Economic Evaluation of the Collaborative Care Demonstration Project In Nova Scotia

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Final Results
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Summary

Chronic diseases, such as hypertension, cardiovascular disease, and diabetes, are extremely costly to health-care systems world wide. Interventions that better manage and/or reduce the cost of treating chronic diseases are widely sought. In the last few decades, there have been a plethora of studies examining the effectiveness, and to a much lesser extent the cost effectiveness, of pharmacists' care in managing chronic disease, including pharmacist-directed care and pharmacist collaborations with other health-care professionals.

Several systematic reviews report that it is difficult to draw an overarching conclusion regarding 'pharmacists' care' as studies tend to be heterogenous in; the types of intervention (e.g., medication review, patient assessment and care planning, prescribing, etc.), health-care systems, and locations (e.g., hospital, clinic, community, etc.). In general, the literature concludes that pharmacist care in heterogenous formats is at least as good as usual care. The limited economic evaluations focusing on pharmacist-physician collaborations tend to show, as many health-care and public-health interventions do, that pharmacists' collaborative interventions improve patient outcomes but also increase costs.

The Pharmacy Association of Nova Scotia, Doctors Nova Scotia, and the Nova Scotia Department of Health and Wellness designed and implemented a Collaborative Care Demonstration Project (CCDP). The goal of the project was to develop and evaluate a model of collaboration between family physicians and community pharmacists to support patients with chronic disease. A sample of pharmacies with physician-pharmacist collaborations was chosen to represent demographic and economic circumstances in the province, after representation, pharmacies were chosen randomly, 448 patients with multiple chronic conditions and/or risk factors were enrolled, and 317 patients completed the study (more than half of the attrition was due to pharmacist/physician leaving the study rather than patients choosing to drop out).

Study results indicate that pharmacist-physician collaborative care led end-of-study improvements, compared to baseline, in all outcome measures (blood pressure, hemoglobin A1C, low-density lipoprotein cholesterol, total cholesterol, nonhigh-density lipoprotein cholesterol, ten-year CVD Risk, clinical COPD Questionnaire, COPD Assessment Test, Morisky

Medication-Taking Adherence Scale (4 item), and PPD=packs/day smoked) except one (high-density lipoprotein cholesterol). Similar to many studies in the literature, outcome improvement was substantially better for high-risk patients than for lower-risk patients and in the treated group analyses compared to the intent-to-treat analyses. The outcome improvements are comparable to outcome improvements found in the literature; all be it at the lower range of results.

Economic evaluations of the CCDP were performed using outcome and resource measures from the CCDP and other Canadian studies. The outcomes measures in the study were not consistent across patients but depended on chronic conditions and/or risk factors present when the patient was enrolled. As a result, the distribution of costs across outcomes was not straight forward. The average cost per significant change in outcome ranges from $174 to just under $11,000 in the intent-to-treat analyses. In the treated analyses both costs and outcome changes were higher, with average costs per significant change in outcome ranging from $170 to just over $6,000. Weighted average cost/outcome change ranges from $136 to just under $4,500 with just over half the results at less than $500. Average costs/significant outcome for higher-risk patients were substantially lower ranging from $2 to about $1,800, depending on distribution of costs. Using historical clinical measures, on average, as comparators, incremental costs/incremental outcome results range from approximately $100 to $6,000 for significant changes.

Taking long-term health consequences of clinical changes into account, the cost-utility analyses, using a Markov Model with a simulated cohort, show that the CCDP generates more quality-adjusted life years at a lower cost than usual care over the lifespan of the simulated cohort; CCDP is shown to be dominant. Sensitivity analyses around assumptions and resource distributions lead to similar dominant results in all cases but one (a constant mortality rate). Sensitivity analyses were also performed on labour costs as qualitative analyses and the literature indicated that training and face-to-face meetings between physicians and pharmacists were likely a redundant component of the intervention. The training and face-to-face collaborative meeting costs were close to 1/2 of the per patient costs with training costs alone being about 1/3. Eliminating these costs would substantially improve the average and incremental costs per change in outcome (similar outcomes are expected).

In sum, using CCDP outcomes and resource consumption and assumptions consistent with those used in other Canadian studies in the literature, the CCDP indicates that pharmacist-physician collaborations can be a cost-effective way of managing chronic disease if long-term health consequences are taken into consideration.

I. Introduction and Literature Review

The exorbitant costs to health-care systems of chronic disease, particularly cardiovascular disease (CVD) and diabetes (DM), has been well documented in many countries (see for example: Franklin, Farland, Thomas, et al, 2013; Simpson, Johnson & Tsuyuki, 2001). In 2005, the cost of CVDs (ischaemic heart disease (IHD), cerebrovascular diseases (CeVD), and hypertensive (HTN)) was estimated to be $20.9 billion ($2008 CDN), with well over a third of that being health-care costs. The costs were expected to grow to $28.3 billion by 2020 (Conference Board of Canada, 2010). An estimate of the health-care costs of diabetes is $15.36 billion ($CDN- base year not stated) between 2011 and 2021 (Bilandzic & Rosella, 2017). Simpson, Johnson, & Tsuyuki (2001) estimated CVD to account for over 1/3 of all deaths and 1/20 hospitalizations.

Many of the studies cited[1] herein begin by noting the large proportion of the population with HTN and DM (~1/4 of Canadians and ~1/3 of US population have HTN; about 8% of the US population has DM) and the high costs of morbidity (an annual cost of $178billion in the US), because HTN and DM are major risk factors for CVD, stroke, and other chronic conditions. There is often mention of the fact that HTN and DM are poorly controlled though they are manageable, and pharmacists' availability in the community makes them more accessible to assist than other health-care providers (see for example Marra, Johnston, Santschi, et al., 2017; Polgreen, Han, Carter, et al., 2015). Blood Pressure (BP), particularly systolic BP (SBP), have been strongly correlated with CVD (O'Donnell & Elosua, 2008; Lewington, Clarke, Qizilbash, et al., 2002). In an overview of the Framingham study results, O'Donnell & Elosua (2008) remark that systolic and diastolic blood pressure have a 'continuous, independent, graded, and positive association with cardiovascular outcomes' (page 302). The well-documented, independent relationships enable BP to be used to estimate future risk, and consequentially, costs when examining interventions for CVD management.

[1] Although the literature review was extensive, it was not designed as a systematic review and thus, may not be exhaustive. As with any literature review, publication bias may exist.

The expansion of pharmacists' roles in health care, aimed at improving patient health outcomes and delivering lower-cost health care, has occurred over several decades (Franklin, Farland, Thomas, et al., 2013; San-Juan-Rodriguez, Nemand, Hernandez, et al., 2018). As with many health-care innovations, much of the early research comes out of the US where a substantial proportion of the population finds it challenging to attend medical doctors' (MD) offices and/or pay for MD visits. Pharmacists are more readily available in the community and as a result, may be able to offer care to individuals who may not be able to access other health-care providers (San-Juan-Rodriguez, Nemand, Hernandez, et al., 2018) whether due to time, resource, or location restraints. The early literature tended to focus on pharmacist interventions including medication review, education (particularly modification of life-style risk factors, including smoking cessation), and/or assisting patients with self-monitoring (e.g., glucose levels for diabetics) (see for example: Brown, Chung, Rrisch, et al., 2016; Franklin, Farland, Thomas, et al., 2013; Jokanovic, Tan, Sudhakaran, et al., 2017).

In the last 20 years, there have been a plethora of studies examining the effectiveness of pharmacists' care (either pharmacist-directed or in collaboration with other heath-care providers) in managing disease, particularly chronic disease. As a result, several systematic reviews of the literature have been produced (see for example: Altowaijri, Phillips, Fitzsimmons, et al., 2013; Greer, Bolduc, Geurkink, et al, 2015; Santschi, Chiolero, Burnand, et al., 2011; Santschi, Chiolero, Colosimo et al., 2014; Brown, Chung, Rrisch, et al., 2016). Systematic reviews tended to examine the effectiveness (and to a lesser extent, the cost effectiveness) of pharmacist care on a single (see for example: CVD (Santschi, Chiolero, Burnand, et al., 2011;); DM (Machado, Bajcar, Guzzo, & Einarson, 2007); HTN (Santschi, Chiolero, Colosimo et al., 2014); smoking cessation (Brown, Chung, Rrisch, et. Al., 2016) or multiple health outcomes (Evans, Watson, Eurich, et al., 2011; Jokanovic, Tan, Sudhakaran, et al., 2017) but few studies examined broader consequences on health-care utilization and mortality (for exceptions see Geurts, Talsma, Brouwers & Gier, 2012; Holland, Desborough, Goodyer, et al., 2007).

Given the large number of studies found in the literature, it may seem surprising that a consensus on the effectiveness of pharmacist care has yet to be arrived at. However, like many public health interventions, pharmacist care can include a wide range of possible interventions including

patient education, medication reviews (some including recommending changes to physicians), obtaining, and review, laboratory results with patients, follow-up visits, meeting with health-care teams to discuss medical care, and more recently, prescribing medications. Systematic reviews often amalgamate disparate interventions aimed at producing the same health outcomes. The quality of individual studies is often in question and is often presented as a limitation to providing a consensus on the effectiveness of pharmacist care. Most systematic reviews find few studies that include economic evaluations, so evaluating the cost effectiveness of interventions has been difficult.

An overview of systematic reviews on pharmacist-led medication review concluded that evidence in moderate- and high-quality systematic reviews indicate that it is effective on a range of outcomes but call for more rigorous economic analyses to determine cost effectiveness (Jokanovic, Tan, Sudhakaran, et al., 2017). Santschi, Chiolero, Burnand, et al., (2011) performed a systematic review and meta-analysis of randomized control trials (RCTs) and concluded that pharmacist care (directed or in collaboration with physicians or nurses) resulted in improvements in CVD risk factors including significant reductions in blood pressure (BP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), and smoking risk. However, they cautioned that significant heterogeneity was present in study results. Similar conclusions were drawn in a meta-analysis of RCTs of pharmacist interventions to control BP (Santschi, Chiolero, Colosimo et al., 2014) and BP control for DM patients (Santschi, Chiolero, Paradis, 2012) with further warnings from by Santschi, Chiolero, Colosimo et al., (2014) that further economic evaluation research was needed to determine the most efficient interventions.

Machado, Bajcar, Guzzo, & Einarson's meta-analysis of pharmacists' DM interventions found that hemoglobin A1C (A1C) was significantly reduced but too few studies were available on other outcomes and they called for more research (Machado, Bajcar, Guzzo, & Einarson, 2007). San-Juan-Rodriguez, Nemand, Hernandez, et al. (2018) state that 'The provision of preventive services at US pharmacies is feasible and effective and has potential for improving patient outcomes and health system efficiency. However, high-quality evidence is still lacking." (San-Juan-Rodriguez, Nemand, Hernandez, et al., 2018; page 145). Evens, Watson, Eurich, et. al., (2011) provided a systematic review of interventions by community pharmacists to improve

CVD and DM outcomes and concluded that poor-quality studies and lack of proven clinical significance demonstrated the necessity of high-quality studies. The systematic reviews found in the literature resoundingly call for further high-quality research before any consensus can be reached on a broad range of interventions and outcomes (Machado, Bajcar, Guzzo, & Einarson, 2007; Rankin, Cadogan, Patterson, et. al., 2018; Rollason & Vogt, 2003).

A very recent Cochrane review and meta analysis (de Barra, Scott, Scott, et al., 2018) focused on RCTs examining non-dispensing services from pharmacists to ambulatory patients in various settings (e.g., community, primary or ambulatory-care) in high-income countries. Well over 100 trials with over 40,000 patients were included in the review, with 76 trials included in the meta-analyses. Most trials targeted chronic conditions. Compared with usual care, the results indicated that pharmacists' care seemed to reduce the percentage of patients whose BP was outside target range but the evidence was ambiguous for A1C. Pharmacist services slightly improved physical functioning but led to little or no difference in adverse drug effects, hospital admissions, in-hospital stays, or mortality. The authors state that the results (pharmacists have varying effects of patient outcomes) need to be interpreted cautiously due to major heterogeneity in study populations, interventions delivered, and reported outcomes.

There were systematic reviews that found solid evidence for the effectiveness of pharmacists' interventions (see for example, Pousinho, Morgado, Falcão, & Alves, 2016; Wang, Yeo, Ko, 2015). Wang, Yeo, Ko reviewed 25 economic evaluations of pharmacist-managed services for DM patients that included targeted education, medication monitoring, health screening, laboratory testing, immunization, and pharmacokinetic monitoring. While many of the studies in the review showed an increase in medication costs, over-all health-care costs were reduced. The interventions were shown to be cost-saving compared to usual care and generated higher quality-adjusted life years (QALYS) (Wang, Yeo, Ko, 2015). Pousinho, Morgado, Falcão, & Alves (2016) included 36 studies evaluating pharmacist interventions on various DM outcomes in several countries and health-care facilities (e.g., community pharmacies, primary care clinics, and hospitals). Greater reductions in A1C were found in the intervention group in 2/24 studies with a 0.18% to 2.1% improvement. BP was found to improve by between 3.3 and 23.5 mmHg for systolic (SBP) and between 0.21 mmHg and 9.1 mmHg for diastolic (DBP). Cholesterol (TC,

LDL and high-density lipoprotein (HDL)), triglycerides, body mass index (BMI), 10-year CVD risk (10yCVDR), health-related quality of life (HRQL), and nonadherence to meds (NAHM) were also improved more in the intervention than control groups in the majority of studies. Cost-effectiveness was examined in just three studies but was improved. The authors of these studies concluded that findings 'clearly support' pharmacists as collaborators in the management of patients with Type 2 Diabetes (T2DM). However, they called for future economic studies of high quality to investigate the cost-effectiveness of further increasing pharmacists' scope in the care of DM. (Pousinho, Morgado, Falcão, & Alves, 2016).

The heterogeneity of results found in the systematic reviews may be due to evaluating interventions that were dissimilar in nature, took place in different settings (community pharmacy, hospital pharmacy, outpatient clinic, etc.), included different health-care professionals (pharmacists only, pharmacists and physicians, pharmacists and nurses, etc.) and/or took place in different countries. Although, the Canadian and US health-care systems have substantially different insurance and payment mechanisms, the health-care systems (including pharmacies) are similar and the populations are relatively comparable. Thus, the remainder of the literature review focuses on evaluations that examine pharmacist-physician collaborations (PPC) in the US and Canada and, when possible, include economic evaluations. Many of the collaborations reported herein take place in the primary-care setting; an attempt was made to focus on PPC in the community (PPCC) but studies are more limited. Studies in the US tend to have larger and more diverse populations (include multiple centres). Most studies were well designed with an intervention and control group or provided simulations using a Markov model drawing data from other studies. The majority of PPC studies found in the literature focused on BP control alone or BP and other risk factors for CVDs (see for example, Padwal, So, Wood, et al., 2019). Studies identified that examined DM (see for example, McAdam-Marx, Arati Dahal, Jennin, et al., 2015, Yu, Shah, Ip, & Chan, 2013) or other outcomes (see for example, Matzke, Moczygemba, Williams, et al., 2018), tended to use BP as an outcome measure as well.

Pharmacist-physician collaborations in Diabetes Management

Pousinho, Morgado, Falcão, & Alves (2016) and Santschi, Chiolero, Paradis G, et al. (2012), mentioned earlier, concluded that the results from their systematic reviews clearly supported

including pharmacists as members of health care teams in the management of patients with T2DM. The studies in the review included pharmacist interventions taking place in varied health care facilities (e.g., community pharmacies, primary care clinics, and hospitals) in different countries.

Studies examining PPC in DM management tended to include PPCs in the primary care setting. Franklin, Farland, Thomas, et al., (2013) performed a cost analysis of a PPC for DM care based on a prospective observational study conducted in seven primary care practices in Tennessee, US. Adults with an A1C >7%, SBP >130 mm Hg, a diastolic blood pressure >80 mm Hg, or LDL concentration >100 mg/dL were eligible for the study. The study followed an intention-to-treat (ITA) methodology. All patients who had at least one appointment with a pharmacist and consented to be enrolled in the study were included in the analysis with the last outcome measure taken used as the end-point measure. There was no control group.

The PPC included a collaborative practice agreement; appointments scheduled for patients to see both a pharmacist and a nurse practitioner or physician; and/or patient appointments with a pharmacist who reviewed each case with a physician to develop a treatment plan. Follow-up visits (in-person or phone) were scheduled as clinically necessary. Pharmacists' roles included medication therapy management (MTM) (initiate, adjust, or discontinue medications for T2DM, HTN, and dyslipidemia); patient education; review of self-monitored blood glucose records; ordering and monitoring of laboratory tests; performing sensory foot exams; referring patients for dilated retinal exams; and ordering or recommending immunizations. Pharmacists had 1,612 interactions with 206 patients for 226 minutes/patient, on average and an additional 207 minutes on intervention activities. Projected cost savings associated with reductions in A1C or BP (1% or 5.6 mm Hg reduction in SBP, respectively) were taken from the literature. Study participants' A1C and blood pressures were reduced by 25 and 24 percentage points over the study period, respectively. The authors reported program costs of $528/patient leading to an average cost per outcome of $160. Including only added labour costs led to a program savings of $420/patient. The authors called for further cost-effectiveness analyses to investigate whether the total cost/patient outcome was efficient.

McAdam-Marx, Dahal, Jennings, et al., (2015) provide an evaluation study that examined the association between a pharmacist-led DM collaborative care management (DCCM) program and patient outcomes, including glycemic control, health-care costs, and short-term economic outcomes in a primary care setting in Utah, US. The study used administrative medical record data to complete a retrospective cohort analysis. Participants suffering from uncontrolled T2DM, (defined as A1C $\geq$ 7.0%) were included. Outcomes were compared between patients referred to the DCCM intervention and patients who were not. A difference-in-difference model was used to estimate the effect of the program on resource utilization. Patients in the DCCM (N=303) slightly younger and had higher A1C than the control group (N=394) at baseline but were statistically the same at 9 and 12 months after inclusion in the study. DCCM program was associated with just under 0.5% reduction in A1C at follow-up relative to the comparison group controlling for potential confounders, including baseline A1C. Difference-in-difference analysis indicated that DCCM patients experienced a smaller average increase in medical charges ($250) than comparison patients ($1,341) between end of study and one year prior to study. The authors concluded better glycemic control and smaller increases in health-care costs were experienced by patients with uncontrolled T2DM enrolled in a pharmacist-led DCCM program than those who were not which could translate into reduced costs and improved outcomes to managed care payers.

The long-term preventive effects and cost-effectiveness of a PCC intervention on CVD outcomes among T2DM patients was investigated by Yu, Shah, Ip, & Chan (2013) using a Markov model and matched cohort data from a study in two outpatient primary care settings in Northern California (one primary care physicians (control) and one with primary care physicians and pharmacists (intervention)). Clinical data were collected from administrative records. Life years and quality-adjusted life years gained were included to measure incremental cost and effectiveness. Both deterministic sensitivity analysis (SA) and probabilistic SA were conducted to examine the robustness of the results.

Given the matched cohorts, baseline measures were similar for the control and intervention groups. After one year the intervention group had significantly better results compared to the control group: SBP (131 vs 126.2 ($p < 0.001$)); A1C (8.4 vs 6.9 ($p < 0.001$)); TC (179.2 vs 154.4

($p < 0.001$)); and HDL (44.4 vs 44.9 (insignificant (NS)), respectively. By the end of the study, estimated risks for coronary heart disease (CHD) and stroke were consistently lower in the intervention group than in the control group. The absolute risk reduction (ARR) between the groups increased over time. Results from the Markov model suggested that having a pharmacist in the primary care team was less expensive and more effective (a dominant strategy) compared to physicians alone in the 10-year evaluation period with base-case assumptions. Sensitivity analysis around inputs (e.g., pharmacists' wages, utility measures for health states, 10-year CVD risk, etc.) showed that cost-effectiveness depended on the time horizon adopted in the study and the magnitude of CVD risk reduction. The authors concluded that adding pharmacists to the health-care-management team for diabetic patients improved the long-term CVD risks and the intervention to be efficient.

A RCT in Edmonton, Alberta (Simpson, Majumdar, Tsuyuki, et al., 2011) questioned whether the addition of pharmacists to a primary-care team would lead to better management of HTN and other CVD risk factors in patients with T2DM (an economic evaluation was not included). Pharmacists performed medication assessments, limited history and physical examinations, provided recommendations on medication management, and followed-up with intervention patients (N=131) as necessary; control patients (N=129) received usual care. Over the one-year study, the ITG results showed that intervention patients had an average reduction in systolic blood pressure of 7.4 mmHg (p=0.001), 4.9 mmHg more than the control group (p=0.01). The primary outcome of a ten percent decrease in BP was met by 37% of the intervention group compared to 23% of the control group (p=0.02). The 10yCVDR was predicted to decrease by two percentage points more for intervention patients than the controls (3% vs 1%; p=0.005), respectively. Other outcomes such as glycemic control, lipid parameters, emergency-room visits, hospitalizations, or all-cause mortality were not statistically different for the two groups. Patients with inadequately controlled HTN at baseline had significantly greater reduction of SBP and a greater proportion reaching the primary outcome in the intervention group (N=82) than the control group (N=71) (13.9 mmHg vs 6.7mmHg (p=0.002) and 0.5 vs 0.28 (p=0.007), respectively). In addition, 54% of the intervention group and only 30% of the controls achieved recommended blood pressure targets at 1 year (p=0.003). A sub-group study of the trial patients without established CVD (Ladhani, Majumdar, Johnson, et al., 2012) showed a significantly

greater improvement in 10yCVDR for the intervention group by just over one percent. The studies concluded that adding pharmacists to primary care teams can improve the care of T2DM patients.

Simpson, Lier, Majumdar, et al., 2015 performed a cost-effectiveness analysis with data collected in the Simpson, Majumdar, Tsuyuki, et al., (2011) study. The subgroup of patients who returned exit surveys (N=123) containing data on utilization of healthcare specialists, healthcare facilities, and allied health-care professionals were included in the study. Pharmacist tracked their time at 3.0 (± 1.9) hours of additional service, on average, for the intervention group. During the study, pharmacists met with patients 2 (± 2) times and contacted them by phone 6 (± 3) times, on average. Intervention patients had fewer visits to ophthalmologists and nurses compared with controls; all other health-care utilization was not significantly different between groups. Clinical outcomes indicated that the intervention was efficient. There were no significant differences in sex, baseline 10yCVDR score or DM duration between the intervention and control groups at baseline but 10yCVDR decreased from 14.6% (±10.1%) to 12.0% (± 7.6%), on average, in the intervention group and from 14.2% (± 10.0%) to 13.4% (± 11.1%), on average in controls (p=0.035). The authors reported a significant difference in the annualized reduction in risk of CVD events as well. Pharmacist costs during the intervention were calculated at $226 (± $143)/patient, on average. Per patient total costs were insignificantly different at $1803 vs $1993 for the intervention and control groups, respectively. In the Monte Carlo results, the intervention dominated usual care in over half of the estimations with sensitivity analyses presenting similar results. The authors concluded that adding pharmacists to primary care teams was cost-effective for T2DM management, and in most circumstances, may also be cost saving.

Studies examining the addition of pharmacists to primary-care teams seem to show effectiveness and, where cost studies were completed, likely efficiency, however few studies examining community pharmacists' collaborations with physicians in the community were identified. A notable exception is Doucette, Witry, Farris, & McDonough's (2009) examination of an intervention where community pharmacists provided DM management, but the pharmacist-physician collaboration was limited to pharmacist faxing visit reports and recommendations to the patient's MD. The study randomized adults with T2DM to extended DM care or usual care.

Pharmacists developed, implemented, and monitored a management plan customized for each patient, and followed up with the patient and physician to ensure optimal outcomes. Intervention patients received up to four visits with the community pharmacists at their local pharmacy. Pharmacists assessed clinical parameters (e.g., A1C, LDL, and BP) and provided patient education and recommend drug therapy changes and self-care activities. Pharmacists faxed a one-page progress note to patients' physicians summarizing each visit and offering recommendations for therapy changes for consideration. Patients in the control group received usual DM care from their primary-care provider. The intervention group (N= 31) and control groups (N=35) were substantially smaller than the planned 50 per group. There were no significant between-group differences at baseline with mean A1C of 7.95% and LDL at 102.5 mg/dL both above recommended levels. SBP was 118.2 mmHg and DBP was 66.7mmHg which were lower than the study target at baseline.

Pharmacists carried out just over 87% of the quarterly meetings. For those who received the treatment (treated group (TG)) study results showed that SBP (DBP) decreased by 4.5 ± 15.19 mmHg (0.3 5 ± 8.45 mmHg) for the control group and 7.1 ± 10.38 mmHg (1.2 ± 7.79 mmHg) for the treatment group. The mean change in LDL was -12.0 (-83 to 29) mg/dL for the control group and - 19.6 (-106 to 32) mg/dL for the intervention group. However, the differences between groups were insignificant for clinical measures. Patients who received the intervention significantly increased engagement in diet and wellness activities by 1.25 and 0.73 days/week more than the control group, respectively. The authors concluded that pharmacists' care significantly improved life-style and self care activities while the clinical outcomes trended towards improvement indicating that pharmacists' collaboration showed promising results when caring for DM patients. The authors went on the explain that the lack of significance in clinical outcome changes could have been due to the smaller sample sizes or fewer meetings than planned in the study protocol and called for further research with larger sample sizes and economic analyses.

Hypertension

A meta-analysis including 39 RCTs (N=14,224) evaluating the effects of pharmacist interventions on outpatients' BP is oft quoted in recent studies (Santschi, Chiolero, Colosimo et

al., 2014). The main components of the interventions were patient education, feedback to physicians, and medication management by pharmacists (working alone or in collaboration with others). Pharmacist interventions were more effective at reducing BP than usual care; with higher reductions of SBP by 7.6 mmHg and DBP by 3.9 mmHg. However, the authors commented that there was extensive heterogeneity in the studies with results varying for very large significant effects to no effects and the reasons for the heterogeneity could not be identified. One reason for the heterogeneity in results could have been the substantial differences in types and delivery (collaborations or not) of pharmacists' interventions. Focusing on studies more closely related to physician-pharmacist collaborations may provide a better indication of their effectiveness.

A US study examined pharmacist-physician collaborations in community-based medical offices by randomizing offices between intervention (N=3) and control (N=3) with 402 patients in total (Carter, Ardery, Dawson, et al., 2009). The intervention was more restrictive than other studies as the pharmacists' role was limited to making drug therapy recommendations to physicians based on national guidelines. Outcomes were guideline adherence and BP.

The mean guideline adherence scores increased in the intervention (control) group from 40.4 to 62.8 (49.4 to 53.4) over the six-month trial ($p=0.09$). The mean SBP decreased by 6.8mmHg in the control group and 20.7 mm Hg in the intervention group ($P<0.05$), however the difference became insignificant after adjusting for confounders. DBP decreased by 4.5 mm Hg in control group and 9.7 mm Hg in the intervention group (insignificant difference between groups). Blood pressure controlled was significantly better in the intervention group (63.9% vs 29.9; ($p<0.001$). The authors concluded that the physician-pharmacist collaborative intervention achieved significantly better mean BP, even though only SBP was significantly better before controlling for confounders, and overall BP control rates compared with a control group and called for additional research. No economic analysis was performed.

Kulchaitanaroaj, Brooks, Ardery, et al., (2012) compared the costs associated with a physician-pharmacist collaborative intervention with those of usual care. The intervention included MDs (primary care, specialists, and, in some clinics, residents) from 11 community-base medical offices, clinical pharmacists (all had PharmDs). The intervention group (N=252) received direct

patient care from the pharmacist including assessment, recommendations to during clinic visits, and phone follow-ups. Patients saw MDs when necessary. Pharmacists and other providers collaborated when needed. The control group (N=244) received usual care. Health-care costs including costs of provider time, laboratory tests, and antihypertensive drugs were collected retrospectively via survey and publicly available sites. The intervention group had, on average, slightly fewer anti-hypertensive prescriptions and co-morbidities, had slightly higher BPs and was much less likely to be African-American, so outcomes and total costs were adjusted for patient characteristics.

The intervention group's outcomes were significantly better than the control groups by the end of the study. More intervention patients achieved BP control than the control group (66.0% vs 41.4%; $p<0.001$) and SBP dropped by 9.08 mmHg and DBP by 3.49 mmHg more in the intervention group ($p<0.001$). The incremental cost-effectiveness ratio (incremental cost/incremental outcome) (ICER) was $1338.05/additional patient achieving BP control over 6 months. The cost to lower SBP and DBP 1 mmHg was $36.25 and $94.32, respectively. As with many interventions, the conclusion of the study was that the physician-pharmacist collaborative intervention increased BP control but also the cost of care. The authors called for additional research, such as a cost-benefit, to assess whether financial savings related to reduced morbidity and mortality achieved from better BP control would outweigh the cost of the intervention.

Kulchaitanaroaj, Brooks, Chaiyakunaprukd, et al., (2017) went on to perform that economic evaluation using a Markov model cohort simulation, employing the data from Kulchaitanaroaj, Brooks, Ardery, et al., (2012), to establish the probability of acute coronary syndrome, stroke, and heart failure over patients' projected lifetime. Quality adjusted life years (QALY) was the outcome of interest and ICERs were estimated. The estimated QALYs gained was 0.14 with a life-time incremental cost per QALY simulated at $26,808. Higher risk patients benefited more than lower risk patients. Simulations indicated that the ICER, on average, was under the accepted $50,000 threshold (Jaswal, 2013) in 47% of the Monte Carlo estimations.

The Collaboration Among Pharmacist and Physicians to Improve Blood Pressure Now (CAPTION) trial (Isetts, Buffington, Carter, et al., 2016; Polgreen, Han, Carter, et al., 2015)

randomized 32 medical offices in 15 states to one of two interventions (a 9-month or a 24-month BP intervention; the interventions were identical in the first nine months) or usual care for patients with uncontrolled HTN (SBP >140 mmHg (>130 if DM or chronic kidney disease) or DBP >90 mm Hg (>80 if DM or chronic kidney disease)). The groups were statistically similar, except for marital and insurance status, with approximately 1/3 of the total of 625 patients per group. BP control at 9 months was the outcome of interest. Pharmacists performed a medical review, a baseline patient interview regarding their medications, barriers to BP control (eg, side effects and nonadherence), and lifestyle changes when necessary. Pharmacists were to call patients at 2 weeks, have structured face-to-face visits with them at 1, 2, 4, 6, and 8 months, and any additional visits as warranted. The pharmacist created a care plan and recommending therapy adjustments to MDs. Pharmacist-physician interactions tended to be in person both worked in the same office.

At the end of the 9-month intervention, the average SBP and DBP were 6.1mm Hg and 2.9 mm Hg, respectively lower in the intervention group than in the usual-care group (p=0.002 and p=0.009, respectively). HTN control was 43% vs 34% in the intervention vs control group (insignificant difference), and the intervention group had 4.9 BP-medication changes, on average, while the control group had only 1.1 (P=0.0003). Costs were assigned to medications and providers' time. Total costs for the intervention were $1462.87 and $1259.94 for the control group, a difference of $202.93 (insignificant at usual levels). The cost to lower SBP and DBP by 1 mm Hg was $33.27 and $69.98, respectively. The cost to increase the rate of HTN control by 1 percentage point in the intervention group was $22.55. The authors state that given the better outcomes in the intervention group and the insignificant differences in costs, the results highlight the cost-effectiveness of a clinical-pharmacist intervention for HTN control in primary care settings. However, care should be taken with their interpretation as many of the outcome measures were not significantly different between the two groups. In fact, Gums, Uribe, Vander, et al., (2015) reported that the results "demonstrate that clinical pharmacists increased medication intensification. However, PPCM models will need to develop non-adherence identification and intervention methods to further improve the potency of the care team." (Gums, Uribe, Vander, et al., 2015; page 10).

CVD risk factors (including HTN)

As noted previously, Santschi, Chiolero, Burnand, et al., (2011) systematic review and meta-analysis of RCTs concluded that pharmacist care (directed or in collaboration with physicians or nurses) was found to improve CVD risk factors including significant reductions in BP, TC, LDL, and smoking risk with significant heterogeneity in the study results. Their review included 30 RCTs (N=11,765 patients). Interventions conducted by pharmacists or by a pharmacist in collaboration with physicians or nurses included patient educational interventions, patient-reminder systems, measurement of CVD risk factors, medication management and feedback to physician, and/or educational intervention to health care professionals. The meta analysis indicated that pharmacist care was associated with significant decreases in SBP of 8.1mm HG ($p<0.001$) in 19 studies (N=10,479 patients), on average, and a mean DBP drop of 3.8mmHg ($p<0.001$). TC was reduced by 17.4 mg/L ($p<0.001$) in 9 studies (N=1,121 patients), LDL by 13.4 mg/L ($p<0.006$) and a reduction in the risk of smoking (2 studies (N=196 patients) by just over 20% ($p<0.001$). As with other reviews, the interventions were varied in their type and delivery.

The Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP) (Tsuyuki, Johnson, Teo, 2002; McLean, McAlister, Johnson, et al., 2008) was mentioned in the Santschi, Chiolero, Burnand, et al., (2011) review. The SCRIP, a randomized, multicenter (44 sites in Alberta and Saskatchewan) trial, was designed to evaluate the efficacy of a community-pharmacist intervention to improve the *process* of cholesterol risk management in patients at high risk for CHD events, however the data were used to explore several other research questions (see Tsuyuki, Johnson, Teo, et al., 1999). High risk patients were identified as having at least one of the following: previous acute myocardial infarction, stable or unstable angina, coronary revascularization by coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, vascular disease, or DM with one or more other cardiovascular risk factors (including cigarette smoking, HTN, positive family history of premature CVD, obesity, sedentary lifestyle, hypercholesterolemia, or age >45 for men or age >55 for women). Intervention patients received a brochure and education about CVD risk factors. Pharmacists completed a physician contact form listing the patient's risk factors, medications, the results of a cholesterol test that was performed, and any recommendations the pharmacist thought

appropriate and the form was faxed to the MD. If appropriate, the patient was asked to see their MD for further follow-up. Patients were followed up at two, four, eight, 12, and 16 weeks. During those visits, pharmacists provided educational reinforcement and checked for primary outcomes (a composite measurement indicating improvement in the *process* of cholesterol risk management including: 1) a complete lipid panel by the physician, 2) addition and 3) modification of lipid-lowering drug therapy). The individual measures in the composite were considered secondary outcome measures. Patients allocated to usual care received the brochure and minimal follow-up. The study design called for1000 patients to be enrolled but the study was halted after the recruitment of only 675 by the external monitoring committee due to the 'striking evidence of benefit' (page 1150). The SCRIP study is closely related to the current study given focus on CVD risk factors including HTN and DM and it is one of the few Canadian trials. In addition, the data have been used as the basis for other evaluations (e.g., Houle, Chuck, McAlister & Tsuyuki, 2012; McLean, McAlister, Johnson, et al., 2008; Simpson, Johnson, Tsuyuki, 2001) and the SCRIP intervention design was used as a basis for other trials (SCRIP-plus (Tsuyuki, Olson, Dubyk, et al., 2004), SCRIP-HTN (Houle, Chuck, McAlister, & Tsuyuki, 2012; McLean, McAlister, Johnson, et al., 2008).

The ITG results of the SCRIP trial (Tsuyuki, Johnson, Teo, 2002) reported that the primary outcome was achieved by 57% (31%) of the intervention (control) a 26 percentage-point difference (p=0.001) by the termination of the study. Secondary outcomes also showed significantly different measures; 53% vs 29% of intervention and control groups, respectively had fasting cholesterol panels (p=0.001). A new (increasing the existing) cholesterol prescription was met by 10% (3%) of the intervention group compared to 4% (1%) of the control group (p=0.003 (p=0.07)). There were no differences in the results by age or geography but there was a significantly greater effect for women vs men and in patients with DM. Tsuyuki, Johnson, Teo (2002) concluded that the SCRIP trial conclusively demonstrated that community-pharmacists' interventions improved the *process* of cholesterol management. They went on to explain that the trial reported *process* and not clinical outcomes because the evidence of cholesterol-lowering therapy was already well documented.

An economic evaluation of the trial (Simpson, Johnson, &Tsuyuki, 2001) reported clinical outcome measures, taken at baseline and exit visits, that were used to predict 10yCVDr for the intervention group (no data on controls were reported). Over the 4-month trial, the intervention group saw declines in: TC from 4.99 to 4.85 mmol/L ($p<0.001$), SBP 140 to 137mmHg ($p<0.001$), and 10yCVDr, from 17.3% to 16.4% ($p<0.0001$). Smoking cessation was not significantly different between the two groups.

Intervention resource usage was collected as part of the study. Patients reported number of MD visits, nature and frequency of adverse drug events, and treatment of the adverse events in an exit survey. Unit costs were taken from available health benefit and fee structure documents. Pharmacists provided 102.4 minutes in intervention activities. There were no significant differences in the number of visits to physicians between the two groups, thus no difference in costs of physician visits. The average cost of the intervention to a community pharmacy manager was $48.44/patient. The main differences in resource utilization between patients in the intervention and usual care groups were in the lab tests and prescriptions included as outcomes. The total costs (in 1999 $CDN) to the provincial governments were $11,913 and $9,246 for the intervention and usual-care groups, respectively; an incremental cost of $6.40/patient, on average, over 4-month study. Patient out-of-pocket payments were not included, so government costs were sensitive to the proportion of patients qualifying for government insurance plans. The authors concluded that the incremental costs were minimal for the intervention even though there were no control-group measures.

The SCRIP-plus trial (Tsuyuki, Olson, Dubyk, et al., 2004) was based on the SCRIP intervention but used a before-after design for the evaluation (it was considered unethical to randomize patients to a control group due to the very positive results of the SCRIP intervention). Patients from 42 community pharmacies who were at “very high” risk of CVD events were included in the study (419 patients). As with SCRIP, pharmacists completed intervention forms detailing assessment results and therapeutic recommendations and faxed them patient’s MDs. Pharmacists had follow-ups by telephone at two and four weeks and in-person at three and six months where patient progress was assessed.

The ITG data (last known outcomes were used for 60 patients who did not complete the trial) showed that enhanced pharmacists' care improved patients' outcomes for patients at very high risk of CVD events. Patients experienced a mean decrease in LDL of 0.5 mmol/L; a relative reduction of 13.4% ($p < 0.0001$). At the end of the study 27% of patients where within target range for LDL (compared to zero at start of trial). A total of 16% of patients started a new lipid-lowering medication,1% had medications added, 5% changed medications, and 9% had a dosage increase. Adherence in those receiving lipid-lowering medications was 84%. Of the 359 patients with data at the end of the trial, 162 (45%) were contacted to explore outcomes approximately one-year post trial (extended follow-up) (Yamada, Johnson, Robertson, et al., 2005). Characteristics for the original and extended groups were similar. The LDL level for the extended group was not significantly different approximately one year later (2.79 mmol/L vs 2.85) and neither was the proportion at target LDL. Patients' treatments remained stable over the follow-up period, on average. The extended follow-up results were taken as further evidence that enhanced pharmacist interventions have positive and lasting effects for the patients at high risk of CVD events.

The Study of Cardiovascular Risk Intervention by Pharmacists–Hypertension (SCRIP-HTN) was another study based on the original SCRIP trial. It was implemented in 14 pharmacies in Alberta but was delivered by pharmacist-nurse teams (McLean, McAlister, Johnson, et al., 2006; 2008). The study population was patients with DM and HTN and the outcome of interest was reduction in SBP. The groups were similar at baseline and most patients had multiple CVD risk factors including DM and HTN. SBP decreased in both arms of the trial during the 6 months, but the adjusted reduction in the intervention group (N=115) was 5.6 mm Hg more than the control group (N=112) (p=0.008). In a subgroup of patients with SBP>160 mm Hg at baseline, experienced larger differences at 24.1mm Hg (p<0.001). The percentage of patients who met recommended BP targets (<130/80 mm Hg) increased from 2.6% (3.6%) to 47.0% (33.0%) in intervention (control) group, a 14-percentage-point improvement (p=0.02). The authors pointed out that the intervention not only improved outcomes for well-controlled patients, but it was 'extremely efficacious' at doing so for patients who were poorly controlled. Furthermore, Houle, Chuck, McAlister & Tsuyuki (2012) showed the intervention to be cost-effective with Monte Carlo simulations using the study outcomes and resource data found in the literature. The authors

estimated annual incremental cost savings (2011 $CDN) of $131/patient for the 6 months and $115/patient for a year-long intervention. An annual total cost savings/patient remained ($40.69 for a 6-month program or $24.45 for the year) even if the pharmacist's time with patients was doubled. The authors called for wider adoption of pharmacist-managed HTN care for patients with DM and HTN.

Finally, the Alberta Clinical Trial in Optimizing Hypertension (RxACTION) (Tsuyuki, Houle, Charrois, et al., 2015) was a randomized trial of the effect of pharmacist prescribing on BP reduction in the community. Although pharmacist prescribing did not occur in the current study, the results of RxACTION, including its economic evaluation (Marra, Johnston, Santschi & Tsuyuki, 2015), are discussed briefly as they are widely cited. The RxACTION trial randomized patients with above-target BP through **c**ommunity pharmacies, hospitals, or primary care teams in 23 communities in Alberta. The intervention included pharmacists providing patients with an assessment of BP and CVD risk, education on HTN, prescribing of antihypertensive medications, laboratory monitoring, and monthly follow-up visits for 6 months (N=181 patients). The control group (N=67) received a wallet card for BP recording, written HTN information, and usual care from their pharmacist and physician. The outcome of interest was SBP at 6 months. The intervention and control groups were similar at baseline. The intervention group saw a reduction in SBP of 18.3mm HG, on average, compared to the 11.8 mm Hg average drop in the control group; an adjusted difference of 6.6 mm Hg (p=0.0006). The adjusted odds of the intervention group achieving BP targets were more than double the control group. The Markov model (Marra, Johnston, Santschi & Tsuyuki, 2015), using these results and others from the literature (Santschi, Chiolero, Colosimo, et al., 2014), found a reduction in costs of long-term CVD and end-stage-renal disease more than offset the cost of the intervention, with a resulting cost savings of $6,365 over 30 years for an intervention that led to an 18.3 mmHg reduction in SBP; the intervention was more effective and less costly than usual care (assumed to have no effect on SBP which was not the case in the RxACTION study). The sensitivity analysis showed that an intervention that saw decreases in SBP in the 7.6 mmHg (more in line with incremental changes found in the literature) led to improved outcomes but also increases in costs; leading to an ICER of $40,000/QALY.

The results of the pharmacist-physician collaborations just described tend to show, as many health-care interventions do, that the collaborative interventions improve patient outcomes but also increase costs. The current trial was designed for both qualitative and quantitative evaluations (see Research Power Inc (2019) for further detail). The current study presents the economic evaluation of the trial. The next section presents the methodology and data, section III presents the results, and section IV conclusions and discussion.

II. Methodology and Data

The Pharmacy Association of Nova Scotia (PANS), Doctors Nova Scotia (DNS), and the Nova Scotia Department of Health and Wellness (NSDHW) designed and implemented a Collaborative Care Demonstration Project (CCDP). The goal of the CCDP was to develop and evaluate a collaborative care model of collaboration between family physicians and community pharmacists. The collaboration's goal was to support patients with chronic disease. Briefly, physicians paired with up to two pharmacists normally at two pharmacies. A sample of pharmacies with physician-pharmacist collaborations was chosen to represent demographic and economic circumstances in the province, after representation, pharmacies were chosen randomly. Pharmacist/physicians in chosen pharmacies discussed the projects with patients and obtained consent from 448 patients.

Physicians and pharmacists attended a one-day orientation workshop on the CCDP and pharmacists received additional training in chronic disease management and developing care plans. Patient recruitment took place from July 2017 to January 2018. CCDP inclusion criteria were: registration with Nova Scotia Pharmacare, presence of two chronic diseases of interest (DM, ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), or HTN), or have one of the specified chronic diseases and one identified risk factor (obesity, smoking, or non-adherence to medication (NAHM)). Pharmacists developed a care plan for each patient with input from the patient and physician. Protocol called for pharmacists to have in-person follow-up visits with patients at least every two months to support achievement of the care plan. In addition, pharmacists followed up with patients by phone as needed. Pharmacists were to meet with their physician collaborators once/month to discuss patient status and any additional

supports needed. Patient-pharmacist interactions and pharmacist-physician meetings were logged during the project and patient outcome data were reported at baseline and at the end of the 12-month intervention. Patients also completed a mail-in survey addressing subjective outcomes and demographic information. Funding was not available for a control group, but pre-study patient outcomes were documented as comparison data. Qualitative data were also collected (See Power Research Inc. (2019) for further details and a descriptive analysis of the results).

This study presents an economic analysis of the CCDP. Typically, partial economic analysis or a costing study is presented when control group is available (see Hoch & Dewa, 2005). The average total cost of the intervention is divided by the average change in outcomes found in the intervention to calculate a cost per unit change in the outcome of interest. The results of these analyses are presented in the results section. A cost-effectiveness analysis provides the change in cost between two or more treatments (typically usual care and the intervention) per incremental change in an identical outcome. Herein, the difference in costs between usual care and intervention are estimated using the assumption is that usual care produced no improvement over the CCDP (see results section for further discussion).

Many recent studies in the literature present the change in BP (particularly SBP) as a result of pharmacists' interventions for patients with CVD and/or CeVD. The Framingham study indicates that systolic BP is strongly correlated with CVD and CeVD and may be used alone to predict changes in 10yCVDr if other parameters are not available (see for example: D'Agostino, Vasan, Pencina, et al., 2008). Incremental changes in the 10yCVDr were included in this study as an outcome as it provides a single measure that envelopes change in several clinical outcomes. However, the sample of patients with 10yrCVDr reported is 36 percent smaller than the sample of patients with SBP recorded. Given that the largest subgroup in the study sample has a SBP measure, like many in the literature, this study uses changes in SBP to predict changes in RR changes for CVD and CeVD. These relative risks are used to perform a more complex economic evaluation – a cost utility analysis.

A cost-utility analysis predicts the changes in quality-adjusted life years (QALY (also referred to as utility)) that result from changes in clinical outcomes due to an intervention. There are several

survey instruments that have been constructed to evaluate the QALYs related to different health conditions, but most cost-utility studies obtain the QALY values from the literature (as is done in this study) as surveying participants to obtain the data to construct QALYs is often difficult, time consuming, and expensive. The incremental cost effectiveness ratios (or incremental cost/ incremental QALY) (ICER) were estimated using a Markov model with simulated cohorts. The ICER is a statistic that can be presented to policy makers and/or payers who can then compare the results of disparate interventions (e.g., the CCDP could be compared to an intervention that introduces a new chemotherapy for breast cancer). If the intervention provides higher QALYs at lower costs than usual care, the ICER will be negative and the intervention is classified as dominant. If, as is often the case, the ICER is positive with the intervention providing higher QALYs at higher costs than usual care, then it is the policy maker's/payer's decision as to whether the ICER ratio is one they are willing/able to accept given their budgetary realities. Typically, health interventions that deliver cost/QALY's under $50,000/QALY are considered 'acceptable' (Jaswal, 2013).

a. Patient Outcomes

The study design had patient outcomes of interest collected at baseline and at the end of the 12-month trial. An historical measure of each outcome, from patients' medical charts, taken 6 months before enrollment in CCDP was also to be included in the data. Patients' clinical measurements depended on the conditions existing when patients were enrolled in the study (e.g., patients with DM had A1Cs recorded, patients with HTN had BPs recorded, etc.), thus the number of patients (N) with data for each outcome differs depending on their eligible conditions and their care plan. Patient outcomes examined in this study included BP, A1C, TC, LDL, and HDL. Other behavioral measures and indices were also documented (e.g., packs of cigarettes smoked per day (PPD), Clinical COPD Questionnaire (CCQ), COPD Assessment Test (CAT), Morisky Medication-Taking Adherence Scale (MMAS)). Given the pharmacist-physician collaboration was designed to address multiple chronic conditions, clinical measures were used to estimate a 10yCVDr and heart age. As discussed previously, the 10yCVDr and heart age demonstrate the estimated long-run effects of addressing multiple risk factors. Multivariate regression analyses were completed for each outcome to test for underlying baseline differences

in outcomes across socio-economic determinants of health to determine whether adjustments were necessary; none were identified.

Typically, an intention-to-treat analysis (ITA) is completed during an economic evaluation, however as over half the attrition in the CCDP was not driven by patient choice (see results section for discussion), both intention-to-treat analysis and a treated analysis (TA) are presented herein. The intention-to-treat group (ITG) includes anyone with a baseline clinical measure. It is assumed that those with missing endpoint outcomes had identical baseline and endpoint values (e.g., no difference resulting from the intervention). The treated group (TG) includes any patient that did not drop out and has clinical outcome measured at baseline and at the end of the CCDP. Outcome measures differed across patients depending on their chronic conditions and needs, thus some of the outcome measures have very small sample sizes and results using these measures should be viewed carefully. Finally, many studies in the literature presented results for high-risk groups (HRG) which include patients with clinical outcome measures that are out of range at baseline (see for example, Matzke, Moczygemba, Williams, et al., 2018); high risk results are presented herein.

b. Probabilities, Utilities and Relative Risks for Markov Model

A Markov model cohort simulation with a one-year cycle was used to predict MI, stroke, and HF events, and death (from an event or other) throughout the lifetime (40 years). In the first year of the base case, patients are 60 years of age and receive either usual care or CCDP. At the end of the first year, and for remaining cycles, participants will remain in their original state, suffer an event (MI, stroke, HF) or die. Those that survive an event, remain in that state for following cycles until they die as a result of the event.

Baseline QALYs (utilities) and risks for disease states were modeled using results from the literature (Houle, Chuck, McAlister, & Tsuyuki, 2012; Kulchaitanaroaj, Brooks, Chaiyakunaprukd, et al., 2017; ,Marra, Johnston, Santschi, et al., 2017; Palta, Chen, Kaplan, 2011). Age adjusted population death rates were used (Statistics Canada, 2019b). Modified risks were estimated using CCDP results and meta-analysis studies from the literature (Houle, Chuck, McAlister, & Tsuyuki, 2012; Marra, Johnston, Santschi, et al., 2017; Padwal, So, Wood, et al.,

2019). Changes in relative risk (RR) of different conditions and the utility measures associated with those conditions were used to perform the cost-utility analysis. The relative risk (RR) for major cardiac or CeVD events have been well documented in the literature (e.g., Marra, Johnston, Santschi, et al., 2017 find a relatively linear relationship between SBP reduction and the reduction of CVD and CeVD risk of approximately 0.026 for each mmHg SBP reduced). The probabilities for health states, RR, utilities, assumed distribution, and sensitivity analyses are listed in Table Seventeen. Mean values are used to estimate the deterministic results and Monte Carlo analyses (1,000 repetitions) were used to estimate the probabilistic results.

c. Resource Measures

The study perspective is the health-care payer. The resources used in the CCDP project were recorded during the project and include pharmacists' time spent counselling patients in person and on the phone, physicians' and pharmacists' time collaborating with each other (typically face-to-face), start up training for pharmacists and physicians, and the purchase of a blood pressure equipment for the pharmacy. The CCDP study had a menu of payments that were agreed upon in the consultation stage, however opportunity costs were used to price the resources expended during the intervention. Labour for pharmacists and physicians was tracked in the project. Hourly wages for pharmacists were obtained from a survey of Nova Scotia pharmacists (Pharmacy Association of Nova Scotia, 2019), Pharmacist wages across the province were somewhat heterogeneous, but the distribution was tight, so the mean wage for Nova Scotia pharmacists (including 20% benefits package) was used in the analysis. Physician payments were somewhat more variable. The average hourly wage for physicians in Nova Scotia (expert opinion) was used to estimate physician resources expended. The complex care consultation fee paid by Nova Scotia Medical Services Insurance (NS MSI) was used in the sensitivity analysis (the fee paid to physicians when attending to patients with multiple chronic health issues (as in the project)). The estimated project costs were used in the first cycle of the Markov Model. For the remaining cycles, following Marra, Johnston, Santschi, et al., (2017), it is assumed that patients have a 30-minute visit with the pharmacist each quarter and, as a result, outcome improvements remain stable. The pharmacist-physician collaboration is maintained via email, text, or fax and not face-to-face (qualitative data indicated that the face-to-face meetings were not necessary and electronic means of communication would likely be more effective for

the collaboration (Research Power Inc., 2019). The resource values for health care used by patients projected to suffer an acute event (MI, HF, or stroke) were taken from the literature (Marra, Johnston, Santschi, et al., 2017) and adjusted by Nova Scotia price index for health and personal care to 2018 prices (Statistics Canada, 2019) and hospital cost differences between Alberta and Nova Scotia (CIHI, 2019). All costs are presented in 2018 Canadian dollars.

Cost for those who died from 'other' conditions were not included as it was assumed that the probabilities were identical for the usual care and intervention arm (Drummond, Stoddart, Torrance, 1998). Laboratory tests were also assumed to be similar between usual care and the intervention arm. If more laboratory tests were needed in the intervention, the costs per test are small relative to labour costs thus excluding them from the analysis should affect results little (Drummond, Stoddart, Torrance, 1998). Visits to the physician were assumed to be the same for the usual care group and the intervention (four per year as Nova Scotia billing rules allow). Sensitivity analyses were completed on this assumption (1/2 as many and twice as many MD visits in the intervention as the usual care arm) as the literature reported ambiguous results on this. The average cost per patient in the ITG group is the total cost of the CCDP divided by the number of patients enrolled in the study (N=448). The costs per patient in the TG are the total intervention costs divided by the total number of patients did not drop out of the study (N=317).

Finally, qualitative results (Research Power Inc., 2019), regulations concerning pharmacists' licensing and scope of practice, and other similar trails (see SCRIP trials) indicate that pharmacists would not receive additional training if the current project were to spread and physician/pharmacist collaborations would be dealt with electronically (fax, email, text, etc.). Sensitivity analyses were performed excluding physician and pharmacist training and face-to-face meetings.

III. Results

Initially 23 MDs and 39 Pharmacists in 41 Pharmacies agreed to participate in the CCDP study and attended a one-day training workshop. Additionally, pharmacists participated in a review program of the targeted disease states (for a total of 27.5 hours of training). By the end of the study 18 MDs, and 25 Pharmacists in 25 Pharmacies remained active in the study. The study

experienced substantial issues with obtaining the projected study sample size; less than half of the projected patient population was enrolled (N=448). Study attrition was also high (29.2%), but more than half of the attrition was driven by the pharmacist and/or physician leaving the study (55.4%) rather than the patient refusing/unable to continue participation (44.7%). Documented reasons for patient withdrawals from project were: physician/pharmacist left study (55.4%), personal/family (27.3%), worsening health and/or institutionalization (11.4%), and death (6.1%). Reasons for physicians'/pharmacists' attrition were: pharmacist dropped out, left project or did not complete data collection and/or follow up (52%), pharmacist left pharmacy and/or area or departed (36%), and physician dropped out (12%).

Table One displays descriptive statistics for those who completed the study compared to those who dropped out. The results demonstrate that, on average, the two groups are very similar. The only significant differences between the two groups are the percentage of patients eligible for the study due to HTN and other conditions (lower in the drop-out group) and as a result, the BP measurements are slightly better in the drop-out group. If the two groups were statistically identical, one might assume, the observations were missing at random, the drop outs would react similarly to the treated group had they remained in the study. The small differences between the two groups and the fact that the attrition was not determined by the patients in over half the cases may make the TG results reliable. Table Two, compares descriptive statistics between ITG and TG groups, also demonstrates that the two groups have similar characteristics and outcome measures.

Tables Three and Four present the mean difference in each clinical outcome for the ITG and the TG, respectively. The clinical measures in both the ITG and the TG groups show significant improvement, on average, between beginning and end of CCDP, except for High-density HDL (mmol/L) where there was no statistically significant change. The more subjective measures have small sample sizes and, thus should be viewed with caution (e.g., CCQ, CAT, MMAS, and number of cigarette packs per day smoked (PPD). As expected, the TG had substantially larger beginning to end differences resulting from the intervention, on average. SBP improved by 4.0 mmHg in the ITG group and 5.27 mmHg in the TG, DBP by 1.87 and 2.40, in ITG and TG, respectively. A1C dropped by 2.5% and 3% for the ITG and TG, respectively. Improvements in

all measures except HDL lead to statistically significant improvements in both 10yrCVDr and heart age. 10yrCVDr declined by 0.912 (4%) in the ITG and by 1.5 (6%) in the TG while heart age declined by 1% and 2% in each group, respectively (note that those with the outcomes necessary to predict 10yrCVDr and heart age may not be representative of the entire sample). The sample of smokers in the CCDP was small, but over the intervention there was a 19% drop in PPD in the ITG and a 25% drop in the TG. The number of abstainers (zero PPD) increased from 3 (6%) at baseline to 11 (22%) at end of study, a 16% drop (results not shown).

HRG subgroup analyses are provided in Table Five (ITG) and Six (TG). Consistent with most studies, the improvement between base-case and end-point clinical measures were substantially better for higher-risk groups, on average, and all results are statistically significant. Patients with SBP>130 (SBP>160) experienced a 10 mmHg (31 mmHg) decline in the ITG. Those with DBP>80 saw a 9.5 mmHg drop. Higher risk A1C patients (>7) had more than double the effect of the average A1C effect, while those with A1C>9 had 6 times the drop. The TG showed similarly large increases in effect size for those at higher risk.

Although improvements in clinical measures lead to better outcomes for most patients, the long-run goal of clinicians and their patients typically is to move towards a 'normal' or in-range measure. The proportion in 'normal range' and 'high range' at base line and at study end are included in Table Seven. The Pearson Chi2 indicates that there was a significant increase in the proportion of patients in 'normal range' and a significant decrease in the proportion of patients in the 'high range', on average, for every measure for the TG. There was a 24% increase in hypertensive patients in-range, an 18% increase in-range for A1C and a 43% decrease in very high A1Cs. The proportion with 10yrCVDr<10 more than doubled and 10yrCVDr>20 fell by about 6%.

The results in Tables One through Seven indicate the intervention was effective (led to better clinical measures) for both ITG and TG. The study did not have a control group thus it is not possible to compare the changes in outcome measures for the intervention group with changes in outcome measures for a control group, per se. However, historic measures of clinical outcomes were recorded for many patients. For most clinical measures the patient's baseline indicators

were statistically no different than the historical measures (see Table 8). The only two outcomes that were statistically different were SBP (significantly higher at baseline than historic measure by 4 mmHg) and PPD (significantly lower at baseline by 0.12 PPD). Patients would have received usual care in the time between the historical and the baseline measures. Given this, the assumption is that usual treatment (continuing the same treatment as received historically) resulted in no clinical improvement over the intervention timeframe (i.e., the pseudo-control outcome changes were zero). This is a conservative assumption for SBP.

The intervention has been demonstrated to be effective; the analyses of costs can now be completed (if effectiveness had not been shown, an analysis of costs is not required). Table Nine presents the resources consumed by the intervention, the prices of those resources and the sources (see methodology for further details). The intervention was labour intensive with 27.5 hours of training time for pharmacists and 1,230 hours spent in patient meetings (in-person or by phone). Physicians also had 7.5 hours of training, were assumed to have four complex care consultations with intervention (and usual care) patients and physicians and pharmacists spent an additional 292 hours in face-to-face consultations regarding CCDP patients (see Table Ten). Pharmacists saw patients an average of just over an hour for the initial meeting and then just over 3 visits (4 visits) in the ITG (TG) for just under (over for TG) 30 minutes each. Pharmacists spoke to patients an average of just over one time for around 15 minutes. Average total costs were $694/patient in the ITG and $895/patient in the TG. Average total costs for usual care was assumed to be $208/patient. The incremental change in costs/patient for intervention compared to usual care was $486 and $687 in ITG and TG, on average, respectively.

Cost Analysis

The change in average cost per unit change in clinical outcomes at the one-year completion date are listed in Table Eleven for the ITG and TG groups. The average cost per outcome change ranges from $174 to over $173,000 in the ITG. In the TG where both costs and outcome changes are higher, the average cost per outcome change ranges from $170 to over $125,000. If HDL is presented but not reviewed further, as there was no statistical change in the measure, the highest costs per outcome are for other cholesterol measures and A1C. As the intervention protocol called for focus on different outcomes, depending on the patient's relevant conditions and

treatment plan, assigning all costs to all patients may over estimate the costs as some patients were not 'treated' for some issues (e.g., only diabetic patients had A1C screened and only hypertensive patients had BPs screened). In the last column of Table Eleven, a weighted cost/outcome is displayed. The weight is the proportion of the patients treated for that condition. The weighted cost/outcome change ranges from $136 to just under $4,500 and about half the average costs per outcome are less than $500. Tables Twelve and Thirteen present the average costs per improvements in high risk and in-range results. The average costs for the TG and the weighted TG group for high BP and very high outcome measures are relatively small. While the average cost per outcome provides some information, the incremental costs per incremental outcome or cost-effectiveness analysis is what government and other payers are interested in.

Cost-Effectiveness Analysis

Tables Fourteen through Sixteen present the incremental cost per incremental change in outcome. The results range from $122 for systolic SBP reductions to approximately $7,600 for LDL reductions for the ITG and $130 to $58773 for the TG. The weighted cost/outcome ranges from $105 to $3,424 and is under five hundred dollars for the majority of the outcomes. The incremental costs for changes in cholesterol and A1C are relatively high. Tables Fifteen and Sixteen present the results for patients in the HRG and for changes in/out of range. The incremental costs of lowering very high BP are around $50 and only a few dollars in the weighted TG. The in/out of range results also show a relatively low incremental cost/incremental change in outcome for most measures.

Cost Utility Analysis

The incremental costs/incremental outcomes are taken at a point in time and while it is widely known that better clinic outcome measures indicate better health outcomes, the analysis does not take into consideration the fact that improving the clinical outcomes lead to positive long-run consequences including fewer negative health events, meaning lower costs to the health-care system and more and better years of life. A cost-utility analysis predicts the long-run consequences of changes in clinical measures by estimating the incremental quality of life years (QALY) gained relative to the incremental costs expended over some time horizon.

A Markov model with cohort simulation is used to estimate the incremental costs per QALY (utility) resulting from the changes in clinical outcomes experienced by patients in the CCDP (see section II). The cost inputs are presented in Table Nine and the base-case probabilities, utility measures, and other assumptions are presented in Table Seventeen. Table Seventeen also presents the sensitivity analyses completed. All sensitivity analyses use the base-case parameters with only the parameter of interest changing. Sensitivity analyses around assumptions of physician payments, discount rates, physician visits for CCDP patients, utility scores, RRs, start age, and time horizon were completed. Deterministic results are presented in Tables Eighteen (ITG) and Twenty (TG) and probabilistic results are presented in Tables Nineteen (ITG) and Twenty-one (TG).

In each table, the first row of results presents the base case, the remaining rows present sensitivity analyses as labelled. The base-case results in each table indicate that over the 40-year time horizon, the cohort in the CCDP will cost the government around $130,000 (discounted at 3%) in program and other health costs. However, the usual-care group will cost the government slightly over $140,000 over their life-times. The usual-care group experiences more health-care costs due to their higher probability of suffering an event and the health costs associated with the events. The CCDP cohort also accumulates slightly more QALYs or higher utility over their life span (around 0.12 more QALYs than the usual-care group). Higher QALYs at a lower cost indicate that the CCDP dominates usual care under our base-case inputs and assumptions. The results in each table indicates that the payer saves approximately $7,000 (ITG) to $10,000 (TG) in health-care costs by investing in the CCDP and CCDP patients gain a little over $1/10^{th}$ more QALYs than they would have experienced had the received usual care. ICERs around -$56,000 per QALY (or 56,000 saved per QALY) are generated by the CCDP in each of the models.

Sensitivity Analyses

All sensitivity analyses except adjusting the mortality rate continue to show an over arching dominant result. Cost savings remained after reducing health-care costs by 50% at around $4,000 and an ICER of over $20,000 in the four models. The only input that changed results drastically was a constant death rate of 0.23 for those in the cohorts experiencing a health event (Padwal, So, Wood, et al., 2019) rather than the RR of 1.7 times the age-adjusted mortality rates (Marra,

Johnston, Santschi, et al., 2017). The relative mortality rates approach 100% as individuals become very aged; the constant rate does not. Patients live longer in unhealthy states generating more costs and lower QALY states leading to lower long-run QALYs in the CCDP arm than in the usual care arm. The costs remain lower in the CCDP arm but negative incremental QALYs are generated. However, the assumption of a constant mortality rate that leads to this result does not seem realistic.

Finally, excluding physician/pharmacist training and face-to-face collaborations reduces costs substantially. Excluding training costs reduced costs by 27% in the ITG and 30% in the TG. Excluding both training costs and face-to-face meetings reduced costs by 46% and 50% in the ITG and TG, respectively. The percentage reductions would lead to the similar relative reductions in the costing (tables 11 through 13) and cost-effectiveness analyses (tables 14 through 16). The cost savings from eliminating physician and pharmacist training and face-to-face meeting costs leads to relatively small increases in cost savings per QALY in the CU analysis because training costs per patient are small relative to hospital costs.

IV. Discussion and Conclusions

This study presented an extensive literature review regarding the effectiveness of pharmacists' care of patients with chronic conditions, particularly hypertension and diabetes. A focus on the effectiveness of pharmacist-physician collaborations in community pharmacies was attempted. However, few studies were identified that specifically addressed collaborations in community pharmacies. Many physician-pharmacist collaboration studies originate in the U.S. and the collaborations tend to be located in medical offices of some description. In general, trial sample sizes tended to be small and systematic reviews and meta analyses claimed studies were not the best quality. Studies typically concluded that pharmacists' care was at least as good as usual care although the evidence was limited in some cases. Most authors of systematic reviews called for better quality trials and studies and economic evaluations of the trial results.

This study provides an economic evaluation of the CCDP, a pharmacy-physician collaboration in community pharmacies in Nova Scotia. The results indicate that the CCDP was effective in its goals to support patients with multiple chronic conditions. Multiple outcome measures showed

statistically significant improvements from baseline to study end for both ITG and TG. Improvements were larger for the TG as were the costs.

The improvement in outcomes are in line with lower limits found in the literature (see for example: Pousinho, Morgado, Falcão, & Alves, 2016). The low-end results could be due to the fact that, on average, pharmacists met with patients 3 (ITG) or 4 times (TG) when study protocol called for meetings at least every two months during the study year. As with many treatments, a positive dose response is likely. The CCDP study was not able to enroll the desired number of patients and almost 1/3 of the enrolled sample dropped out. It is possible that the patients who stayed had more recalcitrant health issues (there was no historical information on persistence of disease states), however analyses of the sample before and after attrition indicated the sample characteristics measured in the study were similar between the two groups (likely because physicians/pharmacists leaving the study was responsible for over half of the attrition rate). The small sample size limited the analyses of some of the outcomes that showed promising results (e.g., PPD, MMAS, and CCQ).

As a result of the attrition issue, TG results were presented alongside the ITG results. In addition, the multiplicity of conditions and the lack of common measurements across all patients lead to extremely high costs/outcomes in some outcomes with small sample sizes. To adjust for these factors, TG costs were weighted by the proportion of the sample that had outcomes recorded providing an ad hoc but perhaps more realistic distribution of costs across outcomes.

The study lacked a control group but did obtain pre-study outcome measures. Comparison of pre-study and baseline measures showed that patients receiving usual care between pre-study and baseline measure showed no statistical improvement in that time. This result offered a basis for the assumption of zero improvement in the pseudo-control group. (Marra, Johnston, Santschi, et al., 2017) assume a no improvement control group as well.

The program costs and costs per individual outcomes are at the upper end of those found in the literature (Franklin, Farland, Thomas, et al., (2013) had program costs that were about ¾ of the CCDP program costs). The training protocol for pharmacists and physicians and the face-to-face

meetings between pharmacists and physician were resource heavy (many of the collaborations found in the literature included shorter training times and pharmacist faxing reports to the physician for review (see for example: Doucette, Witry, Farris, & McDonough, 2009; SCRIP trials). Isetts, Buffington, Carter, et al., (2016) and Polgreen, Han, Carter, et al., (2015) found the cost of lowering SBP and DBP by 1 mm Hg to be in the $33 and $70 range, respectively, the CCDP costs were at least double that. However, the ICERs generated in the Markov model indicated that the CCDP was cost efficient in the long run with lower costs than usual care and higher QALYs produced (CCDP was dominant in the base case analysis and 16/17 sensitivity analyses). The QALYS produced were in line with those found in the literature given similar improvement in outcome measures (see for example: Kulchaitanaroaj, Brooks, Chaiyakunaprukd, et al., 2017; Marra, Johnston, Santschi, et al., 2017). Some of the economic evaluations found in the literature used changes in outcomes that were extremely unusual (e.g., Marra, Johnston, Santschi, et al., 2017) and not comparable to this study.

The study results indicate that, given the very high costs of health care, pharmacist-physician collaborations to reduce CVD risk can be effective and cost-effective when the intervention provides moderate changes in CVD risk factors. The lessons learned from the CCDP qualitative results (Research Power Inc., 2019) and other study protocols (e.g., SCRIPs), show that collaborations between pharmacist and physicians could be much less time consuming and therefore, less costly if done electronically and not face-to-face. If the program were rolled out to more pharmacies and more pharmacists, patients would more likely to be able to continue care if a single pharmacist left the pharmacy and not necessitating patients to leave the program. The sensitivity analyses completed that excluded training costs or training costs and face-to-face meetings decreased costs by between 30% and 50%, indicating that a spread out of the program to addition pharmacies could be even more cost efficient than this study finds depending on the mode of communication between pharmacists and physicians and training protocols.

The Nova Scotia Department of Health and Wellness 2017/2018 Business plan (Department of Health and Wellness, 2017) promoted a shift in health care towards collaborative care involving more broadly defined health-care providers working in an integrated manner with the patient at the centre of their work. It states that ‘improving access to collaborative teams will provide Nova

Scotians with more systematic, comprehensive care. Collaborative teams will allow for same day/next day service, by connecting patients with the right providers. And collaborative care will provide care needed for patients with complex needs in a more patient-oriented way.' (page 4). The economic evaluation presented here provides evidence that pharmacist-physician collaborations may be a cost-effective way of following through on the plan.

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Table 1 Descriptive Statistics of Study Sample and Attrition Sample

Characteristic	Completed Study (N=Obs)	Mean	SD	Dropped Out (N=Obs)	Mean	SD
Female	(N=317)	0.50	(0.50)	(N=127)	0.54	(0.50)
Age	(N=316)	70.06	(10.6)	(N=127)	69.94	(11.1)
Height	(N=314)	166.72	(10.2)	(N= 96)	165.05	(10.4)
Weight	(N=313)	88.33	(23.2)	(N= 92)	85.39	(21.6)
BMI	(N=313)	31.77	(8.24)	(N= 91)	31.07	(6.74)
Eligible						
DM	(N=317)	0.52	(0.50)	(N=131)	0.56	(0.49)
HTN	(N=317)	0.90	(0.30)	(N=131)	0.83	(0.37)^
IHD	(N=317)	0.35	(0.48)	(N=131)	0.32	(0.46)
COPD	(N=317)	0.17	(0.38)	(N=131)	0.15	(0.36)
Obese	(N=317)	0.50	(0.50)	(N=131)	0.44	(0.49)
Smokes	(N=317)	0.16	(0.37)	(N=131)	0.09	(0.28)
NonAdhere	(N=317)	0.14	(0.35)	(N=131)	0.13	(0.33)
Other	(N=317)	0.84	(0.37)	(N=131)	0.69	(0.46)*
#Eligible	(N=317)	2.74	(0.87)	(N=131)	2.53	(0.84)^
BP treat HX	(N=317)	0.71	(0.46)	(N=131)	0.44	(0.49)*
BP treat BL	(N=317)	0.85	(0.36)	(N=131)	0.47	(0.50)*
SBP BL	(N=284)	135.69	(16.5)	(N= 65)	132.55	(14.5)
DBP BL	(N=284)	76.26	(10.8)	(N= 65)	71.92	(10.1)^
LDL BL	(N=254)	2.05	(0.85)	(N= 56)	2.18	(1.05)
TC BL	(N=250)	4.01	(1.14)	(N= 55)	4.09	(1.38)
HDL BL	(N=253)	1.25	(0.39)	(N= 55)	1.17	(0.27)
NHDL BL	(N=249)	2.81	(1.17)	(N= 53)	2.94	(1.30)
A1C BL	(N=155)	7.83	(1.66)	(N= 38)	7.66	(1.50)
CVD RISK BL	(N=237)	23.90	(7.37)	(N= 49)	23.19	(8.28)
Heart Age BL	(N=237)	78.18	(4.96)	(N= 49)	76.73	(6.70)
PPD BL	(N= 55)	0.73	(0.47)	(N= 14)	0.94	(0.46)
MMAS BL	(N= 35)	1.38	(1.11)	(N= 9)	1.33	(0.50)
CCQ BL	(N= 26)	2.30	(1.73)	***		
CAT BL	(N= 14)	25.93	(11.1)	***		
SBP HX	(N=195)	130.05	(14.0)	(N= 57)	133.16	(15.5)
DBP HX	(N=195)	74.37	(9.96)	(N= 57)	75.39	(11.1)
LDL HX	(N=199)	2.12	(0.86)	(N= 50)	2.28	(1.16)
TC HX	(N=198)	4.01	(1.07)	(N= 49)	4.16	(1.49)
HDL HX	(N=201)	1.19	(0.34)	(N= 48)	1.18	(0.36)
NHDL HX	(N=198)	2.82	(1.00)	(N= 48	2.93	(1.38)
A1C HX	(N=119)	7.75	(1.62)	(N= 31)	7.37	(1.42)
CVD RISK HX	(N=168)	23.18	(7.82)	(N=44)	23.29	(8.26)
Heart Age HX	(N=168)	77.32	(5.62)	(N=44)	77.80	(5.93)
PPD HX	(N= 50)	0.91	(0.45)	(N= 11)	0.97	(0.51)
MMAS HX	(N= 35)	1.43	(0.88)	(N= 5)	1.60	(0.55)

BMI=Body Mass Index, BP=Blood Pressure, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, LDL= Low-density lipoprotein cholesterol, TC=Total Cholesterol(mmol/L), HDL=High-density lipoprotein cholesterol(mmol/L), NHDL= Nonhigh-density lipoprotein cholesterol(mmol/L), CVD Risk= 10-year CVD Risk(%)using Framingham Risk Score, A1C= Hemoglobin A1C test, CCQ= Clinical COPD Questionnaire, CAT= COPD Assessment Test, MMAS= Morisky Medication-Taking Adherence Scale(4 item), PPD=packs/day smoked, BL=Baseline, HX=history.
*** too few observations for analysis.
* and ^ significant difference between groups p-value=0.000 and p-value≤0.05, respectively.

Table 2 Descriptive Statistics of Intention to Treat and Treated Samples*

Characteristic	Intention to Treat (N=Obs)	Mean	SD	Treated (N=Obs)	Mean	SD
Female	(N=444)	0.51	(0.50)	(N=317)	0.50	(0.50)
Age	(N=443)	70.02	(10.7)	(N=316)	70.06	(10.6)
SBP BL	(N=349)	135.11	(16.2)	(N=254)	136.53	(16.8)
DBP BL	(N=349)	75.46	(10.8)	(N=254)	76.09	(10.9)
LDL BL	(N=310)	2.07	(0.89)	(N=188)	2.05	(0.87)
TCH BL	(N=305)	4.03	(1.18)	(N=182)	4.00	(1.18)
HDL BL	(N=308)	1.23	(0.37)	(N=182)	1.21	(0.37)
NHDL BL	(N=302)	2.83	(1.19)	(N=180)	2.80	(1.07)
A1C BL	(N=193)	7.80	(1.63)	(N=132)	7.79	(1.64)
CVD RISK BL	(N=286)	23.78	(7.52)	(N=163)	24.44	(7.28)
Heart Age BL	(N=286)	77.93	(5.31)	(N=163)	78.18	(5.11)
PPD BL	(N= 55)	0.73	(0.47)	(N= 51)	0.75	(0.49)
MMAS BL	(N= 54)	1.37	(1.03)	(N= 40)	1.33	(1.10)
CCQ BL	(N= 27)	2.28	(1.70)	(N= 24)	2.22	(1.60)
CAT BL	(N= 16)	26.19	(10.8)	(N= 11)	25.09	(12.4)
SBP>130	(N=198)	145.49	(12.5)	(N=156)	146.19	(13.0)
SBP>160	(N= 25)	171.84	(9.14)	(N= 23)	171.61	(8.97)
DBP>80	(N= 93)	88.67	(7.04)	(N= 73)	88.93	(7.48)
LDL>3.5	(N= 23)	4.12	(0.44)	(N= 11)	4.11	(0.34)
LDL>4.0	(N= 14)	4.40	(0.30)	(N= 8)	4.28	(0.21)
TCH>5.2	(N= 46)	6.06	(0.78)	(N= 29)	5.95	(0.77)
TCH>6.2	(N= 16)	6.95	(0.62)	(N= 7)	7.06	(0.78)
AC1>7	(N=120)	8.62	(1.54)	(N= 76)	8.39	(1.72)
AC1>9	(N= 35)	10.58	(1.38)	(N= 12)	10.52	(2.39)
CVDR>10	(N=264)	25.08	(6.23)	(N=151)	25.73	(5.85)
CVDR>20	(N=197)	28.30	(2.98)	(N=117)	28.47	(2.97)

*Intention to Treat includes all patients with a baseline outcome measure. Missing end point measures were assumed equal to baseline (i.e., no improvement). Treated includes patients who did not drop out and have both base line and end of study results. See footnote Table 1 for acronyms and definitions

Table 3 Outcome Differences Baseline to End of Study
Intention to Treat Analysis

Outcome	N	Mean	t-test	[95% CI]	
SBP	349	-3.997	4.633	[-5.694	-2.300]*
DBP	349	-1.871	3.526	[-2.915	-0.827]*
LDL	310	-0.064	2.063	[-0.125	-0.003]^
TCH	305	-0.071	1.883	[-0.144	0.003]
HDL	308	-0.004	0.482	[-0.023	0.014]
NHDL	302	-0.080	2.259	[-0.149	-0.010]^
A1C	193	-0.196	2.448	[-0.354	-0.038]^
CVD Risk	286	-0.912	3.915	[-1.371	-0.454]*
Heart Age	286	-0.902	3.665	[-1.387	-0.418]*
PPD	69	-0.139	3.359	[-0.221	-0.056]*
MMAS	54	-0.670	5.900	[-0.844	-0.416]*
CCQ	27	-0.443	3.723	[-0.687	-0.198]^

See footnote Table 1 for acronyms and definitions
CAT sample sizes too small for comparison.
* and ^ significant group difference p-value=0.000 and p-value≤0.05, respectively.

Table 4 Outcome Differences Baseline to End of Study
Treated Analysis

Outcome	N	Mean	t-test	[95% CI]	
SBP	254	-5.265	4.525	[-7.543	-2.969]*
DBP	254	-2.398	3.374	[-3.797	-0.998]*
LDL	188	-0.119	2.425	[-0.216	-0.022]*
TC	182	-0.139	2.312	[-0.257	-0.020]*
HDL	182	-0.007	0.467	[-0.023	0.038]
NHDL	180	-0.158	2.802	[-0.269	-0.047]*
A1C	132	-0.241	2.174	[-0.461	-0.022]*
CVD Risk	163	-1.500	3.859	[-2.268	-0.733]*
Heart Age	163	-1.632	3.878	[-2.463	-0.801]*
PPD	51	-0.188	3.450	[-0.297	-0.079]*
MMAS	40	-0.825	6.418	[-1.085	-0.565]*
CCQ	24	0.50	3.844	[-0.230	-0.766]*

See footnote Table 1 for acronyms and definitions
CAT sample sizes too small for comparison.
* significant with p-value≤0.05.

Table 5

Outcome Differences Baseline to End of Study
High Risk Patients
Intention to Treat Analysis

Outcome	N	Mean	t-test	[95% CI]	
SBP>130	198	-10.08	8.589	[-12.39	-7.762]*
SBP>160	25	-31.32	7.908	[-39.49	-23.15]*
DBP>80	93	-9.409	8.583	[-11.59	-7.232]*
LDL>3.5	23	-0.374	2.748	[-0.656	-0.092]^
TCH>5.2	46	-0.510	4.309	[-0.748	-0.272]*
TCH>6.2	16	-0.574	2.144	[-1.145	-0.003]^
A1C>7	120	-0.478	4.451	[-0.691	-0.265]*
A1C>9	35	-1.063	3.734	[-1.641	-0.484]^
CVDR>10	264	-1.083	4.552	[-1.551	-0.614]*
CVDR>20	197	-1.342	5.115	[-1.860	-0.825]*

See footnote Table 1 for acronyms
CAT sample sizes too small for comparison.
* and ^ significant group difference p-value=0.000 and p-value≤0.05, respectively.

Table 6

Outcome Differences Baseline to End of Study
High Risk Patients
Treated Analysis

Outcome	N	Mean	t-test	[95% CI]	
SBP>130	156	-12.09	8.485	[-14.90	- 9.28]*
SBP>160	23	-34.04	8.975	[-41.91	-26.28]*
DBP>80	73	-11.99	9.700	[-14.45	- 9.52]*
LDL>3.5	11	-0.782	3.388	[-1.296	- 0.27]*
TCH>5.2	37	-0.634	4.531	[-0.917	-0.350]*
TCH>6.2	9	-1.021	2.393	[- 2.01	- 0.37]*
A1C>7	98	-0.514	4.208	[- 0.76	- 0.27]*
A1C>9	28	-1.064	3.181	[- 1.75	- 0.38]*
CVDR>10	151	-1.785	4.572	[- 2.56	- 1.01]*
CVDR>20	117	-2.062	5.051	[- 2.87	- 1.25]*

See footnote Table 1 for acronyms
CAT sample sizes too small for comparison.
* and ^ significant group difference p-value=0.000 and p-value≤0.05, respectively.

Table 7
Changes in Proportion 'normal' and 'high'Range from Baseline to End of Study Treated

Outcomes	N	Baseline	Intervention	Pearson Chi2	Pr
BP <130/80	254	0.373(0.317, 0.430)	0.461(0.402, 0.520)	13.8212	0.000
A1C<7	132	0.333(0.252, 0.415)	0.394(0.309, 0.478)	22.9096	0.000
A1C>9	132	0.159(0.096, 0.222)	0.091(0.041, 0.141)	44.8551	0.000
LDL<3.5mmol/L	188	0.941(0.908, 0.975)	0.952(0.921, 0.983)	42.3924	0.000
TC<5.2mmol/L	182	0.830(0.775, 0.885)	0.890(0.844, 0.936)	53.4260	0.000
TC>6.2mmol/L	182	0.038(0.010, 0.067)	0.016(-0.002,0.035)	32.5499	0.000
CVDR<10	163	0.043(0.011, 0.074)	0.098(0.052, 0.144)	31.3645	0.000
CVDR>20	163	0.718(0.648, 0.788)	0.675(0.602, 0.748)	61.1172	0.000

See footnote Table 1 for acronyms
CAT sample sizes too small for comparison.
* and ^ significant group difference p-value=0.000 and p-value≤0.05, respectively.

Table 8

Difference in Outcomes from Historic^ Measure to Baseline

Variable	Obs	Mean	|t-test|	[95% Conf.	Interval]
SBP	233	4.047	3.258	1.599	6.495*
DBP	233	0.723	0.970	-0.753	2.212
LDL	211	-0.035	0.871	-0.113	0.044
TCH	207	0.007	0.136	-0.099	0.113
HDL	208	0.014	1.173	-0.010	0.038
NHDL	205	0.012	0.242	-0.088	0.113
CVDRisk	171	0.551	1.385	-0.235	1.334
Heart Age	171	0.649	1.473	-0.221	1.519
A1C	136	0.155	1.583	-0.039	0.349
CCQ	7	-0.371	1.749	-0.891	0.148
MMAS	40	-0.125	1.955	-0.254	0.004
PPD	61	-0.121	2.550	-0.215	-0.026*

^Protocol called for historic measures to be from 6 months before CCDP enrollment but no information on the timing of the measure was included in the data.
See footnote Table 1 for acronyms
CAT sample sizes too small for comparison.
* and ^ significant group difference at p-value≤0.05.

Table 9 Resource Use and Costs

Resource	Mean(SD)		Sources/Assumptions
Pharmacist Hourly Wage	$54.90(4.95)*		(Nova Scotia Pharmacy Assoc, 2019)
Pharmacist training	27.5hrs		(assumed once for intervention)
Pharmacist labour CCDP(hours)	1230(829)^		(Study data – Intervention)
Pharmacist follow-up	2hrs/pt/yr		(assumption - Marra et al.,2018)
Physician Consultation fees			
High (base case)	$146.88		(Expert calculations)
Low	$52.00		Complex Care Consultation Fee (NS MSI))
Physician training	7.5hrs		(Study protocol)
Physician Meetings(hours)	292(308)^		(Study data – Intervention)
Patient Medical Care			(Marra et al., 2017; Padwal, 2019)
Myocardial Infarction	$ 9,003	Gamma(25, 360)	
Heart Failure	$10,356	Gamma(25, 414)	
Stroke	$62,512	Gamma(197, 317)	
Post MI(after first year)	$ 2,633	Gamma(25, 105)	
Post HF(after first year)	$10,356	Gamma(25, 414)	
Post Stroke(after first year)	$ 9,484	Gamma(25, 380)	
BP Monitor	$850/pharmacy		(every 5 yrs (online warranties))

*Includes 20% benefit package (Houle et al., 2012).

Table 10 Pharmacist-Patient and Pharmacist-Physician Meeting Times

	Intent to Treat (N=448)				Treated (N=317)			
Meetings	Mean	Std.Dev.	Min	Max	Mean	Std.Dev.	Min	Max
Pharmacist-patient								
Initial Visit	1.0	0.0	1	1	1.0	0.0	1	1
Total minutes/pt	61.87	19.81	2	150	62.54	21.82	2	150
In-person Follow-up	3.17	2.70	0	17	4.03	2.59	0	17
Total minutes/pt	90.13	97.69	0	595	112.89	100.07	0	595
Phone Follow-up	1.11	1.62	0	15	1.37	1.74	0	15
Total minutes/pt	12.80	19.80	0	105	15.19	20.65	0	105
All Meetings	5.28	3.38	1	26	6.40	3.18	1	26
Total minutes/pt	164.81	111.15	30	720	190.62	113.88	40	720
Training minutes/pt	3.68	-	-	-	5.21	-	-	-
Pharmacist-physician								
Meetings/pharmacy	10.02	10.20	0	31	12.46	9.95	1	31
Minutes/pharmacy	427.32	452.15	0	1960	493.30	462.16	70	1130

*results are rounded

Table 11 Average Cost/Change Outcome^
Intention to Treat and Treated

Outcome	ITG(N=448)	TG(N=317)	TG(prop* to N)
SBP	$ 174	$ 170	$ 136
DBP	$ 371	$ 373	$ 299
LDL	$ 10,844	$ 7,251	$ 4,460
TCH	$ 9,775	$ 6,439	$ 3,697
HDL~	$ 173,500	$ 127,857	$ 73,407
NHDL	$ 8,675	$ 5,665	$ 3,216
A1C	$ 3,541	$ 3,714	$ 1,546
CVD Risk	$ 761	$ 597	$ 307
Heart Age	$ 769	$ 548	$ 282
PPD	$ 4,993	$ 4,761	$ 766
MMAS	$ 1,036	$ 1,085	$ 137
CCQ	$ 1,567	$ 1,790	$ 136

^Cost Study results
* a weighted cost/outcome is displayed. The weight is the proportion of the patients treated for that condition.
See Table 1 for acronyms.
See Table 3 and 4 for Outcomes.
~No significant difference in HDL.
Results are rounded.

Table 12 Average Cost/Change Outcome^ High Risk Group
Intention to Treat and Treated

Outcome	ITG(N=448)	TG(N=317)	TG(prop* to N)
SBP>130	$ 69	$ 74	$ 36
SBP>160	$ 22	$ 26	$ 2
DBP>80	$ 74	$ 75	$ 17
LDL>3.5	$ 1,856	$ 1,155	$ 40
TCH>5.2	$ 1,361	$ 1,411	$ 165
TCH>6.2	$ 1,209	$ 876	$ 25
A1C>7	$ 1,452	$ 1,741	$ 538
A1C>9	$ 1,653	$ 841	$ 74
CVDR>10	$ 640	$ 501	$ 238
CVDR>20	$ 517	$ 434	$ 160

^Cost Study Results
* a weighted cost/outcome is displayed. The weight is the proportion of the patients treated for that condition.
See Table 1 for acronyms.
See Tables 5 and 6 for Outcomes
Results are rounded.

Table 13

Average Cost per Percentage Point change in/out range (TG)

Outcomes	Percentage Point Change	Cost/unit change (N=371)	Cost/unit change (prop to N)
BP <130/80	8.8	$ 102	$ 81
A1C<7	6.1	$ 147	$ 61
A1C>9	-6.8	$ 131	$ 55
LDL<3.5mmol/L	1.1	$ 814	$ 483
TC<5.2mmol/L	6.0	$ 149	$ 86
TC>6.2mmol/L	-2.2	$ 407	$ 234
CVDR<10	5.5	$ 163	$ 85
CVDR>20	-4.3	$ 208	$ 107

^Cost Study Results
*a weighted cost/outcome is displayed. The weight is the proportion of the patients treated for that condition.
See Table 1 for acronyms.
Unit change=percentage point change.
See Table 1 for acronyms.
See Table 7 for Outcomes.
Results are rounded.

Table 14

Incremental Change Cost/Incremental Change Outcome^
Intention to Treat and Treated

Outcome	ITG(N=448)	TG(N=317)	TG(prop* to N)
SBP	$ 122	$ 130	$ 105
DBP	$ 260	$ 286	$ 230
LDL	$ 7,594	$ 5,773	$ 3,424
TCH	$ 6,845	$ 4,942	$ 2,837
HDL~	$ 121,500	$ 98,143	$ 56,347
NHDL	$ 6,075	$ 4,348	$ 2,469
A1C	$ 2,480	$ 2,851	$ 1,187
CVD Risk	$ 533	$ 458	$ 236
Heart Age	$ 539	$ 423	$ 216
PPD	$ 3,496	$ 3,654	$ 588
MMAS	$ 725	$ 833	$ 105
CCQ	$ 1,097	$ 1347	$ 104

Cost-Effective Results
^difference between cost(outcome) of CCDP and of usual care.
* a weighted cost/outcome is displayed. The weight is the proportion of the patients treated for that condition.
See Table 1 for acronyms.
See Table 3 and 4 for Outcomes.
~No significant difference in HDL.
Results are rounded.

Table 15

Incremental Change Cost/Incremental Change Outcome^
Intention to Treat and Treated

Outcome	ITG(N=448)	TG(N=317)	TG(prop* to N)
SBP>130	$ 48	$ 57	$ 28
SBP>160	$ 16	$ 20	$ 2
DBP>80	$ 52	$ 57	$ 13
LDL>3.5	$ 1,299	$ 879	$ 30
TCH>5.2	$ 953	$ 1,084	$ 126
TCH>6.2	$ 847	$ 673	$ 19
A1C>7	$ 1,017	$ 1,337	$ 413
AC1>9	$ 457	$ 646	$ 57
CVDR>10	$ 449	$ 385	$ 183
CVDR>20	$ 362	$ 333	$ 123

Cost-Effective Results
^difference between cost(outcome) of CCDP and of usual care.
* a weighted cost/outcome is displayed. The weight is the proportion of the patients treated for that condition.
See Table 1 for acronyms.
See Tables 5 and 6 for Outcomes
Results are rounded.

Table 16

Change in Cost per Percentage Point increase in Category (TG)

Outcomes	Percentage Point Change	Cost/unit change (N=371)	Cost/unit change (prop* to N)
BP <130/80	8.8	$ 78	$ 63
A1C<7	6.1	$ 113	$ 47
A1C>9	-6.8	$ 101	$ 42
LDL<3.5mmol/L	1.1	$ 625	$ 370
TC<5.2mmol/L	6.0	$ 114	$ 66
TC>6.2mmol/L	-2.2	$ 312	$ 179
CVDR<10	5.5	$ 125	$ 64
CVDR>20	-4.3	$ 160	$ 82

Cost-Effective Results
* a weighted cost/outcome is displayed. The weight is the proportion of the patients treated for that condition.
See Table 1 for acronyms.
See Table 7 for Outcomes.
Results are rounded.

Table 17 Base-case Probabilities used in Markov Model

Characteristic	Value(SD)	Distribution	Source
Myocardial Infarction (MI)			Padwal et al. 2018
60-69 years old	0.0209		Houle et al., 2017
70-79 years old	0.0417		
80-89 years old	0.0696		
Heart Failure			
60-69 years old	0.0192		
70-79 years old	0.0383		
80-89 years old	0.0536		
Stroke			
60-69 years old	0.0116		
70-79 years old	0.0197		
80-89 years old	0.0237		
Relative Risk Event Death	1.7		Marra et al., 2017
Death from Healthy State			
60-69 years old	0.0219(0.003)		Statistics Canada, 2019
70-79 years old	0.0560(0.008)		
≥80 years old	0.2570(0.024)		
RR Intent to treat	0.90	Normal	Marra et al., 2017
Utility Values			Marra et al., 2017
Chronic Disease	0.867	Beta(11049, 1680)	
MI	0.725	Beta(61446, 23307)	
Heart Failure	0.636	Beta(480, 275)	
Stroke	0.694	Beta(7090, 3126)	

Discount Rate	3%		
Start Age	60 years		
Time Horizon	40 years		

Sensitivity Analysis

Utility Values			Jai et al., 2018
Chronic Disease	0.868	Beta(11049, 1680)	
MI	0.660	Beta(4113, 2124)	
Heart Failure	0.578	Beta(140983, 102932)	
Stroke	0.606	Beta(2951, 1923)	
RR Treated	0.86	Normal	Marra et al., 2017
RR Multiple effects	0.61	Normal	
Risk Event Death	0.23		Padwal et al., 2019

0% Discount Rate
5% Discount Rate
Start Age 40 years
Start Age 50 years
Start Age 70 years
5 year Time Horizon
10 year Time Horizon
20 year Time Horizon
¾ Health Care Costs
½ Health Care Costs
MD paid for Chronic care visit
Benefits and Overhead — Simpson et al., 2015
½ MD visits for intervention
Double MD visits for intervention
Labour costs (No Training)
Labour costs (No Training nor face-to-face meetings)

Table 18

Markov Model Results
Intent to Treat
Deterministic (result from mean inputs)

Scenario	CCDP		Usual Treatment		Incremental		Cost per QALY
	Cost	QALY	Cost	QALY	Cost	QALY	
Base Case	$134,704	12.93	$141,429	12.81	-$6,724	0.12	-$56,165
Sensitivity Analyses							
5% Discount rate	$101,743	10.80	$107,191	10.71	-$5,4448	0.09	-$59,056
0% Discount rate	$215,449	17.84	$226,142	17.64	-$10,693	0.21	-$51,502
Low MD Wage	$134,280	12.93	$141,429	12.81	-$7,148	0.12	-$57,342
1/2 MD visits	$134,274	12.93	$141,429	12.81	-$7,154	0.12	-$57,390
Twice MD visits	$134,587	12.93	$141,429	12.81	-$6,841	0.12	-$54,879
Benefits & Overhead^	$134,775	12.93	$141,429	12.81	-$6,653	0.12	-$55,572
¾ Health Care Costs	$101,907	12.93	$106,600	12.81	-$4,693	0.12	-$39,201
½ Health Care Costs	$69,109	12.93	$71,771	12.81	-$2,662	0.12	-$22,237
Utilities	$134,704	12.51	$141,429	12.36	-$6,724	0.15	-$46,008
Multiple Effects	$106,778	13.36	$141,429	12.81	-$34,650	0.56	-$62,268
Risk Event Death	$231,541	16.24	$242,888	16.27	-$11,347	-0.03	$437,177
5 yr Horizon	$10,277	3.97	$10,366	3.96	-$89	0.01	-$11,349
10 yr Horizon	$33,770	7.11	$35,685	7.08	-$1,914	0.03	-$68,734
20 yr Horizon	$94,551	11.17	$100,196	11.09	-$1,914	0.03	-$68,734
Start Age=40	$136,775	17.46	$144,309	17.36	-$7,535	0.10	-$72,358
Start Age=50	$136,468	16.30	$143,479	16.19	-$7,011	0.11	-$64,604
Start Age=70	$101,399	9.34	$106,279	9.23	-$4,879	0.11	-$44,397
No Training costs	$134,516	12.93	$141,429	12.81	-$6,912	0.12	-$57,735
No Training/meetings	$134,385	12.93	$141,429	12.81	-$7,043	0.12	-$58,829

^Adds 14% vacation pay, 18% benefits and 15% facility overheads to base pharmacist salary (Simpson et a., 2015) compared to 20% benefits in base case.
Results are rounded.

Table 19

Markov Model Results
Intent to Treat
Probabilistic Results (Mean of 1,000 repetitions)

Scenario	CCDP		Usual Treatment		Incremental		Cost per QALY
	Cost	QALY	Cost	QALY	Cost	QALY	
Base Case	$134,292	12.92	$141,870	12.79	-$7,578	0.13	-$57,371
Sensitivity Analyses							
5% Discount rate	$101,589	10.81	$107,453	10.71	-$5,864	0.10	-$57,979
0% Discount rate	$213,796	17.87	$225,764	17.64	-$11,968	0.24	-$50,206
Low MD Wage	$133,207	12.91	$141,182	12.77	-$7,974	0.14	-$57,842
1/2 MD visits	$133,823	12.89	$141,249	12.76	-$7,425	0.13	-$57,106
Twice MD visits	$134,091	12.96	$141,348	12.83	-$7,257	0.13	-$56,428
Benefits & Overhead^	$134,806	12.91	$141,441	12.79	-$6,636	0.12	-$55,139
¾ Health Care Costs	$101,734	12.94	$106,459	12.83	-$4,726	0.11	-$41,992
½ Health Care Costs	$68,606	12.98	$71,790	12.84	-$3,183	0.14	-$22,857
Utilities	$133,377	12.96	$141,228	12.82	-$7,851	0.14	-$56,630
Multiple Effects	$106,863	13.36	$141,805	12.80	-$34,942	0.56	-$62,472
Risk Event Death	$230,213	16.23	$243,188	16.27	-$12,976	-0.04	$335,166
5 yr Horizon	$10,267	3.98	$10,368	3.97	-$102	$0.01	-$12,912
10 yr Horizon	$33,561	7.14	$35,692	7.11	-$2,132	0.03	-$72,438
20 yr Horizon	$93,787	11.23	$100,241	11.14	-$6,454	0.09	-$70,214
Start Age=40	$135,604	17.40	$144,350	17.29	-$8,746	0.11	-$76,294
Start Age=50	$135,666	16.20	$143,376	16.08	-$7,709	0.12	-$66,866
Start Age=70	$100,623	9.34	$106,261	9.21	-$5,637	0.13	-$43,803
No Training costs	$134,170	12.90	$141,621	12.78	-$7,451	0.13	-$58,420
No Training/meetings	$132,956	12.92	$141,016	12.79	-$8,061	0.13	-$61,335

^Adds 14% vacation pay, 18% benefits and 15% facility overheads to base pharmacist salary (Simpson et a., 2015) compared to 20% benefits in base case.
Results are rounded.

Table 20 Markov Model Results
Treated
Deterministic (result from mean inputs)

Scenario	CCDP		Usual Treatment		Incremental		Cost per QALY
	Cost	QALY	Cost	QALY	Cost	QALY	
Base Case	$131,503	12.98	$141,429	12.81	-$9,925	0.17	-$57,901
Sensitivity Analyses							
5% Discount rate	$99,509	10.83	$107,191	10.71	-$7,682	0.13	-$60,676
0% Discount rate	$211,114	17.92	$226,142	17.64	-$15,028	0.29	-$52,460
Low MD Wage	$131,365	12.98	$141,429	12.81	-$10,063	0.17	-$58,706
1/2 MD visits	$131,400	12.98	$141,429	12.81	-$10,028	0.17	-$58,502
Twice MD visits	$131,712	12.98	$141,429	12.81	-$9,716	0.17	-$56,682
Benefits & Overhead^	$131,605	12.98	$141,429	12.81	-$9,823	0.17	-$57,306
¾ Health Care Costs	$99,572	12.98	$106,600	12.81	-$7,028	0.17	-$40,999
½ Health Care Costs	$67,640	12.98	$71,771	12.81	-$4,132	0.17	-$24,104
Utilities	$131,503	12.57	$141,429	12.36	-$6,523	0.15	-$44,633
Multiple Effects	$106,778	13.36	$141,429	12.81	-$34,650	0.56	-$62,268
Risk Event Death	$226,315	16.23	$242,888	16.27	-$16,573	-0.04	$429,262
5 yr Horizon	$10,121	3.97	$10,366	3.96	-$246	0.01	-$22,295
10 yr Horizon	$32,760	7.12	$35,685	7.08	-$2,924	0.04	-$74,593
20 yr Horizon	$91,818	11.21	$100,196	11.09	-$8,378	0.11	-$75,384
Start Age=40	$133,013	17.51	$144,309	17.36	-$11,296	0.15	-$76,277
Start Age=50	$132,974	16.34	$143,479	16.19	-$10,505	0.15	-$67,855
Start Age=70	$99,123	9.38	$106,279	9.23	-$7,155	0.16	-$45,426
No Training costs	$131,238	12.98	$141,429	12.81	-$10,190	0.17	-$59,447
No Training/meetings	$131,052	12.98	$141,429	12.81	-$10,376	0.17	-$60,532

^Adds 14% vacation pay, 18% benefits and 15% facility overheads to base pharmacist salary (Simpson et a., 2015) compared to 20% benefits in base case.
Results are rounded.

Table 21 Markov Model Results
Treated
Probabilistic Results (Mean of 1,000 repetitions)

Scenario	CCDP		Usual Treatment		Incremental		Cost per QALY
	Cost	QALY	Cost	QALY	Cost	QALY	
Base Case	$130,816	12.99	$141,155	12.81	-$10,339	0.18	-$56,324
Sensitivity Analyses							
5% Discount rate	$99,371	10.82	$107,434	10.68	-$8,063	0.13	-$59,902
0% Discount rate	$210,682	17.93	$226,949	17.61	-$16,266	0.32	-$51,428
Low MD Wage	$130,374	12.95	$141,319	12.77	-$10,944	0.18	-$59,959
1/2 MD visits	$130,919	13.02	$141,544	12.84	-$10,625	0.18	-$57,924
Twice MD visits	$130,663	12.99	$141,340	12.80	-$10,677	0.19	-$57,037
Benefits & Overhead^	$131,467	13.04	$141,486	12.86	-$10,019	0.18	-$55,190
¾ Health Care Costs	$99,040	13.00	$106,568	12.81	-$7,528	0.19	-$39,953
½ Health Care Costs	$67,112	12.96	$71,692	12.78	-$4,580	0.19	-$24,440
Utilities	$130,816	12.99	$141,155	12.81	-$10,339	0.18	-$56,324
Multiple Effects	$106,863	13.36	$141,805	12.80	-$34,942	0.56	-$62,472
Event Death risk	$224,867	16.24	$242,861	16.29	-$17,994	-0.04	$429,876
5 yr Horizon	$10,115	3.98	$10,380	3.97	-$265	0.01	-$23,510
10 yr Horizon	$32,528	7.10	$35,752	7.06	-$3,224	0.04	-$78,301
20 yr Horizon	$91,251	11.20	$99,915	11.09	-$8,664	0.11	-$75,714
Start Age=40	$132,596	17.37	$143,987	17.23	-$11,390	0.14	-$80,945
Start Age=50	$132,569	16.25	$143,714	16.09	-$11,146	0.15	-$72,004
Start Age=70	$98,418	9.43	$106,572	9.25	-$8,154	0.18	-$45,539
No Training costs	$134,170	12.90	$141,621	12.78	-$7,451	0.13	-$58,420
No Training/meetings	$129,998	12.92	$141,048	12.735	-$11,051	0.18	-$60,604

^Adds 14% vacation pay, 18% benefits and 15% facility overheads to base pharmacist salary (Simpson et a., 2015) compared to 20% benefits in base case.
Results are rounded.