Health Policy and Community Pharmacy Provision of Oncology Medications

An assessment of the effect of a changing health policy environment on the medication adherence, cost and safety of oncology medications provided by community pharmacies

by

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ABSTRACT

Introduction: Oral cancer therapy has more than doubled in the past 10 years and all indications are that the pipeline of new and emerging cancer therapies continues to include a higher percentage of oral drugs. With the increased availability of oral oncology products, patients can have access to their medications in community pharmacies and avoid the burden of travel and waiting time in cancer clinics or hospitals. However, this shift in care may also pose some challenges such as adherence to the treatment, safe use of the oncology products and increased costs to patients and the health care system. This study examined the impact of this shift to greater use of oral chemotherapy, looking at adherence, drug interaction management and cost through a series of health policy changes.

Methods: Administrative health data between April 1, 2000 and March 31, 2015 from the Manitoba Centre for Health Policy Repository were used for this study. Dispensation records were used to assess drug utilization, measure adherence, analyze drug interactions and calculate medication costs.

Results: Adherence was examined using imatinib as the case example. High levels of adherence (>90%) were found throughout the study period regardless of insurance coverage. The clinically important drug interaction between tyrosine kinase inhibitors and proton pump inhibitors was assessed for medication provided by community pharmacies. Over 1/3 of patients received these interacting drugs together with little evidence of interventions to manage this interaction. During the study period, the cost of oral oncology medications rose more than 7 fold from $2,682,805 to

$21,311,652, with increases in the rate of prescribing (20 to 29 per 1000 people) and increases in the cost of oncology prescriptions ($113 to $549 per prescription).

Conclusion: Although oral therapy provides advantages and greater flexibility for cancer patients which is reflected in a high degree of adherence, additional policy reform and support need to be given to ensure that these medications can be used safely and effectively in the community setting.

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LIST OF ABBREVIATIONS

ATC – Anatomical therapeutic chemical classification system

CI – Confidence interval

DPIN – Drug program information network

HCDP – Home Cancer Drug Program

HIPC – Health Information Privacy Committee

H2RA – Histamine2-receptor antagonists

IV - Intravenous

ICD-9-CM – International classification of diseases, 9th revision, clinical modification

ICD-10-CA – International classification of diseases, 9th revision, Canadian enhancement

MCHP – Manitoba Centre for Health Policy

MPR – Medication Possession Ratio

OTC – Over-the-counter

PPI – Proton pump inhibitors

TKI – Tyrosine kinase inhibitors

Chapter 1 Introduction

Oral agents have been used in the treatment of cancer since the development of alkylating agents in the 1950's and 1960's (DeVita & Chu, 2008). In the 1970's and 1980's the majority of new therapies used in the treatment of cancer were administered by the parenteral route. As such, IV therapy became the mainstay of most oncology regimens. However, in the past 10-15 years an increasing number of new cancer therapies have been developed as oral formulations. Oral cancer therapy has more than doubled in the past 10 years (Timmers, Beckeringh, van Herk-Sukel, Boven, & Hugtenburg, 2012) and all indications are that the pipeline of new and emerging cancer therapies continues to include a higher percentage of oral drugs (Moore, 2007).

There are some obvious benefits of this move to increased use of oral therapy. Oral administration is more convenient for patients than the traditional intravenous method and when asked, patients generally prefer oral therapy (Partridge, Avorn, Wang, & Winer, 2002). From a system perspective, oral therapy takes some of the burden off of outpatient clinics where chair time can be a limiting resource.

Despite the advantages, replacing IV chemotherapy regimens with oral therapies raises a number of concerns. The use of IV therapy ensures adherence, while oral therapy is left in the hands of patients. Adherence with oral cancer therapy given in the community setting is an important issue in this new paradigm. If we consider the situation in Manitoba, IV therapy is provided at no cost to patients but oral therapy must generally be obtained from community pharmacies with the associated logistical burden and costs. Finally, community administered oral chemotherapy raises a variety of safety

concerns. The special handling procedures followed in cancer centres may not be followed or available in community pharmacies. Appropriate handling of waste may also be an issue from both an environmental and cost perspective. Clinically oral chemotherapies may be a relatively uncommon event in community pharmacies. Some community pharmacists have acknowledged that there are limitations in their training and knowledge related to oncology products (Abbott, Edwards, Whelan, Edwards, & Dranitsaris, 2014). This lack of familiarity may limit their ability to effectively deal with issues such as drug-drug interactions.

1.1 Adherence and Oral Chemotherapy

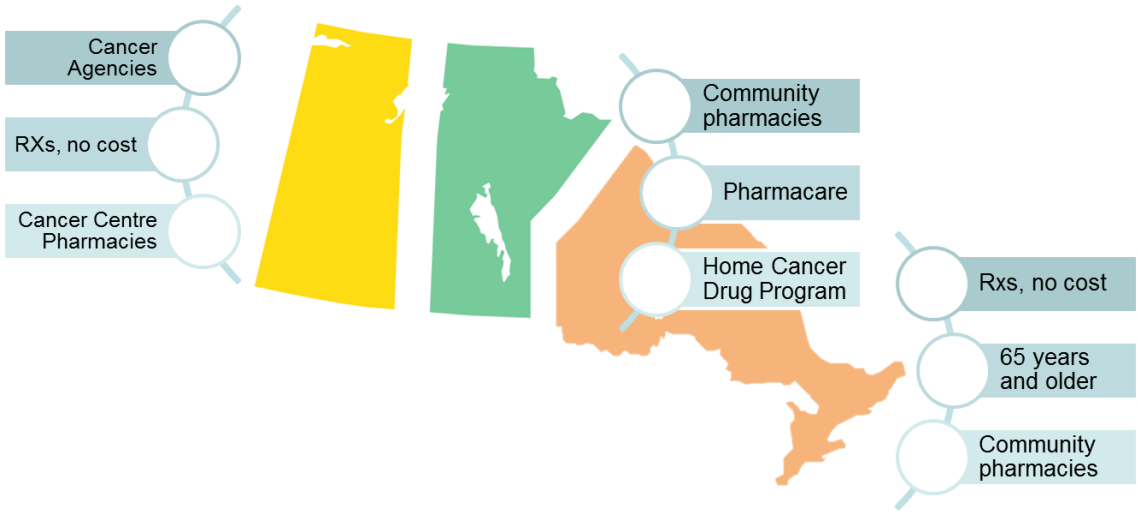
Medication-taking behavior is an important public health issue. Non-compliance with medication is associated with increased hospitalizations, mortality risks and costs for the health care system (Roebuck, Liberman, Gemmill-Toyama, & Brennan, 2011; Vik, Maxwell, & Hogan, 2004). Medication compliance and adherence are frequent terms used in the medical literature to describe “the extent to which a person’s behavior-taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (World Health Organization, 2003). Cancer patients, in general, display better adherence to the therapy, possibly because of their clinical condition and consciousness of the importance of drug therapy (Kimura et al., 2014). However, optimal adherence is still not observed in all patients being treated with oral anticancer medications (Mccue, Lohr, & Pick, 2014). Adherence to oral anticancer agents among the adult population varies widely from 16.8% to 100% (Partridge et al., 2002). Cancer can also be associated with over-adherence where patients take more than the prescribed dose in an effort to cure

their disease. Over-adherence has been reported with gefitinib and capecitabine in patients with metastatic breast cancer (Mayer et al., 2009). Because of the narrow therapeutic index of some oral cancer therapy, over-adherence may place patients at considerable health risk.

1.2 Oral Chemotherapy and Cost

Financial status can be a barrier in medication adherence, particularly for high cost medications where a high level of out-of-pocket expenditure is expected. Patients without drug insurance coverage may not adhere to the treatment because of its financial impact (Kaisaeng, Harpe, & Carroll, 2014). The cost of new oral chemotherapy agents may be hundreds of dollars a day (PCODR, 2015). This level of cost presents challenges for patients, insurers and pharmacies. In the past, cancer therapies have been provided without cost as part of IV regimens. In Canada, the delivery administration in health is a provincial responsibility. As a result, different provinces have developed their own unique policy approaches to supporting patients receiving oral chemotherapy. The provinces that border Manitoba exemplify the range of policy alternatives (Figure 1-1). In Saskatchewan, these oral cancer therapies are provided without cost to patients and are dispensed directly from the Cancer Agency locations. In Ontario, oral medications are dispensed from community pharmacies and are usually paid directly by patients, by private insurance, or by government programs for those on either social assistance or over the age of 65. It is not clear what the best policy approach is in terms for care of patients, cancer outcomes and cost. The different policy approaches in different provinces represent a natural experiment for examining the effects of these varied policy approaches.

Figure 1-1 Oncology drug coverage in Canada (Saskatchewan, Manitoba and Ontario)



1.3 Oral Chemotherapy and Safety

The safety issues of oral chemotherapy manifest themselves in 2 major ways. The first is directly to patients. Many anticancer agents have a narrow therapeutic index, meaning that small dosage errors could either compromise the efficacy of the treatment or expose the patient to potent toxicities. Therapy with oral agents may involve complex regimens and patients may struggle with self-administering their medications, monitoring doses and managing or reporting the occurrence of side effects. Severe side effects are commonly reported during the treatment with oncology drugs and include edema, nausea, vomiting, diarrhea, muscle cramps, rash and fatigue, any of which can lead to abandonment of treatment. It is unclear if patients receive sufficient support to deal with all of these issues when oral therapies are provided in the community.

Drug-drug interactions can be assessed using administrative data (Becker et al., 2007; Friesen & Bugden, n.d.). There have been a number of high profile cases of

patient harm occurring due to the failure of community pharmacists to respond appropriately to drug-drug interactions (Tomlinson, 2014). Important drug-drug interactions are common among cancer patients. Examples include the potential for elevated International Normalized Ratio (INR) and the risk of bleeding when capecitabine is combined with warfarin (Yildirim, Ozyilkan, Akcali, & Basturk, 2006) and decreased absorption of tyrosine kinase inhibitors (TKIs) when they are used with Proton Pump Inhibitors (PPIs) (Peters, Zimmermann, & Adjei, 2014).

The second safety issue involves the health care personnel handling these antineoplastics in the community pharmacy setting. Some national surveys suggest that some community pharmacy sites are not fully prepared to handle these agents (Goodin et al., 2011). Guidelines on how to handle oral chemotherapy may not always be followed. Community pharmacists may lack a specific area to store and manipulate the drugs and may not be using protective clothing (e.g. gloves for safe handling of the oral antineoplastic agents) (Abbott et al., 2014).

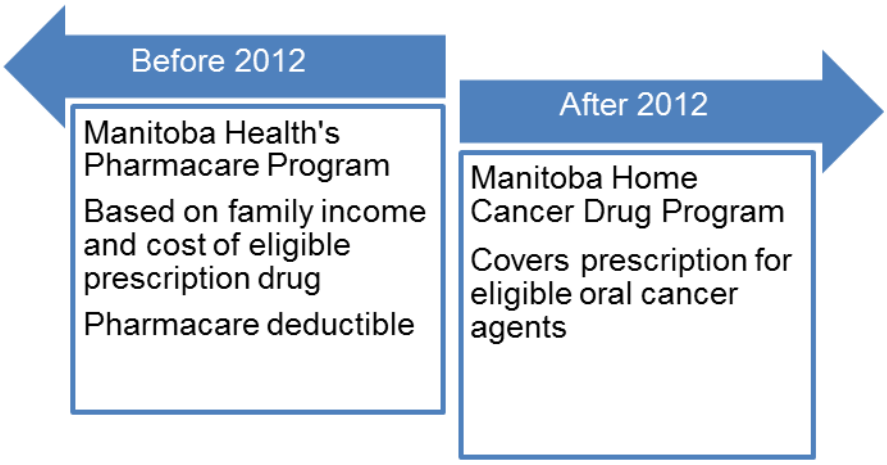
1.4 Manitoba and the Evolving Cancer Medication Policy Environment

Manitoba's approach to the provision of cancer therapy differs from Saskatchewan and Ontario and has also evolved over time. Prior to 2012, oral chemotherapy was provided by community pharmacies and was supported for all Manitobans through its income-based Pharmacare program. In this system, patients would pay out of pocket for these medications until they reached their income-based deductible (3.09% to 6.98% of income), after which the medications would be provided without cost. The deductible is applied on an annual basis so long-term patients could

potentially cycle through high cost periods and no-cost periods. In 2012, the Manitoba government introduced the Home Cancer Drug program. Under this program listed medications are provided without cost to patients. Medications continue to be provided by community pharmacies, but are not subject to the usual deductibles and are completely covered (full first dollar coverage).

There are also some unique features of the pharmacy business in Manitoba. The dispensing fees (the amount that pharmacists can charge for dispensing the drug) were not regulated in Manitoba. Market forces were expected to regulate fees charged to Manitoba patients. More recently very high cost medications have presented some challenges for pharmacies in terms of carrying costs, wastage and enhanced storage and handling requirements. High dispensing fees are known to be associated with other high cost products (e.g. biologic products for arthritis and Crohn's disease). The interplay of cost and policy changes on dispensing fees in this unregulated market is unknown.

Figure 1-2. Policy evolution for coverage for oral cancer agents in Manitoba



Chapter 2 Study Objectives and Methods

In this study we conducted a review of the utilization of cancer medications and the associated supportive medications using an observational retrospective longitudinal approach while focusing on adherence, costs and safety issues. Using a population-wide database, the study seeks to better understand the impact of policy on the safe and effective use of cancer-related agents in the community setting.

2.1 Study Objectives

Medication Adherence (Chapter 3)

1. To measure adherence of imatinib provided in the community setting
2. To assess any differences in adherence between the period where outpatient oral chemotherapy was covered by Pharmacare only and the period where the Home Cancer Drug Program provided drug coverage
3. To compare adherence to imatinib in Manitoba to historically reported values from other provinces

TKI and Acid Suppressive Agents Interactions (Chapter 4)

1. To assess safety related to tyrosine kinase inhibitors and acid suppressive agents provided in the community setting
2. To assess the distribution and volume of prescriptions at individual pharmacies

Cost and Dispensing Fees for Oral Oncology Medications (Chapter 5)

1. To conduct a longitudinal cross-sectional review of the volume and cost of cancer medications used in the community setting from 2000 to 2015

2. To assess costs and dispensing fees associated with drugs used in the Home Cancer Drug Program

2.2 Methods

An observational retrospective longitudinal study using administrative data from the Manitoba Center for Health Policy (MCHP) was conducted between April 1, 2000 to March 31, 2015. All products listed as eligible for the Home Cancer Drug Program in Provincial Oncology Drug Formulary (latest update June 2015) and/or Manitoba Health Listing of Covered Supportive Medications (Manitoba Health Program Launch Document 2012) and/or Manitoba Health Listing of Part 2 or 3 covered oncology products and/or approved by Oncology P&T committee were included. Anatomical Therapeutic Chemical (ATC) codes for oncology products are primarily: LO1-4 Antineoplastic and Immunomodulating Agents. Patients that did not have prescriptions for oral chemotherapy, community-delivered injectable therapy or related supportive drugs covered under the Home Cancer Drug Program were excluded.

The Manitoba Centre for Health Policy (MCHP) maintains the Manitoba Population Research Data Repository, a collection of administrative health care databases containing records of all interactions between Manitoba residents and the health care system. All data in the Repository are de-identified (names and addresses are removed) and each record has a unique scrambled number, which allows records to be linked through time and across datasets.

For this study, the Drug Program Information Network (DPIN) and the hospital discharge abstracts were accessed. The DPIN database, which is used to adjudicate

and conduct drug utilization reviews for all prescription drugs dispensed by community pharmacies in the province, was used as the source of dispensation records data. Hospital discharge abstracts contain data on patient's hospitalizations in the province. In this database it is possible to access information such as admission dates, discharge dates, the ICD-9 CM and/or ICD-10 codes for diagnosis and procedures as well as hospital information.

2.2.1 Longitudinal Oral Chemotherapy Utilization

Claims and costs of oral chemotherapy, community-delivered injectable therapy or related supportive drugs covered under the Home Cancer Drug Program were assessed over the study period in terms of the volume and cost of community cancer medications used in Manitoba. Where possible, the World Health Organization (WHO) ATC Classification System and Defined Daily Dose (DDD) methodology were used to assess the volume of use. Where this was not possible the number of patients treated and the milligrams of use of individual products were assessed.

2.2.2 Adherence to Selected Oncology Medications

All imatinib prescriptions (ATC code L01XE01) from 2005-2015 were extracted using administrative data from the MCHP. Imatinib 400mg is the typical dose for conditions such as chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST) therefore prescriptions for 400mg imatinib tablets were used to assess patient's adherence. Adherence was assessed using the electronic pharmacy claims data to determine the Medication Possession Ratio (MPR) method. MPR was calculated as follows:

$$MPR = \frac{total\ days'\ supply}{days\ \ in\ the\ interval}\ x\ 100$$

An MPR ≥ 80% was considered as optimal adherence. MPR was capped at 100% in order to avoid inflated adherence estimates. Since information of use of medication when a patient was hospitalized was not available, patients' hospitalization records were linked to the data and lengths of stay were excluded from their MPR calculations.

2.2.3 Drug Interactions in Community Oncology Medications

The safety of community oncology medications was assessed using selected drug interactions (TKIs and acid suppressive agents) from a cohort that included all individuals dispensed a TKI prescription between April 1 2000 and March 31 2015 in Manitoba. ATC codes were used to identify drugs of interest, including H2RAs (ATC codes starting with A02BA) or PPIs (ATC codes starting with A02BC), with TKI prescriptions also identified by ATC and split into two groups stratified by the risk level of the TKI-acid suppressive agent interaction (Table 2-1). TKIs included were bosutinib (L01XE14), dasatinib (L01XE06), erlotinib (L01XE03), pazopanib (L01XE11), dabrafenib (L01XE23), gefitinib (L01XE02) and nilotinib (L01XE08). Concomitant use of interacting drugs was assessed to determine both the incidence of clinically significant drug-drug interactions and the clinical response to the interaction. Duration of a prescription was based on the days' supply variable, with an end date calculated by adding this variable to the prescription dispensation date. A prescription was classified as interacting when one of the acid suppressive agents and a TKI prescription had overlapping timeframes. Each interaction was assessed for the presence of a response

code M1-3 (Table 2-2) indicating a drug-drug interaction and the pharmacists' intervention code when appropriately provided (Table 2-3).

Table 2-1 Drug-drug interaction risk rating according to Lexicomp© Interactions Module

Risk	Action	Description
A	No Known interaction	Data have not shown relevant interactions between the drugs
B	No Action Needed	Data shows that the drugs may interact, but there is not sufficient clinical evidence concerning the concomitant use.
C	Monitor Therapy	Data shows that the drugs may have clinically significant interactions. Benefits of concomitant use can outweigh the risks. Monitoring is recommended. Adjustments of the dosage of one or both agents may be necessary.
D	Consider Therapy Modification	Data shows that the drugs may have clinically significant interactions. Patient assessment of the patient is recommended to assess risk/benefit. Intense monitoring, empiric dosage changes, or alternative therapies may be necessary.
X	Avoid Combination	Data shows that the drugs may have clinically significant interactions. Risks usually outweigh the benefits. Concomitant use of the two drugs should typically be avoided.

* Adapted from Lexicomp® Interactions Module, Hudson, Ohio: Lexi-Comp, Inc.; 2017; [cited 2018 Jun 14]; Available from: http://online.lexi.com.uml.idm.oclc.org (Lexicomp Online®, 2017)

Table 2-2 DPIN Response Code Chart		
Response code	**Description**	**Action required**
ME	adverse drug interaction (replaced by M1, M2, M3)	Potential drug/drug interaction with a prescription being filled and another that the patient currently takes. Appropriate intervention code(s) should be provided
M1	drug interaction, level 1	
M2	drug interaction, level 2	
M3	drug interaction, level 3	

* Adapted from Manitoba Health, Seniors and Active Living, Pharmacy claims submission manual (DPIN pharmacy manual). Winnipeg, Manitoba; 1994; [cited 2018 Jun 14]; Available from: https://www.gov.mb.ca/health/pharmacare/profdocs/dpin_manual.pdf (Government of Manitoba, 1994)

Table 2-3 Examples of Intervention and Exception Codes in DPIN	
Code	**Description**
DU	For drug utilization review only
ED	Exception drug status prescriber choice
EP	Exception drug status pharmacist choice
ES	Override concurrent therapy requirement
ET	Override questionable concurrent therapy
MG	Override – various reasons
MU	Limited-use product
MV	Vacation supply
UA	Consulted prescriber & filled Rx as written
UB	Consulted prescriber & changed dose
UC	Consulted prescriber & changed instructions for use
UD	Consulted prescriber & changed drug
UE	Consulted prescriber & changed quantity
UF	Patient gave adequate explanation & filled as written
UG	Cautioned patient Rx filled as written
UH	Counselled patient Rx not filled
UI	Consulted other source Rx filled as written
UJ	Consulted other sources altered Rx and filled
UK	Consulted other sources Rx not filled
UL	Rx not filled – pharmacist decision
UM	Consulted prescriber, Rx not filled
UN	Assessed patient, therapy is appropriate
UO	Valid reason to use alternative therapy

* Adapted from Manitoba Health, Seniors and Active Living, Pharmacy claims submission manual (DPIN pharmacy manual). Winnipeg, Manitoba; 1994; [cited 2018 Jun 14]; Available from: https://www.gov.mb.ca/health/pharmacare/profdocs/dpin_manual.pdf (Government of Manitoba, 1994)

2.2.4 Oncology Prescription Volume

Rare filling of oncology prescriptions may make it difficult to maintain knowledge and competency related to oncology products in some pharmacy locations. The number of oncology-related prescriptions per community pharmacy were assessed as a surrogate for safety. The number of oncology prescriptions per individual pharmacy was assessed across a variety of medications and cancer types to assess the likelihood that individual pharmacies have sufficient prescription volume to maintain experience and competency.

2.2.5 Cost in Community

Aggregated cost breakdowns were used to assess the margins over-list price and the dispensing fees associated with oral oncology products. An assessment of the costs of providing chemotherapy products in community pharmacies has not been previously reported. Manitoba's relatively unique environment of universal complete coverage and recent regulation in the dispensing fees should make this a particularly worthwhile exercise. All oral oncology prescriptions (ATC codes starting with L01) dispensed from April 1, 2000 to March 31, 2015 in Manitoba were collected. They were categorized into the following classes: Alkylating agents (L01A), antimetabolites (L01B), endocrine therapy (L02), immunotherapies (L04AX02 and L04AX04), plant alkaloids (L01C), protein kinase inhibitors (L01XE) and other antineoplastic agents (L01XB01, L01XX14, L01XX35, L01XX11, L01XX05, L01XX23, L01XX43). Descriptive statistics (average dispensing fee, dispensing fee range, average cost per prescription) were performed as the main outcome of this objective. The impact of capping dispensing fees at $30 was assessed by retrospectively examining the average dispensing fees. The

impact of the introduction of the Home Cancer Drug program on the mean dispensing fee was examined using piecewise regression. Both a stepwise increase in mean fee and an increase in the rate of change of the mean were examined separately for the period surrounding the policy change in April 2012.

Chapter 3 The impact of a full coverage policy on imatinib adherence

3.1 Abstract

Introduction: Imatinib mesylate is an oral tyrosine kinase inhibitor used primarily in the treatment of chronic myeloid leukemia. Oral oncology drugs, like imatinib, are more convenient for patients compared to intravenous chemotherapy, but place more responsibility for the treatment on the patients. Poor adherence to imatinib has been reported in the literature, which is believed to be one of the reasons for treatment failure. Out-of-pocket costs can be a significant barrier for patients prescribed oral oncology drugs that may cost thousands of dollars a month. This study assessed the adherence of patients taking imatinib over a 10-year period where insurance coverage changed from partial to full coverage.

Methods: A population-based, observational retrospective cohort study was conducted using administrative data. All imatinib prescriptions (ATC code L01XE01), 400mg strength, from 2005-2015 were collected and included in the study. Medication Possession Ratio (MPR) was used to calculate adherence in this study, with a threshold of ≥80%. MPR was capped for values above 100%. Amount of imatinib dispensed in a two-year period, before and after the full coverage policy change, was also assessed based on the days' supply records.

Results: Overall adherence to imatinib was high and mean MPR was consistently over 90% for up to 9 years of treatment. When adherence was assessed for patients taking imatinib before and after the change to full insurance coverage, MPR did not change significantly (91% vs 91%; p=0.65) and the proportion of patients with

low adherence (MPR <80%) also did not change (18% vs 17%; p = 0.83). Early filling of prescriptions at the end of the benefit year to delay the new annual deductible was eliminated with full coverage.

Conclusion: Due to an apparent ceiling effect of high adherence, there was no impact of full coverage on adherence with imatinib.

3.2 Introduction

Imatinib (Gleevec®, Novartis Pharmaceuticals Canada, Inc), is an oral tyrosine kinase inhibitor (TKI) that has shown significant improvements in survival of patients with chronic myeloid leukemia (CML) when compared with patients treated with interferon-alfa plus cytarabine (Druker et al., 2006). Complete cytogenetic remission has been observed in over 70% of newly diagnosed CML patients treated with imatinib (O'Brien et al., 2003). Results from a recent study show that life expectancy of patients with CML rose to levels similar to the general population with successful imatinib treatment (Bower et al., 2016). However, lack of adherence has been shown to reduce the likelihood of achieving proper molecular response (Marin et al., 2010). Imatinib is also indicated as first line therapy for other malignancies like gastrointestinal stromal tumor (GIST) (Lexicomp Online, 2016).

Oral chemotherapy, like imatinib, can offer considerable convenience to patients compared to intravenous chemotherapy. However, these oral regimens place increasing responsibility on patients to follow the treatment regimens and to avoid treatment interruptions. This transition from provider-administered IV therapy to patient-managed daily oral doses has the potential to impact treatment adherence. Poor

adherence with imatinib has been reported in the literature among patients with both CML and GIST and has been cited as one of the potential reasons of disease recurrence and disease progression (Al-Barrak & Cheung, 2013).

The aim of this study was to measure adherence of patients taking imatinib provided in the community setting in Manitoba, Canada and to assess any impact of drug insurance policy changes on adherence. There have been a number of health policy changes since the brand-named product, Gleevec®, was first marketed in Canada in 2001 (Health Canada, 2016). The initial cost of treatment with Gleevec® was approximately $3,800 per month and had a substantial financial impact on patients receiving imatinib (T Darkow, Maclean, Joyce, Goldman, & Lakdawalla, 2012; Theodore Darkow et al., 2007). This cost was reduced with the introduction of generic versions of imatinib in 2013 at a cost of $1,000 per month. Generic imatinib was considered fully interchangeable under the government Pharmacare program when it was added to the formulary. The financial impact was moderated through the government drug insurance program available to all citizens of Manitoba. However, the Pharmacare program still required patients to pay the full cost of their prescriptions up to an annual deductible based on the family income (3.05% to 6.90% of income) (Manitoba Health, 2016). Finally, this financial burden was also eliminated in April 2012 with the introduction of the Manitoba Home Cancer Drug Program. The Home Cancer Drug program provides full coverage and allows patients to fill eligible drugs at no cost. The drugs covered by this program are oral cancer medications such as tyrosine kinase inhibitors (imatinib, dasatinib), endocrine therapies (tamoxifen), antimetabolites (capecitabine) and

supportive cancer treatment drugs such as propulsives (domperidone, metoclopramide) and antiemetics (ondansetron, olanzapine) (CancerCare Manitoba, 2016).

3.3 Methods

The current study was a population-based, observational retrospective cohort study that used administrative data. All imatinib prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System code L01XE01) from 2005-2015 were extracted from administrative data from the Manitoba Centre for Health Policy (MCHP). MCHP houses the Manitoba Population Research Data Repository that contains health information for all of Manitoba's residents. In this study, the Drug Program Information Network (DPIN) database was included in order to access pharmacy records. All data in the Repository are de-identified (names and addresses are removed) and each record has a unique scrambled number, which allows records to be linked through time and across datasets.

Imatinib is available as 100mg and 400mg tablets. The recommended dose for the common indication (chronic phase CML) is 400mg daily with higher dosages (600mg to 800mg) given in the accelerated phase or blast crisis (CPS). As 400mg tablets would be part of 400mg, 600mg and 800mg doses, the prescriptions for 400mg imatinib tablets were used to assess adherence. Since 100mg tablets would be typically used as supplemental therapy, 100mg tablets were excluded from the study. Pharmacy records were used to calculate adherence levels. Adherence was calculated using the Medication Possession Ratio (MPR), which divides the total days' supply by the number of days in the interval. MPR ≥80% was considered optimal (Dicus, Lyons, Olson, Tran,

& Blackburn, 2015. MPR was capped at 100% in order to avoid inflated adherence estimates (Hess, Raebel, Conner, & Malone, 2006).

$$MPR = \frac{total\ days'\ supply}{days\ \ in\ the\ interval}\ x\ 100$$

Total days' supply was obtained by summing each prescription's days' supply, except for the last prescription dispensed. For each prescription, the time to the next prescription was calculated from the number of days that elapsed from one prescription to the subsequent one. For overall adherence, the first and last prescription ever of each patient in the entire follow-up was considered beginning and end of treatment. In the analysis by calendar year, the first and last prescriptions of each patient in each calendar year were considered for the MPR calculation, meaning that in each calendar year that a patient had a treatment course with imatinib, their MPR was calculated. In the analysis by treatment year, each patient was followed for intervals of 365 days from their first prescription, each interval being considered a year of treatment.

Since records of medication use during hospitalizations were not available, the MPR calculations excluded hospital time. MPR was calculated for the period before and after April 1st, 2012 (the date when the Home Cancer Drug program was introduced in the province) for patients who received imatinib in both periods. A paired t-test was used to compare patients' MPR before and after the introduction of the program. In addition, the average of days' supply by month was obtained for the 2 full years before (2010-2011) and the 2 full years after (2013-2014) the year of the policy change to full coverage (2012) to test for changes in prescription filling patterns.

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all data analyses. Approvals were granted by the University of Manitoba Health Research Ethics Board and the Manitoba Health Information Privacy Committee. In Manitoba, the legislative framework does not require individual level consent for research conducted on de-identified data where the privacy of patients is protected.

3.4 Results

During the study period (2005-2015), 188 patients filled prescriptions for imatinib. Patients who had not filled two or more consecutive imatinib prescriptions were excluded from the MPR analysis (n=25). Overall adherence to imatinib was high during the study period with an average MPR of 89% (95% CI 86-92) and 79% of patients in the optimal adherence group (MPR ≥80%). We were able to analyze 163 patients by treatment year. Greater than 80% of patients maintained high adherence (MPR≥80%) over multiple years of treatment (Table 3-1). This was also reflected in the high overall average adherence (90% to 97%) for patients using imatinib for up to 9 years (Table 3-1).

In order to examine the potential impact of health policy on imatinib adherence, the MPR was also examined by calendar year. The year 2005 was excluded from the analysis due to low number of observations (i.e. less than 5 patients). Adherence levels by calendar year were high (mean MPR 88-94%), throughout the study period (Figure 3-1). There was no indication that removing any financial barrier with the Home Cancer Drug program had an impact on imatinib adherence, when analyzing the MPR for patients that had prescriptions before and after the introduction of the program (n=72).

The mean MPR was 91% before the introduction of the Home Cancer Drug Program and 91% after it was introduced {t(71) = 0.45 p = 0.65}. In addition, the proportion of patients with low adherence (MPR <80%) did not significantly change after the introduction of the Home Cancer Drug Program (Table 3-2). Before the introduction of the program, the average total cost of imatinib per patient per fiscal year was $34,331 (CI 33,042-35,620) with a median of $36,914 {interquartile range (IQR) 20,887-44,162}. However, the majority of this cost was paid by the government insurance program and patients paid out-of-pocket an average of $2,817 (CI 2,518-3,117) per fiscal year, median $1,839 (IQR 604-3,645). Patients were required to pay out-of-pocket a portion of the prescription cost for 21.3% of the imatinib prescriptions filled, which translated into patients only paying 8.2% of the overall cost. The only obvious impact of the Home Cancer Drug program policy change was a change in prescription fill patterns at the end of the benefit year (Figure 3-2). Prior to the implementation of the Home Cancer Drug program there was an increase in the days' supply filled during March (the end of the benefit year). After the start of the Home Cancer Drug program the filling of prescriptions was relatively even in all months of the year (Figure 3-2).

3.5 Discussion

The purpose of this study was to measure patients' adherence to the oral oncology medication, imatinib. The study also assessed the potential impact of policy changes that removed all financial barriers on adherence to imatinib. The majority of imatinib users in Manitoba had optimal adherence during the study period with 79% of patients showing MPR ≥ 80% from 2005 to 2015. Good adherence to oral treatment is crucial for positive clinical outcomes and it has been shown to improve survival

(Ganesan et al., 2011; Hochhaus et al., 2017; Ibrahim et al., 2011). In a study where CML patients were surveyed regarding adherence to TKIs, 90% of the patients responded that they never discontinued their therapy and were mindful about the nonadherence consequences (Breccia et al., 2015). The results of our study are consistent with previous studies (Anderson et al., 2015; Dicus, Lyons, Olson, Tran, & Blackburn, 2015; Santoleri, Sorice, Lasala, Rizzo, & Costantini, 2013). In a study in Alberta, the majority of patients maintained high adherence levels during the follow-up period with median MPR above 95% and 30.6% of the patients in the lower adherence groups (Anderson et al., 2015). Santoleri et al. found that although patients taking imatinib had slightly lower adherence than other TKIs, these patients seem to be highly persistent to the therapy with 90% of patients taking the drug for more than one treatment year (Santoleri, Sorice, Lasala, Rizzo, & Costantini, 2013). While a study conducted in Saskatchewan, Canada also found overall high adherence, they found more of a decline in long-term adherence than found in our study. In patients receiving imatinib from the Saskatchewan Cancer Agency, optimal adherence (MPR>80%) fell from 82% in the first year of treatment to 71% in the 5th year of treatment (Dicus et al., 2015). In Manitoba, adherence remained above 80% in all 9 years of treatment reviewed (Table 3-1). Patients in Saskatchewan receive imatinib at no cost directly from their cancer treatment centre. In Manitoba, patients are required to fill prescriptions at community pharmacies. This additional barrier of filling prescriptions at a community drug store does not seem to have impacted adherence. In fact, it could be seen as a benefit as some patients might have closer access to community pharmacies than they do to a cancer treatment centre. In some cases, patients visiting their regular

community pharmacies may be more convenient than travelling to a cancer centre. However, the Saskatchewan cancer centres also send medications to some patients in the mail. This makes the lower adherence in Saskatchewan difficult to explain, but it may be possible that the convenience of a local community pharmacy and the interaction with the pharmacist help support the higher level of adherence seen in Manitoba.

Imatinib adherence was high throughout our study period when analyzed by calendar year, with mean MPR between 88% and 94% per year. In Manitoba, oral chemotherapy was partially supported for all Manitobans through a deductible-based Pharmacare program prior to 2012 and switched to the Home Cancer Drug program, where listed medications were provided without cost (no deductible) to patients. There was no indication that the switch to complete drug cancer coverage program impacted patients' adherence behaviour to imatinib. Adherence was already high with the majority of patients maintaining adherence levels above the 80% MPR threshold. Given the high cost of imatinib, most patients exceeded their deductible early in the year and were essentially already receiving their medications at no cost for much of the year. This may help explain the apparent lack of impact of the Home Cancer Drug on imatinib adherence. However, the dispensing pattern did change with the introduction of the Home Cancer Drug Program. The spike in the mean number of tablets of imatinib dispensed by the pharmacies occurred in the month of March, which is the last month before the end of the Pharmacare fiscal year. The increase in medication being dispensed right before the beginning of a new fiscal year can be related to the fact that patients would likely be stocking up to avoid starting their annual deductible at that time.

Interestingly, this pattern was then not observed after the implementation of the Home Cancer Drug program, when patients no longer had to pay out-of-pocket for their medication in order to reach their annual deductible.

3.6 Limitations

The use of a province-wide population-based administrative database is a strength of our study. However, there are also important limitations in the use of dispensing data to calculate adherence. Precision in the patients' adherence estimate is dependent on the days' supply and the prescription dates provided in the community pharmacies. In addition, our study, like all studies using administrative database, cannot assess whether the patients are actually taking the mediations. Another factor to be considered is that adherence calculations based on MPR have the potential to overestimate the estimates when prescriptions are filled early. Capping the values at 100% was used in order to avoid elevation of the results. This could potentially represent over-adherence of the drug or more simply early filling of prescriptions (Anglada-Martinez et al., 2015; Parker, Moffet, Adams, & Karter, 2015). This issue was particularly important when patients refilled prescriptions early at the end of the fiscal year.

3.7 Conclusion

As cancer therapy shifts from primarily intravenous therapy to oral therapy, patients play a greater role in ensuring adherence with therapy. This population level review found adherence to imatinib was high throughout the 10-year study period. Even when patients received imatinib over an extended period of time, adherence remained

high. While out-of-pocket costs can be an important barrier to access oral chemotherapy agents, only limited impact of a policy to provide complete coverage for oral therapy was evident.

3.8 Acknowledgements

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Table 3-1. Patients' adherence rates for imatinib in Manitoba by patient treatment year

Year	Sample size	Mean MPR (95% CI)	Median (IQR)	% of patients with MPR ≥80%
1	163	91% (88-93)	100% (89-100)	83
2	116	92% (89-95)	99% (92-100)	87
3	92	92% (89-95)	100% (94-100)	84
4	69	92% (89-96)	98% (92-100)	87
5	55	94% (92-97)	99% (92-100)	91
6	42	90% (85-95)	95% (88-100)	80
7	23	93% (89-96)	94% (88-100)	92
8	14	94% (88-100)	98% (94-100)	88
9	10	97% (94-99)	98% (95-100)	100

Figure 3-1 Patients' adherence rates for imatinib in Manitoba by calendar year

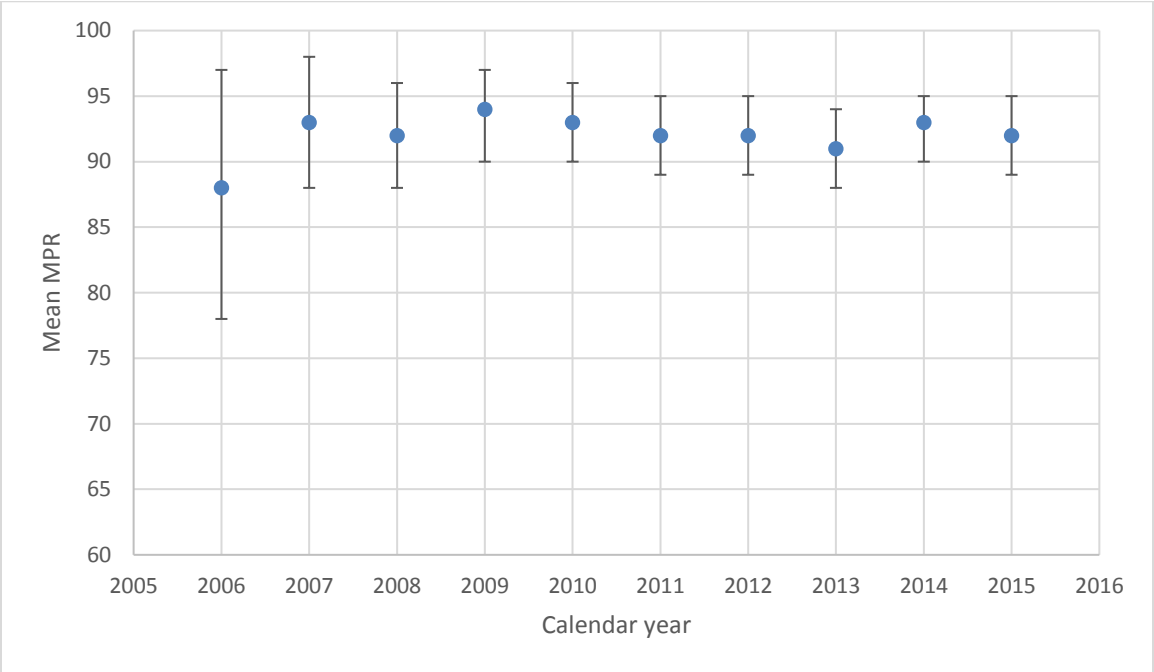
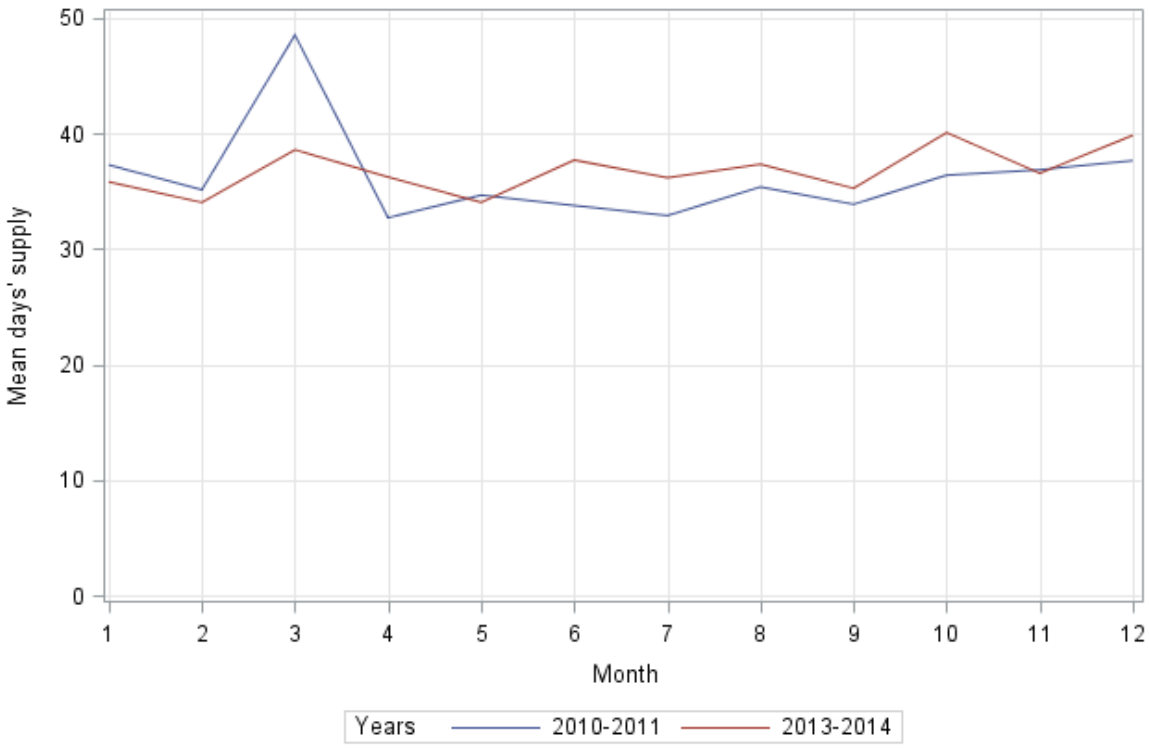


Table 3-2 Number of patients with low and high adherence before and after the introduction of the Home Cancer Drug Program			
	Before the Home Cancer Drug Program	**After the Home Cancer Drug Program**	
Optimal adherence (MPR ≥80%)	59	60	119
Poor adherence (MPR <80%)	13	12	25
	72	72	144
Chi-square 0.0484; p-value .825865			

Figure 3-2 Average days' supply per month before and after the introduction of the Home Cancer Drug coverage program



Note: 2010 and 2011 (before the introduction of the cancer coverage program); 2013 and 2014 (after the introduction of the program)

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Chapter 4 Community Pharmacy and the Management of Tyrosine Kinase Inhibitor Interactions with Acid Suppressive Therapies

4.1 Abstract

Background: Utilization of oral oncology drugs, such as tyrosine kinase inhibitors (TKIs), has increased. The shift of care from centralized cancer centres to community pharmacies may pose issues for patients, particularly regarding the management of drug-drug interactions (DDIs). The aim of this study was to assess this issue by examining clinically important drug interactions between TKIs and acid suppressive agents.

Methods: A population-based study assessed the prevalence of DDIs and the volume of oncology prescriptions from April 1, 2000 to March 31, 2015 in Manitoba by using administrative health databases housed at the Manitoba Centre for Health Policy. All TKI and concomitant acid suppressive agent prescriptions, identified using the Anatomical Therapeutic Chemical Classification System (ATC), were included in the study. Interaction warnings and responses were quantified. Volume of oncology prescriptions was collected and selected TKIs were reviewed to evaluate community pharmacists' knowledge regarding these products and their competence in patient education.

Results: Over 1/3 of the patients who received TKI prescriptions overlapped with a concomitant prescription for a histamine 2 receptor antagonist (H2RA) or a proton pump inhibitor (PPI). In these patients, an average of 54% of their time on a TKI overlapped with days when acid suppressive therapy was prescribed. When the first

interacting prescription for each patient was examined, the warning code resulted in a pharmacy response code in only 22% of cases.

Conclusions: TKIs and acid suppressive agents such as PPIs and H2RAs are often prescribed concomitantly. Given the substantial reduction in TKI blood levels seen with this interaction, more awareness and education in community pharmacies is needed to support appropriate management of this clinically important drug interaction.

4.2 Introduction

Chemotherapy and in particular targeted chemotherapy, has been evolving rapidly. Nearly 30% of new drugs approved have a cancer indication (Davidson et al., 2016). Increasingly, these new treatments are oral therapies. While such therapies are convenient and preferred by patients, they frequently shift cancer management from centralized cancer centres to community pharmacies. It is unclear if patients, pharmacies and pharmacists are prepared for this shift in care (Abbott, Edwards, Whelan, Edwards, & Dranitsaris, 2014). The advantages of oral therapy may be eroded if patients receive insufficient support when receiving oral therapies that are provided in the community. Adherence may be an issue compared to intravenous (IV) therapies, as patients may struggle with self-administering their medications, monitoring doses and managing or reporting the occurrence of side effects. Drug interactions may also be an issue. More than 60% of cancer patients are exposed to drug-drug interactions (Jansman et al., 2005; Riechelmann & Del Giglio, 2009). It has been estimated that in approximately 4% of cases, drug-drug interactions contributed to the death of cancer patients (Buajordet, Ebbesen, Erikssen, Brérs, & Hilberg, 2001). Only 9% of community

pharmacists indicated they felt comfortable educating patients on oral cancer therapies, or were fully prepared to handle, store and provide these agents (Abbott et al., 2014; Goodin et al., 2011).

One prominent class of new molecularly targeted anticancer therapies is the tyrosine kinase inhibitors (TKIs). TKIs act by blocking the tyrosine kinase enzymes. Tyrosine kinases work in the cell's signal-transduction pathways, interfering with cellular growth and proliferation. Mutated tyrosine kinases can cause unregulated cellular activity. Therefore, TKIs are used to decrease cell division and cancer progression (Arora & Scholar, 2005; Roelof W F van Leeuwen, van Gelder, Mathijssen, & Jansman, 2014). In Canada, there are currently over 20 types of oral TKIs available on the market for a wide range of oncology indications. Like with other therapies, TKI use has given rise to some concerns despite the many advantages. TKIs are among the most expensive therapies provided in the retail pharmacy setting with a monthly cost between $1,000 and $5000 (Dusetzina, Winn, Abel, Huskamp, & Keating, 2014). TKIs are also associated with clinically important drug interactions with commonly prescribed medications (Peters, Zimmermann, & Adjei, 2014).

Studies have shown that acid reducing medications such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) can decrease the absorption of TKIs (Keller, Franquiz, Duffy, & Trovato, 2016; Smelick et al., 2013; R W F van Leeuwen et al., 2013; Roelof W F van Leeuwen et al., 2014; Yin et al., 2010). For example, omeprazole can decrease serum concentrations (Cmax) of erlotinib and dasatinib by 61% and 42%, respectively, while ranitidine can decrease erlotinib by almost 54% (Roelof W F van Leeuwen et al., 2014). According to Lexicomp®

Interactions Module (Lexicomp Online®, 2017), treatment with a TKI and an acid suppressive agent should be avoided when there is a risk rating of X, as risks of concomitant use outweigh the benefits. With a risk rating of D, modification of therapy should be considered as the interaction is considered to be clinically important (Table 4-1).

The objectives of this study were to assess the prevalence of concomitant use of acid reducing agents and TKI therapy, pharmacists' responses to the interactions and the persistence of the interaction during TKI therapy.

4.3 Methods

A population-based cohort study examining prescriptions for TKIs and their co-prescription with acid suppressive agents was conducted in Manitoba using administrative health databases from the Manitoba Centre for Health Policy (MCHP) during the time period from April 1,2000 to March 31, 2015. Study data was obtained from the MCHP, which maintains the Manitoba Population Research Data Repository, a collection of administrative health care databases containing records of all interactions between Manitoba residents and the health care system. The Drug Information Program Network (DPIN) database, which is used to adjudicate and conduct drug utilization reviews for all prescription drugs dispensed by community pharmacies in the province, was used as the source of dispensation data. Although all records in the data repository have been de-identified, a unique identifier allows information about individual persons to be linked across the many datasets available in the Repository.

Anatomical Therapeutic Chemical (ATC) codes were used to identify drugs of interest: H2RAs (ATC codes starting with A02BA) or PPIs (ATC codes starting with A02BC), with TKI prescriptions: bosutinib (L01XE14), dasatinib (L01XE06), erlotinib (L01XE03), pazopanib (L01XE11), dabrafenib (L01XE23), gefitinib (L01XE02) and nilotinib (L01XE08). Agents were split into two groups stratified by the risk level of the TKI-acid suppressive agent interaction (Table 4-1).

The study cohort included all individuals dispensed a TKI prescription between April 1, 2000 and March 31, 2015. In addition to all TKI prescriptions, H2RA or PPI prescriptions to these patients dispensed after the first TKI prescription, but before the end of the last TKI prescription, were collected. H2RA and PPI prescriptions dispensed outside of this time frame were excluded. Duration of a prescription was based on the days' supply variable, with an end date calculated by adding this variable to the prescription dispensation date. A prescription was classified as interacting when one of the acid suppressive agents and a TKI prescription had overlapping timeframes. The duration of overlap was defined as the number of days where both drug classes were concurrently used. Each interaction was flagged and counted. In order to calculate overlapping days' supply, the overlapping timeframes of the acid suppressive agent prescriptions were divided by the total duration of TKI prescriptions for each patient.

In the provincial DPIN system a drug interaction warning code is displayed to the pharmacist filling the prescription when it overlaps with a prescription for an interacting medication. Pharmacists have an opportunity to enter a response code when interaction warnings appear in order to indicate what measures they took to deal with the interaction. Pharmacists' response codes to the interaction warning, prompted by the

very first instance when TKI-PPI or TKI-H2RA overlap occurred, were collected and analyzed.

Since TKIs are not commonly used in general practice, an effort was made to assess the volume of these prescriptions filled by individual pharmacies. The rationale for this was to assess the opportunity for pharmacies to develop competency and experience with these medications. Pharmacies were classified into 3 groups based on TKI prescription volume per year (never dispensed, 1-2 prescriptions, 3 or more prescriptions).

The analysis for this study was done using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) and Microsoft Excel 2013 (Microsoft Corporation, Redmond, Washington). Prior approvals were received by the University of Manitoba Health Research Ethics Board and the Manitoba Health Information Privacy Committee.

4.4 Results

Between 2000 and 2015 there were 3,146 TKI prescriptions dispensed to 442 individuals in Manitoba (Table 4-2). Over 1/3 (172 patients) of these patients received TKI prescriptions that overlapped with a concomitant prescription for an H2RA or a PPI. The combination of TKI and acid suppressive agent prescriptions generated 1,114 warning codes. However, pharmacists only responded to these codes 32% (359) of the time. When the first interacting prescription for each patient was examined, the warning code resulted in a response code for a minority of cases. Less than 3% of the response codes entered by the pharmacist were directly related to the interaction (Figure 4-1).

In an effort to look beyond the response codes, the degree of persistence of concomitant use of TKIs and acid suppressive agents was assessed by evaluating days of overlap between a TKI and an H2RA or a PPI prescription. In the 172 patients using TKIs and H2RAs/PPIs a mean of 54% (95% confidence interval (CI) 51%, 57%) of TKI days overlapped with days where acid suppressive agents were also prescribed (Figure 4-2). An average of 4 PPI prescriptions and 2 H2RA prescriptions were filled by patients taking TKIs. Only 13 patients had both a PPI and an H2RA prescription dispensed concurrently with a TKI prescription. A t-test analysis showed no significant difference in percent of days' supply overlap between risk groups X and D of TKIs and PPIs/H2RAs $t(189)=-0.58$, $p=0.56$; TKIs and PPIs $t(121)=1.11$, $p=0.27$; TKIs and H2RAs $t(73)=-2.16$, $p= .034$. The percentage of days overlap between TKIs and PPI/H2RAs showed no trend over time when examined in a regression model analysis ($p=0.69$).

Table 4-3 summarizes the volume of TKI prescriptions. The majority of pharmacies had never dispensed a TKI. Only erlotinib was dispensed with any regularity, with 9% of pharmacies dispensing it at least once a year. Other TKIs were dispensed so irregularly that less than 0.5% of pharmacies dispensed more than 3 prescriptions per year.

4.5 Discussion

More than a third of the patients that had been prescribed a TKI filled prescriptions for acid suppressive agents during their course of the treatment. While warning codes were generated for these interactions, pharmacists infrequently responded to these codes. Furthermore, there was little evidence of corrective action

taken to address the interaction. The percentage of days of overlap between TKI and acid suppressive agent prescriptions was calculated and an average of 54% concomitant use was observed. Furthermore, during the period of TKI use, patients filled multiple prescriptions for acid suppressive agents.

In clinical practice, potential drug interactions related to cancer are commonly reported and have been associated with adverse patient outcomes (Riechelmann & Del Giglio, 2009). Some exploratory reviews of drug interactions and oral anticancer medications in the community have been performed, but these high-level studies examined the general prevalence for all drug interactions and all oral cancer therapies (Roelof W F van Leeuwen et al., 2014). Ko and colleagues conducted a review of clinically important interactions with oral anticancer agents in Singapore, but did not find or did not consider PPI and H2RA interactions (Ko et al., 2012). More recently, a small study examined PPI use and TKIs (axitinib, sorafenib and pazopanib) in metastatic renal cell carcinoma (Au et al., 2016). Of 128 treatment lines, concomitant PPI use was seen in 49 or 38%. However, no difference in time of treatment with TKI was seen between patients who received an interacting PPI and patients who did not. Keller and colleagues found lower rates of drug-drug interactions in 356 TKI users from 2 outpatient clinics. Only 19, or 5% of patients, had been prescribed an interacting PPI with a further 13 (4%) patients prescribed an interacting H2RA (Keller et al., 2016).

The impact of acid suppressive agents on TKI levels has been demonstrated in a variety of small scale kinetic studies showing that concomitant use of TKI and a PPI/H2RA decreased TKI absorption by 30-60% (Haouala et al., 2011; Tan et al., 2013). While a great deal of attention has been paid to the availability, cost and

insurance coverage of TKI therapies (Darkow, Maclean, Joyce, Goldman, & Lakdawalla, 2012), less attention has been paid to ensure that these clinically important interactions are avoided. While the real-world impact on patient outcomes is unknown, it seems likely that a 30-50% reduction in blood levels would have an impact on patient outcomes. For imatinib in chronic myeloid leukemia (CML), a level of non-adherences (missing 3 doses per month) that would produce a modest reduction in blood levels has been associated with poor patient outcomes (Druker et al., 2006; Marin et al., 2010). Although avoiding the combination of a TKI and an acid suppressive agent is recommended, other options have been suggested. When concomitant use cannot be avoided, it has been suggested that the TKI and PPI interaction could in theory be minimized by using an enteric-coated PPI once a day and taking the TKI at least 2 hours before the intake of the PPI (Roelof W F Van Leeuwen, Jansman, & Hunfeld, 2017).

In the provincial database, drug interaction codes are generated to inform the pharmacist when two or more interacting drugs are being dispensed. Pharmacists have an opportunity to document their response to these interaction codes in this electronic system. Very few pharmacists entered response codes into the system and almost none entered response codes that would be considered clinically relevant. This low level of response to clinically important drug interactions and warnings has been seen in other clinical settings (Ojeleye, Avery, Gupta, & Boyd, 2013). The high number of interacting warning codes are known to contribute to an alert fatigue and contribute to pharmacists over-riding or ignoring warnings (Malone et al., 2005; Murphy, Forrey, & Desiraju, 2004; Tomlinson, 2014). Despite this low level of response, we cannot rule out that other

forms of documentation (e.g. paper documentation on the original prescription) may have occurred. However, the high level of overlapping of TKI and PPI/H2RA days and number of PPI/H2RA prescriptions filled during TKI use suggest that the lack of code response could reflect a real lack of response to the interaction. A low level of response to contraindicated or potentially serious drug interactions with oncology drugs was also reported by Weingart et al. where alerts only changed prescribing in 15% of cases (Weingart, Zhu, Young-Hong, Vermilya, & Hassett, 2014).

A possible contributing factor to the relatively high level of concomitant prescribing of PPIs/H2RAs and TKIs in our study may be the relative rarity of TKI use in the community pharmacies that are dispensing the medications. The vast majority of community pharmacies did not fill prescriptions for TKIs and <1% of pharmacies filled 3 or more prescriptions per year for most TKIs. It would be difficult for a pharmacist to develop sufficient expertise to adequately intervene in cases of medications that are dispensed so rarely. If we assume that the frequency of dispensing medications is a reasonable surrogate for competency, then the decentralized approach to providing TKIs from community pharmacies is problematic. This challenge has been recognized in surveys of Canadian community pharmacists (Abbott et al., 2014): fourteen percent of the pharmacists answered that they had education background in oral oncology drugs and only 1 in 5 had attended a continuing education event related to oncology in the past 2 years. Over 90% of community pharmacists did not feel comfortable educating patients on these medications. Similar results were reported in a study from Ireland, where a third to a half of pharmacists surveyed did not feel that they had enough information (e.g., treatment plan, patient details) to properly dispense oncology drugs

(Hammond et al., 2012). Furthermore, both surveys suggested that use of personal protective equipment, safe handling of oral oncology agents and proper procedures for disposal of hazardous waste were also lacking (Bartel, 2007; Goodin et al., 2011). It seems clear that further supports and education need to be provided to community pharmacists who are providing oral TKIs. Consideration should be given to establishing centralized dispensation sites with pharmacist and pharmacies that specialize in the management of oral oncology products, although having the TKI and acid suppressive agent dispensed from the same pharmacy may present an opportunity for pharmacy-based intervention without complicated communication among different pharmacies (Jones, Fife, Curkendall, Guo, & Shannon, 2001).

Our study has strengths as it was a population-based study that captured the dispensing of all prescription medications to the entire population of the province and it extended over a long period of time. However, it also has a number of limitations. Dispensing of a medication does not necessarily indicate the medication was taken by the patient. The study was also not able to capture over-the-counter (OTC) PPIs and/or H2RAs use. Over-the-counter H2RAs were available throughout the study periods but OTC PPIs have only been available since 2014. While this is a limitation of the study, our results could be considered a conservative estimate as the use of the OTC products would increase the number of patients using TKIs who were taking interacting medications. Finally, we cannot assess pharmacists' knowledge through administrative databases, so we have used the low number of prescriptions by individual pharmacies as a sign of limited ability to gain knowledge, experience and competency in the management of these agents and their interactions.

4.6 Conclusion

The increased availability and dispensation of oral oncology products, such as TKIs, may decentralize care to community pharmacies. Surveys of community pharmacists suggest that they may not be fully prepared for this shift in care. The relative rarity of some cancers and the use of TKIs make it difficult for pharmacists to develop and maintain competency in this area. However, the role of pharmacists in the management of clinically important drug-drug interactions is clear. In this study we found that more than a third of patients were exposed to acid suppressive therapy during the period they were taking TKI therapy. Furthermore, the majority of these patients have more than 50% overlap of their acid suppressive therapy and their TKI therapy. Pharmacy response to this interaction appears to be suboptimal. Increased awareness and education may help support pharmacists in helping patients manage this important interaction in a more appropriate manner.

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Table 4-1. Potential drug interactions between TKI and PPI/H2RA according to LEXICOMP

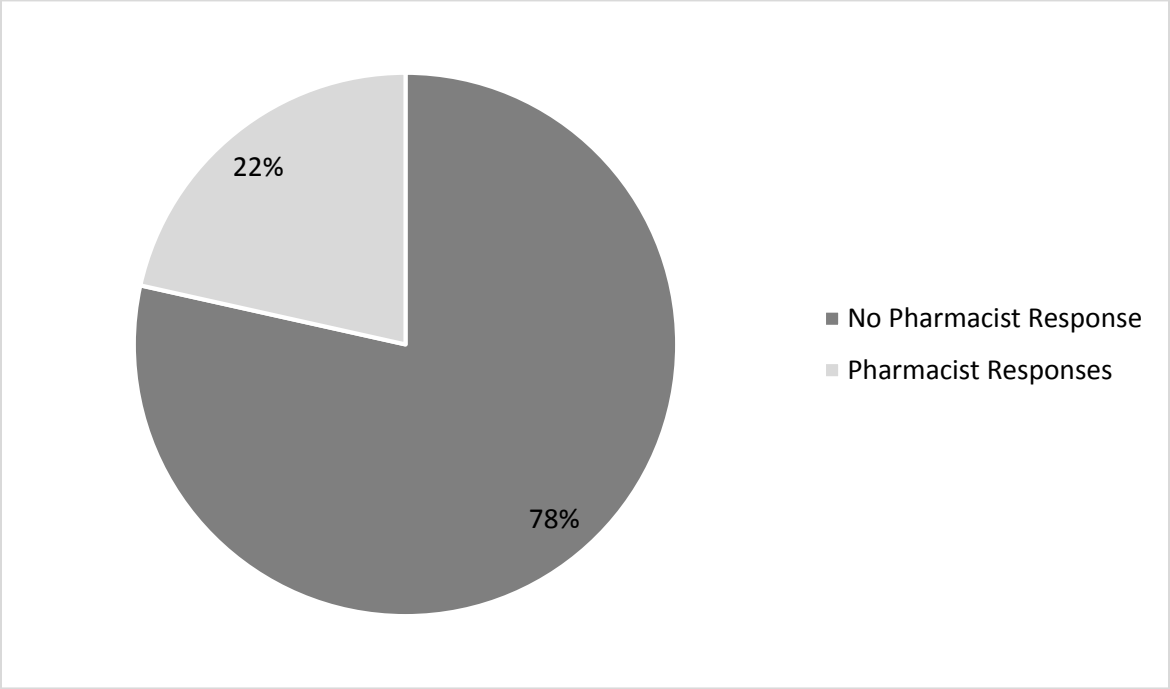
	PPIs*	H2RAs**
Risk X Avoid Combination	Dasatinib Erlotinib Pazopanib	Dasatinib Pazopanib
Risk D Consider Therapy Modification	Dabrafenib Bosutinib Gefitinib Nilotinib	Bosutinib Erlotinib Gefitinib Nilotinib

*PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)

**H2RAs (cimetidine, famotidine, nizatidine, ranitidine)

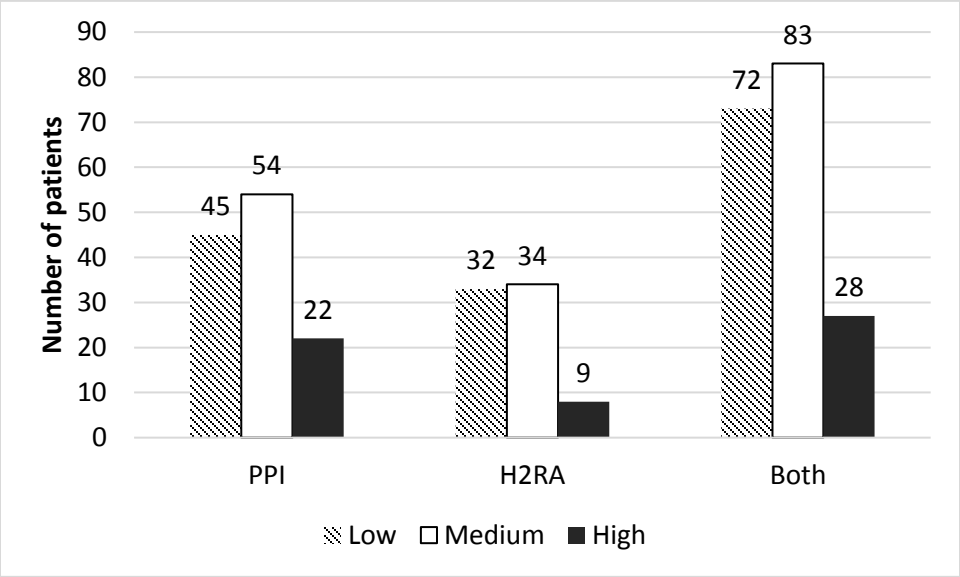
Table 4-2. Number of TKI users and prescriptions identified		
Drug	**Users, n**	**Prescriptions, n**
Dasatinib	65	901
Erlotinib	329	1614
Pazopanib	15	73
Bosutinib	<5	<5
Dabrafenib	17	129
Gefitinib	9	23
Nilotinib	22	351

Figure 4-1. Percentage of patients that had a response code entered by the pharmacist in the first interaction between a TKI and an acid suppressive agent at dispensation.



Total number of prescriptions: 172; Number of patients that had a response code: 37; Response codes identified: 39; Codes entered by the pharmacist: Related to drug coverage {ED (Exception drug status prescriber choice); DU (For drug utilization review only); EP (Exception drug status pharmacist choice).}, Potentially related to drug interaction management {UG (Cautioned patient Rx filled as written); UI (Consulted other source Rx filled as written)}.

Figure 4-2. Number of patients with low, medium and high percent of days' supply overlap between TKI and acid suppressive agents.



PPI: proton pump inhibitor; H2RA: histamine-2 receptor antagonists; Frequency of days of overlap between a TKI and an acid suppressive agent: low (less than 50% of the time); medium (50-75% of the time); high (more than 75% of the time).

Table 4-3. Experience of pharmacies based on number of TKI prescriptions dispensed							
Number of prescriptions	**% of pharmacies**						
	Dasatinib	Erlotinib	Pazopanib	Dabrafenib	Gefitinib	Nilotinib	Bosutinib
0	95.3	91.0	99.5	99.6	99.7	98.3	99.9
1-2	3.3	4.7	0.2	0.1	0.2	0.4	0.1
≥3	1.4	4.3	0.3	0.3	0.1	1.3	0

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Chapter 5 Cost and health policy in the management of oral oncology drugs provided in the community: A 15-year population-based longitudinal observational study

5.1 Abstract

Introduction: The introduction of new oncology medications such as targeted therapies and immune therapies is changing the cancer treatment paradigm. Many of these medications are being introduced in oral formulations and are often dispensed from community pharmacies. The aim of this study was to assess the impact of oral cancer therapy on health system costs and the pharmacy business model.

Methods: A population-based retrospective study was conducted using data from the Manitoba Centre for Health Policy (MCHP). All oral oncology drugs dispensed in Manitoba from 2000/01 to 2014/15 fiscal years were included in the study. Total cost and dispensing fees related to oral oncology medications dispensed in the community were assessed. The impact of policy changes (income-based deductible, first dollar-full coverage and capped dispensing fee) were assessed. Piecewise regression was used to examine the impact of the introduction of the cancer drug program (full coverage) on the mean dispensing fee in the province.

Results: The total cost of oral anticancer agents dispensed in the province increased by more than 7-fold from $2,682,805 in 2000/01 to $21,311,652 in 2014/15. The average cost of an oral cancer prescription has also risen from $113 in 2000/01 to $549 in 2014/15. Protein kinase inhibitors represent 39% of total cost with an average annual cost of more than $5,000,000/year. The mean dispensing fee increased from

$9.36 to $29.85 from 2000/01 to 2014/15. There was neither a stepwise increase in mean prescription dispensing fee (p=0.66), nor was there an increase in the slope of upward trend in the fee after the first dollar full coverage was implemented (trend line; p=0.27). While the average dispensing fee has increased, the actual fee percentage of the total cost steadily declined. Scenario analysis projected that a dispensing fee cap would result in almost $600,000/year in government savings, but it would potentially reduce pharmacy margins on these products to unsustainable levels, challenging the community pharmacies to carry medications that are expensive and require specific demands.

Conclusions: The shift to oral chemotherapy, particularly for high cost products like protein kinase inhibitors and immunotherapies, has placed some new pressures on the health care system, as well as community pharmacies and the business model that supports them. As government payers struggle to support the costs associated with new expensive oral medications in the community pharmacy setting, policy directed at saving government expenditure simultaneously undermines the business model that supports the dispensing of these products in community pharmacies.

5.2 Introduction

Cancer therapy is continuously evolving with recent advances occurring particularly in targeted and immune system based therapies (Shih, Smieliauskas, Geynisman, Kelly, & Smith, 2015). Targeted therapies are notable for their precise mechanism of action in cancer treatment, which offers the promise of efficacy with less systemic side effects. The positive aspects of these therapies compared with traditional

chemotherapy make them a focus for drug development. Increasingly, these new therapies are developed as oral dosage forms (Felton, Londen, & Marcum, 2014). In some cases, these therapies can be highly effective and can make cancer more of a chronic condition whereas the general idea of cancer as a fatal illness. Patients with chronic myeloid leukemia (CML) treated with imatinib, a tyrosine kinase inhibitor (TKI), have increased overall survival (Howard et al., 2016) and can achieve a life expectancy approaching that of a person not affected by cancer. (Bower et al., 2016). This shift to long-term oral therapies can present unique challenges for both patients and health care systems. Many systems and associated health policies have been built around a shorter-term acute delivery of intravenous therapies.

These innovations, however, come with considerable cost and open speculation about the ability of health care systems to afford the increasing cost of oncology medications (Darkow, Maclean, Joyce, Goldman, & Lakdawalla, 2012). It is estimated that cancer expenses will rise from $125 billion in 2010 to $173 billion in 2020 in the U.S (Mariotto, Robin Yabroff, Shao, Feuer, & Brown, 2011). Part of this increase is due to the increasing use of new and more expensive therapies, but the number of people with cancer is also rising. Globally, new cases of cancer are estimated to rise from 13.3 to 21.5 million in 2010 and 2030, respectively (Beaulieu, Bloom, Bloom, & Stein, 2009). The switch from intravenous therapy that is administered at a clinic or cancer centre to oral formulations can also pose some health policy challenges. Oral therapies have traditionally been provided by community pharmacies. Particularly for rare forms of cancer, community pharmacies may be not fully prepared to provide these medications. Some medications may be rarely seen by the pharmacists making it more difficult for

them to gain experience in order to better assist the patient's needs. (Abbott, Edwards, Whelan, Edwards, & Dranitsaris, 2014). In addition, at a cost of thousands of dollars a month, out-of-pocket costs can be a significant barrier for patients and a challenge for pharmacy business models and health care system budgets (Dusetzina, Winn, Abel, Huskamp, & Keating, 2014). From 2004-5 to 2009-10, cancer drugs were one of the three largest classes in drug expenditure in Canada (wholesale spending) with an average annual growth of 13.4% (Canadian Institute of Health Information, 2012).

In Canada, health is a provincial responsibility and each Canadian province handles the provision of health care differently. In this study, the population-based linked administrative data for the province of Manitoba were used to assess the cost implications of this shift to oral therapy provided by community pharmacies. There have been a number of significant health policy changes in the government support for the provision of oral chemotherapy in the community. Intravenous cancer therapies are provided by a province-wide network of cancer centres and are fully covered by the provincial health care system. Oral therapies, however, are provided by community pharmacies and covered under the provincial Pharmacare system. All residents of Manitoba are covered by a system that fully covers the medication after the payment of an income-based deductible (3.09 to 6.98% of family income). This income-based deductible was seen as a barrier for oral chemotherapy, particularly because IV therapy was provided at none cost. In 2012, a Home Cancer Drug Program was launched that provided first dollar full coverage for oral chemotherapy products. Initially there were no limits on the dispensing fees that could be charged for a prescription as competition with market forces was expected to effectively regulate fees. However, in August 2017, a

dispensing fee cap of no more than $30 per prescription for all prescriptions regardless of ingredient cost was implemented. The aim of this study was to assess the impact of oral cancer therapy on health care system costs and the pharmacy business model.

5.3 Methods

A population-based retrospective study was conducted in the province of Manitoba, Canada, using data from April 1, 2000 to March 31, 2015. Data were obtained from the Manitoba Population Research Data Repository maintained by the Manitoba Centre for Health Policy (MCHP). The Repository contains data generated during the everyday operation of Manitoba's universal public health care system. The Drug Program Information Network (DPIN), containing dispensation records from community pharmacies, was specifically accessed for this study. All data are de-identified, but containing scrambled identifying variables, allowing records to be linked across and within databases.

Drug therapies were classified using the Anatomical Therapeutic Chemical (ATC) system. All oral oncology prescriptions (ATC codes starting with L01-04) were collected. They were categorized into the following classes: alkylating agents (L01A), antimetabolites (L01B), endocrine therapy (L02), immunotherapies (L04AX02 and L04AX04), plant alkaloids (L01C), protein kinase inhibitors (L01XE) and other antineoplastic agents (L01XB01, L01XX14, L01XX35, L01XX11, L01XX05, L01XX23, L01XX43). Extent of dispensation and utilization were quantified, based on total number of oral oncology prescriptions dispensed and number of users.

Annual total prescription costs and mean dispensing fees were calculated overall, as well as by drug class and drug. Data were then grouped in bands based on the prescription costs and in dispensing fee categories. Average dispensing fees and the percentage of the dispensing fee of the total prescription were calculated for each year across the study period. The impact of the policy change capping dispensing fees at $30 was assessed by retrospectively examining the impact of the policy on average dispensing fees.

The impact of the introduction of the HCD program on the mean dispensing fee was examined using piecewise regression from 2008 to the end of the study period. Both a stepwise increase in mean fee and an increase in the rate of change of the mean were examined separately for the period surrounding the policy change in April 2012.

All data analysis was done using SAS 9.4 (SAS institute, Cary NC). This study was conducted with approval from The University of Manitoba Health Research Ethics Board and the Manitoba Health Information Privacy Committee.

5.4 Results

During the study period, total cost and utilization of cancer medications dispensed in the community increased substantially (Figure 5-1). The total cost of oral anticancer agents dispensed in the province increased by more than 7-fold from $2,682,805 in 2000/01 to $21,311,652 in 2014/15. The number of prescriptions dispensed increased from 23,847 to 38,955 prescriptions over the same period. The average cost of an oral cancer prescription rose from $113 in 2000/01 to $549 in

2014/15. The rate of oral cancer drug use also increased from 20 to 29 prescriptions per 1000 people (45% increase).

Overall, the most commonly prescribed oral cancer therapies were the hormonal/endocrine therapies used as adjunctive therapies primarily for breast and prostate cancer (Table 5-1). Endocrine therapies accounted for nearly 70% of all oral oncology prescriptions but only 27% of the cost. On the other hand, protein kinase inhibitors (imatinib, sunitinib, dasatinib) represented 3.5% of oral cancer prescriptions but 39% of total cost, with an average cost per prescription of $3,677 and an average annual cost of more than $5,000,000/year. Immunotherapies significantly impacted cost after 2010, with lenalidomide becoming the medication with the highest expenditure by the end of the study period. Overall, protein kinase inhibitors and immunotherapies were responsible for 52% of the increase in oral cancer therapy prescriptions (Figure 5-1). When examining total expenditures on a drug-by-drug basis, a similar pattern emerged. Low cost but high volume endocrine therapies (bicalutamide, anastrozole, letrozole) were well represented in the top 10 drugs based on expenditure (Table 5-2). However, protein kinase inhibitors as high cost agents prescribed to fewer patients were also prominent. Imatinib represented the drug with the highest expenditure in the province for 10 consecutive years (2003 to 2012) and dropped to the 4th position only in the last year of the analysis.

The overall mean dispensing fee was $20.32 (CI 20.19-20.45); however, in a few cases, dispensing fees were as high as $999.99 (maximum allowed in reimbursement software). These extreme fees (>$900) were relatively rare and made up only 0.017% of all dispensing fees. However, with higher prescription costs, higher dispensing fees

were generally more common (Table 5-3). For prescriptions costing over $600, the majority of dispensing fees charged were more than $100 per prescription (Figure 5-2). The average dispensing fee increased steadily (9% per year) from $9.36 to $29.85 from 2000/01 to 2014/15 (Table 5-4). There was no indication that the full first dollar government coverage of all oral oncology medications in 2012 was associated with an increase in the rate of increases in dispensing fees. There was neither a stepwise increase in mean prescription dispensing fee (p=0.66), nor was there an increase in the slope of upward trend in the fee after 2012 trend line (p=0.27).

The potential impact of the implementation of a dispensing fee cap of $30 per prescription in 2017 was assessed by examining its impact through a scenario analysis that retrospectively evaluated the impact of this policy on past years. The percentage of fees above $30 rose steadily over the study period, reaching almost 12% by 2014/15 (Table 5-4). While the average dispensing fee was increasing, the actual fee percentage of the total cost was declining. The implementation of a $30 fee cap cut the average dispensing fee in half and reduced pharmacy revenue by almost $600,000 for 2014/15. The fee percentage of total cost also declined to 2.6%.

5.5 Discussion

In Manitoba, the cost of cancer drugs dispensed in community pharmacy increased 7-fold in the last 15 years. This increase in cost is partially driven by the higher costs of new oral therapies with an almost 5-fold increase in the cost of the average prescription. Protein kinase inhibitors and immunotherapies are responsible for over half of this increase. In addition, a 45% increase in the population rate of

prescribing indicates that more oral cancer prescriptions are being used by more people. While lower cost endocrine therapies are the most frequently used therapies with thousands of users, drugs like imatinib, which is prescribed only to a few hundred of users, had a dominant impact on overall drug costs.

These results were similar to findings from previous studies out of the United States, where mean expenditures per month increased from $1,869 in 2000 to $11,325 in 2014 (Dusetzina, 2016). As in our study, there were large contributions from immunotherapies (thalidomide, lenolidomide) and TKIs (imatinib). These agents are known to be cost drivers. Data from Ontario, Canada estimated that lenalidomide and imatinib were expected to cost $131,765 and $74,490 per patient per year, respectively (Taylor, 2014). In addition to the higher cost of medication, the number of users and prescriptions dispensed also doubled in our study. Conditions like kidney cancer and CML have been shown to cause a 4-fold increase in cost due to the introduction of new oral drugs but also by the fact that patients appeared to be using more of these drugs for longer periods of time (Howard et al., 2016). Tyrosine kinase inhibitors, although representing only 3.5% of prescriptions, contributed to 39% of total costs. Imatinib had the highest impact in total cost for multiple subsequent years. Generic imatinib was introduced in Canada in 2012 and government coverage requires automatic substitution with generic products at the pharmacy level. This change was primarily responsible for the drop in expenditure on imatinib ($5.2 million 2012 to 1.3 million 2015; Table 5-2).

The high cost of oral cancer medications can pose challenges for the health care system at many levels. With an average cost of almost $4,000, the first prescriptions for a protein kinase inhibitor could present a significant barrier for patients (Santoleri,

2013). In a cross-sectional study with elderly Medicare beneficiaries, the mean daily out-of-pocket costs for 5 oral cancer drugs ranged from $2.96 to $37.47 ($1,080.40 to $13,676.55 annually) and a large number of patients in this study (35% to 70% of the patients), especially the ones who had higher out-of-pocket costs, were more likely to delay or to discontinue their treatments (Kaisaeng, Harpe, & Carroll, 2014). While this may have been a barrier for patients during the 2000 to 2012 portion of the study period, after 2012 oral chemotherapy was provided without cost (without deductible) to oral cancer patients. This helped to rationalize a system that provided full coverage for intravenous but only limited coverage for patients that received oral therapy from community pharmacies.

The shift to oral chemotherapy, particularly for high cost products like protein kinase inhibitors, has placed some new pressures on community pharmacies and the business model that supports them. While private insurance plays a role in paying for the total prescription cost, Manitoba primarily has a single government provider for drug coverage that allows no mark-up over the wholesale price but a fee regulated only by market forces. The average dispensing fee was $20.32 in our study period, with higher fees associated with higher cost prescriptions (Table 5-3, Figure 5-2). As the cost of oral oncology prescriptions increased there was a steady increase in dispensing fees. Only a small percentage of fees were extreme, as high as $900 (0.017%) and it is notable that the percentage of the fee of total cost (margin) declined throughout the study period.

Government payers have been paying increasing attention to ways of managing the costs of providing medication coverage. This has included generic pricing reform,

the pan-Canadian drug purchasing arrangements, risk-sharing agreements (RSA's), market surveillance and performance measurement (Taylor, 2014). In a cost-driver analysis for public drug plan dispensing fees that was conducted by the Patented Medicine Prices Review Board in Canada, the average annual growth rate of dispensing fees in Manitoba was 11.3%, making up a 17.4% share of total prescription expenses (Canada. Patented Medicine Prices Review Board., 2011). This study showed a lower annual increase (9%) and a smaller percentage of total cost (5.3 to 8.3%) for oral oncology medications. Despite this, Manitoba's attention has shifted to a policy of governing allowable dispensing fees as a way to control costs, for high cost drugs supported by provincial programs.

The potential implications of the introduction of a $30 dispensing fee cap policy in August 2017 were estimated retrospectively by conducting a scenario analysis that capped all past fees at $30. Since oral chemotherapy is now fully covered by the government program, this change will have no impact on patient care or on their out-of-pocket costs. However, it was estimated that this policy change would produce government savings of approximately $600,000 per year. It is notable that this translates to a loss of $600,000 from community pharmacies and reduces the percentage of the fee of total prescription cost down to 2.6%. This margin is less than half of what it was under the unregulated policy environment. It is too early to determine the actual full impact of the policy, but for some products (average protein kinase inhibitor $3,677) a $30 fee represents only 0.8%. It is unclear if all community pharmacies will continue to provide these products with such low rates of return.

This study has a number of strengths but also some limitations. The study was strengthened by the complete population level data that extend over a decade that included important health policy changes. The single payer framework was also a strength, as it allowed the assessment of the exact cost per prescription dispensed and the related dispensing fees charged in community pharmacies. However, observational studies using administrative data also have a number of limitations. Out-of-pocket costs are known to be a barrier to adherence (Kaisaeng, Harpe, & Carroll, 2014). If medication cost prevents patients from filling their prescriptions this complete lack of adherence would not be captured in our data, since administrative data are only able to capture dispensation records and would not include prescriptions that are not filled. While several important health policy transitions were captured, given the recent nature of the dispensing fee cap, only a retrospective scenario analysis was possible. The actual impact of this policy and any unintended consequences remain to be determined.

5.6 Conclusion

The annual cost for oral oncology medications increased by 7-fold during the study period. The primary driver of this increase in cost was high-cost protein kinase inhibitors and immunotherapies. The impact of new therapies available and of the use of therapy for longer periods was evident in the increasing rate of prescribing (20 to 29 prescriptions per 1,000). The increase in cost of oral chemotherapy has placed financial strain on both patients and government payers. To address the patient's financial burden, the government provided first dollar coverage for patients. This only further increased government costs and led to a policy of capping dispensing fees to control costs. While this policy change is expected to produce almost $600,000 in annual

savings, it is unclear if the resulting reduction in pharmacy margins will have unintended consequences.

5.7 Acknowledgements

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project #2015-033 (HIPC# 2015/2016 – 30). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health.

Figure 5-1. Total cost of prescriptions dispensed in Manitoba from 2000 to 2015 by drug class

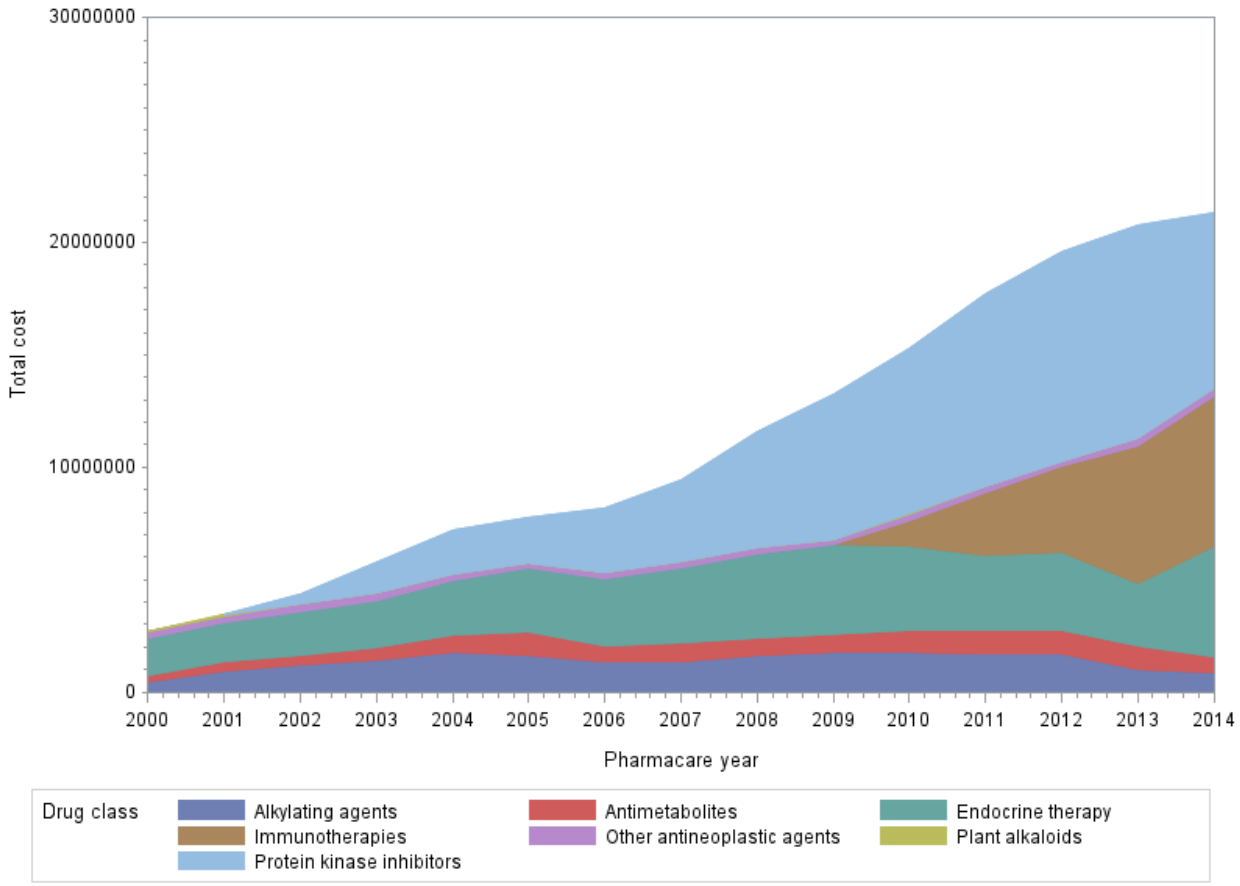

Table 5-1. Most common oral oncology medications dispensed in Manitoba from 2000/01 to 2014/15			
Generic drug name	**Drug class**	**Number of prescriptions**	**Number of users**
Tamoxifen	Endocrine therapy	124,158	7,189
Anastrozole	Endocrine therapy	85,684	3,100
Letrozole	Endocrine therapy	65,848	3,605
Methotrexate	Antimetabolite	51,470	2,137
Bicalutamide	Endocrine therapy	45,534	5,645
Capecitabine	Antimetabolites	22,216	2,239
Hydroxyurea	Other antineoplastics	19,851	910
Exemestane	Endocrine therapy	15,945	1,111
Megestrol	Endocrine therapy	13,494	1,701
Imatinib	Protein kinase inhibitors	11,952	342

Table 5-2. Most Costly Oral Oncology Medications Dispensed in Manitoba from 2000/01 to 2014/15							
2000	2002	2004	2006	2008	2010	2012	2014
Bicalutamide $706,875	Temozolomide $1,127,071	Imatinib $1,936,050	Imatinib $2,708,400	Imatinib $3,296,452	Imatinib $4,811,562	Imatinib $5,219,348	Lenalidomide $6,722,523
Temozolomide $380,584	Bicalutamide $750,235	Temozolomide $1,665,849	Temozolomide $1,270,148	Anastrozole $1,854,952	Anastrozole $2,081,703	Lenalidomide $3,834,913	Abiraterone $3,101,527
Anastrozole $368,910	Anastrozole $532,449	Bicalutamide $791,101	Anastrozole $1,189,513	Temozolomide $1,592,100	Temozolomide $1,701,050	Temozolomide $1,657,041	Sunitinib $1,716,284
Tamoxifen $210,771	Imatinib $451,045	Anastrozole $720,738	Letrozole $640,133	Sunitinib $1,103,863	Sunitinib $1,365,009	Sunitinib $1,457,517	Imatinib $1,273,664
Capecitabine $160,874	Capecitabine $255,357	Capecitabine $637,782	Capecitabine $518,118	Letrozole $740,187	Lenalidomide $1,111,473	Anastrozole $1,112,728	Dasatinib $1,211,537
Hydroxyurea $145,508	Tamoxifen $216,305	Letrozole $382,580	Bicalutamide $490,369	Capecitabine $586,013	Capecitabine $759,265	Letrozole $872,910	Temozolomide $820,286
Megestrol $127,834	Letrozole $161,329	Tamoxifen $196,687	Exemestane $303,271	Erlotinib $463,856	Letrozole $650,065	Capecitabine $831,500	Dabrafenib $752,396
Flutamide $88,846	Megestrol $130,458	Anagrelide $165,919	Tamoxifen $166,751	Bicalutamide $448,385	Erlotinib $585,615	Dasatinib $591,504	Letrozole $689,478
Letrozole $74,651	Anagrelide $130,407	Megestrol $125.316	Megestrol $130,481	Exemestane $375,262	Bicalutamide $438,960	Everolimus $530,376	Erlotinib $682,850
Chlorambucil $67,395	Hydroxyurea $122,093	Exemestane $103,408	Erlotinib $128,621	Dasatinib $158,265	Dasatinib $356,127	Abiraterone $526,143	Capecitabine $538,400

Table 5-3. Drug cost and dispensing fees grouped by prescription cost				
Prescription cost	**Number of prescriptions**	**Type**	**Sum**	**Mean (95 CI)**
0-25	129,583	Drug Cost	$1,652,386	$12.80 (12.76, 12.82)
		Dispensing fee	$1,127,992	$9.96 (9.94, 9.98)
25-100	154,192	Drug Cost	$7,304,751	$47.37 (47.28, 47.47)
		Dispensing fee	$1,477,781	$10.37 (10.35, 10.39)
100-200	140,608	Drug Cost	$21,224,000	$150.94 (150.81, 151.07)
		Dispensing fee	$1,724,237	$12.64 (12.61, 12.68)
200-300	18,594	Drug Cost	$4,320,722	$232.37 (231.99, 232.75)
		Dispensing fee	$259,165	$14.48 (14.33, 14.63)
>300	76,934	Drug Cost	$133,851,301	$1,739.82 (1,723.87, 1,754.77)
		Dispensing fee	$5,301,941	$69.13 (68.38, 69.89)

Figure 5-2. Distribution of prescriptions by dispensing fees based on the total cost of prescriptions

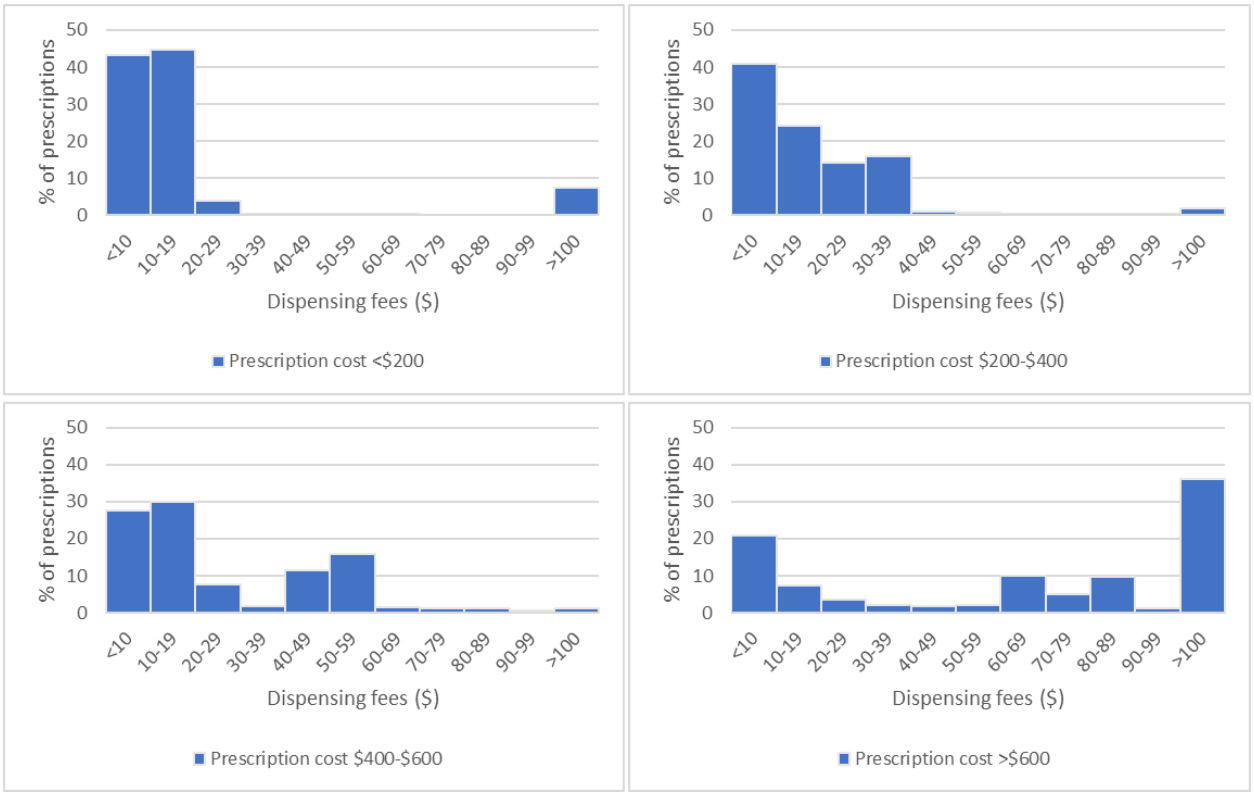

Table 5-4. Distribution of the average dispensing fee cost with a cap of $30 and estimated savings from 2000/01 to 2014/15

Fiscal year	Average rx cost ($)	Average fee ($)	Fee % of total cost (%)	% of rx dispensing fees above $30 (%)	Average fee capped at $30 ($)	Fee % of total cost, with $30 cap (%)	Estimated savings ($)
2000	112.65	9.36	8.3	2.26	8.16	7.2	27,699
2001	132.63	11.17	8.4	3.37	9.03	6.8	53,587
2002	161.74	12.75	7.9	3.98	9.79	6.1	77,321
2003	207.50	15.67	7.6	5.38	10.95	5.3	126,670
2004	243.54	17.35	7.1	6.92	11.86	4.9	156,510
2005	243.27	17.44	7.2	7.35	12.37	5.1	154,324
2006	245.32	17.50	7.1	6.93	12.49	5.1	158,781
2007	259.01	18.32	7.1	7.31	12.86	5.0	185,167
2008	298.75	20.15	6.7	7.99	13.21	4.4	244,887
2009	332.73	21.83	6.6	9.3	13.73	4.1	293,858
2010	364.69	22.20	6.1	9.36	13.86	3.8	318,580
2011	422.93	24.55	5.8	9.8	13.95	3.3	401,557
2012	465.10	26.16	5.6	10.1	14.08	3.0	460,889
2013	515.05	27.54	5.3	10.93	14.09	2.7	519,092
2014	548.77	29.85	5.4	11.65	14.18	2.6	576,857

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Chapter 6 Thesis Conclusions

Historically, cancer therapies have been primarily administered through IV routes. However, availability of oral oncology products has increased and shifted an aspect of cancer care to community pharmacies. This evolving decentralized model of care has a variety of impacts on patients, pharmacies and the health care system. In this thesis the impacts on adherence to oral cancer medications, safety issues related to drug-drug interactions and the high cost of oral cancer medications were considered.

With oral chemotherapy agents, patients have a greater role in ensuring adherence with therapy. In this study we found that adherence to imatinib was high. Adherence remained high even when patients were receiving it over a number of years. Furthermore, there was no indication that removing the financial barrier with first dollar full coverage had an impact on imatinib adherence. MPR remained high before and after the introduction of the Home Cancer Drug Program.

Surveys of community pharmacists have indicated that they feel they are not fully prepared for this shift in care (Abbott et al., 2014). For relatively rare cancers and their oral treatments it may be practically difficult for community pharmacists to develop and maintain competency related to these medications. To examine this issue, the frequency of concomitant dispensation of TKI and acid suppressive agents was assessed. These medications are known to interact and substantially reduce the level of the TKI. A third of patients were exposed to acid suppressive therapy during the period they were taking TKI therapy. This result suggests that system changes may be

required to better support the optimal use of oral cancer medication in the community setting.

Finally, costs of oral chemotherapy were reviewed. The annual cost of oral oncology medications increased by 7-fold from 2000/01 to 2014/15. Protein kinase inhibitors and immunotherapies were the biggest cost drivers. In addition, there was evidence that Manitobans were using more oral cancer therapies (20 to 29 prescriptions per 1000) and that these oral cancer prescriptions were more expensive ($113 to $549). The increase in cost of oral chemotherapy has placed financial strain on both patients and government payers. Patient costs were addressed with the first dollar full coverage Home Cancer Drug Program in 2012. This shifted more costs to the government program. In an effort to address costs, a dispensing fee cap was recently introduced. While this policy change is expected to produce almost $600,000 in annual government savings, it is unclear if the resulting reduction in pharmacy margins will have unintended consequences.

Chapter 7 Thesis References

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Chapter 8 Appendix A: Research Approvals

8.1 Manitoba Centre for Health Policy Approval Letter

UNIVERSITY OF MANITOBA | Faculty of Health Sciences

College of Medicine
Manitoba Centre for Health Policy
Community Health Sciences
408-727- McDermot Ave Winnipeg MB
Canada R3E 3P5
Phone (204) 789-3819
Fax (204) 789-3910
Email info@cpe.umanitoba.ca

November 13, 2015

Juliano Amador da Silva
College of Pharmacy
University of Manitoba
750 McDermot Ave
Winnipeg, MB R3E 0T5

Dear Juliano:

Re: Health Policy and Community Pharmacy Provision of Oncology Medications: An Assessment of the Effect of a Changing Health Policy Environment on the Medication Adherence, Cost and Safety of Oncology Medications Provided by Community Pharmacies
MCHP project number: 2015-033

Enclosed is a copy for your records of the fully executed Researcher Agreement, representing approval to proceed with the above research project at the Manitoba Centre for Health Policy (MCHP) using Manitoba Health, Healthy Living and Seniors data. It is important that the requirements outlined in this agreement be shared with all members of your project team, specifically Section 5 obligations respecting use and disclosure and Section 6 regarding reports, monitoring and enforcement. It is also important that all correspondence with MCHP relating to this project reference the MCHP project number.

We look forward to facilitating access to the Population Health Research Data Repository for your project. To proceed, please contact Charles Burchill (Manager, Program and Analysis System) at [redacted] Sophie Buternowsky, Senior grants Accountant, at MCHP will be contacting you regarding invoicing for your project.

If any changes are made to the original approved study protocol, they must be submitted to the Health Research Ethics Board for approval and the data providers. A copy of the submissions and approvals must also be sent to MCHP.

We would be glad to assist you in meeting ongoing project requirements for maintaining access to the data, as outlined at our website: http://umanitoba.ca/medicine/units/mchp/resources/access_reporting.html
Should you have any questions, please do not hesitate to contact me at (204) 975-7770.

Sincerely,

[redacted]

Kara Dyck
Repository Access Coordinator

cc Sophie Buternowsky, Senior Grants Accountant

http://umanitoba.ca/medicine/units/mchp/

8.2 University of Manitoba Health Ethics Review Board Approval

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS Research Ethics Board

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Telephone 204-789-3255
Fax 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Juliano Amador da Silva	U of M/Pharmacy	HS18783 (H2015:315)
APPROVAL DATE: August 4, 2015	**EXPIRY DATE:** August 4, 2016	
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. Shawn Bugden		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
N/A	Health Policy and Community Pharmacy Provision of Oncology Medications: An assessment of the effect of a changing health policy environment on the medication adherence, cost and safety of oncology medications provided by community pharmacies
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: U of M Internal Funds	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
July 31, 2015	August 4, 2015

THE FOLLOWING ARE APPROVED FOR USE:

Document Name	Version(if applicable)	Date
Protocol: Proposal		
Consent and Assent Form(s):		July 31, 2015
Other: Data Capture Sheet		July 31, 2015

CERTIFICATION
The above named research study/project has been reviewed in a ***delegated manner*** by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form.**
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report.**

Sincerely,

[redacted]

John Arnett, PhD. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone:** (204) 789-3255/ **Fax:** (204) 789-3414

UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada, R3E 0W3
Telephone : 204-789-3255
Fax: 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Juliano Amador da Silva	U of M/Pharmacy	HS18783 (H2015:315)
HREB MEETING DATE (if applicable):	**APPROVAL DATE:**	**EXPIRY DATE:**
	July 12, 2016	**August 4, 2017**
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (if applicable):		
Dr. Shawn Bugden		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
Na	Health Policy and Community Pharmacy Provision of Oncology Medications: An assessment of the effect of a changing health policy environment on the medication adherence, cost and safety of oncology medications provided by community pharmacies
SPONSORING AGENCIES AND/OR COORDINATING GROUPS:	
U of M Internal Funds	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
June 30, 2016	June 30, 2016

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

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7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD., C. Pysch.
Chair, Health Research Ethics Board
Bannatyne Campus

UNIVERSITY OF MANITOBA | Research Ethics - Bannatyne
Office of the Vice-President (Research and International)

P126-770 Bannatyne Avenue
Winnipeg, Manitoba
Canada, R3E 0W3
Telephone : 204-789-3255
Fax: 204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Juliano Amador da Silva	U of M/Medicine/Pharmacy	HS18783 (H2015:315)
HREB MEETING DATE (if applicable):	**APPROVAL DATE:** July 20, 2017	**EXPIRY DATE:** August 4, 2018
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (if applicable): Dr. Shawn Bugden'		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Health Policy and Community Pharmacy Provision of Oncology Medications: An assessment of the effect of a changing health policy environment on the medication adherence, cost and safety of oncology medications provided by community pharmacies
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: U of M Internal Funds	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
June 6, 2017	June 8, 2017

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

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7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD., C. Pysch.
Chair, Health Research Ethics Board
Bannatyne Campus

UNIVERSITY OF MANITOBA | Research Ethics and Compliance

Research Ethics - Bannatyne
P126-770 Bannatyne Avenue
Winnipeg, MB
Canada R3E 0W3
Phone +204-789-3255
Fax +204-789-3414

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Juliano Amador da Silva	U of M/Medicine/Pharmacy	HS18783 (H2015:315)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:**	**EXPIRY DATE:**
	July 23, 2018	**August 4, 2019**
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable):		
Dr. Shawn Bugden		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Health Policy and Community Pharmacy Provision of Oncology Medications: An assessment of the effect of a changing health policy environment on the medication adherence, cost and safety of oncology medications provided by community pharmacies
SPONSORING AGENCIES AND/OR COORDINATING GROUPS:	
U of M Internal Funds	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
July 13, 2018	July 13, 2018

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval

*Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.*

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

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7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

John Arnett, PhD., C. Pysch.
Chair, Health Research Ethics Board
Bannatyne Campus

8.3 Manitoba Health Information Privacy Committee Approval

Manitoba
Health, Healthy Living and Seniors
Health Information Management
4040-300 Carlton Street, Winnipeg, Manitoba, Canada R3B 3M9
T 204-786-7204 **F** 204-944-1911
www.manitoba.ca

October 19, 2015

Juliano Amador de Silva
University of Manitoba
750 McDermot Avenue
Winnipeg, MB R3E 0T5
dasilvaj@myumanitoba.ca

HIPC No. 2015/2016 – 30
File number to be quoted on correspondence

Dear Juliano Amador de Silva,

Re: Health Policy and Community Pharmacy Provision of Oncology Medications: As Assessment of the Effect of a Changing Health Policy Environment on the Medication Adherence, Cost and Safety of Oncology Medications Provided by Community Pharmacies

The Health Information Privacy Committee has considered and ***approved*** your request for access to data for the purposes of the above named project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that any manuscripts and presentation materials resulting from this study must be submitted to Manitoba Health, Healthy Living and Seniors for review. Specifically, manuscripts must be submitted *at least **30** calendar days* prior to the intended publication and presentation materials must be submitted *at least **10** calendar days* prior to the presentation.

Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by **MCHP**. If you have any questions or concerns, please do not hesitate to contact Saila Parveen, Committee Coordinator at (204)786-7204.

Yours truly,

[redacted]

Shirley Treacy, B.S.P., M.Sc.
Chair, Health Information Privacy Committee

c.c. D. Malazdrewicz

Manitoba
spirited energy

8.4 CancerCare Manitoba Research Resource Impact Committee

CancerCare
MANITOBA
ActionCancerManitoba

○ 675 McDermot Avenue
Winnipeg MB R3E 0V9
Canada

○ 409 Taché Avenue
Winnipeg MB R2H 2A6
Canada

www.cancercare.mb.ca

October 12, 2015

Juliano Amador da Silva
750 McDermot Ave.
Winnipeg MB R3E 0T5

Re: RRIC #2015-054: Health Policy and Community Pharmacy Provision of Oncology Medications: An Assessment of the Effect of a Changing Health Policy Environment on the Medication Adherence, Cost and Safety of Oncology Medications Provided by Community Pharmacies

The above-named study has been approved by the CancerCare Manitoba (CCMB) Research Resource Impact Committee (RRIC) pending receipt of a copy of the HIPC approval letter. Please send a copy of this approval letter to the RRIC coordinator as soon as it is available.

According to the CCMB RRIC submission form that you completed, NO CCMB paper charts will be required for this study and the study expected duration is 2 years.

A copy of the CCMB PHIA form for research is appended to this letter.

ANY SIGNIFICANT CHANGES TO THIS RESEARCH PROJECT MUST BE REPORTED TO THE RRIC BY SUBMITTING A "REQUEST FOR AMENDMENT FORM" FOR CONSIDERATION IN ADVANCE OF IMPLEMENTATION OF SUCH CHANGES. Significant changes include (but are not limited to): a change in the study design or in the data to be collected; a change in the study duration, the patient cohort to be studied, or the number of participants to be studied; the need to review CCMB paper charts (when not originally planned) or the need to review significantly more CCMB paper charts than originally planned; the addition of other trainees or co-investigators to the project; or the inclusion of additional individuals who will have access to the data or database.

Please cite the RRIC number for this study in all future correspondence with the RRIC about it. Please note that annual approval is not required if there are no changes to the project (as outlined above).

This approval is for RRIC use only. For ethics of human use and/or regulatory bodies, approval should be sought from the relevant parties as required.

Yours sincerely,

[redacted]

Rochelle Yanofsky, MD FRCPC
Chair, CCMB Research Resource Impact Committee

Enclosure: CCMB PHIA Form for Research

cc: Cheryl Clague – Cancer Registry/Epidemiology
Jacqueline Sholdice – Privacy Officer
Maureen Crump – Paper Charts
File copy

CancerCare Manitoba
ActionCancerManitoba

RRIC #: 2015-056

THE PERSONAL HEALTH INFORMATION ACT OF MANITOBA

AGREEMENT FOR ACCESS TO
PERSONAL HEALTH INFROMATION
FOR RESEARCH PURPOSES
BETWEEN:

CancerCare Manitoba
(hereinafter referred to as the "CCMB")

-and-

Juliano Amador da Silva
(hereinafter referred to as the "Principal Investigator")

This agreement is used to access personal information for research purposes. Once the Principal Investigator has signed this form and the terms and conditions of access have been approved by CCMB, it becomes a legal agreement between the Principal Investigator and CCMB. The Research Resource Impact Committee application form must be appended to this agreement and forms part of the legal agreement.

The collection of the information referenced on this form is authorized by *The Personal Health Information Act* and will be used only to administer the research project. The CCMB Privacy Officer or designate can answer any questions concerning this agreement or the collection of the information on this form.

Identification of Principal Investigator

Name (last name/first name/initials): Amador da Silva, Juliano

Address: Apotex Centre, 750 McDermot Avenue, Winnipeg, MB R3E 0T5

Telephone: [redacted]

E-mail: [redacted]

Fax:

Title of Research Proposal:
Health Policy and Community Pharmacy Provision of Oncology Medications: An assessment of the effect of a changing health policy environment on the medication adherence, cost and safety of oncology medications provided by community pharmacies

Please provide the following additional information if applicable:

Institutional Affiliation and/or Department: College of Pharmacy

Position: Master's Student

Academic Advisor (if PI is a trainee): Dr. Shawn Bugden

The Principal Investigator has requested access to the following records that contain personal information and are in the custody or under the control of CCMB and agrees to the following terms and conditions:

- not to publish the personal health information in a form that could reasonably identify the individuals concerned.
- to use the information requested solely for the purposes of the above-named approved research project.
- to destroy or remove the study information/data at the earliest opportunity.

1. Describe the safeguards used to protect the confidentiality and security of the personal data/information and/or personal health information:

All of the data for the analysis will reside within the secure computer environment of the Manitoba Centre for Health Policy (MCHP). All of the analyses will be conducted within the secure computer environment of the Manitoba Centre for Health Policy (MCHP).

2. Specify potentially identifying information (ie: name, address, date of birth, initials, PHIN/MHSC numbers) which will be collected and requirement rationale.

Date of birth and scrambled PHIN will be used to link databases within the Data Repository at MCHP. Date of birth will also be used for calculating age (e.g., at date of service) which is necessary to make comparisons with alternative policy approaches. Health care provider and pharmacy will be used to determine trends in prescribing patterns and volume but results will be aggregated and all small cells (<5) suppressed.

3. How will this identifying study information be linked to a study participant?

All linkages will be made via computerized files in the repository at the Manitoba Centre for Health Policy (MCHP). The record linkage will not be used for purposes that can be detrimental to the individuals involved, and the benefits to be derived from such a linkage are clearly in the public interest. In order to link database records across data files, Manitoba Health has undertaken the translation process, where all personal identifiers have been removed and numeric identifiers encrypted.

4. Specify how long study information (stored in any media) will be retained?

All study associated data and programming code will be archived at the time of study completion and removed from MCHP's analysis system. Study completion is identified by the principal investigator or by the submission of a final REB notification of study completion. Consistent with University of Manitoba protocols, archives will be maintained at MCHP for a period of at least seven (7) years and no more than ten (10) years after completion to allow time for questions and clarifications of publications and then all study associated data will be destroyed. The programming code may be retained indefinitely.

5. Specify how will you secure this study information throughout this duration?

Locked room with access given only to MCHP authorized persons. The computer is password protected, requiring a username, four static digits plus 6 continously varying digits unique to each username, distributed through RAS keys. All data will remain on the MCHP main server, no files can be downloaded or removed from the remote terminal.

6. Specify the procedures to destroy study information, stored in any media)? (shred, burn, erase)

Data used at MCHP are de-identified at the source. Manitoba Health datasets created for the

purposes of this study will be deleted after completion of analysis for scholarly articles. Source data are maintained in the Population Health Research Data Repository.

7. Identify all AGENCIES and list the NAMES OF ALL INDIVIDUALS who will have access to the study information now or in the future (including the PI).

University of Manitoba Health Research Ethics Board, PI (Juliano Amador da Silva) and Co-Investigators (Dr. Shawn Bugden, Jordan Nash, Kevin Friesen, Erika Lehmann, and Pat Trozzo)

8. Have all individuals who have access to study information:

Completed PHIA Orientation: ☒ Yes ☐ No

Signed the Pledge of Confidentiality: ☒ Yes ☐ No

If no, contact the Privacy Officer Designate for CCMB (Jacqueline Sholdice [redacted])

CancerCare Manitoba agrees to grant access to the records on the terms and conditions stated above.

Signed at: _____ this _____ day of _____, 2015

Signature of Principal Investigator

[redacted]

Name of Principal Investigator (printed)

Juliano Amador da Silva

Signature of Representative of Institution

Privacy Officer (or designate)
Health Information Services
CancerCare Manitoba
Telephone: (204) 787-2266