CPAM COSTING STUDY

Final Results

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March 10, 2020

I. Introduction

Warfarin is a common oral anticoagulant therapy that is effective in the prevention and treatment of thromboembolic disease. Although warfarin is a relatively inexpensive medication, frequent monitoring may be necessary to maintain therapeutic levels. Prothrombin times, measured by international normalized ratio (INR), must be maintained in a tight therapeutic range as risk of thrombosis increases with subtherapeutic anticoagulation and the likelihood of hemorrhage increases with supratherapeutic levels. Physician monitoring of patients on warfarin is currently considered usual care in Canada and elsewhere. However, other modalities of anticoagulant monitoring are being implemented in many countries including patient-self monitoring, specialized clinics, and pharmacist-managed anticoagulation in clinics and the community.

The Pharmacy Association of Nova Scotia (PANS) and Doctors Nova Scotia (DNS) developed a Community Pharmacist-led Anticoagulation Management Service (CPAMS) similar to one piloted in New Zealand (Harrison et al., 2015). In the Nova Scotia demonstration project, pharmacists provided anticoagulation management, in collaboration with family physicians, using point-of-care testing and decision support software. Similar pharmacist provided services have been shown to increase the quality of the patient experience, maintain or improve clinical outcomes, and decrease resource utilization (Harrison et al., 2015; Ingram et al., 2018). This report examines data collected from Nova Scotia's CPAMS demonstration project to evaluate its effectiveness compared to usual care. Given patient outcomes, a cost study from the payer's perspective (Nova Scotia Department of Health and Wellness (NSDHW)), should the CPAMS model be scaled up to the provincial level, is completed.

The paper proceeds as follows, the next section presents a review of studies that have evaluated the components of CPAMS: point-of-care INR testing; warfarin dosing decision support software; pharmacists' provision of anticoagulant management; and other CPAMS models. Section III presents the data and methodology and section IV presents results. Section V offers some conclusions.

II. Literature Review

Patients undergoing treatment for chronic atrial fibrillation, pulmonary embolism, venous thromboembolism, myocardial infarction, or stroke, and those with mechanical heart valves require anticoagulant therapy to reduce the risk of embolisms. Warfarin, an oral anticoagulation therapy (OAT), has been commonly used for more than six decades. It is a convenient medication for patients and, when administered properly, is highly effective. A tight therapeutic range must be maintained to balance the risk of thrombosis if anticoagulation is ineffective with the risk of hemorrhage if it is excessive (see for example, White et al., 2007; Connock et al., 2007; Bungard et al., 2009; Bungard et al., 2012; Reiffel, 2017). Maintaining the therapeutic range may be difficult due to pharmaceutical interactions, comorbidities, diet, and heterogeneity in patient responses to warfarin doses (see for example, Bungard et al., 2009; Hou et al., 2017; Reiffel, 2017). This necessitates frequent monitoring of prothrombin times (reported as in international normalized ratio (INR)) (see for example, Reiger et al., 2006; Reiffel, 2017).

Anticoagulant management (including monitoring of INR and warfarin dosage changes to maintain therapeutic ranges) has historically been the purview of physicians in Canada and many other countries. Physician management (usual care (UC)) typically requires patients to obtain INR testing at a laboratory, the laboratory reports the INR to the physician and the physician in turn contacts the patient with necessary dosage changes (see for example, Reiger et al., 2006; Health Technology Assessment, 2007; Bungard et al., 2009). A recent Canadian study (McAlister et al., 2018) reported that only 41% of warfarin treated patients who were regularly monitored in UC exhibited levels of control in line with those in randomised trials and that percentage decreased over time. For warfarin to be a reliable anticoagulant treatment, INR must be better controlled. Thus, alternative models of anticoagulant management are being evaluated.

Over the last two decades, alternate models of anticoagulant management have evolved with advances in INR testing technology and health practitioners, other than physicians, who are able to monitor and adjust warfarin dosages. There are a plethora of studies evaluating anticoagulant management provided by primary care physicians (PCP) relative to: anticoagulation clinic care, usually provided by registered nurses or pharmacists; management by community pharmacists; and patient self-testing or self-management. The movement of anticoagulation management out

of the physician's office has been facilitated by the availability of affordable and effective point-of-care (POC) monitors (see for example, Medical Advisory Secretariat, 2009; Canadian Agency for Drugs and Technologies in Health (CADTH), 2014; Norrie, 2016) and decision support software (DSS) to assist with dosage regulation (Wieloch, 2011; Harper et al., 2014). Thus, new modalities in monitoring and maintaining patients on long-term warfarin may exhibit POC monitoring, DSS, and/or health-care practitioners other than physicians or even the patient themselves managing their INR tests and warfarin dosing.

The remainder of the review will focus on studies which place the current study in the context of the broader literature. This study examines a community pharmacist-led anticoagulation management service (CPAMS) demonstration project in Nova Scotia (NS). CPAMS models utilize POC testing, computer DSS, and community pharmacists to provide anticoagulation management services in collaboration with physicians. Similar CPAMS models have been shown to be efficient (Harrison et al., 2011; Harrison et al., 2014; Ingram et al., 2018). It was hypothesized that the demonstration project would show that CPAMS would better utilize pharmacist's training, reduce the workload of primary care physicians and blood collection services, and improve patient accessibility and convenience (PANS, 2017).

Point-of-care monitoring and Decision Support Software

As previously noted, the ability to test and monitor INR results in venues other than traditional settings (laboratory and PCP office (or UC)) came about with the advancement in affordable and effective POC monitors and reliable and accessible DSS for warfarin dosing. INR POC monitoring uses portable coagulometers which only need a drop of blood, obtained by fingerstick, applied to a disposable test strip or cartridge to obtain a reading. An INR result is reported within a short period (usually under three minutes). (Medical Services Advisory Committee, 2005). Studies have shown patient support for routine capillary INR testing using portable monitors for the management of their anticoagulation. Woods et al. (2004) fount that patients expressed a strong preference for capillary over venous INR monitoring. Patients also rated capillary monitoring to be significantly less painful and to be substantially less time consuming (Woods et al., 2004; Shaw et al., 2014).

Evaluation studies routinely examine UC compared to an alternate modality including the use of POC and DSS but few studies intend to evaluate the individual components (for exceptions see, Jackson et al, 2005; Perry et al., 2010; CADTH, 2014; Norrie, 2016 which focus on the difference between POC and laboratory testing and Harper & Pollock, 2011; Wieloch et al., 2011; Harper et al., 2014 which focus on the use of DSS). Perry et al., (2010) pointed to the clinical issues with POC but did evaluate clinical outcomes per se. Norrie (2016) presented a 'proof of concept' study in a Canadian province with a relatively small sample size. Patients reported less burden and higher satisfaction with POC compared to laboratory testing. TTRs were higher with POC, mainly due to immediacy of results, so patients spent fewer days out of range while waiting for test results. Lower adverse events and emergency room visits were also recorded, however due to the small sample size, the authors cautioned that statistical significance was difficult to show in some instances.

Jackson et al., (2005) compared INR measures taken by pharmacists using POC monitoring directly with laboratory testing in rural pharmacies in Australia. They found the measures to be highly correlated (r=0.88) and that the POC monitoring was well received by patients, physicians and pharmacists. Harper & Pollock (2010) compared anticoagulant control using self-testing and decision support provided over the internet to standard laboratory testing. They found no statistically significant difference between the two methods of anticoagulant control (TTR 72% (laboratory) vs 81% (DSS)) but INR was below range significantly less in the DSS group. A small cohort with poor control showed marked improvement with self testing using DSS (TTR increased from 38% under UC to 71% using DSS).

Harper et al, (2014) examined anticoagulant control in patients managed by doctors and community pharmacists. Both groups used DSS to assist with warfarin dosage regulation. They concluded that the computer algorithm provided appropriate dose recommendations for INR results ranging from 1.5 to 4. Clinicians' doses differed from the DSS recommendation in just under one quarter of tests, but the changes were not needed to correct algorithm inaccuracies. Clinicians predominantly changed the dose when the INR was below therapeutic range; physicians adjusted the dose more often and made larger adjustments than pharmacists. Physicians achieved poorer TTR control than pharmacists (75.1% compared to 67.4%), in part due to their higher level of overriding the algorithm. The clinicians' behaviour was believed to

be in part due to their confidence in their own decisions, however the changes tended to underdose patients. So, the authors concluded that better anticoagulant control could be obtained if clinicians more closely followed the computer algorithm. Wieloch et al. (2011) suggested that the high level of warfarin control found in a national registry of anticoagulant users in Sweden (better than randomized control trials) was in part due to the registry and in part due to the DSS used within the registry.

A systematic review of 47 studies (Canadian Agency for Drugs and Technologies in Health (CADTH), 2014) showed that for in-range INR values, POC and laboratory monitoring produced similar results but POC testing took substantially less time. The use of POC monitors resulted in statistically significantly higher TTRs but no differences in major bleeding, thromboembolic events (TE) or strokes. Nine older systematic reviews (Cepoiu et al., 2010; Dolor et al., 2010; Health Quality Ontario, 2009; Bloomfield et al., 2011; Brown et al., 2007; Christensen et al., 2007; Gailly et al., 201; Garcia-Alamino et al., 2010; Heneghan et al., 2006) summarized within the CADHT (2014) study found heterogenious results. Of the four studies reporting TTR, Christensen et al., (2007) and Connock et al., (2007) found increases in INR as a result of POC monitoring but Bloomfield et al. (2011) and Cepoiu et al. (2010) found no significant differences in TTRs between testing methods. While the earlier systematic reviews mirrored the CADHT (2014) non-significant results for major bleeds, they reported lower risk for TE and stroke with POC monitoring than for laboratory testing of INR.

A full economic evaluation was completed comparing several INR monitoring models to standard practice (laboratory testing via PCP) from the health-care payer's perspective (CADTH, 2014). The results showed that POC models were more costly than laboratory testing. However, patient-self management (PSM) using POC monitoring led to higher quality-adjusted-life years (QALYs) than did UC. The incremental cost-effectiveness ratio (ICER) for PSM compared to UC was just over $13,000/QALY gained (well within acceptability limits). Clinical use of POC monitoring and patient self testing (PST) were dominated by PSM. When the perspective was expanded to include patient costs (travel time and lost wages), PSM dominated all models.

Norrie (2016) provided a simple costing of laboratory vs POC testing from the payer's perspective and found that for every $1 spent on ongoing POC testing, laboratory testing would

cost $1.64. However, the POC costing did not include initial investment in equipment (coagulometers). Medical Advisory Secretariat (2009) found that UC was the least expensive model when comparing health-care staff testing (HCS), PST and PSM (annual care costs where $234.74, $779.0, $662.24, and $649.52, respectively). When total costs were extrapolated (including adverse events) UC = $6,068/QALY, Health-care staff testing = $4,702/QALY, PST =$4,786/QALY, and PSM = $3,268/QALY.

Using data from a Canadian RCT, Reiger et al. (2006) estimated a Markov model and found PSM using POC to be a cost-effectiveness alternative at $14,129/QALY gained. Lafata et al., (2000) estimated a similar model comparing UC (PCP and laboratory testing) to PST with POC monitors and INR results called into an anticoagulant management service to obtain dosage changes. While the risk of adverse events was lower in the PST scenario, the health-system cost savings due to adverse events were more than offset by the costs of more frequent INR testing in the PST model. However, when patient and care-giver costs were included, PST was more cost-effective than UC. Connock et al., (2007) completed a systematic review and a used a Markov model to estimate costs and benefits of PSM compared to UC. PSM was not found to be a cost-effective alternative for usual anticoagulation care in the UK population but the authors suggested that patients who are not satisfactorily controlled in their clinical setting might be better off with it.

In general, research findings support the use of POC and DSS in combination as an effective alternative to the UC model of laboratory testing and informing medical practitioners of INRs to obtain warfarin dosage changes. The immediacy of the results and dosage changes is particularly helpful.

Pharmacists' Anticoagulation Management (in non-community settings)

The evaluation of pharmacist involvement in anticoagulant management is complicated by the variability of settings that pharmacist function in. Studies in the literature include pharmacists who work in: primary care clinics, specialized anticoagulant management clinics, hospital settings, and community settings (typically pharmacies). In this section, studies focusing on

pharmacist provision of anticoagulant management in settings other than community are reviewed.

A recent systematic review compared physician care using laboratory testing (UC) to pharmacist management of warfarin therapy (PMWT) (Entezari-Maleki et al., 2016). In reviewed studies, PMWT typically included a trained pharmacist directing warfarin management therapy in a primary care clinic using physician-approved designated protocols. The pharmacists' activities could have included seeing patients and assessing their medical conditions, adjusting warfarin doses based on INR results usually using POC testing, patient consultation and education, monitoring of patients regarding anticoagulation-related adverse effects, and checking drug and dietary interactions with their medications. Twenty-four studies (four RCTs and 20 observational studies (OS) were included in the analysis. Most of the studies were carried out in the United States (US – 50%), Canada (25%), and the United Kingdom (UK – 21%), so the study was relative to the Canadian experience. While the results varied by type of study (RCT vs OS), PMWT was always at least as good as UC. Specifically, there were no significant differences in outcomes in the RCTs. OS showed significantly better outcomes for PMWT than UC: TTR (72.1% vs 56.7%), major bleeding (0.6% vs 1.7%), TE (0.6% vs 2.9%), hospitalization (3% vs 10%), and emergency room visits (7.9% vs 23.9%). In both RCTs and OS, patient satisfaction was higher in PMWT and where reported, both pharmacists and physicians were satisfied with pharmacists' care and patients found pharmacist to be better managers of anticoagulation therapy than UC. Other reviews found limited differences between PMWT and UC. Saokaiw et al. (2010) found a significant reduction in overall bleeding but no significant differences between PMWT and UC for major bleeding, TE, or mortality (all-cause and warfarin related). Zhou et al., 2016 and Hou et al., 2017 found similar results; RCTs tended to show insignificant differences between pharmacist care and UC, while OS indicated pharmacist care led to better outcomes.

A study comparing clinical pharmacists' (CP) to registered nurses' (RN) to physicians' (UC) anticoagulant management in primary care settings in a health network in the US (Rudd et al., 2010) is of interest. The TTR of 83.6 for CP care was significantly higher than the other two modalities (UC=57.4; RN=71.8). Hospitalizations (UC=13.9; RN=12.3; CP=5.4) and emergency

department visits (UC=5.6; RN=5.6; CP=1.2) were also significantly lower for CPs compared to RNs and UC.

A cost-effectiveness analysis on pharmacist-managed anticoagulation compared with UC care in the same clinic setting was also of note. Medical claims data were obtained on anticoagulation cost, overall medical care costs, anticoagulation-related adverse events, hospitalizations and emergency department visits, and frequency of INR testing. The INR values were obtained by laboratory and clinical reports. The pharmacists had significantly more INR tests performed than did physicians. The percentage of INR values in range and the TTR were significantly higher in the pharmacists' group compared to physicians (67.2% vs 54.6%, and 73.7% vs 61.3%, respectively). The pharmacists' group also had significantly fewer anticoagulation-related adverse events, hospital admissions, and emergency department visits. The direct anticoagulation care and overall medical care costs were $35,465 and $754,191, respectively for pharmacist group, compared to $111,586 and $1,480,661, respectively for usual care. The pharmacists' anticoagulation service demonstrated a net cost savings of $647,024. The authors concluded that pharmacist-managed anticoagulation leads to reduced health-care expenditures while improving therapeutic outcomes compared with UC.

Cost-effectiveness analyses were also included in the Entezari-Maleki et al. (2016) review; one RCT and four OS. The RCT (Lalonde et al., 2008) found PMWT to be less cost-effective by CAN$123.80 per patient/year due to follow-up costs. The OS studies found the opposite (PMWT services were more cost effective than UC). For example, Rudd et al. (2010) reported that PMWT saved more than US$147,000 in health-care resources over UC, Wilt et al. (1995) calculated US$4000/patient-year, in hospitalizations and emergency department savings, Bungard et al. (2009) reported over CAN$1220,000 savings/patient-year and Hall et al (2011) reported an overall savings of approximately US$726,000.

A set of Canadian studies examined clinical care provided by pharmacist rather than their UC. The pre- post-studies evaluated a pharmacist-run ambulatory clinic (PAC) with a physician advisory committee (Bungard et al, 2009: Bungard et al, 2012) and CP care provided in a similar primary care setting (Young et al., 2011) compared to UC. All INRs were obtained in the same

manner (laboratory testing). Therefore, the main difference in the two modalities of anticoagulation management was whether it was delivered by a pharmacist or a physician.

Bungard et al, (2009) reported that PAC showed significantly better results (TTR of 66.5%) than those obtained pre-enrollment in UC (TTR of 48.8%). The difference increased for those with longer periods of data to 65.3% vs 81.7% for PAC vs UC. Prior to admission to PAC care, there were significantly more patients with emergency room visits and hospital stays for TE than during it (0.492 events/patient year for PAC versus 0.036 events/patient year for UC). The decrease in health-care resource used led to a cost savings of just over CDN$122,000. Young (2011) found similar differences in UC and pharmacist care. TTR was significantly higher for CP at 73% than for UC at 65%. Bungard (2012) performed a follow-up to the Bungard (2009) study; randomizing a small number of patients (approximately 30) to return to UC (their PCP) and an equivalent number to remain in PAC care. There were no significant differences in TTR (73.5 vs 76.9 PAC vs UC) after 4.5 months nor TE nor hemorrhages. Patient satisfaction was significantly higher for the PAC group and, given the choice most patients would have chosen to remain in PAC care over returning to PCP care. There was some discussion by the authors that the education received in PAC may have assisted the patients in anticoagulant management after returning to their physician's care.

The reported studies provide strong evidence that pharmacists provide at least as good care as physicians when it comes to anticoagulant management and in some instances the care may be more effective. In addition, patient satisfaction seems to be higher with pharmacists' care.

Community Pharmacist-led Anticoagulation Management Service (CPAMS)

Until this point, the review has focused on the individual elements that make up the collaborative model of care which is the foundation for CPAMS. As previously noted, CPAMS models utilize POC testing, computer DSS, and community pharmacists to provide anticoagulation management services, in collaboration with physicians, to their patients (see for example recent evaluations by, Ingram et al., 2018; Harrison et al., 2014; Harrison et al., 2011).

Ingram et al. (2018) completed a retrospective study examining a CPAMS offered by a large pharmacy chain in the UK. The move to the CPAMS model was a result of the National Health Service (NHS) desire to move health-care services into communities where people lived. The CPAMS offered care by CP for noncomplex patients over the age of 16 who were stable (at least two out of four INRs, immediately before referral, in range). Pharmacists received training and mentoring in INR testing and anticoagulant management and provided care within pharmacies. Their competency was reviewed regularly. INR was measured by POC monitors and DSS was used to assist in dosing, INR retesting appointments, and collecting of patient data. Patient's were instructed on INR results and follow-up appointments verbally and in writing. Target INR ranges were specified by the referring clinician and verified by pharmacists against recommended targets for given indications. Evaluation outcomes were percentage readings within the specified ranges (RR) and mean TTR using (Rosendaal et al., 1993) for each patient. Patients were surveyed regarding qualitative outcomes (patient satisfaction).

The results of the Ingram et al., (2018) analysis showed an average RR of 65.4% and a mean TTR of 72.5%. On average, the RR and the TTR increased as patients were in the service longer. Patients who left the service had statistically significantly lower outcomes than those who remained; RRs of 69.3% vs 61.4% and TTRs of 78.0 vs 67.0, respectively. The mean CPAMS TTR of 72.5% compared favourably to the mean TTR from other providers of 71.5%. CPAMS RRs and TTRs also exceeded local and national targets. Overall satisfaction, satisfaction with interpersonal relations and communication were very high. Up to one third of patients stated they wanted more information on side effects and reasons for taking warfarin. The authors stated that CPAMS provided good clinical outcomes and high patient satisfaction and as a result suggested that community pharmacies are well positioned to support the delivery of anticoagulant management.

As discussed previously, Harper et al., (2014) compared services provided by the National Community Pharmacy Anticoagulant Management service (similar to a CPAMS model) to UC in New Zealand. Accredited pharmacists had been managing established anticoagulant patients since 2010. While the study's main focus was on evaluating the DSS, it did show that

community pharmacists achieved significantly higher TTR control than physicians with TTRs of 75.1% compared to 67.4%, respectively.

The NS CPAMS demonstration project closely followed a New Zealand CPAMS pilot which ran from November 2010 to July 2011 (see Shaw et al., 2014; Harrison et al., 2015). The pilot included 15 community pharmacies across New Zealand that represented a wide range of urban/rural, socioeconomic and ethnic-based communities. Pharmacists participating in the pilot received training and accreditation from the Pharmaceutical Society of New Zealand. Pharmacists provided patients with POC INR testing. INR results were available immediately and pharmacists made dosage recommendations with the assistance of a DSS. Pharmacists were able to override the recommendation at their discretion. Patients were referred by their PCP and the PCP retained overall responsibility for the patients. A quantitative study of all patients and a pre–post comparison methodology were completed (Harrison et al., 2015). The data were extracted from the DSS. The final study sample was 671 patients including 84 who left CPAMS (22 patients were excluded due to too few INR tests to complete TTRs). Pre-CPAMS enrollment data were obtained from the physicians for 221 patients who provided consent, enabling the pre-post-data necessary for the comparison study. Outcomes included TTR (Rosendaal, 1993), time above and below range (TBA and TBR, respectively), and number and proportion of results outside efficacy and safety thresholds.

The mean TTR in the pilot study was 78.6%, the mean TBA and TBRs were 10.4% and 11.0%, respectively. Statistically significant increases in TTRs were recorded over time (79.4% for patients completing 16 weeks and 80.3% for those completing 26 weeks). In the matched CPAMS-UC data, patients had measurements over longer periods in CPAMS (median = 228 days) than UC (median = 178 days). CPAMS patients showed a statistically significant increase in mean TTR from 61.8% under UC to 78.5% in the matched data. The authors also reported a significant reduction in time below range (no values were recorded). The percent above range (not reported), the median number of tests per month (3.4 for pharmacists and 2.8 for PCP), and the results outside safety and efficacy thresholds (INR more than 1.0 outside target range, INR >5.0, and INR>8.0) were not significantly different in the two modalities of anticoagulation care.

The authors conclude that community-pharmacist anticoagulation management using POC and DSS was safe and effective and resulted in marked improvements in TTR compared to UC.

A cost-benefit analysis performed using the outcome data from the pilot study, estimated changes in untoward events from the literature and health-care costs from New Zealand health services (Harrison et al., 2011). The study was completed from a government-payer perspective. They found that the CPAMS costs were about 30% lower than UC cost ($908.16 compared to $1301.76/patient/year, respectively). When the improvement in TTR found in CPAMS was extrapolated to decrease in thromboembolic and major bleeding events, CPAMS produced substantial cost savings for the New Zealand government. They concluded that with 80% of anticoagulation patients managed under a CPAMS model in New Zealand, the government would save approximately $177million over 5 years (Harrison et al., 2011).

A qualitative follow-up study on attitudes towards CPAMs (Shaw et al., 2014) indicated that patients experienced improved access and convenience. Patients preferred capillary testing including the immediacy of test results and dose changes. They indicated that they had a better understanding of their health problems than previously. While sample sizes were small, the majority of general practitioners and practice nurses felt there were positive benefits for patients (convenience) and themselves (time saved) and expressed confidence in pharmacists' ability to provide the service. Pharmacists reported greater satisfaction and better use of their clinical knowledge in direct patient care and that their relationships with both patients and health professionals had improved. Physicians reported some concerns regarding potential loss of involvement in patient management while having responsibility for negative outcomes. The authors concluded that the CPAMS model was highly supported by patients and valued by both pharmacists and physicians. Given the promising results obtained in the New Zealand study, the Pharmacists' Association of Nova Scotia undertook a similar CPAMS demonstration project.

III. Methodology and Data

CPAMS Demonstration Project Nova Scotia

In the Nova Scotia CPAMS model, community pharmacists provided POC INR testing and adjusted warfarin doses as needed using DSS (INR Online). PCPs provided a diagnosis and

collaborative warfarin management plan. Pharmacist were enabled to prescribe and monitor patients as per the Nova Scotia College of Pharmacists Prescribing Standards of Practice. INR Online calculated: the dose of warfarin, the optimal date of subsequent INR tests, and the patient's TTR and the mean TTR for each pharmacy. INR Online also tracked untoward events and patients' compliance with appointments.

The project began in fall 2017 with the training of pharmacists. Pharmacists were required to be trained and accredited by the University of Waterloo's *Management of Oral Anticoagulation Therapy (MOAT)* program (or equivalent) for the demonstration project[1]. Training was also offered on the use of POC testing with the CoaguChek XS Pro and INR Online. General practitioners and their patients were recruited to participate in the program by the participating pharmacies. Pharmacies were chosen for representativeness of the NS population. Patients provided informed consent to take part in the study. Patient enrollment was completed between February 1 to July 31, 2018 and patients were to participate in the study for 12 months after their first INR test was recorded. In addition to the Online data, general practitioners were asked to submit at least five historical INR readings for their enrolled patients, and patients were also asked to complete a qualitative survey documenting their experiences.

Effectiveness of CPAMS

This study uses the data collected as part of the NS CPAMS demonstration project to examine its effectiveness. Scenarios associated with a CPAMS scaled up to the broader NS population will be costed using data and resource values from the CPAMS results, the literature, and expert opinion where needed.

Patient outcomes examined follow the literature and the New Zealand CPAMS safety markers and include days in study, number of INR tests, percent INR tests in range, percent INR tests above range, percent INR tests below range, percent days INR is in Range or time in therapeutic range (TTR), percent INR tests below 1.5 and percent INR tests above 4.0 (INRs at which the

[1] While pharmacists were required to undergo training for the demonstration project, they would not be required to do so if CPAMS were to be scaled up to the provincial level. However, it is assumed that most pharmacists would want some training (PANS communication)

physician received an automatic message from the INR Online system regarding out of range INRs).

Two populations are examined[2]. The Original study population includes patients meeting the original study design; patients enrolled and followed for one year. The second population includes only patient whose INRs were taken from November 1, 2018 onward (Post Nov population)[3]. The comparator used in the effectiveness analysis is historical data obtained from physicians. As the historical data were highly variable in number and time period covered, the quality was questioned. Comparator data obtained from the literature is used as an alternate comparator for some scenarios. Specifically, costing is performed for three resource pricing assumptions for a scaled up in CPAMS in NS (Scenarios One, Two, and Three). Scenarios Four and Five use resource values from Scenario Three and alternate assumptions regarding outcomes. The Scenarios are as follows:

Scenario One

CPAMS is scaled up with the format and payment structures similar to those of the demonstration project. Resource values were derived from CPAMS demonstration project costs on an intent to treat basis. Pharmacies are reimbursed by the Nova Scotia Department of Health and Wellness (NSDHW) for their costs and physicians receive their usual fees for anticoagulation management for their collaboration. Physicians' fees and laboratory costs are covered by NSDHW for patients' INR monitoring under UC. It is assumed that additional health-care resource use is similar between CPAMS and UC[4].

[2] Results from third population – all patients INRs recorded between the beginning and end of the demonstration project – are presented in the Appendix. The results are very similar to the original study sample.

[3] A manufacturing error with the test strips used by CPAMS pharmacies to test INR in the Coaguchek XS Pro was identified in October 2018. The error could result in test values greater than 4.5 INR having an increasing positive bias (i.e., inflated results). These test strips may have been used by pharmacies anytime between March 2018 and October 2018. Once CPAMS pharmacies were aware of this issue, they had patients with test values greater than 4.5 duplicate the test in a laboratory to confirm the results and provide them to the pharmacy to manually enter into INR Online until new test strips could be provided.

[4] As TTRs are statistically the same for CPAMS and UC in the effectiveness analysis that follows.

Scenario Two

CPAMS is scaled up with the format similar to that of the demonstration project. The payment structure includes pharmacies reimbursed from the NSDHW for their CPAMS costs and physicians no longer reimbursed for patients who are managed through CPAMS. Resource values are derived from costs in demonstration project on an intent to treat basis. Physicians' fees and laboratory costs are covered by NSDHW for patients' INR monitoring under UC. It is assumed that additional health-care resource use is similar between CPAMS and UC[3].

Scenario Three

CPAMS is scaled up with the format similar to that of the demonstration project except the NSDHW reimburses pharmacies $50/patient/month for patients enrolled in CPAMS and the pharmacies cover all CPAMS costs for those patients. Physicians are not reimbursed for patients who are managed through CPAMS. Physicians fees and laboratory costs are covered by NSDHW for patients' INR monitoring under UC. It is assumed that additional health-care resource use is similar between CPAMS and UC[3].

Scenarios Four and Five

Assume resource values from Scenario Three and uses outcomes including the significantly different TTRs from Post November 1, 2018 sample for Scenario Four and Usual Care TTRs from literature for Scenario Five.

IV. Results

Effectiveness Study

Forty pharmacies and 106 pharmacists participated in CPAMS. As per study design, pharmacies were distributed evenly across NS health management zones with almost half of the pharmacies located in small towns. The average length of time pharmacy staff spent on patient appointments and follow up activities (e.g., scheduling appointments, phone calls with patients or PCPs) was 12.7 minutes. Times were longer at the beginning of the project and declined over time. (see, Research Inc., 2019).

All results presented in this study are intention to treat results (ITT). Table One presents descriptive statistics from INR Online data[5] (n=928) and the patient survey data (n=436). A little more than half of the patients were female, the mean age was just over 75 years, and most patients were on warfarin for Atrial Fibrillation. A little over 20% of the 944 patients enrolled in the project left at some point; 199 patients (21%) left; 16 patients (1.7%) had fewer than two INRs, so were not included in the ITT analyses (183 who exited had two or more INRs, so were included in the ITT analyses). The attrition rate is somewhat better than the rate recorded in the New Zealand pilot where three percent of patients had fewer than two INRs and 24% of patients left the study at some point (Harrison et al., 2015). Attrition proportions and reasons are presented in Table One: five percent of the sample died, two percent left because they were admitted to hospital or long-term care, one percent moved, two percent returned to their physician, eight percent had a treatment change (including ceasing anticoagulation or moving to a better suited anticoagulent), and the attrition reason was unknow in two percent of the sample. Of the deaths, 13% were related to anticoagulation (hemorrhage or TE), 40% were classified as unrelated to warfarin and 47% were for unknown reasons. According to the survey data, most of the study population classified their residence as rural, most were married or widowed, and most had high school diploma or less; characteristics consistent of an older population. Regression analyses (not shown) were completed to ascertain significant associations between TTRs and patient demographics that would necessitate adjustments; none were identified.

Appendix Table A1 displays the demographic characteristics for those who remained in the study and for those who left. The attrition sample is a little older with substantially lower anticoagulation control, on average, than those who remained in the study. The attrition sample is not statistically different with regards to reason for warfarin treatment, or other demographics. The mean time in study, including those who left is almost 11 months for the original sample (maximum 12 months), almost 8 months for the post sample (maximum 9 months) and just over 13 months (maximum 18 months) for all recorded INRs (see Table A2).

[5] To be included in the quantitative analyses, patients had to have had at least two INR values recorded; the minimum needed to calculate at TTR. Sixteen (1.7%) of the 944 enrolled patients did not have two INR values leaving a sample of 928 for the evaluation analysis. The attrition rate for the sample of 928 is 19.7% (183 patients).

Study outcomes are presented in Tables Three through Six and A2 through A5. Table Three presents the Intention to Treat (ITT) data for the original and historical samples (INR data submitted by physicians). The TTRs are similar at 68.8% and 68.5%, in original and historical sample, respectively. Patients spent slightly less time in range in the study sample than the historical sample (62.9% vs 65.7%, respectively), less time below range (19.5% vs 22.6%, respectively), and more time above range (17.6 vs 11.7%, respectively). Patients in the historical sample had fewer INRs below 1.5 than the comparator (2.9% vs 4.6%, respectively). Consistent with the higher likelihood of being above range, the proportion of the study sample above 4.0 was 0.04 while the historical group was 0.02. The matched sample is slightly smaller (Table Four) and the point estimates change slightly but results are consistent. TTRs are statistically the same (68.9% vs 68.5%, study vs control). The other outcomes are statistically significant in the same direction and similar magnitude as reported in Table Three (Tables A2 and A3 present the results for all patient INRs recorded and provide similar results).

Tables A4 and A5 exclude patients with any INRs above 4.5 before November 1, 2018 when faulty strips were in circulation (see footnote 2). The strips caused an upward bias on higher results (INRs>4.5). The sample size is reduced by 20% to 742 and the magnitude of the outcomes increase slightly but the trends remain. TTR and INR in range are now statistically the same (in all three samples). The proportion below range remains higher in the historical data and the opposite is true regarding proportion above range. As expected, the proportion of INRs >4.0 declined substantially. In the matched data differences are all statistically significant except for TTR and % INR in range. In order to avoid losing 20% of the sample, only data from November 1, 2018 (Post sample) is included in Tables Five and Six. The TTR is substantially higher in this group[6]. The matched data in Table Six now shows CPAMS patients in the study as of November 1, 2018 to have statistically significantly higher TTRs than their matched historical data (73.8% vs 69.4%, respectively). The percent INR in range is also statistically significantly higher (68.7 vs 66.4, respectively), and the percent above and below range remain significantly different in the same direction as previous results, however, as expected, the magnitude of the difference in percent above range is smaller.

[6] This is not a surprise, many studies showed TTRs to increase over time (see for example, Harrison 2015) and there were no data available on some of the attrition sample in the later months of the study.

In sum, the outcome results consistently indicate that CPAMS is at least as good as usual care with no statically significant differences in TTRs in the original study sample. The proportion INRs in range is significantly less in the study data than the historical data, mainly driven by a substantially higher proportion of INRs above range. This is likely due, at least in part, to the issue with faulty strips prior to November 2018. The data excluding all patient data prior to November 1, 2018 shows significantly lower proportion of patients above range (almost 25% lower) and a corresponding increase in the proportion in range. The quality of the historical data may be suspect due to the substantial variation in the number of INR tests (indicated by standard deviations that are substantially larger than in the study sample) and the mean number of months of historical data (small but heterogenous, with some patients having data recorded over a few days with others over years) thus alternate assumptions regarding UC TTRs are used in the costing analyses.

Costing Study

Cost-effectiveness studies routinely use outcome data extracted from the literature (see for example, Reiger et al., 2006; CADTH, 2014). An alternative to using the historical data collected in the CPAMS is to do so. TTRs from primary-care settings found in the literature vary widely. Liu et al. (2019) report TTRs as high as 80.3% in a large Swedish registry study (Wieloch et al., 2011) and as low as 51.0% in a meta-analysis of US studies (Cios et al., 2009). They obtained a TTR of 71.0% for INR target ranges of 2.0 to 3.5 and 67.8% for a target INR range of 2.0 to 3.0. Health Quality Ontario (2009) reported TTRs from over 20 studies ranging from 34.2% to 70.4%. A simple mean of the values is approximately 64% which is consistent with the other studies (Liu et al., 2019; Young et al., 2011).

Costs used in this study are presented in Table Seven and include: health-care practitioners' wages/fees for patient visits, laboratory testing, and POC monitoring costs. Cost drivers include the number of INR tests, and the clinicians' time spent with patients. It is assumed that any additional use of health-care resources is identical across CPAMS and UC as the anticoagulant outcomes were similar in the two modalities in the original sample. Table Eight presents the per patient per month costs and incremental costs for Scenario One. Tables Nine and Ten present the per patient per month costs and incremental costs for Scenarios Two and Three. Tables Eight

through Ten are set up identically with the first two rows of data presenting costs as a result of the Original and Post Nov study samples, respectively. Costs include training fees as it is assumed that there will be demand for the training when CPAMS is scaled up. CPAMS cost estimation used demonstration project data, so standard deviations and minimums and maximums are reported. Physician fees for anticoagulant management are presented in the third row and UC lab costs in the next 3 rows (the mean from the literature in the first row, lowest value from the literature in the second row, and highest value in the third row); the costs are point estimates. The next panel includes calculations of the incremental costs (CPAMS – UC) and present the costs for the two samples from CPAMS data compared to UC. A positive value indicates UC is more cost effective than a scaled-up CPAMS (given there are no statistical differences in TTRs – a cost minimization study is possible). If the values are negative, a scaled-up CPAMS will be more cost-effective than the current UC. Finally, the bottom panel presents sensitivity analyses, using the different resource values obtained from the literature.

The monthly/patient cost of CPAMS ranges from $42.15 to $44.98 (the difference is due to the lower number of INR in the Post Nov sample than in the original sample). Physicians continue to receive their usual anticoagulant management fees from NSDHW whether providing anticoagulant management or collaborating with CPAMS in Scenario One. So, the costs compared in this scenario are resources used by CPAMS pharmacists compared to physician laboratory costs. Given physicians retain their fees, it is not surprising that CPAMS is less cost-effective than UC (incremental costs are all positive). Sensitivity analyses shows that CPAMS is only cost effective if physicians obtain the highest number of INRs at costs in the highest range identified in the literature.

Scenario Two may present a more realistic picture (see Table Nine). Physicians are no longer paid fees for patient's anticoagulation management when it is received through CPAMS. The costs presented are identical to those in Table Eight but the incremental costs are now calculated as CPAMS pharmacists' costs minus UC which includes physician fees and laboratory costs. The incremental costs show CPAMS to be more cost-effective by between approximately $10 and $13/patient/month. Sensitivity analyses do not change the cost-effective of CPAMS except if the very lowest resource costs from the literature are used for UC. In this extreme case, UC is a little

more cost-effective (at approximately $1.25/patient/month). In all other analyses CPAMS is more cost-effective than UC by up to $36/patient/month. Table Nine indicates that, on average, physicians could be paid a small fee to maintain collaboration with pharmacists in the CPAMS and it would still be cost-effective alternative for anticoagulation management in Nova Scotia.

Table Ten repeats the analyses in Table Nine but assuming the NSDHW pays each pharmacy a flat fee of $50/patient/month to provide anticoagulation management to patients (Scenario Three). The incremental analysis shows that CPAMS remains cost effective, at the mean, but the difference is becoming marginal. The sensitivity analyses indicate that the finding is not stable over possible resource fees identified in the literature. UC is more cost effective if the lower resource values are realistic and CPAMS care is more cost effective if the higher resource values found in the literature are.

Table Eleven presents data used to calculate the cost-effectiveness for Scenarios Four and Five. The literature indicates that the significantly higher TTR results obtained in the Post Nov sample should be correlated with significantly lower adverse-event rates (see for example, Amin et al., 2014). The top panel of Table Eleven presents extrapolated event rates for TTRs between 55% and 75% for Ischemic stroke (IS), hemorrhagic stroke (HS), systemic embolism (SE), Major Bleed except HS (MBEHS), Clinically Relevant Non-major Bleed (CRNB), and Minor Bleed (MBld) (Amin et al., 2014). The second panel shows the estimated costs for each of the events in CDN$2018 (Goere et al., 2005; Regier et al., 2006; Brown et al., 2007; CADTH, 2009; Nova Scotia Health Authority, 2019; Amin et al., 2014) and the bottom panel calculates the cost differences per five percentage point differences in TTR. These values are used to estimate cost differences between CPAMS and UC for Scenarios Four and Five.

Scenario Four assumes the TTRs obtained Post November 2018 sample are more realistic than those obtained for the Original sample. If this assumption holds, the CPAMS TTR is significantly higher than the UC TTR (73.8% vs 69.4%, respectively). If the assumptions hold, CPAMS is likely to see a reduction in health-care resources due to fewer adverse events of approximately $102/patient/year or about $8.50/patient/month (TTR moving from just below 70 to just below 75). Adding this cost savings to the incremental cost savings in Scenario Three

shows a CPAMS cost savings of $13.89/patient/month. CPAMS remains the cost-effective alternative in both the lower and higher resource costs cases in the sensitivity analyses. The incremental costs savings ranges from $2.24/patient/month to $36.55/patient/month.

Finally, Scenario Five uses UC TTRs from the literature (64.3%) rather than the historical values due to the suspect quality of the historical data. In this scenario, TTRs increase from just below 65% for UC to just under 75% for CPAMS. This TTR difference would be associated with a $213/patient/year or $17.77/patient/month savings for CPAMS in health-care resources due to fewer adverse-event costs. Adding event cost savings to incremental cost differences in Scenario Three shows CPAMs to be cost savings at $23.16/patient/month. The sensitivity analyses results range from a resource costs savings of $11.51/patient/month to $45.82/patient/month in the low- and high-resource cost cases.

A health-care resource savings of $17.77/patient/month added to the incremental cost savings in Scenario Two would lead to a cost savings in the range of $30/patient/month. If the TTRs from Scenario Five are more representative of CPAMS, costing structures from either Scenario two or three would allow a small monthly fee to be paid to physicians for collaboration with CPAMS while retaining cost savings for the NSDHW. The only scheme that would not see CPAMS being at least marginally cost effective is continuing to pay physicians their UC fees and paying CPAMS to manage the anticoagulation care.

V. Summary and Conclusions

A literature review of the effectiveness and cost-effectiveness of component factors of Nova Scotia's Community Pharmacists Anticoagulation Management Service (CPAMS) and similar CPAMS located in the UK and New Zealand is presented. The general conclusion out of the literature is that the components and CPAMS are found to be at least as effective as usual care (UC – typically primary-care physicians providing anticoagulation management). The cost effectiveness weighs heavily on the assumptions regarding which health-care resources are included and their values. CPAMS is shown to be preferred over UC by patients and generally accepted by physicians.

The study then examined the effectiveness of Nova Scotia's CPAMS demonstration project. The results show that CPAMS is at least as effective as usual care (primary-care physicians providing anticoagulation management). Using the original sample and historical INR values from the study, CPAMS and UC show statistically equal TTRs. With statistically equal health outcomes, a cost-minimization study can be completed. Several scenarios for costing of a scale-up of CPAMS in Nova Scotia were presented. The only Scenario where CPAMS was not at least as cost effective as UC was the scenario where physicians retain the same payment fee structure in CPAMS as they received for full anticoagulation management. It seems unlikely that a health-care payer would continue to pay physicians fully while paying for an alternate anticoagulation management model.

If TTR levels more consistent with those found in the literature (either the Post Nov results for CPAMS or INR values for UC) are assumed, CPAMS is more effective than UC. CPAMS cost savings increased due to the expectation of fewer adverse events associated with the statistically significantly lower TTR compared to UC. Again, a cost savings is seen in all Scenarios except when physicians maintain the pre-CPAMS payment structure. The cost savings is generally adequate enough to allow NSDHW to provide a small payment for physicians which would maintain their collaboration in CPAMS and still see a savings in health-care resource expenditures for the government if CPAMS scaled up.

Limitations

The CPAMS demonstration project encountered some issues with the data collection, particularly the manufacturing error identified in the testing strips. The error led to possible biases in the data collected in the early part of the study (before November 1, 2018). Thus, the data obtained in the original study design may have led to INRs that were biased upwards and, lower TTRs for the CPAMS. On the other hand, the values obtained in the Post Nov sample, include patients that were in the study for some time and exclude some of the patients who dropped out earlier in the study. This may lead to higher TTRs for CPAMS. Finally, as is the case for most economic studies, many of the resource values and cost drivers were obtained from the literature and assumptions were drawn where necessary. Presenting results for both the

Original and Post Nov samples and multiple sensitivity analyses were particularly important for this study.

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Table 1 Patient Level Descriptive Data

Variable	Obs	Mean	Std. Dev.
INR ONLINE DATA			
Female	928	0.56	0.50
Age	922	75.09	10.32
Reason for Anticoagulant			
AF	928	0.77	0.42
DVT	928	0.06	0.24
MHV	928	0.05	0.22
PE	928	0.06	0.25
Other	928	0.05	0.22
Attrition Reason			
No Attrition	928	0.80	0.39
Death	928	0.05	0.21
Hospital Admit	928	0.01	0.08
Long-term Care	928	0.01	0.11
Moved	928	0.01	0.09
Returned to MD	928	0.02	0.13
Treatment Change	928	0.08	0.27
Unknown	928	0.02	0.14
SURVEY DATA			
Urban	434	0.34	0.47
Marital Status			
Married	436	0.56	0.50
Widowed	436	0.27	0.45
Never Married	436	0.08	0.27
Previously Married	436	0.08	0.28
Education			
No High School	430	0.36	0.48
High School	430	0.24	0.43
College	430	0.20	0.40
University	430	0.19	0.40

Table Two Participation Time in Study

Months in Study	Mean	Std. Dev.	Min	Max
Original Design	10.90	2.54	1	12
Post November 2018	7.92	1.68	1	9
All observations	13.16	3.73	1	18
Historic Data	4.48	5.30	0.07	107

*Intention to Treat – all patients who enrolled are included in means.

Table Three Results Intention to Treat Analysis

Clinical Data Variable	Original Mean/%	Original Std.Dev.	Historical Mean/%	Historical Std. Dev.
TTR	68.75	16.93	68.51	30.29
% INR in range	62.90	16.61	65.74	28.00
% INR below range	19.49	13.80	22.58	26.42
% INR over range	17.62	12.59	11.67	17.28
% INR <1.5	2.85	6.19	4.62	13.06
% INR >4.0	4.10	7.65	1.50	5.94
# INR tests	19.80	7.74	5.06	1.15
Days INR in Range	226.75	77.36	96.81	134.60
Days in Study	322.00	78.71	136.51	161.59
#observations	928		915	

Notes
All samples are Intention to Treat (for those with at least 2 INR readings.
ITT includes the attrition sample).
Original includes patients INRs for 365 days after first INR test as per study design.
Historical includes all historical INRs (for those with at least 2 historical INRs)

Table Four Results Intention to Treat Matched Data
(includes observations with historical and study INRs)

Clinical Data Variable	Original Mean/%	Original Std.Dev.	Historical Mean/%	Historical Std.Dev.
% TTR	68.85	16.90	68.50	30.21
% INR in range	63.10	16.47*	65.58	28.02
% INR below range	19.23	13.65*	22.78	26.53
% INR over range	17.68	12.63*	11.64	17.18
% INR <1.5	2.81	6.11*	4.61	13.09
% INR >4.0	4.03	7.55*	1.48	5.90
# INR tests	19.67	7.69*	5.06	1.16
Days INR in Range	227.33	77.02*	97.35	135.54
Days in Study	322.42	77.99*	137.30	162.74
#observations	899		899	

Notes
All samples are Intention to Treat (for those with at least 2 INR readings.
ITT includes the attrition sample).
Original includes patients INRs for 365 days after first INR test as per study design.
Historical includes all historical INRs (with at least 2 historical INRs)
* significantly different than historical values.

Table Five Intention to Treat Analysis

Clinical Data Variable	Post Nov 2018 Mean/%	Std.Dev.	Historical Mean/%	Std. Dev.
TTR	73.78	17.91	68.50	30.21
% INR in range	68.51	17.85	65.58	28.02
% INR below range	18.42	15.31	22.78	26.53
% INR over range	13.07	12.54	11.64	17.18
% INR <1.5	2.42	7.44	4.61	13.09
% INR >4.0	2.25	5.60	1.48	5.90
# INR tests	13.06	5.36	5.06	1.16
Days INR in Range	172.19	55.18	97.35	135.54
Days in Study	230.63	51.32	137.30	162.74
#observations	845		899	

Notes
All samples are Intention to Treat (for those with at least 2 INR readings.
ITT includes the attrition sample).
Post sample includes all INR tests from Nov. 1, 2018 to end of study
Historical includes all historical INRs (with at least 2 historical INRs)

Table Six Results Intention to Treat Matched Data
(includes observations with historical and study INRs)

Clinical Data Variable	Post Nov 2018 Mean/%	Std.Dev.	Historical Mean/%	Std. Dev.
TTR	73.79	17.91*	69.38	30.05
% INR in range	68.65	17.73*	66.36	27.90
% INR below range	18.30	15.25*	22.51	26.41
% INR over range	13.05	12.55*	11.13	16.73
% INR <1.5	2.42	7.45*	4.58	13.11
% INR >4.0	2.22	5.57*	1.26	5.31
# INR tests	13.04	5.36*	5.10	1.14
Days INR in Range	172.13	55.18*	99.31	138.05
Days in Study	230.51	51.32*	138.24	164.50
#observations	820		820	

Notes
All samples are Intention to Treat (for those with at least 2 INR readings.
ITT includes the attrition sample).
Post sample includes all INR tests from Nov. 1, 2018 to end of study
Historical includes all historical INRs (with at least 2 historical INRs)
* significantly different than historical values.

Table Seven
Costs Related to Providing Anticoagulation Management

CPAMS	Costs/Drivers	Note
Pharmacists Wages	$54.90/hour	PANS, 2019
POC test supplies	$8.15/INR	$7.00 Actual Charge. $8.15 includes 1.164 tests/INR due to errors.
POC Monitor	$2000.00/pharmacy	Over 5-year life span – negotiated by PANS
INR Online (DSS)	$ 3.50/patient/month	Actual charge – negotiated by PANS
Pharmacist Training	$948.75/pharmacist	Voluntary – assumed 2/pharmacy/5 years or None
INR tests	1.9/month (mean)	study results
Pharmacist time	12.7/INR visit (mean)	study results
Usual Care	Costs/Drivers	Note
PCP Management	$24.20/month	Nova Scotia Fee Schedule – Expert opinion
PCP Chronic Care	$39.93 x 3/year	Nova Scotia Fee Schedule – Expert opinion
Physician Total	$34.18/month	calculated
Laboratory Test	$12.19/INR (median)	range $8.24-$17.23[7]
Number INR Tests	1.74/month (mean)	Literature[8] Median=1.7; Range = 1.16 to 2.46; Historical data Mean=2.4; Median=2.16.

[7] Sources: Alberta Health Services, 2016; CADT, 2014; BC Ministry of Health, 2009; Reiger et. al., 2006.
[8] Sources: Bungard et al., 2012; Connock et al., 2007; Reiger et al., 2006; Young et al., 2011; Hall et al., 2011; Harper & Pollock, Lafata et al., 2000; Nichol et al., 2008; CADTH, 2004; Harrison et al., 2015 et al., Rudd et al., 2010.

Table Eight

Scenario One

Monthly Costs per patient for NSDHW

Sample	Mean	Std.Dev.	Min	Max
Pharmacists' Cost (not including physician fees)				
Original~	$44.98	19.50	19.13	254.55
Post Nov~	$42.15	14.78	18.58	139.24
Physician Fees	$34.18 common to both CPAMS and UC			
Usual Care Laboratory Costs				
UC Lab Cost*	$21.21			
UC Lab Cost+	$ 9.56			
UC Lab Cost++	$43.87			
Incremental Cost=Pharmacists' cost-UC lab cost				
Original~-UC*	$23.77			
Post Nov~-UC*	$20.94			
Sensitivity Analyses				
Original~-UC+	$35.42			
Post Nov~-UC+	$32.59			
Original~-UC++	$1.11			
Post Nov~-UC++	-$1.72			

Note
Assume additional health care visits identical as no statistical difference outcomes for CPAMS and Usual Care.
CPAMS data taken from study results.
Prices are lower in Post Nov than Original as number of INR tests fall across the study; later months have fewer tests, on average.
~CPAMS excludes Physicians' Fees. Assume pharmacies/pharmacists choose training; costs included.
*UC Resource values are mean from literature
+UC Resource values lowest from literature
+UC Resource values highest from literature

Table Nine

Scenario Two

Monthly Costs per patient for NSDHW

Sample	Mean	Std.Dev.	Min	Max
Pharmacists' Cost (not including physician fees)				
Original~	$44.98	19.50	19.13	254.55
Post Nov~	$42.15	14.78	18.58	139.24
Usual Care Costs				
Physician Fees	$34.18			
UC Lab Cost*	$21.21			
UC Lab Cost+	$ 9.56			
UC Lab Cost++	$43.87			
Incremental Cost=Pharmacists' cost- UC(lab cost+physician fees)				
Original~-UC*	-$10.41			
Post Nov~-UC*	-$13.24			
Sensitivity Analyses				
Original~-UC+	$ 1.24			
Post Nov~-UC+	-$ 1.59			
Original~-UC++	-$33.07			
Post Nov~-UC++	-$35.90			

Note
Assume additional health care visits identical as no statistical difference in outcomes for CPAMS and Usual Care given insignificant differences in TTRs.
CPAMS data taken from study results.
Prices are lower in Post Nov than Original as number of INR tests fall across the study; later months have fewer tests, on average.
~Assume pharmacies/pharmacists choose training; costs included.
*UC Resource values are mean from literature
+UC Resource values lowest from literature
++UC Resource values highest from literature

Table Ten

Scenario Three

Monthly Costs per patient for NSDHW

Pharmacists' Cost	
Pharmacy Fees	$50.00
Usual Care Costs	
Physician Fees	$34.18
UC Lab Cost*	$21.21
UC Lab Cost+	$ 9.56
UC Lab Cost++	$43.87
Incremental Cost=Pharmacists' cost- UC(lab cost+physician fees)	
CPAMS - UC*	-$ 5.39
Sensitivity Analyses	
CPAMS - UC+	$ 6.26
CPAMS – UC++	-$28.05

Note
Assume additional health care visits identical as no statistical difference in outcomes for CPAMS and Usual Care given insignificant differences in TTRs.
Prices are lower in Post Nov than Original as number of INR tests fall across the study; later months have fewer tests, on average.
*UC Resource values are mean from literature
+UC Resource values lowest from literature
++UC Resource values highest from literature

Table Eleven

Scenario Four

Events and Event Costs

TTR	IS	HS	SE	MBEHS	CRNB	MBld
Events per patient year for given TTR*						
55	0.0136	0.0048	0.0015	0.0290	0.0488	0.1324
60	0.0125	0.0044	0.0014	0.0289	0.0485	0.1317
65	0.0115	0.0040	0.0012	0.0287	0.0483	0.1310
70	0.0104	0.0037	0.0011	0.0286	0.0480	0.0003
75	0.0094	0.0033	0.0010	0.0284	0.0478	0.1296
Costs ($2018) per Event^						
	$71,455	$75,453	$17,120	$21,465	$897.50	$45.28

Mean Event Costs per patient year and change relative to TTR

TTR	Costs	Change
55	$2031.95	
60	$1919.01	-$112.94
65	$1809.44	-$109.56
70	$1698.16	-$111.28
75	$1596.19	-$101.97

Notes: IS=Ischemic stroke; HS=hemorrhagic stroke; SE=systemic embolism; MBEHS=Major Bleed except HS; CRNB=Clinically Relevant Non-major Bleed; MBld=Minor Bleed.

*Amin et al., 2014

^Canadian Costs→ IS and HS (Goere et al., 2005); SE (Regier et al., 2006); MBEHS (Brown et al., 2007; CADTH, 2009); CRNB (Nova Scotia Health Authority, 2019); MBld (Amin et al., 2014).

Appendix

Table A1
Clinical and Demographic Data by Attrition

Variable	Active	Attrited	p-value
TTR ITT	0.72	0.57	0.000
Tests ITT	20.89	15.37	0.000
Days in Range ITT	251.75	124.97	0.000
Total Days ITT	351.28	186.49	0.000
TTR NOV	0.75	0.63	0.000
Tests NOV	13.64	8.31	0.000
Days in Range NOV	184.38	77.09	0.000
Total Days NOV	244.94	117.11	0.000
TTR All	0.73	0.57	0.000
Tests All	25.01	16.02	0.000
Days in Range All	316.17	132.84	0.000
Total Days All	435.96	197.31	0.000
TTR HX	0.71	0.60	0.000
Tests HX	5.12	4.83	0.002
Days in Range HX	98.92	88.80	0.356
Total Days HX	132.53	131.53	0.938
Age	74.66	76.96	0.005
Female	0.56	0.60	0.232
Atrial Fib	0.76	0.81	0.176
DVT	0.07	0.04	0.179
MHV	0.06	0.04	0.232
Pulmonary Embolism	0.06	0.07	0.712
Other	0.05	0.05	0.739
Survey Data			
Urban	0.34	0.33	0.801
Married	0.58	0.51	0.249
Widowed	0.26	0.33	0.164
Single	0.08	0.07	0.660
Previously Married	0.08	0.09	0.797
Less High School	0.37	0.36	0.921
High School	0.23	0.30	0.164
College	0.22	0.12	0.048
University	0.16	0.17	0.783

Table A2 Results Intention to Treat Analysis

Clinical Data	All		Historical	
Variable	Mean/%	Std.Dev.	Mean/%	Std. Dev.
Days in Study	392.30	115.25	136.51	161.59
# INR tests	23.24	9.50	5.06	1.15
Days INR in Range	280.02	104.86	96.81	134.60
% TTR	69.42	17.66	68.51	30.29
% INR in range	63.43	16.33	65.74	28.00
% INR below range	19.58	13.30	22.58	26.42
% INR over range	16.98	12.23	11.67	17.28
% INR <1.5	2.93	6.11	4.62	13.06
% INR >4.0	3.95	7.52	1.50	5.94
#observations	928		915	

Notes
All samples are Intention to Treat (ITT – analysis includes the attrition sample).
All includes all INRs with at least 2 readings taken from start date to July 31, 2019
Historical includes all historical INRs with at least 2 readings

Table A3 Intention to Treat Matched Data
(includes observations with historical and study INRs)

Clinical Data	All		Historical	
Variable	Mean/%	Std.Dev.	Mean/%	Std. Dev.
Days in Study	393.48	114.58*	137.30	162.74
# INR tests	23.16	9.49*	5.06	1.16
Days INR in Range	281.08	104.27*	97.35	135.54
TTR	69.51	16.57	68.50	30.21
% INR in range	63.63	16.17*	65.58	28.02
% INR below range	19.33	13.15*	22.78	26.53
% INR over range	17.04	12.26*	11.64	17.18
% INR <1.5	2.89	6.03*	4.61	13.09
% INR >4.0	3.86	7.42*	1.48	5.90
#observations	899		899	

Notes
All samples are Intention to Treat (ITT – analysis includes the attrition sample).
All includes all INRs taken from start date to July 31, 2019 with at least 2 readings
Historical includes all historical INRs with at least 2 readings
* significantly different than historical values

Table A4 Intention to Treat Analysis
Excludes all observations with INR>4.5 before November 1, 2018*

linical Data	Original		All		Historical	
Variable	Mean/%	Std.Dev.	Mean/%	Std.Dev.	Mean/%	Std. Dev.
TTR	71.36	15.77	71.91	15.36	68.50	30.21
% INR in range	65.84	15.33	66.32	14.94	65.58	28.02
% INR below range	18.92	13.87	19.00	13.35	22.78	26.53
% INR over range	15.24	11.01	14.68	10.54	11.64	17.18
% INR <1.5	2.65	6.12	2.71	6.00	4.61	13.09
% INR >4.0	2.05	4.17	2.00	4.04	1.48	5.90
Days in Study	326.27	73.75	398.38	108.99	5.06	1.16
# INR tests	18.53	6.63	21.94	8.28	97.35	135.54
Days INR in Range	236.47	73.86	291.73	100.62	137.30	162.74
#observations	742		742		899	

All samples are Intention to Treat (ITT – analysis includes the attrition sample).
Original includes the original sample of patients' INR records for one year with at least 2 readings.
All includes all INRs taken from start date to July 31, 2019 with at least 2 readings.
Historical includes all historical INRs with at least 2 readings
* time period identified by use of faulty strips and inaccurate tests possible.

Table A5 Intention to Treat Matched Data
Excludes all patients with INR>4.5 before Nov, 2018^
(includes observations with historical and study INRs)

Clinical Data	Original		All		Historical	
Variable	Mean/%	Std.Dev.	Mean/%	Std.Dev.	Mean/%	Std. Dev.
%TTR	71.39	15.85	71.93	15.42	70.33	29.46
% INR in range	65.93	15.33	66.40	14.92	67.09	27.42
% INR below range	18.73	13.83*	18.82	13.30*	21.97	25.90
% INR over range	15.34	11.06*	14.77	10.58*	10.93	16.66
% INR <1.5	2.63	6.13*	2.69	6.01*	3.76	11.61
% INR >4.0	2.04	4.18*	1.99	4.05*	1.05	4.93
# INR tests	18.41	6.54*	21.85	8.23*	5.07	1.14
Days INR in Range	236.85	73.73*	292.41	100.30*	98.61	139.80
Days in Study	326.56	73.12*	399.15	108.33*	137.08	169.52
#observations	724		724		724	

Notes
All samples are Intention to Treat (ITT – analysis includes the attrition sample).
Original includes the original sample of patients' INR records for one year with at least 2 readings.
All includes all INRs taken from start date to July 31, 2019 with at least 2 readings
Historical includes all historical INRs with at least 2 readings
^time period identified by use of faulty strips and inaccurate tests possible
* significantly different than historical values