSM	7,509	4.2121	1,783	271	0.0176	15,384
	Clinic	8,060	4.2007	1,919	550	-0.0114	-48,420[a]
	PST	8,448	4.1981	2,012	938	-0.0140	-67,141[a]
0.013	Lab	7,443	4.1932	1,775	-	-	-
	PSM	7,752	4.2105	1,841	308	0.0173	17,816
	Clinic	8,278	4.1993	1,971	526	-0.0112	-47,053[a]
	PST	8,661	4.1968	2,064	909	-0.0138	-66,109[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Major hemorrhagic event, if INR value is below target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.008	Lab	6,938	4.1964	1,653	-	-	-
	PSM	7,212	4.2140	1,712	274	0.0176	15,582
	Clinic	7,764	4.2026	1,847	552	-0.0114	-48,478[a]
	PST	8,152	4.2000	1,941	940	-0.0140	-67,133[a]
0.0115	Lab	7,028	4.1958	1,675	-	-	-
	PSM	7,263	4.2136	1,724	235	0.0179	13,163
	Clinic	7,837	4.2021	1,865	574	-0.0115	-49,680[a]
	PST	8,230	4.1995	1,960	967	-0.0142	-68,090[a]
0.015	Lab	7,117	4.1951	1,696	-	-	-
	PSM	7,314	4.2133	1,736	197	0.0182	10,849
	Clinic	7,909	4.2016	1,882	595	-0.0117	-50,827[a]
	PST	8,307	4.1989	1,978	993	-0.0144	-68,999[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Minor hemorrhagic event, if INR value is above target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.06	Lab	7,086	4.2104	1,683	-	-	-
	PSM	7,299	4.2227	1,729	213	0.0123	17,319
	Clinic	7,888	4.2152	1,871	589	-0.0075	-78,866[a]
	PST	8,285	4.2134	1,966	986	-0.0092	-107,074[a]
0.115	Lab	7,031	4.1952	1,676	-	-	-
	PSM	7,265	4.2133	1,724	234	0.0181	12,928
	Clinic	7,839	4.2021	1,866	574	-0.0117	-49,088[a]
	PST	8,233	4.1989	1,961	967	-0.0144	-67,261[a]
0.17	Lab	6,982	4.1832	1,669	-	-	-
	PSM	7,235	4.2059	1,720	253	0.0227	11,142
	Clinic	7,795	4.1909	1,860	561	-0.0150	-37,280[a]
	PST	8,186	4.1874	1,955	951	-0.0185	-51,460[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Minor hemorrhagic event, if INR value is within target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.02	Lab	7,033	4.2395	1,659	-	-	-
	PSM	7,266	4.2653	1,703	233	0.0258	9,026
	Clinic	7,841	4.2488	1,845	575	-0.0165	-34,778[a]
	PST	8,234	4.2450	1,940	968	-0.0203	-47,623[a]
0.05	Lab	7,033	4.1918	1,678	-	-	-
	PSM	7,266	4.2089	1,726	233	0.0172	13,575
	Clinic	7,841	4.1978	1,868	575	-0.0111	-51,774[a]
	PST	8,234	4.1953	1,963	968	-0.0137	-70,922[a]
0.08	Lab	7,034	4.1440	1,697	-	-	-
	PSM	7,267	4.1526	1,750	233	0.0085	27,355
	Clinic	7,842	4.1469	1,891	575	-0.0057	-101,273[a]
	PST	8,235	4.1456	1,986	968	-0.0070	-138,870[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Minor hemorrhagic event, if INR value is below target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.04	Lab	7,079	4.2039	1,684	-	-	-
	PSM	7,292	4.2183	1,729	214	0.0144	14,873
	Clinic	7,878	4.2087	1,872	586	-0.0096	-61,287[a]
	PST	8,274	4.2066	1,967	982	-0.0117	-83,624[a]
0.07	Lab	7,014	4.1924	1,673	-	-	-
	PSM	7,256	4.2117	1,723	241	0.0193	12,491
	Clinic	7,826	4.1994	1,864	570	-0.0124	-46,141[a]
	PST	8,218	4.1965	1,958	962	-0.0152	-63,317[a]
0.1	Lab	6,953	4.1823	1,663	-	-	-
	PSM	7,221	4.2060	1,717	268	0.0237	11,292
	Clinic	7,776	4.1911	1,855	556	-0.0148	-37,465[a]
	PST	8,165	4.1877	1,950	944	-0.0183	-51,730[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Major thromboembolic event, if INR value is above target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.002	Lab	6,754	4.1990	1,608	-	-	-
	PSM	7,095	4.2156	1,683	340	0.0167	20,455
	Clinic	7,593	4.2050	1,806	498	-0.0106	-46,799[a]
	PST	7,968	4.2026	1,896	874	-0.0131	-66,742[a]
0.005	Lab	6,892	4.1974	1,642	-	-	-
	PSM	7,179	4.215	1,703	287	0.0173	16,651
	Clinic	7,715	4.2036	1,835	536	-0.0111	-48,321[a]
	PST	8,100	4.2010	1,928	920	-0.0136	-67,469[a]
0.008	Lab	7,029	4.1958	1,675	-	-	-
	PSM	7,264	4.2137	1,724	235	0.0179	13,141
	Clinic	7,837	4.2021	1,865	574	-0.0115	-49,704[a]
	PST	8,230	4.1995	1,960	967	-0.0142	-68,123[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Major thromboembolic event, if INR value is within target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.001	PSM	5,468	4.2333	1,292	-	-	-
	Lab	5,522	4.2119	1,311	54	-0.0214	-2,518[a]
	Clinic	6,230	4.2196	1,477	762	-0.0137	-55,453[a]
	PST	6,664	4.2164	1,580	1,195	-0.0169	-70,736[a]
0.004	Lab	6,244	4.2042	1,485	-	-	-
	PSM	6,327	4.2239	1,498	83	0.0197	4,230
	Clinic	7,000	4.2112	1,662	672	-0.0127	-52,963[a]
	PST	7,414	4.2083	1,762	1,087	-0.0156	-69,598[a]
0.007	Lab	6,962	4.1965	1,659	-	-	-
	PSM	7,181	4.2146	1,704	220	0.0181	12,158
	Clinic	7,765	4.2029	1,847	584	-0.0117	-50,064[a]
	PST	8,160	4.2002	1,943	979	-0.0143	-68,286[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Major thromboembolic event, if INR value is below target range

Risk of Adverse Event	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.006	Lab	5,697	4.2114	1,353	-	-	-
	PSM	6,507	4.2226	1,541	811	0.0111	72,848
	Clinic	6,762	4.2148	1,604	254	-0.0077	-32,871[a]
	PST	7,077	4.2131	1,680	570	-0.0095	-60,087[a]
0.012	Lab	6,084	4.2069	1,446	-	-	-
	PSM	6,727	4.2200	1,594	643	0.0131	49,208
	Clinic	7,075	4.2112	1,680	347	-0.0088	-39,320[a]
	PST	7,413	4.2092	1,761	685	-0.0108	-63,230[a]
0.018	Lab	6,464	4.2025	1,538	-	-	-
	PSM	6,943	4.2175	1,646	479	0.0150	31,945
	Clinic	7,382	4.2076	1,754	438	-0.0099	-44,217[a]
	PST	7,742	4.2053	1,841	799	-0.0122	-65,572[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

APPENDIX 13: RESULTS OF ONE-WAY SENSITIVITY ANALYSES FOR UTILITY ESTIMATES

Utility of general population

Utility Estimate	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.837	Lab	7,033	3.7856	1,858	-	-	-
	PSM	7,266	3.8005	1,912	233	0.0149	15,624
	Clinic	7,841	3.7908	2,068	575	-0.0097	-59,493[a]
	PST	8,234	3.7886	2,173	968	-0.0119	-81,501[a]
0.93	Lab	7,033	4.1450	1,697	-	-	-
	PSM	7,266	4.1625	1,746	233	0.0175	13,301
	Clinic	7,841	4.1512	1,889	575	-0.0113	-50,776[a]
	PST	8,234	4.1486	1,985	968	-0.0139	-69,553[a]
1	Lab	7,033	4.5044	1,561	-	-	-
	PSM	7,266	4.5246	1,606	233	0.0201	11,580
	Clinic	7,841	4.5116	1,738	575	-0.0130	-44,287[a]
	PST	8,234	4.5086	1,826	968	-0.0160	-60,660[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Utility of acute hemorrhagic event

Utility Estimate	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.648	Lab	7,033	4.1935	1,677	-	-	-
	PSM	7,266	4.2116	1,725	233	0.0181	12,858
	Clinic	7,841	4.2000	1,867	575	-0.0117	-49,038[a]
	PST	8,234	4.1972	1,962	968	-0.0144	-67,175[a]
0.72	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
0.792	Lab	7,033	4.1980	1,675	-	-	-
	PSM	7,266	4.2156	1,724	233	0.0177	13,203
	Clinic	7,841	4.2042	1,865	575	-0.0114	-50,478[a]
	PST	8,234	4.2016	1,960	968	-0.0140	-69,141[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Utility of acute thromboembolic event

Utility Estimate	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.63	Lab	7,033	4.1939	1,677	-	-	-
	PSM	7,266	4.2120	1,725	233	0.0182	12,842
	Clinic	7,841	4.2003	1,867	575	-0.0117	-49,119[a]
	PST	8,234	4.1976	1,962	968	-0.0144	-67,279[a]
0.70	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
0.77	Lab	7,033	4.1976	1,676	-	-	-
	PSM	7,266	4.2152	1,724	233	0.0176	13,220
	Clinic	7,841	4.2038	1,865	575	-0.0114	-50,392[a]
	PST	8,234	4.2012	1,960	968	-0.0140	-69,030[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Utility of temporary disability

Utility estimate	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-effectiveness	Incremental cost ($)	Incremental effectiveness (QALYs)	ICER ($/QALY)
0.648	Lab	7,033	4.1935	1,677	-	-	-
	PSM	7,266	4.2116	1,725	233	0.0182	12,842
	Clinic	7,841	4.1999	1,867	575	-0.0117	-49,018[a]
	PST	8,234	4.1972	1,962	968	-0.0144	-67,145[a]
0.72	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
0.792	Lab	7,033	4.1980	1,675	-	-	-
	PSM	7,266	4.2156	1,724	233	0.0176	13,220
	Clinic	7,841	4.2043	1,865	575	-0.0114	-50,499[a]
	PST	8,234	4.2016	1,960	968	-0.0140	-69,173[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

Utility of permanent disability

Utility Estimate	Strategy	Cost ($)	Effectiveness (QALYs)	Cost-Effectiveness	Incremental Cost ($)	Incremental Effectiveness (QALYs)	ICER ($/QALY)
0.648	Lab	7,033	4.1927	1,677	-	-	-
	PSM	7,266	4.2110	1,726	233	0.0183	12,725
	Clinic	7,841	4.1992	1,867	575	-0.0118	-48,692[a]
	PST	8,234	4.1965	1,962	968	-0.0145	-66,693[a]
0.72	Lab	7,033	4.1957	1,676	-	-	-
	PSM	7,266	4.2136	1,724	233	0.0179	13,028
	Clinic	7,841	4.2021	1,866	575	-0.0116	-49,747[a]
	PST	8,234	4.1994	1,961	968	-0.0142	-68,144[a]
0.792	Lab	7,033	4.1988	1,675	-	-	-
	PSM	7,266	4.2163	1,723	233	0.0175	13,347
	Clinic	7,841	4.2050	1,865	575	-0.0113	-50,849[a]
	PST	8,234	4.2024	1,959	968	-0.0139	-69,658[a]

ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; QALY = quality-adjusted life-year; PSM = patient self-management; PST = patient self-testing.
[a]Dominated.

APPENDIX 14: QUALITY ASSURANCE FOR POINT-OF-CARE TESTING ACROSS CANADA

Context

POC testing is defined as medical testing at or near the site of patient care, without sending the sample to a laboratory setting.[89] POC testing has grown substantially in recent years, both in the scope and the applications of available tests.[90] There are numerous advantages associated with the use of POCT, including convenience, speed, and ease of use. However, the potential disadvantages associated with POCT may be poor quality of analysis, lack of result interpretation, and failure to detect erroneous results.[67] As the methods for applying quality assurance are different for POCT compared with conventional laboratory testing, an understanding of quality assurance programs currently in place in Canada to ensure the quality and accuracy of POCT results is informative for organizations considering implementation of new POCT programs.

Objectives

The purpose of this report is to summarize information on quality assurance practices for POCT internationally and across Canada.

Findings

It is not intended that the findings of this environmental scan provide a comprehensive review of the topic. An Internet search was performed to determine responsibility for POCT quality assurance standards internationally and across Canada. Conventional laboratory quality assurance standards have been included in some instances because there is overlap between standards. This report is based on publicly available information gathered as of August 2013.

International and National Quality Assurance Standards for POC

Internationally, standards have been developed for POCT generally, and for specific items. The international standard for POCT is ISO 22870, *Point-of-care testing — Requirements for quality and competence*. This standard, produced by the International Organization for Standardization (ISO), gives requirements applicable to POCT and is intended to be used in conjunction with ISO 15189, *Medical laboratories — Requirements for quality and competence*. The requirements of ISO 22870 apply when POCT is carried out in a hospital, a clinic, or a health care organization providing ambulatory care. Other related ISO standards are listed in Appendix 14A.

Nationally, the Canadian Standards Association has developed specific requirements applicable to point-of-care testing (CAN/CSA-Z22870-07) and, like the ISO POCT standard, is intended to be used in conjunction with ISO 15189 (see Appendix 14A for more details). However, laboratory regulation and accreditation are not standardized on a national basis.[91]

International and Canadian standards are available for purchase in full text but are not freely accessible in the public domain.

Provincial Standards
Provinces that have publicly accessible POCT standards include British Columbia, Alberta, Saskatchewan, Ontario, and Quebec. New Brunswick and Newfoundland and Labrador follow the Ontario POCT accreditation program.[92]

Prince Edward Island and Nova Scotia rely on Accreditation Canada's Qmentum program for laboratory accreditation. Qmentum was introduced in 2008 and includes a standard specific to POCT.[93] The Qmentum POCT standards reference the CAN/CSA-Z22870-07, which was based on ISO standard Z22870:2006.The program includes information directing organizations through a self-assessment to assess their current performance against the standards and identify areas for improvement. Organizations are directed to use the POCT standards in conjunction with standard laboratory standards. Accreditation Canada changed to a four-year accreditation cycle in January 2013.

Many individual laboratories have also attained further accreditation through international programs, such as the ISO. Table 1 provides a summary of provincial accreditation bodies, POCT standards, and accreditation cycles.

Four provinces (British Columbia, Alberta, Saskatchewan, and Quebec) have posted their full POCT standards online. The British Columbia, Alberta, and Saskatchewan standards are presented as checklists, while the Quebec standard (which is based on CAN/CSA-Z22870-07) is presented in a more narrative format. Manitoba and Ontario also have their own standards programs; however, complete versions of these standards are not freely available to the public online.

Common elements of the full-text POCT standards include:

- Personnel —
  - An interdisciplinary group is established (possibly by the head of the lab) to determine which POCTs are appropriate for the institution.
  - The interdisciplinary group periodically reassesses the POCT practices of the institution.
  - Roles and responsibilities regarding ordering, performing, and monitoring of tests are clearly defined.
  - Staff training, certification, and competency are documented.
- Collection —
  - A procedure manual for specimen collection exists that defines those authorized to take and handle samples, and identifies appropriate methods for identification, preparation, and collection.
- Quality control —
  - POCT should be subject to both internal and external quality control assessment.
  - There must be a periodic evaluation of POC tests and reagents against standard samples.
  - Follow-up actions to quality issues are documented.
- Equipment —
  - Choice of equipment should be made based on precision, accuracy, detection limits, utilization limits, and robustness.
  - An inventory of equipment should be kept.
  - Validation, calibration, and maintenance activities should be recorded.
  - Standard procedures for maintenance and use should be in place.
  - Instructions for troubleshooting problems should be available.
  - Guidelines for cleaning and decontamination practices are in place.

- Results —
  - Results are clearly entered into the patient's permanent medical record with reference ranges and are identified as the result of a POCT.
  - The physician is notified of critical results.
  - Any clinical action resulting from a POCT is recorded in the patient's medical record.

The full versions of these standards can be accessed through the links provided in Appendix 14B: Provincial Laboratory Accreditation.

Table 1: Provincial Accreditation Characteristics

Province	Established Provincial Accreditation Body	Publicly Accessible Customized POCT Standards	Standards Program Used	Regulatory Body	Accreditation Cycle
BC	Y	Y	Provincial	College of Physicians and Surgeons	4 years
AB	Y	Y	Provincial	College of Physicians and Surgeons	4 years
SK	Y	Y	Provincial	College of Physicians and Surgeons	2 to 3 years
MB	Y	N	Provincial	College of Physicians and Surgeons	4 years
ON	Y	Y ISO 22870:2006	Provincial	Ministry of Health and Long-Term Care	4 years
QC	Y	Y CAN/CSA Z22870-07	Provincial	Ordre professionnel des technologistes médicaux du Québec	3 years
NB	N	N	Ontario	NB Department of Health	2 years
PE	N	N	Accreditation Canada	Health PE	4 years
NS	N	N	Accreditation Canada	NA (voluntary)	4 years
NL	N	N	Ontario	NL Department of Health and Community Services	4 years

AB = Alberta; BC = British Columbia; MB = Manitoba; PE = Prince Edward Island; NA = not available; N = no; NB = New Brunswick; NL= Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan; QC = Quebec; Y = yes.

Conclusion

Various standards are in place nationally and internationally for POCT. The publicly available Canadian POCT standards are largely based on the Canadian standard CAN/CSA-Z22870-07 and the international standard ISO Z22870:2006. Laboratory standards are largely regulated by the provincial College of Physicians and Surgeons or provincial health authorities. Accreditation cycles in Canada range from two to four years.

Published Reports (Available Free of Charge on the CADTH Website)
CADTH prepared a Rapid Response report in 2013 pertaining to the clinical and cost-effectiveness of POCT compared with conventional laboratory testing.[94]

In April 2012, CADTH published a Rapid Response report on the testing accuracy and cost-effectiveness of POCT.[95] This report concluded that the precision and accuracy of certain POCT devices used in oral anticoagulation therapy is acceptable compared with conventional laboratory-based testing in a systematic review, and has been demonstrated as cost-effective in a Canadian setting.

APPENDIX 14A: CURRENT INTERNATIONAL AND CANADIAN LABORATORY STANDARDS

Organization	Relevant Laboratory Standard	Description (From Source)
International Organization for Standardization (ISO) Full-text standards are available by purchase only	ISO 15189:2012 — *Medical laboratories -- Requirements for quality and competence* www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=56115	ISO 15189:2012 specifies requirements for quality and competence in medical laboratories. ISO 15189:2012 can be used by medical laboratories in developing their quality management systems and assessing their own competence. It can also be used for confirming or recognizing the competence of medical laboratories by laboratory customers, regulating authorities, and accreditation bodies.
	ISO 22870:2006 — *Point of care testing (POCT) -- Requirements for quality and competence* www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=35173 This standard is applied in conjunction with ISO 15189:2007 (*Medical Laboratories -- Requirements for quality and competence*) www.iso.org/iso/home/store/catalogue_ics/catalogue_detail_ics.htm?csnumber=56115	ISO 22870:2006 gives specific requirements applicable to point of care testing and is intended to be used in conjunction with ISO 15189. The requirements of this International Standard apply when POCT is carried out in hospital, clinic and by a health care organization providing ambulatory care. This International Standard can be applied to transcutaneous measurements, the analysis of expired air, and in vivo monitoring of physiological parameters. Patient self-testing in a home or community setting is excluded, but elements of this International Standard can be applicable.
	ISO 15197:2013 — *In vitro diagnostic test systems -- Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus* www.iso.org/iso/home/store/catalogue_ics/catalogue_detail_ics.htm?csnumber=54976	ISO 15197:2013 specifies requirements for in vitro glucose monitoring systems that measure glucose concentrations in capillary blood samples, for specific design verification procedures, and for the validation of performance by the intended users. These systems are intended for self-measurement by lay persons for management of diabetes mellitus. ISO 15197:2013 is applicable to manufacturers of such systems and those other organizations (e.g. regulatory authorities and conformity assessment bodies) having the responsibility for assessing the performance of these systems.
	ISO 17593:2007 — *Clinical laboratory testing and in vitro medical devices -- Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy* www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=36872	ISO 17593:2007 specifies requirements for in vitro measuring systems for self-monitoring of vitamin K antagonist therapy, including performance, quality assurance, and user training and procedures for the verification and validation of performance by the intended users under actual and simulated conditions of use. ISO 17593:2007 pertains solely to prothrombin time-measuring systems used by individuals for monitoring their own vitamin K antagonist therapy, and which report results as international normalized ratios (INR). ISO 17593:2007 is applicable to manufacturers of such systems and those other organizations (e.g., regulatory authorities and conformity assessment bodies) having the responsibility for assessing the performance of these systems.

Organization	Relevant Laboratory Standard	Description (From Source)
	ISO/TS 22367:2008 — *Medical laboratories -- Reduction of error through risk management and continual improvement* www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=40918	ISO/TS 22367:2008 characterizes the application of ISO 15189 as a system for reducing laboratory error and improving patient safety by applying the principles of risk management, with reference to examination aspects — especially to pre- and post-examination aspects — of the cycle of laboratory medical care. ISO/TS 22367:2008 proposes a methodology for finding and characterizing medical laboratory errors that would be avoided with the application of ISO 15189.
Canadian Standards Association (CSA) Full-text standards are available by purchase only	CAN/CSA-Z22870-07 (R2013) - *Point of Care Testing (POCT) - Requirements for Quality and Competence. (Adopted ISO 22870:2006, first edition, 2006-02-01, with Canadian deviations)* http://shop.csa.ca/en/canada/medical-laboratory-systems/cancsa-z22870-07/invt/27027682007	CAN/CSA-Z22870-07 gives specific requirements applicable to point-of-care testing and is intended to be used in conjunction with ISO 15189. The requirements of this International Standard apply when POCT is carried out in hospital, clinic and by a health care organization providing ambulatory care. This International Standard can be applied to transcutaneous measurements, the analysis of expired air, and in vivo monitoring of physiological parameters. Patient self-testing in a home or community setting is excluded, but elements of this International Standard can be applicable.
	CAN/CSA-Z902-10 - *Blood and blood components* http://shop.csa.ca/en/canada/blood-and-blood-components/cancsa-z902-10/invt/27020812010	CAN/CSA-Z902-10 is intended to ensure that the critical elements and methods of blood safety, efficacy, and quality are incorporated into facility procedures.
CLIA (United States)	US Food and Drug Administration (FDA): Clinical Laboratory Improvement Amendments (CLIA) 1988 www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm	CLIA establishes quality standards for all laboratory testing to ensure the accuracy, reliability, and timeliness of patient test results regardless of where the test was performed. A laboratory is any facility that does laboratory testing on specimens derived from humans to give information for the diagnosis, prevention, or treatment of disease, or impairment of or assessment of health. CLIA is user-fee funded; therefore, regulated facilities cover all the costs of administering the program. Centers for Medicare & Medicaid Services (CMS) assumes primary responsibility for financial management operations of the CLIA program. The categorization of commercially marketed *in vitro* diagnostic tests under CLIA is the responsibility of the FDA. Accrediting organizations include: College of American Pathologists (CAP) www.cap.org/apps/cap.portal The Joint Commission www.jointcommission.org/

APPENDIX 14B: PROVINCIAL LABORATORY ACCREDITATION

Province	Regulatory Body	Laboratory Accreditation Program (If Applicable)	Discussion (From Source)
British Columbia	College of Physicians and Surgeons of British Columbia www.dap.org/Default.aspx and www.cpsbc.ca/programs/dap	College of Physicians and Surgeons of British Columbia: Diagnostic Accreditation Program (DAP) www.dap.org/Default.aspx and www.cpsbc.ca/programs/dap Relevant publication: *Accreditation Standards 2010 Laboratory Medicine* www.dap.org/CmsFiles/file/Standards/2010%20Laboratory%20Standards%20TM%20Update%2022%20July%202013/Laboratory%20Medicine%20Standards%202010%2022%20July%202013.pdf Point-of-Care Testing Standards can be found on page 277.	Since 1971, the Diagnostic Accreditation Program (DAP) has been mandated to assess the quality of diagnostic services in the province of British Columbia through accreditation activities. As a Program of the College of Physicians and Surgeons of British Columbia, the mandate of the DAP derives from the Health Professions Act: Bylaws of the College of Physicians and Surgeons Part 5, Section B. The 2010 edition of the Laboratory Medicine Accreditation Standards have been internationally reviewed and accredited by the International Society for Quality in Health Care (ISQua). Accreditation reassessment is performed on a 4-year cycle.
Alberta	College of Physicians & Surgeons of Alberta (CPSA) www.cpsa.ab.ca/Services/Quality_of_Care_Main/Accreditation_Facilities/Medical_Laboratories.aspx	College of Physicians & Surgeons of Alberta: Laboratory Accreditation Program www.cpsa.ab.ca/Services/Quality_of_Care_Main/Accreditation_Facilities/Medical_Laboratories.aspx Relevant publications: *Accreditation Program Guide Diagnostic Laboratory Facilities (2013)* www.cpsa.ab.ca/Libraries/pro_qofc_laboratories/accreditation-program-guide.pdf?sfvrsn=4 *Diagnostic Laboratory 4-Year Accreditation Assessment Assessor Checklist – Point of Care Testing (POCT) (2013)* www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&ved=0CCoQFjAA&url=http%3A%2F%2Fcpsa.ab.ca%2FLibraries%2Fpro_qofc_laboratories%2Fassessorchecklistspoct.doc	The CPSA administers accreditation programs for those services that Council determines deserve explicit standards and verification of compliance with those standards, whether pertaining to the qualifications of physicians who provide them or the safety of those services to the public. Accreditation looks at compliance, emphasizing continuous quality improvement and promoting optimum performance. More specifically, the CPSA's accreditation program looks closely at policies, processes, and procedures to assess the safety and reliability of the service being provided, as well as the performance of the people involved and the product produced. The Laboratory Accreditation Program examines all aspects of laboratory quality and operations including: organization, management and personnel, quality management systems, physical facilities, equipment, reagent and supplies, laboratory information systems, pre-examination, examination and post - examination activities, quality assurance activities, safety, and point-of-care testing. The Laboratory Accreditation Program is

Province	Regulatory Body	Laboratory Accreditation Program (If Applicable)	Discussion (From Source)
		&ei=SkM_UrXVCcq3rQGUpoGADQ&usg=AFQjCNGbpKScLE1j0YnlOdyJV6CAVEY-yA&sig2=SxJqkum6yNNFpmPDA11MJw	a peer review process with a goal to improve laboratory performance through objective evaluation. Assessors evaluate a laboratory's compliance with the specific requirements of a standard based on objective observation and assessment. All accreditation assessment findings are vetted by the Advisory Committee on Laboratory Medicine to eliminate any potential personal assessor bias, ensure consistent and thorough approach for all facilities, and to review standards for applicability to current best practice. www.cpsa.ab.ca/Libraries/pro_qofc_laboratories/accreditation-program-guide.pdf?sfvrsn=4 Accreditation re-assessment is performed on a 4-year cycle.
Saskatchewan	College of Physicians and Surgeons of Saskatchewan www.quadrant.net/cpss/labqa/	College of Physicians and Surgeons of Saskatchewan: Laboratory Quality Assurance Program www.quadrant.net/cpss/labqa/ Relevant publications: *Laboratory Quality Assurance Policy Manual (2013*) College of Physicians and Surgeons of Saskatchewan Laboratory Accreditation *Point of Care Testing Inspection Checklist (2012)* www.quadrant.net/cpss/docs/Lab_QA_POCT_Inspection_Checklist.doc	The Laboratory Quality Assurance Program of the College of Physicians and Surgeons of Saskatchewan has been granted the authority under the *Medical Laboratory Licensing Act and Regulations* to administer a quality assurance program for medical laboratories. In essence, the LabQA Program is an accreditation program that provides the framework for continuous improvement in laboratory services, through a peer-review process. The Program operates under the principles of a quality system that includes, but is not restricted to, quality system essentials, or QSEs. Some of the major QSEs incorporate process improvements through strategic planning, validation, document control, problem resolution, and audits.
Manitoba	College of Physician & Surgeons of Manitoba (CPSM) http://cpsm.mb.ca/	Manitoba Quality Assurance Program (MANQAP) http://cpsm.mb.ca/manqap Relevant publications: *Manitoba Laboratory Standards (2013)* http://cpsm.mb.ca/cjj39alckF30a/wp-content/uploads/Manitoba_Laboratory_Standards_March-2013.pdf	The Council of the College of Physicians and Surgeons of Manitoba has established a Program Review Committee, which oversees the operation of the MANQAP. The objective of MANQAP is to establish standards for diagnostic facilities, to investigate and inspect diagnostic facilities for accreditation, and to monitor compliance with established standards. Accreditation reassessment is performed on a 4-year cycle.

Province	Regulatory Body	Laboratory Accreditation Program (If Applicable)	Discussion (From Source)
		No mention of POCT in abovementioned documents	
Ontario	Ministry of Health and Long-Term Care (MOHLTC) www.cmlto.com/images/stories/About_CMLTO/Ministry_of_Health_and_Long_Term_Care_POCT_Policy_and_Guideline.pdf	Ontario Laboratory Accreditation (OLA) www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20OLA%20Program%20Information.pdf Under the Quality Management Program — Laboratory Services (QMP-LS) of the Ontario Medical Association (OMA) www.qmpls.org/ Relevant publications: *Quality Management Program — Laboratory Services, Ontario Laboratory Accreditation Division, Ontario Laboratory Accreditation Frequently Asked Questions (2012)* www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20Frequently%20Asked%20Questions.pdf Ontario Laboratory Accreditation Program Information (2012) www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20OLA%20Program%20Information.pdf	According to the OLA, it is Canada's only English-speaking ISO15189 accreditation program aligned with Standards Council of Canada. Therefore, OLA is Canada's only English-speaking accreditation program that leads to an ISO 15189 Certificate of accreditation to ISO 15189:2007 *Medical laboratories — Particular requirements for quality and competence* OLA accreditation requirements are augmented with the following additional standards: ISO 15190:2003 *Medical Laboratories — Requirements for safety*, ISO 22870:2006 *Point-of-Care Testing (POCT) — Requirements for quality and competence*, CSA Z902-10, *Blood and Blood Components,* February 2010 www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20Frequently%20Asked%20Questions.pdf QMP–LS offers accreditation to ISO 15189 under its OLA division. This accreditation program is mandated by three provinces in Canada (Ontario, New Brunswick, and Newfoundland and Labrador), and subscribed to voluntarily by other laboratories. If desired, ISO 15189 accreditation certificates can be issued in conjunction with the Standards Council of Canada (SCC). www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20OLA%20Program%20Information.pdf Accreditation reassessment is performed on a 4-year cycle in Ontario and Newfoundland and a 2-year cycle in New Brunswick. www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20Frequently%20Asked%20Questions.pdf
Quebec	Ministère de la Santé et des Services sociaux (MSSS) www.msss.gouv.qc.ca/en/index.php Ordre professionnel des technologistes médicaux du Québec (OPTMQ)	Relevant publications: *Quality in Biomedical Laboratories – Rules of Practice (2010)* http://optmq.org/wp-content/uploads/2012/12/Quality-in-Biomedical-Laboratories-Second-Edition.pdf	The *Act Respecting Health Services and Social Services* states that every public and private institution shall have the health services and social services it provides accredited by a recognized accreditation body every three years. http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/S_4_2/S4_2_A.html

Province	Regulatory Body	Laboratory Accreditation Program (If Applicable)	Discussion (From Source)
	http://optmq.org/	POTC section starts on page 64. *Point of Care Testing in the Private Sector (2008)* www.inesss.qc.ca/fileadmin/doc/AETMIS/Rapports/Autres/2008_01_res_en.pdf The aforementioned document is a review of Canadian and International standards on POCT, with suggestions for Quebec.	The OPTMQ has adopted CAN/CSA-Z22870-07 Point-of-care testing (POCT)—Requirements for quality and competence. The OPTMQ develops rules of practice that serve as a framework for practice by its members. The second edition of the rules of practice was developed to reflect the requirements of CAN/CSA Standard Z15189-03, ISO Standard 15189-07, and CAN/CSA Standard Z902-04. These standards contain additional requirements, requirements added to reflect the positions taken by the Ordre in order to fulfil its mandate of protecting the public. The specific requirements relating to quality in medical biology target all phases of testing (pre-analytical, analytical, and post-analytical) inside or outside a laboratory. The complete process begins with the medical prescription for the test, and ends with the sending and archiving of the test results report. The quality system targets all stages of the process. These rules of practice were developed taking into account all these elements in compliance with generally recognized laboratory standards and with standards such as those of the Clinical and Laboratory Standards Institute (CLSI) and the International Organization for Standardization (ISO). The objective is to offer tools for implementing procedures that target maintaining and improving the quality of service in biomedical laboratories, and ensuring the safety of personnel and patients. Accreditation reassessment is performed on a 3-year cycle. http://optmq.org/wp-content/uploads/2012/12/Quality-in-Biomedical-Laboratories-Second-Edition.pdf
New Brunswick	Department of Health http://www2.gnb.ca/content/gnb/en/news/news_release.2011.05.0589.html Position Statement	OLA www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20OLA%20Program%20Information.pdf	OLA (see Ontario) is used in New Brunswick. www.qmpls.org/KnowledgeCentre/Newsletter/CurrentIssue/tabid/88/entryid/33/Default.aspx Accreditation reassessment is performed

Province	Regulatory Body	Laboratory Accreditation Program (If Applicable)	Discussion (From Source)
	only: New Brunswick Society of Medical Laboratory Technologists www.nbsmlt.nb.ca/point-of-care-testing.asp		on a two-year cycle. www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20Frequently%20Asked%20Questions.pdf
Prince Edward Island	Health PEI www.healthpei.ca/index.php3?number=news&dept=&newsnumber=7481&lang=E http://www.healthpei.ca/photos/original/hpeiacredrpt10.pdf Results of report: Establishing a Point-of-Care program should be a priority for the organization to ensure the accuracy of results obtained.	Accreditation Canada	Health PEI has received national Accreditation with Condition by Accreditation Canada. All hospitals and services under Health PEI participated in this provincial voluntary Accreditation survey through Accreditation Canada from September 26 to October 1, 2010. www.healthpei.ca/index.php3?number=news&dept=&newsnumber=7481&lang=E
Nova Scotia	NA Position Statement only: Nova Scotia College of Medical Laboratory Technologists (NSCMLT) http://nscmlt.org/index.php?Itemid=659	Accreditation Canada (see discussion)	Accreditation in Nova Scotia is voluntary, though many laboratories are accredited through Accreditation Canada. http://m.thechronicleherald.ca/novascotia/149941-south-shore-health-earns-highest-ranking
Newfoundland and Labrador	Provincial Public Health Laboratory, a Division of the Newfoundland and Labrador Department of Health and Community Services www.health.gov.nl.ca/health/publications/phl_annual_report2011_12.pdf	OLA www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20OLA%20Program%20Information.pdf	In 2010, a memorandum of understanding was signed between the Provincial Government of Newfoundland and Labrador and the OLA program. In May 2010, the Government of Newfoundland and Labrador mandated that all medical laboratories across the province be accredited by OLA to the ISO 15189 standard for medical laboratories. www.health.gov.nl.ca/health/publications/phl_annual_report2011_12.pdf Accreditation reassessment is performed on a 4-year cycle. www.qmpls.org/Portals/0/OLA/PDFs/Master%20-%20Frequently%20Asked%20Questions.pdf