The Effect of Free Distribution of Essential Medicines on Adherence by Income Sources and Level

by

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Abstract

Introduction: Public policies aimed at improving medicine adherence are restricted to people with a low income or to social assistance recipients.

Objective: To determine whether the free provision of essential medicines has a different effect on adherence for people with different income levels and sources.

Methods: In this post-hoc subgroup analysis of results from the CLEAN Meds randomized control trial, binary logistic regression was used as the primary analysis to determine whether free medication provision has different effects at different income levels and sources.

Results: Despite the evidence to suggest that the RCT intervention has a significant effect on adherence ($p=0.02$), there was no substantial difference in the effect of free medicine distribution for people with different income levels or sources ($p=0.73$).

Conclusion: The results of this study do not support the idea that programs aimed at improving access to medicines mostly improve adherence for those of certain income groups.

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Chapter 1

Introduction

1 Background

There is a social gradient in health: people with a higher income or greater wealth are healthier than others. Life expectancy in the highest income neighborhoods in Canada is higher than the life expectancy in the lowest income neighborhoods(1). Among Canadian men, life expectancy is 75.6 years among those living in the lowest income neighborhoods and 80.3 years among those living in the highest income neighborhoods(1); for Canadian women the gap is 81.7 years versus 84 years. The same pattern is seen in the United States, where the life expectancy gap between the richest 1% and the poorest 1% is 14.6 years (95% confidence interval (CI) = 14.4 to 14.8 years) for men and 10.1 years (95% CI = 9.9 to 10.3 years) for women(2). Individuals are more likely to report significantly better health outcomes and are less likely to suffer from long-term illness if they have a higher income(3). In Canada, this is seen through an increase in the rates of a number of various general health indicators, such as diabetes and mental health status over time, except for those of higher income brackets(4). For instance, self-rated mental health has increased in prevalence by 42.5% (95% CI = 14.9%-70.1%) for men and 52.9% (95% CI = 27.3% to 78.5%) for women among Canada's poorest quintile between 2003 and 2013, while rates have remained lower and have stayed steady over time among Canada's wealthiest quintile(4).

The association between health and income exists even when controlling for other characteristics such as age, gender, race, ethnicity, and body mass index(5). These health-related inequalities have shown to increase over time with greater disparities in income(6, 7). Multiple

factors likely contribute to these poor health outcomes, such as access to adequate housing, food, and other environmental factors(8). Among these factors, poor access to health care and specifically access to medications has shown to be a contributing factor to poor health outcomes among the economically deprived(8). Medicines including treatments for hypertension, cardiovascular disease and HIV-AIDS are known to be life-saving, but only some people have access to them.

1.1 Medicine access in Canada

Canada does not have a universal drug coverage program. Public and private insurance schemes exist which provide access to medicines for select individuals. Public insurance schemes are those put in place by a government; and are administered by provinces and territories throughout Canada. For instance, in Ontario, outpatient drug coverage is provided to those 65 and older by the Ontario Drug Benefit Program. For those 24 and under, coverage is available through the Ontario Health Insurance Plan, called OHIP. Furthermore, Ontario residents who have high prescription drug costs relative to their income can apply for public drug coverage through the Trillium Drug Program(9).

Private insurance plans are typically offered by employers. Generally, beneficiaries have access to medications through either full-coverage or co-payment plans. Under co-payment schemes, beneficiaries split the cost of medications with insurers, while no cost is split between insurers and those covered under full coverage plans.

For those uncovered by an insurance plan and unqualified for coverage under a publicly funded program, outpatients pay the cost of medications out-of-pocket.

According to a report published by the Conference Board of Canada, using data from 2017, approximately 22,470,000 of 36,150,000 people, or 62% of the people living in the country, are enrolled in private insurance plans. Approximately 22,360,000 (62%) are eligible for

public plan coverage, with 13,091,300 (36%) individuals enrolled(10). According to Statistics Canada, about 19 percent of Canadians self-report being un-insured, or underinsured for their medical needs(11). With Canada's current population, this equates to about 7,500,000 Canadians having no or insufficient drug coverage(11). In Ontario, using 2015 data, 7,741,000 (55%) individuals are covered under private plans(12). With 4,175,000 (30%) enrolled in public plans, 2,242,000 (15%) individuals are left uninsured(12).

1.2 Adherence and out-of-pocket drug expenditure

Low rates of adherence to prescribed medicines is prevalent on a global scale. In review literature, the total proportion of doses properly adhered to across 76 included studies in low-, middle- and high-income countries was approximately 58%(13). Among other factors, out-of-pocket cost is known to be an important predictor of medicine non-adherence(14, 15). This is seen by evaluating trends in adherence following increases in cost-sharing measures between insurance beneficiaries and insurers, where non-adherence has become increasingly prevalent(16).

Out of pocket drug expenditure can affect adherence in people with chronic conditions. A systematic review of adherence among patients suffering from chronic kidney disease shows that increased spending on medications has an adverse effect on adherence in low, middle and high-income countries(17). Similarly, a review of the available literature on adherence patterns among patients suffering from rheumatoid arthritis shows that out of pocket costs are associated with medicine non-adherence among patients with the disease in countries of all income(18). Further, a systematic review on adherence among patients suffering from hypertension showed an increase in co-payments among countries which rely on co-payment systems for medications is associated with poor adherence to prescribed drug regimens(19).

1.2.1 Other implications of out-of-pocket drug expenditure

Increased out-of-pocket spending on medications is not only associated with lower rates of adherence to prescribed dosing schedules, but is also associated with lower rates of medication prescription(20). Additionally, out-of-pocket drug expenditure is related to higher rates of discontinuation of prescribed treatment through the use of pharmaceuticals(20). Aside from patients suffering from various chronic conditions, higher costs of drugs is furthermore associated with higher use of treatment facilities, such as hospitals and clinics; likely a result of improper adherence to prescribed drug dosing practice(21). The effect of non-adherence on the operation of treatment facilities is well exemplified by systematic review literature, which found that increased cost of medicines for patients results in adverse effects on health outcomes as seen through increases in hospitalization related expenses(21).

The implications out-of-pocket medicine costs has on health systems and patient health outcomes is seen when evaluating Medicare beneficiaries who reach a period of reduced drug coverage known as a “part D coverage gap” within the United States. This coverage gap is a period of decreased insurance coverage for Medicare beneficiaries, and thus higher out of pocket drug expenditure, after having spent a certain amount on medications within a given year. In 2019, this amount is $3,820(22). The part D coverage gap lasts until drug expenditures lead patients to reach a second coverage threshold, referred to as “catastrophic coverage”, where coverage heightens and thus cost of medicines decrease for beneficiaries. In 2019, this second threshold is $5,100(22). In a paper focused on evaluating the outcomes among patients who have reached the part D coverage gap, among 11,732 patients included in the study, patients who had reached the coverage gap had higher rates of hospitalization (relative risk (RR) = 1.02, 95% CI = 0.94-1.10), outpatient visits (RR = 1.16, 95% CI = 1.08-1.25) and other visits (RR = 1.17, 95% CI = 1.02-1.32) compared to those with normal coverage(23). Furthermore, with respect to

economic strain on health systems as a result of a lack of coverage, those in the coverage gap had a 9% higher hospitalization cost (RR = 1.09, 95% CI = 1.01-1.18) and 6% higher outpatient costs (RR = 1.06, 95% CI – 0.97-1.17) compared to those who had not reached to coverage gap. With respect to long term health outcomes, following 1-year follow up, researchers found that patients who had been in the coverage gap had a 20% (hazard ratio (HR) = 1.20, 95% CI = 1.05-1.37) and a 22% (HR = 1.22, 95% = 1.01-1.47) increase in all-cause and cardiovascular related mortality compared with patients had not been in the part D coverage gap(23).

1.2.2 Impact of decreased out-of-pocket expenditure on adherence

Reducing out-of-pocket expenses for patients has the potential to improve medicine adherence. Several research articles in the United States show that prescription drug insurance programs which reduce out-of-pocket cost reduce the use of health facilities among patients and generally improves patient outcomes(24). Among United States Medicare beneficiaries, a review of 47 studies found that generally greater drug coverage among patients (and decreased patient cost-sharing) improved medicine adherence(25). The result of reduced out of pocket expenses improving medication adherence is also shown in a systematic review of 62 studies, which shows the same association among insurance beneficiaries suffering from chronic ailments(26).

Given the trends seen in medicine adherence following decreased cost sharing, research has examined the effect full coverage of medications can have on adherence outcomes among patients. The Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial and the Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study (ARTEMIS) set out to evaluate the effect of cost-free provision of necessary medications among patients who had suffered from a myocardial infarction. The main purpose of both the MI FREEE and ARTEMIS trial was to test the notion that the elimination of out-of-pocket costs for evidence-based therapies may promote appropriate use of medications

and improve health outcomes compared to those with conventional access to pharmaceuticals(27, 28). The trial results show improved adherence among patients in the intervention group, while results pertaining to health outcomes are mixed between the two studies(27, 28).

1.3 History of federal universal drug coverage in Canada

In Canada, there is debate about whether the patchwork of private and public drug coverage should persist, or if a universal drug coverage program similar to one that includes healthcare services should be implemented(29).

Historically, advocacy for the implementation of a federal, universal pharmacare plan has been demonstrated through the recommendations of several reports and panels. Most notably, these include the 1964 Royal Commission on Health Services, the 1997 National Forum on health, and the 2002 Royal Commission on the Future of Healthcare in Canada(30-33). The 1964 Royal Commission on Health Services was established by the federal government to report on the existing facilities and future need of the Canadian population(31). Further, the 1997 National Forum on Health was announced by then Prime Minister Jean Chretien, to advise the federal government on innovative ways to improve our health system(32). Finally, the 2002 Royal Commission, or the Romanow commission, was established by the federal government to review Medicare and recommend policies and measures to improve the system(33). Today, the support for the idea of drug care is demonstrated by the synthesis of reports such as Pharmacare 2020, published in 2015 to discuss the future of drug coverage in Canada(34). Endorsed by hundreds of policy makers and academics alike, the report outlines several policy recommendations, such as the establishment of universal coverage of select medicines at little to no direct cost for patients and the establishment of pharmacare as a single-payer system with a publicly accountable management agency. Though the report does not discuss the logistics of actual implementation,

its publishing and endorsement demonstrates that universal drug accessibility is a program in the current interest of influential decision makers.

Despite historical and recent recommendations from various panels and reports, to date a federal plan has failed to become implemented. Among several factors, politics has proven to play a pivotal role in the lack of implementation of universal pharmacare throughout Canada. In Canada, implementing a national program would require cooperation among the federal government and Canada's provinces(35). Historically, political parties at the federal and provincial levels throughout the country have shown to be misaligned on the topic of pharmacare throughout history(35). Further, industry pressure in favour of the expansion of public coverage has shown to play a role in impeding the implementation of universal public coverage. This bias on behalf of the industry is well illustrated by the Conference Board of Canada in their National Pharmacare Summit 2019 report(36).

In a modern context, the recent implementation of pharmacare plans throughout Canadian provinces may show to have an impeding effect on the implementation of a federal universal drug insurance plan. In Ontario, recent amendments made to the Ontario Drug Benefit program to expand provincial drug coverage supports the constitutionalist stance that programs such as pharmacare are a provincial policy to implement(37). The expansion of similar programs and increase in their frequency throughout Canada has led to a patchwork of drug insurance programs. The patchwork of drug coverage throughout Canadian provinces largely insures only those of specific income levels and sources using private and targeted public insurance plans, and leaves many Canadians throughout the country with inadequate or no medical coverage(38).

1.4 Problem

Research evaluating the outcomes on adherence free provision of prescribed medications can have by income source and level is of high value in crafting a Canadian health system.

Regarding the reformation of the drug insurance system throughout Canada, the calls of the National Advisory Council in 2019, the Pharmacare 2020 report, the 1964 Royal Commission on Health Services, the 1997 National Forum on health, and the 2002 Royal Commission, among other reports and pieces of literature, are united in the suggestion for the implementation of a universal drug care program throughout the country. However, suggestions pertaining to how coverage should be expanded differ. For instance, the Conference Board of Canada, a business membership and research group organization, outlines options such as public coverage with income-based deductibles or individual mandates which require Canadians have a specified standard of drug insurance(39). These either expand the patchwork of coverage which currently exists or subsidize cost for those of lower income.

Gaining an understanding of whether free provision of medicines has a different effect on those of different income levels and sources can shed light on what form drug insurance throughout Canada should take in the future. Thus, it is important to evaluate the impact free provision of medication has on adherence among individuals from various sources and levels of income.

1.4.1 Comparable studies assessing the effect of eliminating out-of-pocket payments

The MI FREEE study demonstrates the effect eliminating copayments of medications can have on patient-related outcomes in patients with private insurance(27). This study was conducted in a highly selected group of previously insured post-myocardial infarction patients, without considering participant income. Further, the study restricted medications to antiplatelet, beta-blockers, ACE inhibitors, angiotensin receptor blockers and statins. The absolute adherence for all patients in the control group showed to be 35.9% to 49.0% higher, with adherence 4% to 6% higher in the full coverage group ($p<0.001$ for all comparisons). As an aside to adherence,

rates of total vascular events or revascularisation were significantly reduced in the full coverage group (21.5% vs 23.3%, HR 0.90; 95% CI = 0.90 – 0.99, p=0.03), as was the rate of the first major vascular event (11.0% vs. 12.8%, HR 0.86, 95% CI = 0.74-0.99, p=0.03). Interestingly, the study furthermore found that the elimination of copayments did not increase total spending, with $66,008 spent for the full coverage group and $71,778 spent in the usual-coverage group (relative spending = 0.89, 95% CI = 0.50 to 1.56, p = 0.68). Furthermore, the patient costs for the trial were reduced for drugs and other services in the control group (relative spending 0.74, 95% CI 0.68 – 0.80, p<0.001)(27).

Further, the Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study (ARTEMIS) provides insight into the effect of free provision of medicines on adherence. The study sought to determine whether cost-free provision of $P2Y_{12}$ inhibitors through the use of drug fee vouchers improved adherence to $P2Y_{12}$ inhibitors and health outcomes among post-myocardial infarction patients compared with patients with conventional access, following a finding that 30% to 60% of patients do not complete the recommended 1 year duration of $P2Y_{12}$ inhibitor therapy(28). The patients were recruited from 301 US hospitals which were randomized into study intervention and control groups in a 1:1 ratio. Patients were eligible for inclusion if they were above 18 year of age, hospitalized with ST-segment elevation myocardial infarction, or non-ST-segment elevation myocardial infarction. Patients had to be treated with $P2Y_{12}$ inhibitor at the time of enrollment and had to have any US-based commercial or government health insurance with prescription drug benefits. Frequently, patients cite cost as the reason of medication nonadherence. Compared to a control group with conventional access to medication, the ARTEMIS study found that the study intervention resulted in a 3.3% (95% CI 1.0%-5.5%) absolute increase in persistence to medication adherence

compared to the control group(28). Further, no significant reduction in major adverse cardiovascular events (MACE) was found(28).

Though the MI FREE and ARTEMIS studies provide insight into the potential effect cost-free provision of medication can have on medication adherence, they do not provide insight into the effect free provision can have on eliminating inequalities in medication access and subsequent adherence between patients from various income levels and income sources. This is because all participants in the MI FREEE study had private drug coverage, a mitigating variable in this respect(40). Similarly, all enrolled participants had drug coverage in the ARTEMIS study. Further, the income of participants was not considered in either analysis.

1.4.2 Gaps in existing research

There is currently no controlled research which allows for analysis to be done among individuals from different income groups.

With respect to existing uncontrolled research comparing medication adherence among various levels of income, using census data, research has found that income is positively associated with medicine adherence throughout the country(41). This analysis however does not provide insight whether this correlation is still present when all individuals are given cost-free access to medicines. Further, the study does not provide insight into determining whether the relationship between income level and adherence is causal, given its uncontrolled nature.

The current body of research that has put emphasis on evaluating causal differences among various levels of income is uncontrolled and largely uses health outcomes as the dependent measure. Research in this regard is plentiful, and has been conducted by various parties, including governmental organizations and research groups. A review on the topic run by the United States Department of Health and Human Services sought to determine whether existing literature demonstrates that a causal relationship exists between various income levels,

referred to as income inequality by the researchers conducting the study, and health. The study finds that the existing literature strongly suggests income inequality has effect on population health and well-being(42). These findings are echoed in a systematic review of 26 studies which sought to evaluate the effect of income level on health outcomes, where it was found that income distribution is strongly related to variance in health status throughout various populations(43). Though causal differences in health status in this regard may be partially attributable to differences in medicine adherence, these works do not provide sufficient insight on differences in medicines adherence between individuals with varying income. Further, they provide no insight into the influence universal access to medications has on the trend between income level and medication adherence or health outcomes.

Excluding levels of income from analysis, other existing research evaluates adherence patterns among those classified as low-income. Among low-income groups, medication adherence has shown to be lowest among those with no or limited coverage, subsequently being subject to high out-of-pocket expenditure of medications(44). Among the low-income cohort, other influential factors such as not receiving adequate information about medications, not regularly visiting a primary care provider, and having abrupt changes to treatment regiments also proved to impact the likelihood of adherence(45).

Furthermore, research is currently lacking in evaluating the discrepancies seen in medicine adherence among individuals from various sources of income. In the context of this study, sources of income include wages, non-worked income with drug benefits such as social assistance and disability pay, and non-worked income without drug benefits such as employment insurance. Alike with the research discussed on income level, the body of research currently available on income source evaluates its impact on health outcomes. In this respect, one Canadian study investigated the relationship of income source and health outcomes among

patients living below poverty, with incomes coming from wages and non-worked, drug insured sources(46). Findings from separate path analyses found that poverty status was differentially related to the health of participants from the different income source groups. Specifically, the working poor were generally found to be healthier than their counterparts in the non-working, insured group; except in cases where the working poor were prevented from filling their prescriptions because of a lack of economic resources to do so(46). Concerning the question of why the unemployed insured income group's health outcomes tend to be lower, many factors are likely relevant, however further research suggests an important predictor of health among this cohort is economic capital. This is suggested in review literature, where it is reported that increases in spending on a per-capita basis among social assistance beneficiaries leads to decreases in all-cause mortality among beneficiaries(47).

Within the Canadian context, controlled research evaluating the impact of free access to medicines on adherence among individuals from various income levels and sources is valuable in its potential to allow researchers and policy makers to gain insight into whether universal drug coverage is likely to differentially impact medicine adherence among individuals from various levels and sources of income. Following a review of existing literature, it is apparent that there is a lack of controlled research to provide a more definitive understanding of the impact free access to medications has on adherence between individuals from these different income groups.

1.5 Improved access and essential medicines

In order to allow for improved access to medicines for patients throughout countries of all income brackets, strategies have been developed which include the creation of essential medicines lists. The World Health Organization recommends that nations develop these lists through the inclusion of essential medicines, which would satisfy the priority health care needs of the population(48).

The suggestion for the creation of a short list of essential medicines made by the World Health Organization from the concern that the pharmaceutical market has expanded past that of which demand truly exists for common ailments. This expansion is the product of pharmaceutical marketing practices, which push to expand sales and subsequently increase revenue on a global basis(48). As up to 40% of a nation's health expenditure can go towards pharmaceutical financing, the inflated market size has increased strain on national drug insurance programs. This problem is worsened among developing countries, due to their shortage of economic resources, shortage of trained health personnel, and lack of organized drug policies(48). Within these countries, communicable diseases are particularly prevalent compared to developed nations, and their health outcomes and ease of transmission are of specific concern(48). To combat the effects of prevalent communicable disease, particular essential medicines are of a heightened priority.

To aid in the availability and accessibility of these drugs from a financing perspective, the World Health Organization suggests that a countries' financial resources be put toward a list of essential medicines specific to the population health needs. All included medicines are to be proven effective therapeutically, have acceptable health outcomes and fulfill the health needs of the population(48). Restricted formularies limit the variability of medication used to treat specific ailments, allowing nations to supply and purchase medications in higher quantities. Bulk purchasing allows for increased access from both the perspective of greater drug availability and cost. With nations dedicated to buying greater quantities of specific medications, the bargaining power of countries increases, providing the potential to reduce cost on a per-dose basis(49).

Jurisdictions around the world currently exist which have followed through with the recommendations of the World Health Organization, providing data which proves the merit of restricted formulary lists. Sweden's "Wise List" of approximately 200 medicines and the United

Kingdom's regional short lists are great examples of successful cost-effective, evidence-based formularies in high-income countries(50-52).

Sweden's "Wise List" formulary consisted of medicines for treating common ailments specific to the countries epidemiological need. Drugs on this list were selected based on their efficacy, safety, suitability and ultimate cost effectiveness(50). In evaluating the outcomes of an intervention aimed at directing prescribing practices in accordance with an essential medicines list, it had been found that between 2000 and 2010, adherence to prescribing in accordance with the formulary among prescribers rose from a rate of 69% in 1999 to 77% in 2009(50). In primary care, adherence increased from 83% in 2003 to 87% in 2009. This figure translates to 4 million euros in savings brought to the Stockholm region alone every year(50).

In the United Kingdom, a study was run out of South Bedfordshire to compare the prescribing practices of 50 general practitioners from 11 practices following the implementation of a restricted drug formulary that is equivalent to an essential medicines lists. Furthermore, the study sought to determine the cost-effectiveness of such a program(51). All practices participating in the study participated in creating a district-specific drug formulary with prescribing data from all other general practitioners in the county. Analysis of data following the trial found that prescriptions written for items in the formulary rose significantly within three therapeutic areas, being cardiovascular, musculoskeletal and obstetrics and gynecology. The results of this study show that as a result of changes in practice, the estimated cost savings resulting from adherence to the drug formulary was about 150,000 pounds (3000 pounds/physician) per year(51).

1.5.1 Benefits of using a Canadian sample

Canada is the ideal setting to study the effects of providing people with access to a list of essential medicines. This is because cost-related non-adherence throughout the country is

prevalent. Using 2007 Canada Community Health Survey data, research shows that the rate of cost-related non-adherence is on average 9.6% throughout the country (95% CI = 8.5%-10.6%), and higher for those of low income(41, 49, 52). Further, healthcare services such as seeing a clinician are generally publicly funded on the provincial/federal level, as outlined by the Canada Health Act(52, 53). This is important as this study can isolate the effect of free provision of medicines on adherence. In this respect, Canada furthermore provides the ideal setting because of the current state of drug coverage throughout the country. The nation is unique on the global stage in that it is the only high-income country with a universal health insurance system that does not provide universal coverage of prescription drugs(52, 54).

1.6 Study implications

1.6.1 Framework to discuss study implications

Research from a trial evaluating adherence among groups with different drug coverage stratified by income source and level can yield substantial insight into the benefits universal drug access can bring. In order to identify the policy implications such research can have, it is useful to conceptualize implications with respect to the universal primary goals of a health system(55). Generally, health systems are theorized to be the product of ethics and politics, which lead to the generation of means to provide a health system through the facets of healthcare delivery, financing, practitioner payment and incentivization, and governmental regulation. The intermediate outcomes of the combined means of healthcare delivery regard improvements in healthcare access, quality and efficiency. Pertaining to the ultimate goals of an implemented healthcare system, governments tend to seek improvements in population health status, financial protection against increased expenditure and consumer satisfaction(55). A diagram of these aspects is seen in Figure 1.

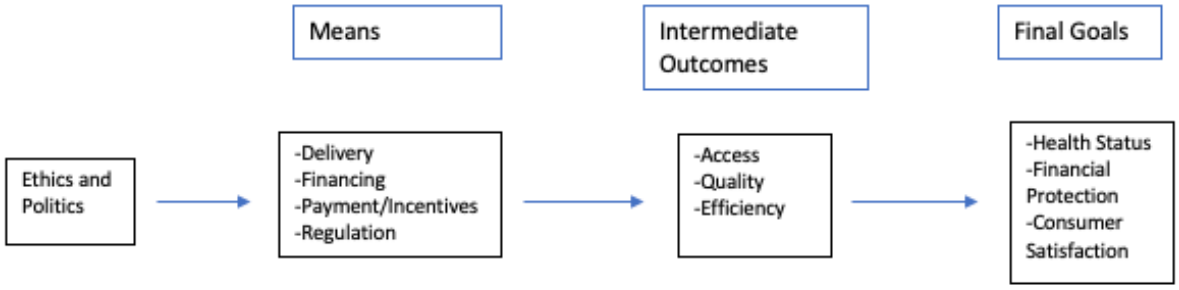

Figure 1: Figure adopted from "What is a Health System? Why Should We Care?". School of Public Health, Harvard University(55).

A discussion of the implications this work has is best focused on the final goals of a healthcare system, as aspects of these goals are further echoed by the Institute for Health Improvement's triple aim framework(56).

1.6.2 Implications

This study's implications are discussed here in the context of the final goals of a health system shown above, being improved health status, financial protection and consumer satisfaction. Regarding health status, as adherence has been shown to be linked to health outcomes throughout various pieces of literature, the results from a study which seeks to evaluate adherence rates between control and intervention groups with focus on identifying patterns of adherence among patients from difference income sources and levels provides profound insight. Specifically, this work determines whether the free provision of medicines has different effects based on income level and income source. With research done in the area, policy makers have the opportunity to make informed choices on the appropriate implementation of a healthcare system with evidence from a controlled trial setting.

Pertaining to financial protection, with respect to consumers, the results of this research sheds light on the potential of a universal access program for essential medicines to improve adherence to medications among particular income level and source groups; through the

alleviation of the financial burden put on them to pay for medications. Concerning financial protection from the governmental perspective, it is important to consider the ultimate effect provision of restricted formularies has had on other health system expenditures from aforementioned trials(21, 23). As adherence is related to health outcomes, this work sheds light on whether free access to essential medicines is likely to lighten the economic burden put on socialized medicine systems present in Canada. This burden is made heavier through patients not adhering to prescribed medications because of cost, subsequently seeking healthcare through other avenues of care. The results of this study will establish whether greater financial protection in this respect will come from providing drug coverage to individuals from particular income levels and sources, or the population as a whole. With this information, policy makers can subsequently make informed decisions on the implementation of a pharmaceutical insurance plan, taking the potential financial benefit of a program's implementation into account.

Finally, the outcomes of this research provide information which allows for policymakers to infer potential beneficiary satisfaction with the program. As the results of this study provide insight into the promotion of equity with respect to medication adherence among individuals from various sources and levels of income, beneficiary satisfaction can be implied from a widespread drug insurance program, should one be implemented.

1.7 Summary

Given the current state of drug coverage in Canada, the intervention in this study may improve adherence to prescribed medications through cost-free access to essential medications, compared with those who hold conventional access to medication. As a direct result of improved medication adherence, the intervention could improve population health if implemented broadly. The specific aim of this analysis is to shed light on whether a universal drug insurance program will benefit only those of specific income level and sources or whether the population as a whole

can benefit. With these results, insight is gained into whether free provision of medicines has a different effect on those of different income levels and sources. Ultimately, the results from this study can help policy makers make informed decisions on the appropriate course of drug coverage in Canada, aiding in shaping a drug health system and settling the debate in government pertaining to implementing a single-payer drug insurance system or maintaining the patchwork of drug coverage which exists today.

1.7.1 Research question

Do income source and level modify the effect of cost-free medicine distribution on adherence?

1.8 Frameworks

1.8.1 Theoretical framework

The theoretical framework motivating the methods and research questions developed for this study are based on the accountability for reasonableness framework. This framework is built around the premise that there is a need to implement limits on health care provisions. As an aim, the framework seeks to outline conditions that must be met in order for organizations to be accepted as legitimate moral authorities for distributing health care fairly(57).

Accountability for reasonableness itself is the idea that the reason or rationale for important limit-setting decisions should be publicly available. These reasons are ones that “fair minded” people can agree are relevant to pursuing patient care under necessary resource constraints. In the context of the framework, “fair minded” people are those who in principle seek to cooperate with others on terms they can justify with one another(57). Four conditions outline the notion of accountability for reasonableness. First is the publicity condition, where decisions regarding both indirect limits and direct limits to care must be publicly accessible.

Secondly, under the relevance condition, the rationale for limit setting decisions should aim to provide a reasonable explanation of how the organization seeks to provide “value for money” in meeting the health needs of a population under resource constraints. A rationale is reasonable if it appeals to evidence, reasons and principles that are accepted as relevant by fair-minded people who are disposed to finding mutually justifiable terms of cooperation. Thirdly, under the revision & appeals condition, there must be mechanisms in place for challenge and dispute resolution regarding limit-setting decisions. Finally, under the regulative condition, there is either voluntary or public regulation of the process to ensure that conditions 1-3 are met.

Ultimately, the purpose of this paper is to support the first and second conditions of the accountability for reasonableness framework; acting as empirical evidence in the implementation of a potential program allotting cost-free access to a restricted drug formulary for Canadian beneficiaries. This proposition is discussed in many sources previously mentioned in this paper (30-34). In addressing the first condition, the methods of this paper ensure limits to care concerning adherence to medication, being the outcome variable of this analysis, are reported and discussed. In addressing the second condition, previously discussed literature supports the notion that restricted formulary lists increase state bargaining power and subsequently reduce the cost of medicines on a per dose basis(49). Further, medicine non-adherence as a result of cost increases net healthcare expenditure, even when factoring in the cost of medications in a controlled setting(21, 24, 27). Thus, through evaluating whether cost-free access to medication improves adherence to medicines differentially between various income sources and levels, this study provides insight into whether public drug coverage with restricted formulary lists can provide “value for money” in meeting the varied health needs of a population.

1.8.2 Conceptual framework

As found from previous research, reduced out-of-pocket expenses for medications is associated with improved adherence. In this analysis, accordingly, it was theorized that the study intervention of cost-free access to essential medicines has a significant, positive relationship with adherence. Furthermore, it was hypothesized that income level and income source effect the relationship seen between the study allocation group and adherence.

The analysis done in this paper used data obtained from the Carefully SeLected and Easily Accessible at No charge Medications (CLEAN Meds) study(52). Thus, the variables included in models run were limited to the variables collected throughout the duration of the trial. Age, gender, income, race and location are all variables which have been reported to be associated with adherence to medications(58, 59). These variables were included in the models used in the analysis as control variables. The conceptual map of the theoretical framework can be viewed in Figure 2.

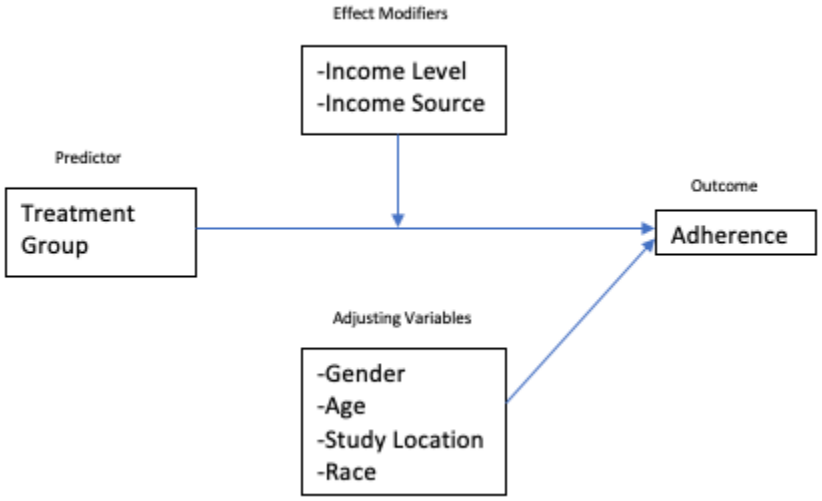

Figure 2: Conceptual map of the conceptual framework proposed in this analysis.

Chapter 2

Methods

2 Study description

The methods description for this analysis is based on the clinical trial information found in the CLEAN Meds study protocol(52).

2.1 Sampling procedures

2.1.1 Setting

The CLEAN Meds trial took place in several practice settings. One setting was an urban family practice affiliated with St. Michaels Hospital in Toronto with six physical sites (Toronto has a population of approximately 2.6 million individuals, with 40,000 rostered patients in practice), and three rural family practices in Ontario. One practice was the Huron Shores Family Health Team in Blind River, Ontario (Blind River has a population of approximately 3,500 individuals). The other practices were the Municipality of Assiginack Family Health Team and the Manitoulin Central Health Family Team in Manitoulin Island, Ontario (Manitoulin Island has a population of approximately 12,000 individuals). All sites were using the same electronic medical record.

2.1.2 Eligibility criteria

Patients aged 18 years or older who had reported medicine non-adherence in the last 12 months prior to the beginning of the study were eligible to take part in the study. In order to identify non-adherence, the study utilized a question which was taken from the Canadian

Community Health Survey, which is similar to surveys used in other countries. The question reads “in the last twelve months, did you not fill a prescription or do anything to make a prescription last longer because of the cost?”(60). Exclusion criteria for participants included family member(s) living at the same address of patients already enrolled in the study, and those who had joined the family practice within the last 6 months. Patients who were eligible for public medicine insurance but who do not have such coverage (e.g., patients who do not have access to their benefit card) were not excluded from the study. Furthermore, patients with public and/or private medicine insurance were not excluded from the study, as long as they reported cost-related non-adherence to medications. Cost-related non-adherence for those covered is commonly due to private insurance companies requiring co-pay, causing 7% of those with prescription medicine insurance in Canada to still report cost-related non-adherence(60). Individuals who have private insurance and were not experiencing cost-related barriers to adherence were not eligible to participate in the study.

2.1.3 Randomization and patient recruitment

Patients for the study were recruited during primary care visits. During visits, clinicians briefly informed patients about the study, and interested patients were provided further information by research assistants. Research assistants across the three sites used in this trial were responsible for ultimately enrolling patients. Eligible patients were centrally randomized into two groups: the intervention group, where patients received free and conventional access to a carefully selected list of essential medicines, and a control group, where patients had conventional access to drugs. In a clinical setting, all participants received usual care. Randomization was concealed using a web-based tool hosted by the Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Institute of St. Michaels Hospital. The

randomization method was designed in R and is stratified by site using permuted blocks of varying sizes. The research investigators and analysts were blinded to treatment allocation in order to reduce ascertainment bias. Considering the nature of the interventions, patients, clinicians and pharmacists were not blinded to treatment allocation.

2.1.4 Sample size rationale for trial

The CLEAN Meds trial was powered for the primary outcome of adherence to prescribed medications. Based on previous studies, an expected adherence rate was 40%-65%(27, 61, 62). It was furthermore expected that at least 90% of patients in the intervention group will be adherent to the intervention, in the sense that they will agree to take at least one of the medicines prescribed. It was furthermore believed that 10% absolute improvement in appropriate adherence is the minimum difference that is important in a clinical setting. A sample size of 392 per group is required to have a power of 80% to detect a 10% absolute difference in adherence for any control group adherence values between 40% and 60%. Inflation for dropouts is applied to the sample size calculation at a two-sided type-1 error of 0.05, as dropouts were considered non-adherent. Based on previous trials, it was expected the dropout rate would be approximately 5%(27, 61, 62).

2.2 Study design

This was a post-hoc subgroup analysis of results from a parallel two-arm, superiority, individually randomized control trial with 1:1 allocation. The trial is furthermore open label as participants are told their allocation group following randomization. The design of the CLEAN Meds trial is summarized in Figure 3.

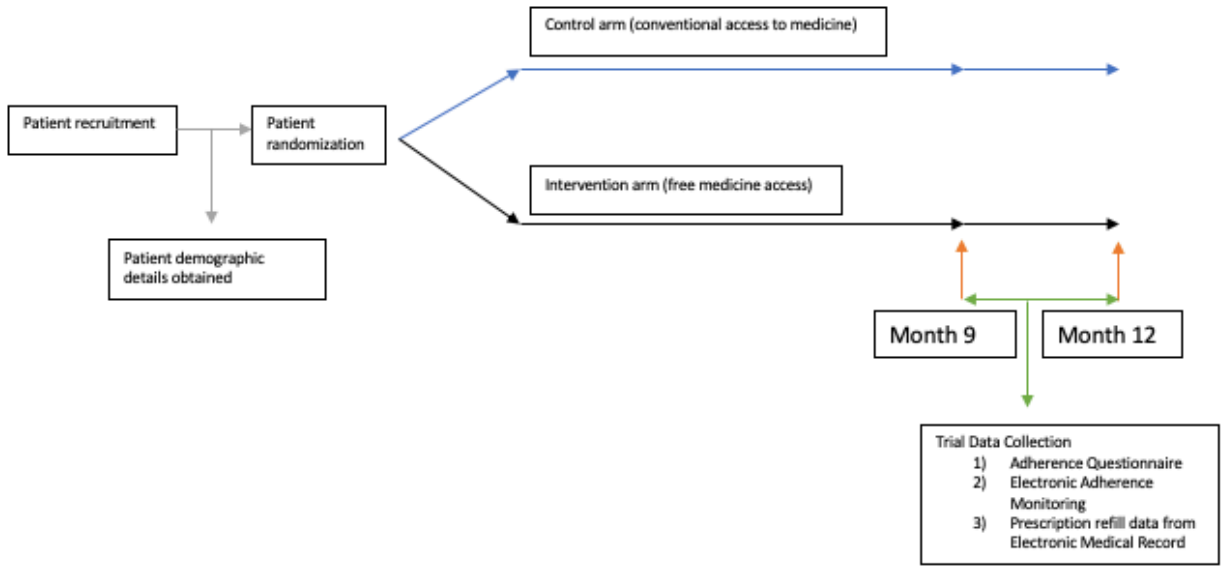

Figure 3: Adopted from the design and timeline of the CLEAN Meds trial(52).

2.2.1 Intervention arm

Patients in the intervention arm of the study received cost-free and convenient access to a list of essential medicines (see http://www.cleanmeds.ca for a list of these medicines). The prescribing clinicians and intervention patients both had access to the list of medicines. Patients still had access to medicines not found on the essential medicines list, however these were accessed in a conventional way.

The essential medicines list was adapted from the 2013 WHO model list of essential medicines(63). A four-step interdisciplinary, clinical peer review process was used in finalizing the list of medications to be used in this study. Additional medicines were added or removed from the list based on clinical suggestions, pharmaceutical industry suggestions and retrospective prescribing data, obtained from electronic medical record data(64). A panel of clinician-scientists who were free of financial conflicts of interest convened every 3 months to evaluate the evidence and vote on recommended changes to the list using a modified nominal group technique(65, 66).

For medicines removed from the list throughout the duration of the study, patients who were initially prescribed these medicines on enrolment remained on them.

Medicine dispensing for the essential medicines was primarily done through mail. A supply of medicines needed for acute care (for example, antibiotics) were stocked at each clinic study site and available for on-site dispensing by the clinician, and dispensing records were kept to prevent contamination. For all other medicines covered on the list, the research pharmacist (who has direct access to patient electronic medical records and prescriptions) dispensed these medicines as prescribed. Medicines had the potential to be delivered to a study participant within the expected geographical region in Ontario in 1 day. Controlled substances, such as opioids, sedatives and stimulants, were not included in the intervention for safety reasons. Patients who were prescribed these medications had access to these medicines in their usual fashion and not through the research study.

After shipment, a pharmacist who has access to interpretation services in 200 languages called to counsel patients about their medicines. Patients without a permanent home address had the option to choose an alternate delivery address (for example, a clinic or a support centre). Potential prescribers outside of the study sites (for example, urgent care providers or secondary care providers) were faxed a letter with the list of essential medicines, and patients were provided with a card with information about the list that can be shared with other providers. Both forms of communication included contact information to reach the research pharmacist.

2.2.2 Control arm

Participants allocated to the control arm had their usual access to medicines and their usual care.

2.3 Data collection

All patients were followed for 12 months from their date of enrolment. Following enrolment, at the beginning of the trial, patient information, including information pertaining to patient demographics, was collected. Medicine adherence was collected during regularly scheduled appointments. No clinic visits were necessary for data collection. There were no differences between the two groups in how data was collected or assessed.

2.3.1 Primary outcome measure

The primary outcome of this trial was adherence to prescribed medicines, and was determined at 12 months by evaluating the number of prescriptions that were taken as prescribed or adhered to for greater than 80% of doses.

The method for assessing medicine adherence was electronic medical record (EMR) chart reviews and self-report data. EMR chart reviews were conducted at the end of the study in order to identify issue dates for prescriptions and determine if chronic-use medicines are re-ordered when expected in a blinded fashion. Prescriptions written within 18 days of the expected renewal date (20% of typical renewal period of 90 days) were classified as adherent. The outcome measure was continuous, and ultimately reported as a percentage of properly adhered to doses based on prescription renewal time. While susceptible to pill dumping, where patients dispose of medications as opposed to taking them, like other objective measured such as pill counts, electronic medical record reviews do not depend on recall(67). Prescriptions for medicines intended to be taken on an “as needed” basis (e.g. analgesics, salbutamol) were excluded from the adherence analysis.

For participants who's EMR chart review data was not available, self-reported adherence was used as the outcome measure. Participants were asked by telephone or email about the number of missed doses in the past week and the percentage of adherence was calculated.

2.4 Analysis

2.4.1 Variable definitions

In the binary logistic regressions run, pertaining to the outcome variable, participants were coded as adherent if they had taken more than 80% of doses which they were supposed to take for all medications prescribed. Participants were coded as non-adherent if they had taken any one of their medications at a rate of less than 80% of the intended dosage. For the Poisson regressions run, the outcome was the number of medicines adhered to on a discrete numerical scale.

The income level variable was stratified into three levels: very low income (<$20 000), below poverty income ($20,000-$40,000), and above poverty income (>$40 000). The very low income cut-off follows closely with figures reported by Statistics Canada, making low income in this analysis classified as those in households making less than $20,000 per year(68). The below poverty threshold was characterized as those with a household income of between $20,000-$40,000, considering the Canadian household poverty line of $37,542(69). The above poverty group consisted of individuals with incomes greater than $40,000. The income level was coded as a single, ordinal variable.

There are three aspects of income source that were coded as three separate binary variables: waged (including job salaries and income from self-employment) versus non-waged income (those who are unemployed uninsured and unemployed insured), unemployed uninsured (including unemployment insurance and job-related retirement pensions) versus all others (those

who are waged and unemployed insured), and unemployed insured (including disability supports and welfare) versus all others (those who are waged and unemployed uninsured).

Race was coded as a binary variable: white participants and all others. Study location was coded as a binary variable: rural or urban. Gender was coded as a binary variable: male and female. The treatment group was coded as a binary variable: control group and intervention group. Age and the number of medicines prescribed remained as single, discrete numerical variables.

In terms of reference groups, for gender, males were used. For race, the all others (not white) group was used as the reference. For location, rural was used as the reference group. For treatment group, the study control is used as the reference group. For income level, those making less than $20,000 annually were used as the reference group.

For the waged versus all others variable, those who are not waged were used as the reference group. For the unemployed insured versus all others variable, those who are not unemployed and insured were used as the reference group. For the unemployed uninsured versus all others variable, those who were not unemployed and uninsured were used as the reference group.

2.4.2 Statistical analysis

The effect of the intervention was evaluated in improving adherence. A Pearson chi-square test was performed, and the p-value was reported and interpreted. Following this analysis, tables of the various income sources and levels were created against adherence, in order to establish the differences in adherence between the control and intervention income level/source groups. The sample size in each income group was given, along with the percentage of individuals in that group.

Models were then run to evaluate the income source by study treatment group and income level by study treatment group interaction terms in predicting medicine adherence. The primary analysis used a binary logistic regression approach, with the outcome variable being adherent or not adherent. To evaluate the predictive value of all of the interaction terms combined, two separate models were run. The first model included the control variables of treatment group, age, gender, race, number of medicines prescribed and study location; along with the income source variables and the income level variable. This model appeared as follows:

Model 1: $\text{Logit}(P)_{\text{Adherence}} = \beta_0 + \beta_{\text{Age}} \times \text{Age} + \beta_{\text{Gender}} \times \text{Gender} + \beta_{\text{Race}} \times \text{Race} + \beta_{\text{Location}} \times \text{Location} + \beta_{\text{Treatment Group}} \times \text{Treatment Group} + \beta_{\text{Income Level}} \times \text{Income Level} + \beta_{\text{Income Sources}} \times \text{Income Sources} + \beta_{\text{Number of Medicines}} \times \text{Number of Medicines}$

The second model included the control variables of treatment group, age, gender, race, number of medicines prescribed and study location; along with the income source and income level variables and their respective interaction terms (income sources*study allocation group, income level*study allocation group). This model appeared as follows:

Model 2: $\text{Logit}(P)_{\text{Adherence}} = \beta_0 + \beta_{\text{Age}} \times \text{Age} + \beta_{\text{Gender}} \times \text{Gender} + \beta_{\text{Race}} \times \text{Race} + \beta_{\text{Location}} \times \text{Location} + \beta_{\text{Treatment Group}} \times \text{Treatment Group} + \beta_{\text{Income Level}} \times \text{Income Level} + \beta_{\text{Income Sources}} \times \text{Income Sources} + \beta_{\text{Number of Medicines}} \times \text{Number of Medicines} + \beta_{\text{Income Level * Treatment Group}} \times \text{Income Level * Treatment Group} + \beta_{\text{Income Sources * Treatment Group}} \times \text{Income Sources * Treatment Group}$

To evaluate the combined predictive value of the interaction terms, a chi-square test was done to evaluate the statistical significance of the difference in the log-likelihood between the models. To obtain the chi-square test statistic, twice the difference in the log likelihoods between the models was calculated(70). To obtain the p-value, the difference in the degrees of freedom

between the two models was used. The chi-square test value was reported, along with the degrees of freedom and respective p-value.

In addition to the previously mentioned reported values aimed at determining the predictive value of the model interaction terms, the variable coefficients, standard errors, Wald-test values and respective p-values, and odds ratios with respective 95% CI's were reported for all continuous and binary categorical variables for Model 1. For income level, as it is categorical and non-binary, the likelihood ratio test statistic and respective p-value were reported in place of the Wald test.

As a sensitivity analysis of methodological approach, Poisson log-linear models were run. For these models, the total number of medicines adhered to were used as the outcome variable. In addition, the log of the total number of medicines prescribed was included in these models as an offset. To evaluate the predictive value of all of the interaction terms combined, two separate models were run. The first model included the control variables of treatment group, age, gender, race, number of medicines prescribed and study location; along with the income source variables and the income level variable. This model appeared as follows:

Model 3: $\log(\mu) = \beta_0 + \beta_{Age} \times \text{Age} + \beta_{Gender} \times \text{Gender} + \beta_{Race} \times \text{Race} + \beta_{Location} \times \text{Location} + \beta_{Treatment\ Group} \times \text{Treatment Group} + \beta_{Income\ Level} \times \text{Income Level} + \beta_{Income\ Sources} \times \text{Income Sources}$

The second model included the control variables of treatment group, age, gender, race, number of medicines prescribed and study location; along with the income source and income level variables and their respective interaction terms (income sources*treatment group, income level*treatment group). This model appeared as follows:

Model 4: $\log(\mu) = \beta_0 + \beta_{Age} \times \text{Age} + \beta_{Gender} \times \text{Gender} + \beta_{Race} \times \text{Race} + \beta_{Location} \times \text{Location} + \beta_{Treatment\ Group} \times \text{Treatment Group} + \beta_{Income\ Level} \times \text{Income Level} + \beta_{Income\ Sources} \times \text{Income Sources} +$

$\beta_{\text{Income Level * Treatment Group}}$ x Income Level * Treatment Group + $\beta_{\text{Income Sources * Treatment Group}}$ x Income Sources * Treatment Group

Alike with what was done for Models 1 and 2, to evaluate the combined predictive value of the interaction terms, a chi-square test was done between the two models to evaluate the statistical significance of the difference in the log-likelihood between them. The chi-square test value was reported, along with the degrees of freedom and respective p-value. Further, the variable coefficients, standard errors, Wald-test values and respective p-values, and incident rate ratios with respective 95% CI's were reported for all continuous and binary categorical variables for Model 3. For income level, the likelihood ratio test statistic and respective p-value were reported in place of the Wald test.

In order to evaluate multicollinearity between the predictor variables, variance inflation factor (VIF) values were calculated. Values of less than 5 were generally considered acceptable. To evaluate the dispersion assumption of a Poisson regression, a negative binomial model was fit with the same variables as were used in the Poisson regression in Model 3. A chi-square test was done between Model 3 and the negative binomial model to evaluate the statistical significance of the difference in the log-likelihood between them. The chi-square test value was reported, along with the degrees of freedom and respective p-value. Should the difference be significant, this will be interpreted as evidence against this assumption being met.

For this study, the method of accounting for missing data was case deletion among participants who had missing data for any of the variables used in the analyses. For descriptive statistics, the participant population was summarized in the control and intervention groups before and after case deletion. Participant demographics in both the included and excluded study sample were summarized in the control group and intervention group. For categorical variables,

the total number of participants in each respective group was reported, in addition to the proportion of individuals in that group. For the number of medicines prescribed, the mean and median value was reported for each group. Further, for age; the mean value was reported along with the standard deviation. The included and excluded samples were compared to determine if the included sample was representative of those excluded. To do this, a chi-square test was run between included and excluded groups for each variable. Following this, the included sample was then reported by their adherence in the control and intervention group to evaluate the respective population's distribution and characteristics. Lastly, the number of participants prescribed different medications was summarized under the anatomical therapeutic chemicals classification system main groups.

All data analysis was done using SPSS version 25.

2.5 Management

The CLEAN Meds research team received implementation assistance from the Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Institute of St. Michaels Hospital. Study data and patient questionnaires were entered and maintained using the REDCap database, which is a secure, password-protected database(71). REDCap was accessed using the internet for data entry purposes. Corrections and changes in the data management system were tracked with the retention of the original data and the corrected data with the data entry and submitting personnel.

2.6 Public involvement

The trial intervention and some of the outcomes were co-designed by a panel consisting of 11 community members, recruited through either canvassing, random digital dialing or public

postings. Recruited community members met with the research team monthly, starting more than 6 months before the study started. These meetings continued throughout the progression of the study.

2.7 Monitoring

2.7.1 Data and safety monitoring board

The Data and Safety Monitoring Board (DSMB) met every three months. The primary purpose of the board was to ensure medicine incidents were properly addressed. Each medicine error was reported to the DSMB immediately. The DSMB made recommendations to the research team about how to mitigate the harm from the medicine incidents and how to prevent future similar errors. The DSMB had the power to recommend discontinuation of the trial if there was an excess of medicine incidents or if identified incidents were not appropriately managed.

2.7.2 Adverse events

Monitoring for medicine incidents and adverse drug reactions occurred from the point of enrollment in the study. Monitoring proceeded until 3 months after the completion of the 12-month study period for each participant. The risk of medicine incidents was mitigated by having the research pharmacist review patients' EMR before initiating or transitioning to alternate treatments. Clinicians were provided with instructions about how to manage patients who experience discontinuation effects. Discontinuation effects were reported as medicine adverse effects. Medicine incidents and serious adverse events were collected in the electronic case report form, and each event was reported to the DSMB. The DSMB assessed ongoing safety of the intervention with this information.

2.8 Ethical considerations

Ethics approval for the conduction of the CLEAN Meds trial was obtained from the St. Michael's research ethics board, the Huron Shores Family Health Team Research Ethics Committee and the Laurentian University Research Ethics Board. There are no restrictions on dissemination of the results.

Chapter 3

Results

3 Results from analysis

3.1 Descriptive statistics

The total trial population was 786, including 391 individuals in the control group (50%) and 395 in the intervention group (50%). For this analysis of income level and source, we excluded 165 (21% of 786) participants missing income level data and 50 (6% of 786) missing income source data and, after other exclusions (see Figure 1), results for 479 (61% of 786) of participants were analyzed. A flow chart of the allocation group sizes before and after case deletion is seen in Figure 4.

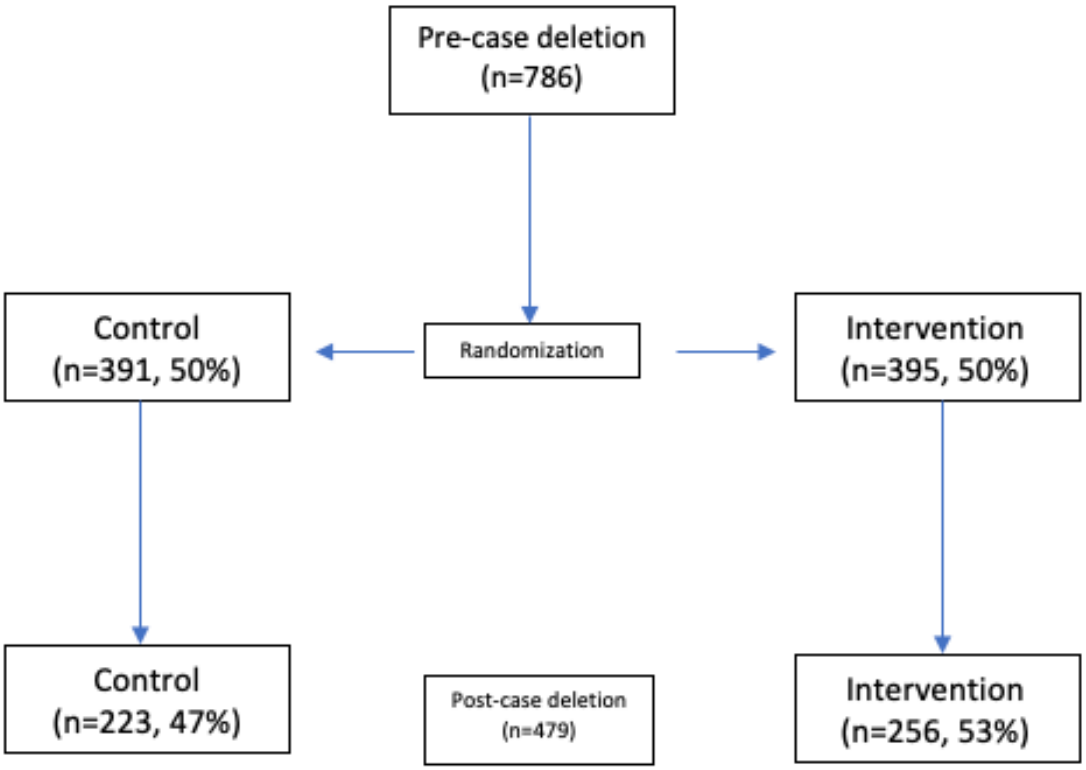

Figure 4: Study allocation group size before and after case deletion. Percentages are based on the proportion of the allocation group size against the total sample size before or after case deletion.

Participants included in the analysis were similar to those excluded with respect to race, gender, age and income level. The included population was generally more urban, unemployed uninsured and unemployed insured, and were less waged. The mean number of medicines prescribed was 3 for both intervention and control in the sample used for the analysis. The median for the control was 2 and was 3 for the intervention. The control group among the excluded population had a mean of 1 medication to adhere to (median of 2). The intervention group had a mean of 2 medications to adhere to (median of 2). Baseline characteristics of the

study participants are shown in Table 1.

		Allocation Group					
		Control		p-value	Intervention		p-value
		Included	Excluded		Included	Excluded	
Gender	Female	53% (118/223)	61% (101/167)	0.143	55% (141/256)	57% (79/139)	0.742
Age		52(13)	48(15)		52(14)	50(15)	
Race	White	67% (149/223)	69% (111/161)	0.660	64% (163/256)	67% (93/138)	0.464
Study Location	Urban	72% (161/223)	63% (106/168)	0.057	73% (188/256)	58% (81/139)	<0.001
Income Source	Wage	57% (126/223)	80% (110/137)	<0.001	45% (115/256)	73% (80/110)	<0.001
Income Source	Unemployed, Uninsured	20% (45/223)	9% (13/137)	<0.001	23% (60/256)	19% (21/110)	0.361
Income Source	Unemployed, Insured	23% (52/223)	10% (14/137)	<0.001	16% (47/256)	8% (9/110)	0.013
Income Level	<20000	37% (83/223)	39% (31/80)	0.891	44% (113/256)	42% (26/62)	0.870
	20000-40000	36% (81/223)	38% (30/80)		34% (86/256)	37% (23/62)	
	>40000	26% (59/223)	24% (19/80)		22% (57/256)	21% (13/62)	

Table 1: Baseline characteristics of all variables in the included and excluded sample populations. Percentage figures are based on the total number of individuals for a given variable in a column. For the age variable, the bracketed number represents the standard deviation. The income level p-value is the result from a single 2x3 chi-square test.

For the number of included participants reported by their adherence in either the control or intervention groups, refer to Table 2 for the categorical variables used in the models. Mean and standard deviation values for age can be found in Table 3. Further, the number and percentage of participants prescribed different medicines can be found in Table 4.

		Allocation Group							
		Control				Intervention			
		Adherence							
		No		Yes		No		Yes	
		Count	Population %	Count	Population %	Count	Population %	Count	Population %
Gender	Female	71	14.8%	47	9.8%	71	14.8%	70	14.6%
	Male	64	13.4%	41	8.6%	57	11.9%	58	12.1%
Race	Other	52	10.9%	22	4.6%	56	11.7%	37	7.7%
	White	83	17.3%	66	13.8%	72	15.0%	91	19.0%
Study Location	Rural	26	5.4%	36	7.5%	24	5.0%	44	9.2%
	Urban	109	22.8%	52	10.9%	104	21.7%	84	17.5%
Income Source	Wage	74	15.4%	52	10.9%	67	14.0%	88	18.4%
	Unemployed, Uninsured	25	5.2%	20	4.2%	38	7.9%	22	4.6%
	Unemployed, Insured	36	7.5%	16	3.3%	23	4.8%	18	3.8%
Income Level	<20000	55	11.5%	28	5.8%	64	13.4%	49	10.2%
	20000-40000	51	10.6%	30	6.3%	38	7.9%	48	10.0%
	>40000	29	6.1%	30	6.3%	26	5.4%	31	6.5%

Table 2: Study population distribution among the variables used.

	Allocation Group							
	Control				Intervention			
	Adherence							
	No		Yes		No		Yes	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Age	51	14	54	13	52	14	51	14

Table 3: Sample descriptive statistics pertaining to age.

Anatomical Therapeutic Chemical main group (Examples Commonly Prescribed)	Study Intervention Group	Study Control Group
Nervous System (acetaminophen, sertraline, gabapentin)	424 (20%)	450 (20%)
Alimentary tract and metabolism (rabeprazole, metformin, insulin)	381 (18%)	403 (18%)
Cardiovascular system (atorvastatin, ramipril, amlodipine)	326 (15%)	366 (16%)
Respiratory system (salbutamol, tiotropium, fluticasone)	274 (13%)	264 (12%)
Dermatologicals (hydrocortisone, betamethasone)	161 (7%)	159 (7%)
Blood and blood forming organs (acetylsalicylic acid, ferrous fumarate)	125 (6%)	140 (6%)
Musculoskeletal system (naproxen, ibuprofen)	117 (6%)	128 (5%)
Genito urinary system and sex hormones (estradiol)	116 (5%)	124 (5%)
Anti-infectives for systemic use (amoxicillin)	86 (4%)	88 (4%)
Systemic hormonal preparations (levothyroxine)	40 (2%)	37 (2%)
Other	21 (1%)	24 (1%)

Table 4: Number and percentage of participants prescribed medicines in the total CLEAN Meds study by Anatomical Therapeutic Chemicals Classification System main groups(72).

3.2 Analysis

3.2.1 Adherence

Overall adherence, being the binary classification of adherent to all prescribed medicines, was higher in the intervention group (128/256, or 50% of the intervention population were adherent) than the control group (88/223, or 39% of the control population were adherent) (chi-squared; 5.35, 1 degree of freedom, p=0.02).

The effect of the study intervention can be seen for individuals of the different income sources and levels in Tables 5, where the percentage adherent of each variable group was higher in the intervention group for every group of income source and level, with the exception of the unemployed/uninsured income source group.

	Study Allocation Group	
Income Category	Control	Intervention
<20000	28% (28/83)	43% (49/113)
20000-40000	37% (30/80)	56% (48/86)
>40000	51% (30/59)	54% (31/57)
Waged	41% (52/126	57% (88/155)
Unemployed/Uninsured	44% (20/45)	37% (22/61)
Unemployed/Insured	31% (16/52)	44% (18/41)

Table 5: Adherence among the various groups of income under respective intervention groups. Percent figure is a reflection of the proportion of the population in each income group.

3.2.2 Study predictors

3.2.2.1 Overview

In the primary analysis (binary logistic regression) to determine if income level or income source modified the effect of the free distribution intervention on adherence, we found little support for effect modification, as adding the interaction terms between income level and treatment group and between income source and treatment group did not make a significant difference in model fit ($p = 0.73$).

Further, it can also be noted that the evidence derived from the primary analysis was not strongly supportive of the notion that income source or level are associated with adherence, as the p-value of income level was 0.12, while the p-value of the income source variables were 0.12 (for the waged versus all others variable) and 0.46 (for the unemployed insured versus all others variable).

Though the main results between the logistic and Poisson regressions are similar, the binary logistic results are considered more reliable as the likelihood ratio test between Model 3 and its negative binomial equivalent yielded a low p-value, suggesting overdispersion, and thus the assumptions of Poisson regressions being violated.

3.2.2.2 Results

For the primary analysis, the chi-square test done between the binary logistic model without interaction terms (Model 1) and the binary logistic model with interaction terms (Model 2) to evaluate the significance of the difference in the log-likelihood between them yielded a chi-square value of 1.286. On 3 degrees of freedom, this result had a p-value of 0.73.

The findings from Model 1 provided supporting evidence for a relationship between adherence and age (odds ratio(OR)=1.02, 95% CI=1.00-1.04, p=0.03), treatment group

(OR=1.99, 95% CI=1.32-2.99, $p=1.0x10^{-3}$), study location (OR=0.37, 95% CI=0.22-0.62, $p=1.4x10^{-4}$) and the number of medicines prescribed (OR=0.69, 95% CI=0.62-0.77, $p=7.7x10^{-11}$) (Table 6). The likelihood ratio test for income level yielded a test statistic value of 2.38, with a respective p-value of 0.12 (β=0.21, Standard Error (SE)=0.14, OR=1.24, 95% CI=0.94-1.62), where those making less than $20,000 annually were used as the reference group.

	B	Standard Error	Wald	p-value	Exp(B)	95% CI (Exp(B))	
Parameter						Lower	Upper
Age	0.019	0.009	4.861	0.027	1.019	1.002	1.036
Gender	-0.246	0.208	1.393	0.238	0.782	0.520	1.176
Race	0.332	0.233	2.031	0.154	1.394	0.883	2.203
Location	-1.001	0.263	14.514	<0.001	0.368	0.220	0.615
Treatment Group	0.686	0.209	10.735	0.001	1.986	1.317	2.994
Income Level	0.212	0.138	2.371	0.124	1.237	0.944	1.620
Waged versus Non-Waged	0.432	0.280	2.380	0.123	1.541	0.890	2.669
Unemployed Insured versus All Others	0.246	0.331	0.553	0.457	1.279	0.668	2.448
Total Number of Medicines Prescribed	-0.369	0.057	42.329	<0.001	0.691	0.618	0.773
Constant	-0.236	0.676	0.122	0.727	0.790		

Table 6: Statistical summary of Model 1. For gender, males are used as the reference group. For race, non-white is used as the reference group. For location, rural is used as the reference group. For treatment group, the study control is used as the reference group. For waged versus all others, those who are not waged are used as the reference group. For unemployed insured versus all others, those who are not unemployed insured are used as the reference group. The unemployed uninsured income source was used as a reference group for the analysis, thus the unemployed uninsured versus all others variable was omitted.

For the sensitivity analysis, the chi-square test done between the Poisson log-linear model without interaction terms and the log number of medicines prescribed as used as the offset (Model 3) and the Poisson log-linear model with interaction terms and the log number of medicines prescribed as used as the offset (Model 4) to evaluate the significance of the difference in the log-likelihood between them yielded a chi-square value of 1.402. On 3 degrees of freedom, this result has a p-value of 0.71.

The evidence derived from Model 3 was strongly supportive of an association between adherence and study location (incidence rate ratio (IRR)=1.05, 95% CI=0.90-1.22, $p=4.0x10^{-3}$) (Table 7). The likelihood ratio test for income level yielded a test statistic value of 0.22, with a respective p-value of 0.64(β=0.11, SE=0.43, IRR=1.09, 95% CI=0.96-1.23), where those making less than $20,000 annually were used as the reference group.

	B	Standard Error	Wald	p-value	Exp(B)	95% CI (Exp(B))	
Parameter						Lower	Upper
Age	0.003	0.003	1.466	0.226	0.539	0.346	0.840
Gender	-0.024	0.063	0.140	0.708	1.003	0.998	1.009
Race	0.046	0.076	0.362	0.547	0.977	0.864	1.105
Location	-0.223	0.077	8.402	0.004	1.047	0.902	1.215
Treatment Group	0.084	0.063	1.787	0.181	0.800	0.688	0.930
Income Level	0.011	0.043	0.069	0.792	1.087	0.962	1.229
Waged versus Non-Waged	0.141	0.084	2.815	0.093	1.011	0.930	1.100
Unemployed Insured versus All Others	0.148	0.093	2.497	0.114	1.151	0.977	1.356
Intercept	-0.619	0.227	7.452	0.006	1.159	0.965	1.392

Table 7: Statistical summary of Model 3. For gender, males are used as the reference group. For race, non-white is used as the reference group. For location, rural is used as the reference group. For treatment group, the study control is used as the reference group. For waged versus all others, those who are non-waged are used as the reference group. For unemployed insured versus all others, those who are not unemployed insured are used as the reference group. The unemployed uninsured income source was used as a reference group for the analysis, thus the unemployed uninsured versus all others variable was omitted.

3.3 Assumptions testing

In testing for multicollinearity, the VIF values among all of the variables included all fall below 5. These values can be seen in Appendix A, Table 1 and 2.

In testing the assumptions of the Poisson regressions run, the likelihood ratio test between the Poisson log-linear regression and the negative binomial equivalent was 326.35. On 1 degree of freedom, the respective p-value was 5.99×10^{-73}.

Chapter 4

Discussion

4 Discussion

4.1 Primary results

Income source and income level do not seem to modify the effect of free essential medicine distribution on adherence based on a post-hoc subgroup analysis of data from a randomized controlled trial. The results of this study do not support the idea that people in certain income groups will benefit more from cost-free access to medicines.

4.2 Meaning and importance

The findings of this study first suggest that the study intervention of free provision of essential medicines does have a significant impact on adherence, where those receiving cost-free access are more likely to adhere to their medications compared to those receiving usual access to drugs. The analysis showed little evidence to suggest a difference in the relationship between any income group and adherence between conventional and cost-free access to medicines. There was also little evidence of a relationship between income source or level and adherence. These results, derived from the binary logistic regressions run were deemed most appropriate in the context of this study, as the assumptions of the Poisson log-linear models were not fully satisfied.

These results are important to consider in settling the debate in Canada which exists pertaining to drug coverage. In linking these results to the issue of pharmacare throughout

Canada, the overall result of the trial suggest that there would likely be a positive impact on adherence by providing essential medicines without charge. Further, we would not expect universal drug coverage to have different effects on adherence among people in different income groups. These results could help to support the argument in favor of the implementation of a universal drug plan, rather than a plan that focuses on people in certain income groups.

4.3 Relation to similar studies

The overall results pertaining to the influence of free provision of medication on adherence outcomes reflects those of a 2011 review study pertaining to the impact of improved access to medication through the alleviation of cost on adherence(25). This review of 47 papers found that lower burden of cost is associated with improvements in adherence to medication. However, the studies included in this review were not controlled and did not seek to evaluate the effect of full coverage on adherence to medications.

Regarding controlled studies evaluating the impact on adherence of cost-free provision of medication, the MI FREEE study and the ARTEMIS study mirror the results of this analysis, in that in all analyses, the cost-free provision of drugs increased the likelihood of adherence. These studies differed from this analysis and the CLEAN Meds trial in several important ways, however. Pertaining the MI FREEE study, the patient population were those subject to co-pay prior to the study on private insurance plans(27). Similarly, all enrolled participants had prior drug coverage in the ARTEMIS study(28), while individuals from all insurance backgrounds were eligible to participate in the CLEAN Meds study. Further, the patients in the MI FREEE and ARTEMIS study were limited to those who were post-myocardial infarction. In the MI FREEE study, the medications were limited to anti-platelet medications, beta blockers, ACE inhibitors, angiotensin receptor blockers and statins(27). Similarly, the ARTEMIS study only sought to determine adherence to treatment through the use of $P2Y_{12}$ inhibitors(28). In the

CLEAN Meds study, a more diverse list of medications was given to patients which suit a variety of ailments. Lastly, the MI FREEE and ARTEMIS studies omitted any analysis pertaining to income source or level and adherence.

Concerning the lack of evidence to support the notion that income level influences adherence, this result is dissimilar to that which is found in a Canadian 2012 census-based study, where they reported a steady increase in odds ratios between income categories going from highest to lowest using an outcome variable of self-reported cost-related non-adherence(41). This study demonstrates an alternate trend between income level and adherence using a Canadian sample. This is attributable to a number of different factors; including the census studies' omission of including income source in their analysis, and thus the effect of income was solely placed on income level. Further, the census study is uncontrolled and uses data solely from the 2007 Canada Community Health Survey, a telephone survey of the community-dwelling population.

4.4 Alternate explanations of findings

Regarding the primary study result of the intervention having an impact on adherence, a possible explanation which could have led to this result is the Hawthorne effect. This effect describes the changing in participant behavior when they are aware that they are being observed(73). As participants were aware of their behaviors being monitored for the purpose of the study, they may have changed their adherence patterns from what they would have been under non-study conditions given identical access to medications. Further, the analysis of this study included self-report data under the outcome variable. Adherence based on self-report data is subject to self-report bias(74), and alike with the alteration of participant behavior following the Hawthorne effect, could have swayed the study result away from the null hypothesis.

Additionally, any changes seen in adherence between allocation groups may have been due to factors other than cost-free provision in the intervention groups. For instance, those in the intervention group also received convenient access to medication through mail. This aspect of the intervention may have contributed to the respective outcome of adherence among the various predictor variables.

Pertaining to the association between income level and adherence, the relationship could be alternately explained by the categorization of income itself. In this study, income was divided into three categories. This categorization of income may have generalized the variable too broadly and thus altered the relationship between income level and adherence.

The results related to income source were possibly due to access to medications apart from an individual's source of income, instead of access to medicines provided solely by their income source. For instance, an unemployed uninsured individual may receive drug benefits from the Ontario trillium plan. The trillium plan is unrelated to income source; however, these individuals would be covered and thus their adherence would likely alter the adherence patterns seen among the truly unemployed and uninsured.

The lack of evidence to support a relationship between income source or level and adherence was furthermore possibly due to both of these variables' inclusion into a single model. In including both variables, the effect of income level or source on adherence was mitigated by the inclusion of one another, as opposed to the entire effect being placed onto one of these variables should either not be included. As income source (particularly the waged versus all others variable) in inevitably associated with income level, it was important to include both of these variables into a single model to avoid omitted variable bias.

4.5 Clinical significance of findings

The clinical significance of this analysis stem from the results which pertain to the impact of the study intervention on adherence, and the interactions between the income groups and study allocation group. The results show that all income groups assessed in this study are likely to improve adherence provided universal coverage, and thus any new program should allow for free access to all Canadians, regardless of income source or level. These results provide support for the argument of implementing a universal drug program, instead of maintaining or expanding the patchwork of programs which exist today.

4.6 Limitations

There are several important limitations of this post-hoc subgroup analysis of randomized controlled trial findings. Firstly, findings from post-hoc subgroup analyses should be viewed as hypothesis generating because they can yield spurious findings that are not reproduced in subsequent studies(75). This is because the sample used does not conform to the randomization model of statistical inference, where individuals are selected at random from a population for a given prespecified analysis(76). However, pursuing this analysis using data from the CLEAN Meds trial provides a unique opportunity to explore the possible relationship between income groups and adherence under conventional and cost-free access to medications. Further, the use of control variables in the regression models run helped mitigate the imbalances in participant characteristics from post-hoc subgroup analysis(75).

Concerning weaknesses pertaining to the CLEAN Meds study design, the sample had been limited, in that the participants recruited for the study from primary care practices. This criteria excluded individuals who were not already connected to a primary care practice, and thus excluded a relevant segment of the Canadian population from the study(52). Though these

individuals were excluded from the analysis, however, there is no evidence to suggest that the included sample is not representative of the Canadian population. Further, the study was unable to determine the contributions of various intervention components (such as the essential medicines list, free provision of medication, mailing medications) toward any effects measured. However, given the extensive literature suggesting a link between adherence and reduced or eliminated out-of-pocket cost for medication, there is good reason to believe the trial results are primarily due to this component of the intervention. Lastly, given the lack of measurement past 12 months, the study could not measure the long term effects of the intervention(52). The link between long term results and cost-free provision of medication is one which should be evaluated in future studies.

Concerning the outcome measure used in this analysis, adherence was measured using mixed methods, being self-report and EMR chart review. The use of multiple methods to obtain an adherence measure results in the entire sample not being the subject to the same biases or limitations. The methods of measuring adherence in this analysis are both subject to their own limitations, as self-reporting is prone to over-estimation, and EMR reviews are susceptible to pill-dumping(77). However, both methods of measuring adherence have high concordance with one another, and using both methods of measurement allowed for an increase in the sample size used for this study(78). Further, the definition of adherence as used in this study is not a universally accepted method. Having a threshold of 80% to classify adherence for multiple medications may classify patients as non-adherent, who may have otherwise been classified as adherent. Reasonable justification for being below this threshold despite proper medication use include appropriately discontinuing medication or substituting them with others(79). However, this threshold of adherence has been deemed valid in the context of this trial following review of

previous literature, explaining its use in similar previous trials, such as the MI FREEE study(27, 79).

In terms of the primary predictor variable of income level, the classification used in this analysis assumes similar characteristics among all participants within the three income level brackets used. These levels of income were broad and did not provide insight into characteristics within narrower income brackets, leading to a potential generalization of the results based on overly broad and few categories. However, the distribution of income among enrolled trial participants made this categorization necessary to ensure a sufficient sample size in each income level group. Pertaining to income source, the classification used in this analysis did not consider sources of drug insurance that are known to be given to individuals apart from their income source. By strictly considering insurance granted by income source, the classification method may have changed the patterns and significance of adherence among the various income source groups. For example, those who were receiving pension, which was classified as an unemployed uninsured income source, and are over 65 are granted insurance by the Ontario Drug Benefit Program. However, given the variety of public and private plans potentially applicable to various study participants, this analysis nonetheless sought to evaluate the association between income source and adherence by strictly interpreting adherence by income source for every study participant.

Regarding the sample size, a significant proportion of the study population had been excluded by omitting participants with any one of the necessary variables missing. Of the 786 study participants initially enrolled in the trial, 479 were included in the analysis (61% of the initial sample size). This smaller sample size detracted from the study power. The effect modifiers used in this study, being income source and level, were gathered from self-reports. Coupled with missing variable information pertaining to adherence, a sample size of 483

participants remained (62% of the entire sample) for the exclusion of these variables alone. As missing information pertaining to income level and income source was likely not missing at random, as such information can be attributed to the presence of other variables such as sex and race, not imputing was a reasonable method of handling missing data(80). Further, as imputation of an outcome variable can bias parameter estimates, complete case deletion was deemed to be the best method of handling the missing data(81). The same approach of handling missing data was subsequently used for the other predictor variables of this analysis. Additionally, the sample size for this analysis was deemed appropriate based on the level of adherence reported in a previous trial under normal access to medicines, being 65%(61). Listwise case deletion was used instead of pairwise deletion in order to omit biased parameter estimates, which can be caused by computation based on different sets of data(82). Ultimately, listwise deletion provided a result reflective of the information present in the dataset.

4.7 Future studies

As a primary outcome of interest following improved adherence to medications is health outcomes, future studies should seek to evaluate the health outcomes directly attributable to improved adherence to medications caused by cost free provision of drugs. Further, as a primary concern with the implementation of a single-payer drug insurance system throughout Canada is economic feasibility(54), future long-term studies should be held to evaluate the total economic cost put on public insurance when these plans include cost-free access to medication, and these results should be compared to the total cost on public health insurance plans which exist today.

4.8 Conclusion

This analysis provides evidence which could help to support the argument that individuals from all income sources and levels should have access to the cost-free provision of

medicines. This work has found that such a program has the potential to benefit people similarly regardless of income level or source. The findings do not support the idea that only low-income individuals would benefit from a change to medicine access public policy which extends coverage. A universal drug coverage program, endorsed by several sources throughout various points in Canadian history, could be implemented over programs which target particular income groups.

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Appendices

5 Appendix A

5.1 Assessing multicollinearity for Models 1 and 2

	Collinearity Statistics	
Parameter	Tolerance	VIF
Age	0.75	1.333
Race	0.825	1.211
Gender	0.953	1.049
Location	0.773	1.293
Treatment Group	0.977	1.023
Income Level	0.845	1.183
Waged versus All Others	0.772	1.295
Unemployed Insured versus All Others	0.782	1.278
Total Number of Medicines Prescribed	0.867	1.153

Table 1: VIF and tolerance values of the variables used in Model 1 and 3.

	Collinearity Statistics	
Parameter	Tolerance	VIF
Age	0.745	1.343
Race	0.829	1.207
Gender	0.957	1.045
Location	0.745	1.341
Treatment Group	0.991	1.009
Income Level	0.387	2.587
Waged versus All Others	0.244	4.106
Unemployed Insured versus All Others	0.399	2.505
Income Level * Treatment Group	0.271	3.684
Waged versus All Others * Treatment Group	0.286	3.491
Unemployed Insured versus All Others * Treatment Group	0.579	1.727
Total Number of Medicines Prescribed	0.864	1.157

Table 2: VIF and tolerance values of the variables used in Model 2 and 4.