EVALUATING THE EFFECT OF PHARMACIST-LED MEDICATION REVIEW IN HIGH-RISK EMERGENCY DEPARTMENT PATIENTS ON HEALTH SERVICES UTILIZATION

by

Sophie Kitchen
B.A., Williams College, 2017

A THESIS SUBMITTED IN PARTIAL FULLFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE in
THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES (Population and Public Health)

THE UNIVERSITY OF BRITISH COLUMBIA (Vancouver)

July 2019

© Sophie Kitchen, 2019
The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

Evaluating the Effect of Pharmacist-led Medication Review in High-Risk Emergency Department Patients on Health Services Utilization

submitted by Sophie Kitchen in partial fulfillment of the requirements for the degree of Master of Science in Population & Public Health

Examining Committee:

Dr. Corinne Hohl, School of Population & Public Health, UBC Co-supervisor

Dr. Kim McGrail, School of Population & Public Health, UBC Co-supervisor

Dr. Michael Law, School of Population & Public Health, UBC Supervisory Committee Member

Dr. Joseph Puyat, School of Population & Public Health, UBC Additional Examiner
Abstract

Background
One in nine emergency department (ED) visits in Canada are caused by adverse drug events, the unintended and harmful effects of medication use. Medication reviews by clinical pharmacists are interventions designed to optimize medications and address adverse drug events to impact patient outcomes. However, the effect of medication review on long-term outpatient health services utilization is not well understood. This research studied the effect of medication review performed by clinical pharmacists on long-term outpatient health services utilization.

Methods
Data included information from 10,783 patients who were part of a prospective, multi-centre quality improvement evaluation from 2011-2013. Outpatient health services utilization was defined as total ED visits and physician contacts, aggregated to four physician specialty groups: general and family practitioners; medical specialists; surgical specialists; and imaging and laboratory specialists. Medication review involved a critical examination of a patient’s medications to identify and resolve medication-related problems and communicate these results to community-based care providers. Interrupted time series analysis compared the effect of the intervention on health services utilization relative to the standard of care controlling for pre-intervention differences in utilization.

Results
ED-based pharmacist-led medication review did not result in a significant level or trend change in total outpatient health services utilization, primary care physician visits, or ED visits relative to the standard of care in the 12 months following the intervention, even when stratified by age, hospital site, and whether patients were admitted to the hospital on their index visit.

Conclusion
This was the first study to measure long term trends of physician visits following an ED-based medication review. The lack of differences in level and trend of GP and ED visits suggest that pharmacist recommendations may not have been adequately communicated to community care providers, and/or recommendations may not have affected health care delivery. Future studies should evaluate patient and physician acceptance of pharmacist recommendations and should encourage patient follow-up to community care providers following medication reviews.
Lay Summary

One in nine emergency department visits in Canada result from adverse drug events, the unintended and harmful consequences of prescription or over-the-counter medication use. Medication review is an intervention designed to detect adverse events related to prescription medication use and improve health outcomes for patients. However, very few studies have examined the long-term impact of medication review on patient’s health services use.

This study did not identify immediate or long-term changes in the number of general practitioner or emergency department visits. These results suggest that recommendations from the ED-based pharmacists may not be adequately communicated to community-based providers and may not result in long-term medication changes for patients. Future medication review interventions should prioritize communication of results between care providers and encourage patients to follow-up on the results of medication review with community-based care providers and prescribers to impact long-term patient outcomes.
Preface

This thesis is an original product of the author, Sophie Kitchen (SK).

SK developed the research objectives, study design, and analysis of the research data with the assistance of the thesis supervisory committee: Drs. Corinne Hohl MD FRCP, Kim McGrail PhD, and Michael Law PhD. This thesis used data from a quality improvement initiative funded by the British Columbia Ministry of Health and Vancouver Coastal Health Authority called the Adverse Drug Event Screening Program. This program was conceptualized by Dr. Corinne Hohl and other faculty at the Center for Epidemiology and Evaluation and the School of Population and Public Health at the University of British Columbia. Preliminary results from this thesis were disseminated at the 2019 Canadian Association for Health Services and Policy Research conference in Halifax, NS and the 2019 Academy Health Annual Research Meeting in Washington, DC. Sections of this thesis will be submitted for publication in peer-reviewed journals.

The University of British Columbia Clinical Research Ethics Board declared this project to be a quality improvement evaluation and waived the need for full board review and informed consent.
Table of Contents

Abstract ........................................................................................................................................ iii
Lay Summary ................................................................................................................................ v
Preface ........................................................................................................................................ vi
Table of Contents ........................................................................................................................ vii
List of Tables ................................................................................................................................ ix
List of Figures ................................................................................................................................. x
List of Abbreviations ..................................................................................................................... xi
Glossary .......................................................................................................................................... xii
Acknowledgements ....................................................................................................................... xiii

Chapter 1: Introduction ................................................................................................................ 1
  1.1 Overview ............................................................................................................................... 1
  1.2 Research Objectives ........................................................................................................... 2
  1.3 Thesis Overview .................................................................................................................. 3

Chapter 2: Background ................................................................................................................ 5
  2.1 Introduction .......................................................................................................................... 5
  2.2 Adverse Drug Events ........................................................................................................... 5
  2.3 Characteristics of Medication Reconciliation and Medication Review ................................ 8
  2.4 Theory of Change for Medication Review ......................................................................... 11
  2.5 Literature Review of In-hospital Medication Review ......................................................... 14

Chapter 3: Methodology ............................................................................................................ 18
  3.1 Intervention ......................................................................................................................... 18
  3.2 Data Sources ....................................................................................................................... 23
  3.3 Study Variables ................................................................................................................... 24
  3.4 Analysis ............................................................................................................................... 27

Chapter 4: Results ....................................................................................................................... 31
  4.1 Descriptive and Bivariate Statistics .................................................................................... 31
  4.2 Primary Results: Outpatient Health Services Utilization ................................................ 32
  4.3 Sensitivity Analyses ............................................................................................................ 33
  4.4 Secondary Analyses: Prescription Drug Utilization ......................................................... 34
  4.5 Tables and Figures ............................................................................................................. 36
Chapter 5: Discussion and Conclusion .................................................................53
5.1 Systematic Allocation .....................................................................................53
5.2 Health Services Utilization Outcomes ..........................................................53
5.3 Prescription Medication Outcomes ..............................................................55
5.4 Strengths and Limitations .............................................................................57
5.5 Conclusion .....................................................................................................61

References ............................................................................................................63

Appendices ...........................................................................................................72

Appendix A. Literature Review ............................................................................72
Appendix B. Anatomical Therapeutic Chemical Codes to Identify Benzodiazepines .78
Appendix C. Clinical Decision Rule .....................................................................79
Appendix D. Addressing Adverse Drug Events .....................................................80
# List of Tables

Table 2.1. Classification of ADE Subtypes ................................................................. 6

Table 2.2 Characteristics of In-hospital Medication Reconciliation vs. Medication Review .............................................................. 10

Table 3.1. Implementation phases of the study protocol and evaluation period .... 18

Table 4.1. Descriptive Statistics of Medication Review and Control ................. 36

Table 4.2. ADE Type Suspected among Patients who received Medication Review .. 37

Table 4.3. Bivariate Statistics of Medication Review and Control ....................... 38

Table 4.4. Health Services Utilization Model Results ............................................. 49

Table 4.5. Potentially Inappropriate Prescription and Benzodiazepine Model Results ........................................................................ 52

Table A.1. Effect of Medication Review on General Practitioner and Total Outpatient Visits ................................................................. 72

Table A.2. Effect of Medication Review on Emergency Department Visits .......... 73

Table A.3. Effect of Pharmacist-led Medication Review on Potentially Inappropriate Prescriptions .......................................................... 75

Table B.1. List of Benzodiazepine derivatives included ................................. 78
List of Figures

Figure 2.1. Framework for the Four-Level Health Care System as Conceptualized by the National Institutes of Health ................................................................. 7

Figure 2.2. Theory of Change adapted and applied to medication review ............... 12

Figure 3.1. Flow diagram .................................................................................. 20

Figure 3.2. Systematic allocation algorithm for Medication Review Intervention ....... 22

Figure 3.3. Ex ante Patient Pathway ................................................................. 26

Figure 3.4. Regression intercepts and slopes for an interrupted time series analysis with a control. ................................................................. 28

Figure 4.1. Number of outpatient physician visits per 1000 patients ............... 39

Figure 4.2. Number of outpatient physician visits per 1000 patients (under 80 years) .... 40

Figure 4.3. Number of outpatient physician visits per 1000 patients (over 80 years) ...... 41

Figure 4.4. Number of GP visits per 1000 patients ......................................... 42

Figure 4.5. Number of GP visits per 1000 patients (under 80 years) ................... 43

Figure 4.6. Number of ED visits per 1000 patients ........................................ 44

Figure 4.7. Number of ED visits per 1000 patients (under 80 years) ................. 45

Figure 4.8. Number of ED visits per 1000 discharged patients (under 80 years) ....... 46

Figure 4.9. Number of ED visits per 1000 patients (over 80 years) ..................... 47

Figure 4.10. Number of ED visits per 1000 discharged patients (over 80 years) ......... 48

Figure 4.11. Number of potentially inappropriate prescriptions per 1000 patients .... 50

Figure 4.12. Number of benzodiazepine discontinuations per 1000 patients ........... 51

Figure C.1 Clinical Decision Rule for identifying high-risk patients ................. 79

Figure D.1 Hypothesized Effect of Addressing ADEs on Medications ............... 80
**List of Abbreviations**

ADE= Adverse Drug Event
ADR= Adverse Drug Reaction
BC= British Columbia
CTAS= Canadian Triage Acuity Score
ED= Emergency Department
GP= General Practitioner
LGH= Lions Gate Hospital
PIP= Potentially Inappropriate Prescription
RH= Richmond Hospital
VGH= Vancouver General Hospital
Glossary

Adverse Drug Event (ADE): unintended and harmful event associated with prescription or over-the-counter medication use

Adverse Drug Reaction (ADR): a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man

Evaluation: the systematic assessment of the outcomes of a program, compared to an explicit or implicit standard, with the aim of contributing to the improvement of the program

Interrupted time series design: quasi-experimental research design in which outcome data from the same individual or group are evaluated at multiple time points before and after a well-defined intervention

Medication Reconciliation: the process of creating a complete and accurate list of a patient’s current medications, including the name, dosage, frequency, and route of administration using multiple sources (e.g. patients, families, community pharmacists, etc.) prior to prescribing medications at care transitions with the purpose of reducing medication discrepancies

Medication Review: a structured, in-person critical examination of a patient’s medications performed by a qualified healthcare provider — typically a pharmacist — with the objective of reaching agreement with the patient about treatment, optimizing the medications’ impact, and minimizing the number of medication-related problems

Outpatient health services: single or multi-disciplinary diagnostic, therapeutic, or education services for non-admitted patients

Polypharmacy: the concurrent use of 5 or more medications by a single individual

Potentially Inappropriate Prescriptions (PIPs): defined by the most recently updated Beers criteria, a widely used explicit list of potentially inappropriate medications recommended to be avoided by older adults, maintained and updated by the American Geriatrics Society

Quasi-experimental design: a nonrandomized or partially randomized pre/post intervention study
Acknowledgements

I am incredibly grateful to the many people who have supported me throughout this process. Firstly, to my co-supervisor Corinne Hohl, for accepting me onto her research team and whose expertise was invaluable to shaping the questions of this thesis. To my co-supervisor, Kim McGrail for her encouragement and methodological eye. And to my committee member, Michael Law, for always being available for a “quick” question, and whose teaching initially inspired this project.

I am thankful for all the contributions from members at the Center for Epidemiology and Evaluation and at the Center for Health Services and Policy Research. Specifically, Amber, Jeff, Maeve, Serena, Stephanie, and Xiaotong, I am profoundly appreciative for all of the guidance, lunchtime talks, and edits. I also want to thank all the friends I have made in Vancouver over the past two years. Thank you for always being around to explore the mountains, exchange ideas, and share a meal.

I would like to thank the Canadian Institutes of Health Research, the Michael Smith Foundation for Health Research, and Vancouver Coastal Health for funding this research.

Finally, I would like to thank my parents and sisters, for their constant supply of encouragement and laughter, and Dan, for being my best friend from across the country.
Chapter 1: Introduction

1.1 Overview
As the prevalence of chronic conditions continues to rise in Canada, so too does the prevalence of polypharmacy, defined as the concurrent use of five or more drug classes by a single patient.\textsuperscript{10-12} Polypharmacy increases the complexity of therapeutic management for care providers and patients, as patients are prescribed medications from multiple prescribers, including primary care physicians and specialists.\textsuperscript{12,13} Unfortunately, this complexity and lack of coordination between care providers can increase the risk of inappropriate medication therapy and adverse drug events (ADEs).\textsuperscript{14-16} ADEs are unintended and harmful events related to medication use, which increase unnecessary health services utilization and are estimated to be between the fourth and sixth leading cause of death in Canada.\textsuperscript{14,15,17-25}

Unfortunately, it is often difficult to detect and address ADEs in clinical encounters. For example, up to 50\% of ADEs are misdiagnosed by physicians, leading to treatment delays and lack of withdrawal of culprit medications.\textsuperscript{26} Furthermore, previous studies have estimated that up to 55\% of older adults admitted to hospital with ADEs are re-exposed to the culprit medication within 6 months.\textsuperscript{27} Finding effective interventions to improve the detection and communication of inappropriate medication therapy and ADEs has the potential to reduce unnecessary health services utilization, and avoid preventable patient harm.

One potential intervention is medication reviews. These reviews are interventions proposed to help patients gain the maximum benefit from their medications, while simultaneously limiting the potential for harm.\textsuperscript{25} Medication review is an in-person, structured, critical examination of a patient’s medications performed by a qualified healthcare provider— typically a pharmacist— with the objective of reaching agreement with the patient about treatment, optimizing the medications’ impact, and minimizing the number of medication-related problems.\textsuperscript{4} While medication reviews have been tested and
evaluated in primary care and hospital settings, few trials have evaluated the effect of pharmacist-led medication review among patients in the ED setting.28

A previous evaluation of the intervention under study in this thesis measured the effect of a pharmacist-led medication review among patients at high-risk for presenting to the ED with an ADE on hospital length of stay.29 This work found ADEs in 2,284 (35.6%) patients in the medication review group. Post intervention, the median number of hospital days within 30 days of the index ED visit was reduced by 0.48 days (95% CI: 0.00 to -0.96, p=0.058) in the review group compared to the control group. While secondary outcomes included ED revisits within 7 days, unplanned hospital readmissions, and all-cause mortality, these analyses were limited in follow-up time, did not account for the impact of the medication review on outpatient physician contacts, and did not control for pre-existing differences in health services utilization between the two groups.

Three recent systematic reviews demonstrated that while there is an evolving body of evidence evaluating the effect of medication review on various outcome measurements, there is a lack of consensus regarding their impact on health services utilization, particularly the effect on number of general practitioner (GP) and ED visits.28,30,31 The effects are generally unclear due to the inconsistent follow-up times, small sample sizes, and restricted study populations. To my knowledge, there has never been a comprehensive interrupted time series analysis, one of the strongest quasi-experimental research designs available, used to evaluate an ED-based medication review intervention. An interrupted time series would allow for time to be included in the analysis, and thus could better inform the debate around the true effectiveness of medication reviews.

1.2 Research Objectives

This thesis builds on the prospective, multi-centre, pharmacist-led intervention described above. It evaluates the effect of ED-based pharmacist-led medication review in patients at high risk of presenting to the ED with an ADE on trends of outpatient health services utilization relative to the standard-of-care, medication reconciliation.

1.2.1 Specific Aims
The specific aims of this dissertation are:

1. To investigate the differences in trends before and after an ED-based medication review intervention of outpatient health services utilization, defined as total ED visits, and physician contacts, including four physician specialty groups: general and family practitioners, medical specialists, surgical specialists, imaging and laboratory specialists relative to a control group. Specifically, to determine if ED-based medication review led to:
   A) an initial change in GP visits
   B) a differing trend of GP visits and total physician visits over time
   C) a differing trend of ED revisits over time
   and if this effect differs among patients admitted to the hospital on their index visit, or by age.

2. To explore the differences in trends of potentially inappropriate prescriptions between the intervention and control groups.

1.2.2 Hypothesis
I hypothesize that ED-based medication review among high-risk patients will result in an initial change in follow-up visits to GPs followed by a longer-term change in trends of total outpatient health services utilization, including outpatient physician visits and ED revisits relative to patients who do not receive medication review.

1.3 Thesis Overview
This thesis consists of five chapters. Chapter 1 contains an introduction to the research problem of ADEs and one intervention proposed to improve outcomes for patients at high-risk of ADEs, medication review. This chapter ends with the specific aims and hypothesis for this study.

Chapter 2 contains a background information of four major areas of research relevant to this thesis: ADEs, medication review and reconciliation, theoretical frameworks for evaluating complex interventions, and previous literature on medication review effectiveness.
Chapter 3 explains the methodology used to conduct the evaluation of medication review on health services utilization. This includes detailed information on the quasi-experimental intervention under study in this thesis and an introduction to the major analytic method used for this thesis, an interrupted time series (ITS) with a control.

Chapter 4 details the study characteristics of the sample under investigation, the primary results focused on health services utilization, including the number of physician visits per 1000 patients in the intervention and control groups, and the exploratory results on potentially inappropriate prescription drug utilization, measured using an ITS.

Chapter 5 discusses the results observed by outcome in relation to the literature, then addresses the overall strengths and limitations of this study and concludes the study with recommendations for future interventions and evaluations.
Chapter 2: Background

2.1 Introduction
The primary aim of this thesis is to conduct an analysis which determines the effect of medication review on health services utilization. The following literature review was conducted to understand the purpose and features of medication review targeting ADEs and incorporate relevant theoretical frameworks to understand how ED-based medication review could impact health services utilization. This review provides a broad overview of the current knowledge of theory and methodology in this area of research which helps to refine the research question and analyses that are the empirical part of this work.

A literature search focused on four different areas of research that are relevant to this thesis: 1) the definition and epidemiology of ADEs; 2) characteristics of medication reconciliation and medication review; 3) theoretical frameworks for evaluating complex interventions; and 4) previous evaluations of medication review.

2.2 Adverse Drug Events

2.2.1 Definition
Adverse drug events (ADEs) are defined as the unintended and harmful complications of over-the-counter or prescription medication use. Historically, there has been significant variation in how ADEs are defined and categorized in research and in clinical practice. The most inclusive definition uses the subtypes designed to describe any “drug-related problem” including eight categories defined in Table 2.1. These categories were constructed to provide practicing clinical pharmacists with a means of identifying, resolving, and preventing drug-related problems in order to contribute to positive patient outcomes. Other studies have used various more restrictive definitions of ADEs, focusing on certain subtypes and excluding others. In an article titled the Clinician’s Guide to the Terminology, Documentation, and Reporting of ADEs, the author described an effective clinical definition of ADEs as “harm caused by a drug or the inappropriate use of a drug”. This definition included the subtypes involved in the use of a drug, such as adverse drug reactions, or subtherapeutic dosage, but excluded subtypes such as non-adherence or untreated indication. The range of definitions has made comparing estimates...
of the prevalence of ADEs in various settings difficult, more recently, this led to the
impetus to standardize the terminology of ADEs and drug-related problems.\textsuperscript{37,38}

The more inclusive definition has been argued to be the most useful when considering
ADEs from a health services research perspective, as many of the subtypes identified
have previously been associated with increased health services utilization and costs, and
many were classified as preventable.\textsuperscript{32,39,40} Therefore, the remainder of this thesis will use
the most inclusive definition of ADEs.

Table 2.1. Classification of ADE Subtypes\textsuperscript{41}

<table>
<thead>
<tr>
<th>Adverse Drug Event Subtype</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse drug reaction</td>
<td>Any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or treatment</td>
</tr>
<tr>
<td>Non-adherence</td>
<td>Any noxious, unintended, or undesired effect caused by failure to receive a drug as prescribed by a health care provider</td>
</tr>
<tr>
<td>Suboptimal dosage</td>
<td>Combines two categories: Subtherapeutic dosage: any noxious, unintended, or undesired effect caused by failure to receive sufficient drug dosage or duration for a given indication or patient Supratherapeutic dosage: any noxious, unintended, or undesired effect caused by excessive drug dose or duration for a given indication or patient</td>
</tr>
<tr>
<td>Untreated indication</td>
<td>Any noxious, unintended, or undesired effect resulting from the failure to treat a known indication</td>
</tr>
<tr>
<td>Improper drug selection</td>
<td>Any noxious, unintended, or undesired effect due to the use of a drug not optimal in the treatment of a confirmed indication</td>
</tr>
<tr>
<td>Other</td>
<td>Including: Drug interaction: any noxious, unintended, or undesired effect caused by the coadministration of 2 or more drugs Drug without indication: any noxious, unintended, or undesired effect</td>
</tr>
</tbody>
</table>
2.2.2 Epidemiology of ADEs

ADEs are estimated to comprise one-third of hospital-related complications and prolong hospital length of stay by approximately 1.7 to 4.6 days, however, some estimates suggest that the consequences and cost of ADEs may be comparable or even greater in outpatient settings.\textsuperscript{42,43} ADEs are estimated to cause or contribute to approximately two million ED visits annually in Canada, and 240,000 visits in British Columbia.\textsuperscript{18} In addition, up to 60\% of ADE-related outpatient visits occur in primary care settings.\textsuperscript{43}

ADEs are multifactorial and could arise from issues at one or more of the four “nested-levels” of the health care system as described by the National Institutes of Health (NIH) (Figure 2.1).\textsuperscript{44} For example, a patient could be experiencing non-adherence because they have chosen not to take their medication (patient-level), because there was a lack of adherence to the treatment guidelines leading to a patient to be on the wrong drug (prescriber-level), because there was an error in how their medication was dispensed (organization-level), or because they could not afford their medication (environment-level & patient-level). Therefore, interventions designed to ameliorate the effect of ADEs must attempt to understand the relative importance of factors at each of these levels and then try to intervene accordingly.

![Diagram of the Four-Level Health Care System](image)

Figure 2.1. Framework for the Four-Level Health Care System as Conceptualized by the National Institutes of Health\textsuperscript{44}
2.3 Characteristics of Medication Reconciliation and Medication Review

2.3.1 Overview
Medication reconciliation and medication review are two distinct interventions that have each been designed to reduce the potential for medication errors at transition points in care and improve patient outcomes. While either of these interventions can be provided in the community or in a hospital setting, this review will focus on the hospital setting.

2.3.2 Medication Reconciliation
In 2008, acute care institutions in Canada started implementing medication reconciliation in response to a national accreditation mandate. Medication reconciliation is the process of creating a complete and accurate list of a patient’s current medications, including the name, dosage, frequency, and route of administration using multiple sources including the patient, family, community pharmacists etc. Medication reconciliation is an intervention generally initiated by physicians, nurses, or pharmacists to reduce medication errors and ADEs resulting from inaccurate medication information at care transitions.

Existing literature generally shows low certainty around the effectiveness of medication reconciliation on optimizing medications, and improving health outcomes. However, one systematic review found hospital-based medication reconciliation to impact patient-oriented outcomes only when the intervention targeted high-risk patients and was performed by pharmacists who assessed medications for appropriateness and ADEs—features usually associated with a medication review.

2.3.3 Medication Review
Medication review is a structured, in-person critical examination of a patient’s medications performed by a qualified healthcare provider—typically a pharmacist—with the objective of reaching agreement with the patient about treatment, optimizing the medications’ impact, and minimizing the number of medication-related problems. Medication review goes a step beyond medication reconciliation to not only carefully assess and document medications, but also to think critically about how to optimize those
medications to impact patient outcomes. Because medication review often requires additional resources and time than a standard medication reconciliation, many studies will target patient populations at high-risk of experiencing ADEs for the intervention. These populations have been identified in past studies using a variety of variables, including age, number of medications, or by disease type. To my knowledge, only one previous evaluation used a clinically validated screening tool to identify patients at high-risk of experiencing an ADE to target for medication review. Using a validated tool may have the advantage of including more patients who could benefit from the intervention, and would allow for different subgroup analyses in younger patient populations who are often excluded from study.

Relative to medication reconciliation, medication review has the advantage of targeting multiple nested level of the NIH Framework, including the patient, frontline care workers, and potentially the organization, depending on how the results of the review are transferred outside of the hospital. Some past interventions have included the resources for the results of the medication review to be transferred via an electronic health database, or faxed to community care providers. Including multiple levels of the NIH framework increases the likelihood of an intervention's success by attempting to close the information discontinuity between different care providers.

Most in-hospital medication review interventions target patients admitted to the hospital ward (Appendix A: Tables A.1 to A.3) despite some benefits of an earlier ED-based intervention. One potential advantage of an ED-based medication review is that a high proportion of all ED visits are attributable to ADEs and a high proportion of these visits are preventable. In addition, EDs have extensive experience with multidisciplinary teams and therefore could adapt to incorporate pharmacists into the existing care team. Finally, research has shown that physicians misattribute up to 50% of ADEs to non-medication related causes. By optimizing the skillset of pharmacists who are specifically trained to identify medication-related issues, ED-based interventions may maximize ADE identification and treatment.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Medication Reconciliation</th>
<th>Medication Review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Ensures that the provider has a complete record of medications when prescribing. (Required Organization Practice by Accreditation Canada since 2008)</td>
<td>Ensures that the provider has a complete record of medications when prescribing AND seeks to enhance a patient’s understanding of, and improve the health outcomes of, their medication regimen AND strives to optimize medication impact (often results in recommendations to change, discontinue, or start new medications)</td>
</tr>
<tr>
<td><strong>NIH Framework Levels Involved</strong></td>
<td>Primarily the frontline care team</td>
<td>Primarily the patient, and frontline care team. Potentially the organization</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
<td>All patients</td>
<td>Often limited to high-risk patients</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>During transition points in care (e.g. arrival in ED, admission, discharge)</td>
<td>During transition points in care (e.g. arrival in ED, admission, discharge)</td>
</tr>
<tr>
<td><strong>Typically conducted by</strong></td>
<td>Nurse, physician, or pharmacist</td>
<td>Clinical pharmacist</td>
</tr>
</tbody>
</table>
2.4 Theory of Change for Medication Review

Theory of Change is a tool popularized by Weiss et al. to evaluate complex interventions with the goal of understanding the empirical basis underlying the intervention.69 This approach has since become widespread in public health literature.60 Theory of Change models start with the desired long-term impact of interventions, and then trace backwards to identify the necessary preconditions and assumptions required for the intervention to be effective. Previous studies have found that evaluating clinical pharmacy interventions such as medication review is particularly challenging, as it strives to change behaviour of both providers and patients in the context of a complex healthcare system.61 Therefore, the Theory of Change approach was used to understand the steps necessary for medication review to impact the intended outcome, health services utilization.

As documented in Figure 2.2, Theory of Change was designed to highlight the specific causal links between the intervention and the intended outcome.62 This framework clearly identifies an explicit population and the hypothesized causal pathway for the initial and downstream impact of the intervention on measurable patient-oriented outcomes such as health services utilization. At stated below, the initial reaction of medication review would result in an immediate increase in GP visits for patients to follow-up on the results of the medication review with their GP. Following the initial reaction, both patients and GPs would have an increased knowledge of medications, leading to improved medication prescribing among GPs and improved medication use (among patients), and a decreased likelihood of experiencing an ADE. The well-being change observed from this intervention would be a decrease in ED revisits.

One of the greatest advantages of this framework is its identification of key assumptions, which are critical factors required for causal links to join as expected. The assumptions as applied to an ED-based medication review intervention (as an example) are the Population, Capacity Change, Behavior Change, and Well-being change assumptions. The Population assumption has three components; first that the recommendations from the pharmacist are appropriate, second that the recommendations are communicated effectively to the patient, and third that they are adopted or accepted by the patient. The
*Capacity Change* assumption details the same three components, however the target group for communication is the prescribing physician. The *Behavior Change* assumption states that increased knowledge of medications influences prescribing and medication use. Finally, the *Well-being change* assumption states that patient’s health services utilization patterns change if there is a decreased likelihood of them experiencing an ADE. All four of these assumptions are required for medication review to effectively impact downstream health services utilization.
Figure 2.2 Theory of Change adapted and applied to medication review. ADE= Adverse Drug Event, GP= General Practitioner, ED= Emergency Department
2.5 Literature Review of In-hospital Medication Review

Previously, in-hospital medication review has been evaluated for its impact on several patient-oriented outcomes including: hospital admissions, length of stay, ED revisits, GP visits, all outpatient visits, and mortality. According to three systematic reviews all conducted before 2016, medication review did not have a significant effect on hospital readmissions or mortality.\textsuperscript{28,31,63} These reviews also found that there was generally an inconsistent effect of medication review on ED revisits, general and all outpatient practitioner visits, with a high level of heterogeneity amongst studies. Therefore, I conducted an updated literature review focusing on these outcomes.

2.5.1 Search Strategy

A comprehensive search of three biomedical databases: EMBASE, MEDLINE (Ovid), and PubMed, and a grey literature search was conducted to estimate the effect of medication review on three outcomes: 1) GP or other outpatient physician visits, 2) ED visits, 3) potentially inappropriate prescriptions, in a hospital-based or ED-based population. Studies that used random or quasi-random methods to allocate patients to medication-review or control were included. Medication review had to specify obtaining a best possible medication history and reviewing medications for appropriateness and ADEs. Compiled studies from past systematic reviews were also evaluated for inclusion in this search. The results of articles included from this search strategy are compiled in Appendix A: Tables A.1 to A.3.

2.5.2 Previous Evaluations of In-hospital Medication Review

Of the four studies conducted in-hospital measuring the effect of medication review on GP or outpatient visits, only the ED-based study found a significant increase between an intervention and control group following medication review (Appendix A: Table A.1).\textsuperscript{51-53,64} Based on this finding, Okere et al. concluded that ED-based medication review may contribute towards transitioning patients towards an appropriate use of GP services, which may result in fewer ED visits downstream.\textsuperscript{64} Although only two studies reported more than one follow-up time and all four studies were limited to only six months follow-
up, Gallagher et al. reported a nonsignificant trend towards a lower frequency of GP visits among the intervention group.\textsuperscript{52}

Of seven studies identified, only two found significant differences in ED revisits following medication review (Appendix A: Table A.2).\textsuperscript{51,54} Notably, Santolaya-Perrín, an ED-based study, found significant differences only among sites with high percentage of pharmacist recommendations accepted by GPs.\textsuperscript{54}

Finally, six studies looking at the effect of in-hospital medication review on prospectively identified potentially inappropriate prescriptions (PIP) were identified (Appendix A: Table A.3).\textsuperscript{52,65-69} All six of the studies found significant decreases in PIPs among those who received medication review relative to the control, however, most of the studies only found a difference from admission to discharge. Two studies found that these changes were not maintained at three months and one year following discharge.\textsuperscript{68,69}

Unfortunately, the comparability of these studies was largely limited due to the variability in the tools used to identify PIPs. According to a systematic review, the only medication class consistently identified as potentially inappropriate across seven different explicit criteria for measuring potentially inappropriate prescriptions — including the Beers and STOPP/START — were long-acting benzodiazepines and tricyclic antidepressants.\textsuperscript{70} Benzodiazepines are known to elicit cognitive deficits and are commonly associated with an increased risk of falls and ADEs.\textsuperscript{71-73} Pharmacists conducting medication reviews are likely to target benzodiazepines for recommendations to discontinue or adjust the dose especially among older adults who presented to the ED after a fall.\textsuperscript{36,74} Two previous studies evaluating the effect of medication review drug optimization found trends towards decreases in benzodiazepine prescriptions among the intervention relative to the control, however, neither were well-powered to detect significant differences.\textsuperscript{68,69} Although some studies show that newer editions of the Beers and STOPP criteria can be used to identify ADEs, the research in this area is conflicting\textsuperscript{75-77} with studies estimating that Beers criteria account anywhere between 3.4\% to 71.2\% of ADEs.\textsuperscript{78,79}
2.5.3 Intervention Under Study

From November 2011 to January 2013, a quasi-randomized study was designed to evaluate a quality improvement initiative in three hospitals in British Columbia, Canada. During the evaluation period at each respective site, triage nurses flagged all incoming ED patients as high or low risk for ADEs, by applying a previously derived and validated clinical decision rule consisting of four variables (co-morbid conditions, antibiotic use within seven days, medication changes within 28 days, and age; Appendix B). The purpose of this study was to assess the effect of ED-based medication review on hospital length of stay. This work found ADEs in 2,284 (35.6%) of high-risk patients in the medication review group. Post intervention, the median number of hospital days within 30 days of the index ED visit was reduced by 0.48 days (95% CI: 0.00 to -0.96, p=0.058) in the review group compared to the control group among patients admitted to hospital. This effect was even greater among patients under 80 years of age (0.60 days; 95% CI: 0.06 to 1.17, p=0.03). Secondary outcomes included ED revisits within 7 days, unplanned hospital readmissions within 30 days, and all-cause mortality within 30 days. However, this analysis did not account for the impact of the medication review on ED visits beyond 7 days nor on other outpatient physician visits and did not control for pre-existing differences in health services utilization between the two groups.

2.5.4 Applications of Findings to Present Study

Previous studies examining the effect of in-hospital medication reviews have produced an overall low quality of evidence with several important limitations. Firstly, most previous medication reviews limited their follow-up time to six months or less, and therefore some important treatment effects may have been overlooked. In addition, there is some evidence to suggest that the effect of the intervention may vary over time, however most studies only analyzed the outcomes at one time point and therefore did were not able to ascertain the trends of the health services utilization. Commonly, studies only examined patients over the age of 65 years. However, previous work has found that there is a distinct effect of medication review on patients under 80 years of age, and therefore, some interaction effects by age may be missed by this restriction. While the ED presents an ideal setting for identifying serious ADEs to outpatient medications, few
studies have tested the effect of medication review in the ED, and only one looked at the effect on outpatient health services utilization.\textsuperscript{54,64,82}

Overall, while previous evidence has suggested that ED-based medication review may lead to an initial increase and subsequent decrease in trend of GP visits, further examination is required to test this hypothesis. In addition, due to the generally short follow-up time in the literature, important effects of the intervention might have been overlooked, and more research looking at clinically important outcomes such as ED contacts with follow-up of at least a year is required to provide more definitive evidence.\textsuperscript{83}

This literature review provides a basis for the distinctiveness of the present study which combines an ED-based setting, a unique patient selection criterion, a large sample size, and a novel longitudinal analysis strategy controlling for pre-intervention differences in outcome. The design of this experiment has an advantage over other RCTs evaluating the effect of medication review by having greater potential for replication, scalability, and generalisability.\textsuperscript{84} This study will build on what has previously been done with multiple follow-up times up to a year post-intervention, a robust statistical method that controls for potential confounding, and a clinically validated patient inclusion criterion.
Chapter 3: Methodology

3.1 Intervention

3.1.1 Setting

This population-based quasi-experimental retrospective evaluation was conducted using data captured from the continuous quality improvement project funded by Vancouver Coastal Health introduced above. The study involved an evidence-based ADE screening algorithm to be implemented in three EDs in British Columbia, including: one tertiary care referral centre (Vancouver General, VGH), and two urban community hospitals (Lions Gate, LGH; and Richmond General, RH).

Following a 6- to 8-week pilot phase, a 12-month evaluation period began at two sites, and a 3-month evaluation at one site between November 2011 and January 2013 (Table 3.1). Given medication review requires additional resources beyond the standard of care, it was not a consistently provided service at the study sites prior to the implementation of this program. As the program only provided the resources for an estimated 30% of high-risk patients to receive medication review, it was deemed ethical to create a control group that received usual care for the purposes of evaluation.

Table 3.1. Implementation phases of the study protocol and evaluation period, by site.

|-------------|---------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------|-------------------|

VGH=Vancouver General Hospital, RH=Richmond Hospital, LGH=Lion’s Gate Hospital

The University of British Columbia Clinical Research Ethics Board reviewed the original study protocol and deemed it to be an evaluation of a quality improvement initiative and waived the need for patients’ informed consent.
3.1.2 Analytic Study Sample

All patients identified as high-risk according to a clinically validated decision rule and aged 19 years or older who presented to the ED at one of the study sites during a pharmacist data collection shift were eligible for enrollment in this study. Individuals with a Canadian Triage Acuity Score (CTAS) of 1 (i.e., resuscitation), those presenting with multisystem trauma (e.g., penetrating trauma), scheduled visits, sexual assaults, postsurgical or pregnancy-related complications or social problems, had a repeat eligible visit (e.g., had a high-risk visit after the first visit), died on arrival, left against medical advice, or out-of-province patients were excluded. Pharmacist coverage was determined based on the documented times of the highest volume of high-risk patients to the ED, including eight hours per day on weekends and holidays at all sites, and between 8 to 12 hours (2 sites), and 16 hours (1 site) per day on weekdays. Double and triple coverage of pharmacists was provided during the busiest hours and days of the weeks. Following these inclusion criteria, there were 10,783 patients eligible for this study (Figure 3.1).
3.1.3 Study Enrolment and Group Allocation

A patient enrolment and allocation algorithm was designed to enable pharmacists to complete the maximum possible number of medication reviews while creating two comparable groups of patients for evaluation purposes. Given a fixed number of available pharmacists, three pre-identified factors created a random availability of pharmacists at
any given point in time: *i)* a variable influx of high-risk patients to the ED, *ii)* a constant pressure to discharge lower-acuity patients, *iii)* a variable amount of time required to complete the medication review.\textsuperscript{13} At the beginning of each shift, medication review pharmacists would sort the ED census by time of patient arrival. Then, pharmacists would determine the highest possible ratio of patients that could be allocated to the intervention relative to the control based on the available resources and demand at that time. (e.g. 1:1, 2:1, 3:1) This ratio was then applied to the sorted list of patients to allocate them to intervention or control based on their time of arrival. If a patient did not receive medication review because they had left the ED before a pharmacist was available, the pharmacists would re-sort the ED census screen by time of arrival starting with the past hour, and would enrol the next randomly selected patient, enrol them into the medication review group, and adjust the ratio of medication review to control patients downward to minimize missed patients. This algorithm is outlined in Figure 3.2.
Figure 3.2. Systematic allocation algorithm for Medication Review Intervention\textsuperscript{13}
3.1.4 Control and Intervention
The control, nurse-led medication reconciliation, involved obtaining a best-possible medication history. This entailed creating a complete and accurate list of a patient’s current medications, including the name, dosage, frequency, and route of administration using multiple sources including patients, families, community pharmacists, etc.

The intervention, pharmacist-led ED-based medication review, involved obtaining a best-possible medication history, discussing the goals of therapy with the patient or caregiver, and reviewing the patient’s medications to identify and resolve medication-related problems, including ADEs. Pharmacists were provided with an electronic patient tracker to document ADE subtypes encountered. All pharmacists delivering the intervention were residency-trained with a minimum of two years’ working experience in an acute care hospital. Following the review, medication review pharmacists attempted to contact the patients’ family or prescribing physicians and community pharmacists by telephone, if possible, and faxed notes to family or prescribing physicians, with their contact information.

3.1.5 Study Time
Each outcome was measured using individual patient-level study time, with time 0 marking the date of the intervention including person-months ranging from 12 months before the intervention to 12 months following the intervention. After allocation, there were 6,403 patients allocated to the medication review group, and 4,380 patients allocated to the control group.

3.2 Data Sources
Longitudinal analyses was conducted using secondary data from de-identified population-based administrative health care databases: PharmaNet, which captures all prescription drug dispensations in British Columbia; Medical Services Plan (MSP), which contains all fee-for-service physician encounters in British Columbia; Client Registry (CR), which contains records for anyone who has received health care services in the province; the Discharge Abstract Database (DAD), which contains national data on hospital admissions, discharges, transfers, and deaths of patients from acute care.
hospitals; and Vital statistics, which contains data on deaths in the province. These data sources were linked to provide comprehensive health services information covering approximately 95% of the population, excluding Federally-insured populations (e.g. First Nations, RCMP, and veterans). I also used the Health Canada Drug Product database to determine the anatomical therapeutic chemical (ATC) code for all dispensed prescriptions. The ATC classification system groups prescriptions based on their acting organ or system and their therapeutic, pharmacological, and chemical properties.

3.3 Study Variables

3.3.1 Outcome Variables

3.3.1.1 Outcomes of Interest

To address the effect of an ED-based medication review on health services utilization, I conducted a high-level overview of health services and prescription drug utilization. An ex ante patient pathway is detailed in Figure 3.3. Outcomes were measured with study-time as defined in the following categories.

1) **Total physician contacts:** I calculated the total physician contacts measured with physician fee-for-service data in British Columbia for the medication review group compared to the medication reconciliation (control) group. Total contacts were measured by grouping all physician fee-for-service records into four predetermined specialty groups: general and family practitioners; medical specialists; surgical specialists; imaging and laboratory specialists. Physician contacts were calculated per study-month of each individual for the medication review versus control group in three ways: 1) as a number of total physician contacts per 1000 individuals; 2) mean physician contacts per group; and 3) median physician contacts per group. Multiple visits to the same practitioner-type on the same day were considered as one unique visit, with the exception of ED visits in which each visit per day was considered as a unique visit.

2) **ED visits and GP contacts:** ED contacts, defined as any unplanned revisit unrelated to trauma, sexual assault, a post-operative or pregnancy-related complication, or social problem, and GP contacts were also analyzed separately from total physician contacts as a 1) number of ED contacts per 1000 individuals...
per group, 2) mean number of ED contacts, and 3) median number of ED contacts. This outcome was recorded per person-month for each patient from 12 months before to 12 months after the intervention and per person-week as 25 weeks before and after the intervention.

3) **Potentially Inappropriate Prescriptions**: Potentially inappropriate prescriptions were identified using 2012 Beers criteria, restricting to patients over the age of 65 years.\(^7,8\)

4) **Benzodiazepine discontinuations and dose alterations**: Used as a measure of medication optimization according to seven explicit criteria, a benzodiazepine prescription was defined as discontinued if the same active ingredient was not re-dispensed within the days’ supply plus 30 days.\(^70\) A benzodiazepine was deemed to have had an alteration of dose if the active ingredient was dispensed but there was a change in strength within the prior 30 days. A prescription was identified as a benzodiazepine using the anatomical therapeutic index. A list of all medications included can be found in Appendix C: Table C.1.

3.3.1.2 Stratification

I performed subgroup analyses to examine which patient-level factors affected the likelihood of these outcomes; specifically, analyses for <80 years of age, >80 years of age, whether the patient was admitted to the hospital on the index visit, and by hospital site.
Figure 3.3. *Ex ante* Patient Pathway for the effect of medication review medication optimization and on health services utilization. The bolded pathway indicates the pathway for a high-risk patient with a suspected ADE.
3.4 Analysis

3.4.1 Statistical Analyses

All unadjusted bivariate statistics were conducted using the two-sample t-test or the Wilcoxon rank-sum test or Chi-square test if the normality assumption was not met.

I used interrupted time series analysis, one of the strongest quasi-experimental research designs, to assess the effect of the medication review on the primary outcomes listed at 24 distinct observations, 12 months before and after the intervention in study-time. This is shown visually in Figure 3.4 where O represents a distinct observation, and X represents the medication review which would only influence the intervention group. Interrupted time series with a control was chosen specifically for this intervention for its ability to provide a more detailed assessment of the longitudinal impact of an intervention than what is typically possible with a randomized controlled trial while minimizing confounding. Other advantages of the interrupted time series design include the ability to control for secular trends in the data, ease of conducting stratified analyses, and a clear graphical presentation of results.
Figure 3.4. Regression intercepts and slopes for an interrupted time series analysis with a control. Where the bottom line indicates the control and the top line indicates the intervention. (Figure from Linden et al.)

I used the following general composition—typical of an interrupted time series with a control—to model the outcomes at time periods, $t$, of one person-month:

$$Y(t) = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t + \beta_4 Z + \beta_5 Z T + \beta_6 Z X_t + \beta_7 Z X_t T$$

Variable definitions:

$Y(t)$: the outcome of interest at time $t$
$T$: time since the start of the study
$X$: dummy variable indicating the pre or post-intervention period
$Z$: represents the intervention ($Z=1$) or control ($Z=0$) group
\( \beta_0 \): the intercept or baseline value of the outcome for the control group
\( \beta_1 \): the pre-existing trend in the outcome for the control group
\( \beta_2 \): the baseline difference between the intervention and the control group
\( \beta_3 \): the pre-existing difference in the trend between the intervention and control group
\( \beta_4 \): the level change in the control group following the intervention
\( \beta_5 \): the trend change in the control group following the intervention
\( \beta_6 \): the difference in level change between the intervention and control group
\( \beta_7 \): the difference in trend change between the intervention and control group

The two parameters of interest are \( \beta_6 \), which indicates the difference in *level* change of the outcome between intervention and control group, where level refers to the immediate increase or decrease in the outcome following the intervention, and \( \beta_7 \), which indicates the difference in *trend* change of the outcome between the intervention and control group, where trend refers to the sustained difference in slope of the outcome over time.

Appropriate autoregressive terms were included when necessary in the model to adjust for the correlation of observations over time.  

### 3.4.2 Statistical Assumptions

An additional benefit of interrupted time series is that it can remove the effects of unobserved or unmeasurable confounding due to time-invariant (fixed) differences between the comparison groups, for example the effect of gender (an unmeasurable covariate) on the outcome of interest.\(^{97}\) In order for this analysis to assume that absent the effect of the medication review, the intervention group would have observed the same post-intervention level and trend change as the control group, the following assumptions must also be met:

1) any large historic events or other concurrent interventions which may influence the outcome (health services utilization) would equally affect the intervention and control group

2) there was no difference in the maturation of the intervention or control groups following the intervention that would affect the outcome of interest
All statistical analyses were conducted with R statistical software package, version 3.5.2. Data preparation was conducted with SAS, version 9.4
Chapter 4: Results

4.1 Descriptive and Bivariate Statistics
During the enrollment period between December 2011 and April 2012, there were 135,323 ED visits at the three participating hospital sites. Of these visits, 124,516 were excluded from analysis. The majority were excluded from the analysis for being identified as “Low-Risk” by the clinical decision rule (93,453, 75%). Of the remaining 10,783 eligible ED visits, 6,403 were systematically allocated to medication review, and 4,380 were allocated to the control.

As shown in Table 4.1, the majority of individuals included in the analysis experienced their index ED visit at VGH (68.9%), the median age was 70 (IQR: 32), 55.9% were female, and 57.9% had an index CTAS score of 2 (Urgent). The sample cohort also had an average of 8.3 medications prescribed in the six months prior to their index visit [standard deviation (SD)= 5.8] and 60.7% were discharged from the ED on their index visit.

The medication review group contained more individuals who experienced their index visit at VGH (74.7%) relative to the control (60.5%). There was an approximately equal distribution between the medication review and the control by age, with marginally more individuals aged 80-105 years included in the medication review group (33.9% relative to 31.7%). The medication review group had an average of 8.4 prescriptions (SD=5.8) relative to 8.1 in the control (SD=5.8), and slightly fewer individuals in the medication review group were discharged (60.3%) relative to the control (61.3%). During the follow-up time 12% of both the medication review (814 individuals) and 11% of the control (520 individuals) died, and therefore any months of these individuals’ data following their death was excluded from the analysis. Suspected ADEs were detected in 2,339 (36.6%) of patients who received medication review.

ADE subtypes suspected among patients who received medication review are displayed in Table 4.2 with differences measured using a Chi-square test. Notably, patients under
80 years of age were more likely to have a suspected ADE (37.4%) relative to patients over 80 years (32.5%; p<0.05). In addition, there were some differences by age in the proportion of ADE subtypes suspected. Patients under 80 were more likely to be suspected with non-adherence or an ineffective drug and were less likely to be suspected with supratherapeutic dose, relative to patients over 80 years old.

Unadjusted bivariate statistics, measured using the Wilcoxon rank-sum test, showed that there were significantly fewer ED visits 0-30 days following the index visit with a mean of 0.466 visits (SD: 0.999) per patient in the intervention and 0.483 visits (SD: 0.958) per patient in the control group (p=0.01). No bivariate differences were observed for total physician or GP visits (Table 4.3).

4.2 Primary Results: Outpatient Health Services Utilization

Interrupted time series models were used to determine the difference in various outpatient health services utilization outcomes for individuals allocated to receive the intervention (medication review) relative to the control (medication reconciliation).

4.2.1 Total Physician Visits

As shown in Table 4.4 the number of total physician visits at the first time point included in the analysis (12 person-months before the intervention) of 2,454 per 1000 control patients (95% CI: 2129.9, 2778.6) and 2,565 per 1000 medication review patients (95% CI: 2095.9, 3023.4) was not statistically different (p=0.64). Similarly, there was a similar and slightly increasing pre-intervention trend of visits for both the control group (61.5 per 1000, 95% CI: 17.2, 105.9) and the medication review group (57.1 per 1000, 95% CI: -5.6, 119.8), but there was no difference in pre-intervention level or trend between the two groups (p=0.64, p=0.89 respectively).

There was no significant change in the differential level or trend of the number of total physician visits per 1000 patients for individuals allocated to the medication review versus control in the 12 months following the intervention even after stratifying by age (Figures 4.1, 4.2, 4.3).
4.2.2 General Practitioner Visits

As with total physician visits, there were no significant differences in the pre- or post-intervention level or trend of GP visits between the medication review and control groups for all individuals (Table 4.4; Figure 4.4). Although patients in both the medication review and control group experienced a sharp increase in GP visits following their index ED visit, there was not a significant differential increase in level or trend of GP visits following the medication review, including when stratified by age. GP visits accounted for 69.3% of the level increase in total physician visits among the entire population.

4.2.3 Emergency Department Visits

The number of ED visits 12 person-months before the intervention was 107.1 per 1000 patients in the control and 101.8 per 1000 patients in the medication review group. The number per 1000 increased by 3.6 visits per 1000 patients per month (95% CI: 0.3, 6.9) for 12 months leading up to the index ED visit. There was not a significant difference in the pre-intervention level (p=0.76) or trend (p=0.39) between the medication review and control group.

There was no significant change in the differential level or trend of the number of ED visits per 1000 patients for individuals allocated to the medication review versus control in the 12 months following the intervention, nor among patients under 80 (Figures 4.7 & 4.8). There was a near significant level differential decrease of 30 ED visits per 1000 patients over 80 years who received medication review in the month following the index visit (95% CI: -61.2, 2.5; p=0.08) relative to the control (Figure 4.10). However, this effect was attenuated when the analysis was further stratified by discharged patients (Figure 4.11).

4.3 Sensitivity Analyses

Additional sensitivity analyses were conducted to test for bias introduced by the selection of the study time period or population. With regards to the study time period, the health services outcomes produced substantially increased health services visits at time point 0, the first month following the medication review. Although the substantial increase in visits was expected, including these points in the model distorted the trends of visits.
Therefore, sensitivity analyses were conducted with these points excluded from the model, and with an indicator term included to adjust for the outliers at time points -1 and 0. Both approaches similarly adjusted for the expected outliers and were used to model the health services outcomes.

Sensitivity analyses on the population were also conducted. Beyond age, stratification of the primary outcomes was conducted on populations admitted to the hospital after their index ED visit, and by hospital site. Patients were stratified if admitted on the index visit to control for any effect in-hospital medication services may have had on long-term outcomes. To test if there was any residual confounding, medication review and control groups were propensity score matched based on age, gender, CTAS, number of medications six months prior to intervention, arrival mode, and arrival time. These sensitivity analyses did not reveal any statistically significant differences across groups compared to the primary results (results not shown).

4.4 Secondary Analyses: Prescription Drug Utilization

In addition to the primary outcomes, interrupted time series models were used to determine the effect of medication review on prescription drug utilization measures relative to the control.

4.4.1 Number of Potentially Inappropriate Prescriptions

As shown in Table 4.5, the baseline number of PIPs 12 person-months before the intervention was 615 per 1000 patients in the control and 678 per 1000 patients in the medication review group. The number per 1000 increased by 14 PIPs per 1000 patients per month in the control group (95% CI: -13.6, 16.1) for 12 months leading up to the index ED visit. There was no significant difference in the pre-intervention level (p=0.11) or trend (p=0.89) between the medication review and control group.

There was no significant change in the differential level or trend of the number of PIPs per 1000 patients for individuals allocated to the medication review versus control in the 12 months following the intervention (Figure 4.12).

4.4.2 Number of Benzodiazepine Changes
As shown in Table 4.5, the baseline number of benzodiazepine discontinuations 12 person-months before the intervention was 15 per 1000 patients in the control and 13 per 1000 patients in the medication review group. The number per 1000 decreased by 0.2 discontinuations per month in the control group (95% CI: -0.4, 0.0) for 12 months leading up to the index ED visit. There was no significant difference in the pre-intervention level (p=0.17) or trend (p=0.40) between the medication review and control groups. There was no significant change in the differential level or trend of the number of benzodiazepine discontinuations per 1000 patients for individuals allocated to the medication review versus control in the 12 months following the intervention (Figure 4.13). The number of benzodiazepine dose adjustments per 1000 patients was also measured, with no significant changes in differential level (-1.52, 95% CI: -7.1, 4.1; p=0.60) or trend (-0.25, 95% CI: -0.4, 0.6; p=0.63) between the intervention and control following the index visit (results not shown).
### 4.5 Tables and Figures

#### Table 4.1. Descriptive Statistics of Medication Review and Control

<table>
<thead>
<tr>
<th></th>
<th>Overall Study Sample (10,783)</th>
<th>Study Sample by Medication Review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (59.4%)</td>
<td>No (40.6%)</td>
</tr>
<tr>
<td>Medication Review</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6,403</td>
<td>59.4</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VGH</td>
<td>7,434 (68.9%)</td>
<td>74.7*</td>
</tr>
<tr>
<td>LGH</td>
<td>2,676 (24.8%)</td>
<td>17.6*</td>
</tr>
<tr>
<td>RH</td>
<td>673 (6.2%)</td>
<td>7.7*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6,031 (55.9%)</td>
<td>56.5</td>
</tr>
<tr>
<td>Male</td>
<td>4,752 (44.1%)</td>
<td>43.5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>70 (32)</td>
<td>71 (31)*</td>
</tr>
<tr>
<td>19-44 years</td>
<td>1,904 (17.7%)</td>
<td>16.9</td>
</tr>
<tr>
<td>45-64 years</td>
<td>2,703 (25.0%)</td>
<td>24.6</td>
</tr>
<tr>
<td>65-79 years</td>
<td>2,326 (21.6%)</td>
<td>21.8</td>
</tr>
<tr>
<td>80-105 years</td>
<td>3,850 (35.7%)</td>
<td>36.7</td>
</tr>
<tr>
<td>CTAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (Emergency)</td>
<td>2,553 (23.7%)</td>
<td>23.2</td>
</tr>
<tr>
<td>3 (Urgent)</td>
<td>6,241 (57.9%)</td>
<td>58.3</td>
</tr>
<tr>
<td>4 (Semi-Urgent)</td>
<td>1,896 (17.6%)</td>
<td>17.6</td>
</tr>
<tr>
<td>5 (Non-Urgent)</td>
<td>93 (0.9%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Number of Prescriptions(^i)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>8.3 (5.8)</td>
<td>8.4 (5.8)*</td>
</tr>
<tr>
<td>Prescription Dispensed(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>2977 (27.6)</td>
<td>27.8</td>
</tr>
<tr>
<td>Discharged on index visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged</td>
<td>6,544 (60.7%)</td>
<td>60.3</td>
</tr>
<tr>
<td>Admitted</td>
<td>4,239 (39.3%)</td>
<td>39.7</td>
</tr>
</tbody>
</table>

\(^i\)Within 6 months of index visit; \(^a\)During 24 month study period, *indicates p<0.05
**Table 4.2. ADE Type Suspected among Patients who received Medication Review**

<table>
<thead>
<tr>
<th>ADE Type Suspected</th>
<th>Age ≤80 (N=4054)</th>
<th>Age &gt;80 (N=2349)</th>
<th>Total (N=6,403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication problem, n(%)</td>
<td>2536 (62.6)*</td>
<td>1586 (67.5)*</td>
<td>4098 (64.2)</td>
</tr>
<tr>
<td>Suspected ADE, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADR</td>
<td>408 (10.0)</td>
<td>222 (9.5)</td>
<td>626 (9.8)</td>
</tr>
<tr>
<td>Subtherapeutic</td>
<td>129 (3.2)</td>
<td>72 (3.1)</td>
<td>200 (3.1)</td>
</tr>
<tr>
<td>Supratherapeutic</td>
<td>61 (1.5)*</td>
<td>63 (2.7)*</td>
<td>124 (1.9)</td>
</tr>
<tr>
<td>Ineffective Drug</td>
<td>221 (5.5)*</td>
<td>61 (2.6)*</td>
<td>281 (4.4)</td>
</tr>
<tr>
<td>Needs Additional Drug</td>
<td>332 (8.2)</td>
<td>213 (9.1)</td>
<td>428 (6.7)</td>
</tr>
<tr>
<td>Non-adherence</td>
<td>324 (8.0)*</td>
<td>99 (4.2)*</td>
<td>422 (6.6)</td>
</tr>
<tr>
<td>Unnecessary Drug</td>
<td>43 (1.0)</td>
<td>33 (1.4)</td>
<td>75 (1.2)</td>
</tr>
</tbody>
</table>

*indicates p<0.05 by Chi-Square test
Table 4.3. Bivariate Statistics of Medication Review and Control

<table>
<thead>
<tr>
<th>Study Sample by Medication Review</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=6,403</td>
<td>n=4,380</td>
</tr>
<tr>
<td><strong>Mean ED Revisits</strong> (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-30 Days</td>
<td>0.466(0.999)*</td>
<td>0.483(0.958)*</td>
</tr>
<tr>
<td>30-60 Days</td>
<td>0.211(0.704)</td>
<td>0.206(0.723)</td>
</tr>
<tr>
<td>60-90 Days</td>
<td>0.181(0.621)</td>
<td>0.169(0.613)</td>
</tr>
<tr>
<td><strong>Mean GP Visits (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-30 Days</td>
<td>3.563(4.975)</td>
<td>3.546(4.973)</td>
</tr>
<tr>
<td>30-60 Days</td>
<td>2.048(3.446)</td>
<td>1.902(3.262)</td>
</tr>
<tr>
<td>60-90 Days</td>
<td>1.672(2.888)</td>
<td>1.632(2.867)</td>
</tr>
<tr>
<td><strong>Mean Total Physician Visits (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-30 Days</td>
<td>8.325(7.984)</td>
<td>8.255(8.184)</td>
</tr>
<tr>
<td>30-60 Days</td>
<td>4.728(6.06)</td>
<td>4.436(5.67)</td>
</tr>
<tr>
<td>60-90 Days</td>
<td>3.841(5.038)</td>
<td>3.756(5.029)</td>
</tr>
</tbody>
</table>

*Excluding index visit; *indicates p<0.05 by Wilcoxon rank-sum test
Figure 4.1. Number of all outpatient physician visits in person-months per 1000 patients enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The intervention led to a nonsignificant positive post-intervention level change differential of 163.6 visits per 1000 patients (95% CI: -270.4, 597.5; p= 0.46), and a nonsignificant negative post-intervention trend change differential of 7.1 per 1000 patients per month for 12 months (95% CI: -93.3, 107.4; p=0.89). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Figure 4.2. Number of all outpatient physician visits in person-months per 1000 patients under 80 years enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The intervention led to a nonsignificant positive post-intervention level change differential of 170.3 visits per 1000 patients under 80 years (95% CI: -241.3, 581.9; p= 0.42), and a nonsignificant positive post-intervention trend change differential of 9.3 per 1000 patients under 80 years per month for 12 months (95% CI: -85.2, 103.8; p=0.84). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Figure 4.3. Number of all outpatient physician visits in person-months per 1000 patients over 80 years enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The intervention led to a nonsignificant positive post-intervention level change differential of 92 visits per 1000 patients over 80 years (95% CI: -189.0, 373.2; p= 0.525), and a nonsignificant positive post-intervention trend change differential of 10 per 1000 patients over 80 years per month for 12 months (95% CI: -61.6, 80.1; p=0.80). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Figure 4.4. Number of all GP visits in person-months per 1000 patients enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The intervention led to a nonsignificant positive post-intervention level change differential of 113.4 GP visits per 1000 patients (95% CI: -68.6, 295.4; p= 0.23), and a nonsignificant negative post-intervention trend change differential of 2.2 per 1000 patients per month for 12 months (95% CI: -46.5, 42.1; p=0.92). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Number of all GP visits in person-months per 1000 patients aged under 80 years enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The intervention led to a nonsignificant positive post-intervention level change differential of 94.4 visits per 1000 patients (95% CI: -53.4, 242.3; p=0.21), and a nonsignificant negative post-intervention trend change differential of 5.5 per 1000 patients per month for 12 months (95% CI: -37.2, 26.3; p=0.74). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.

**Figure 4.5.** Number of all GP visits in person-months per 1000 patients aged under 80 years enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The intervention led to a nonsignificant positive post-intervention level change differential of 94.4 visits per 1000 patients (95% CI: -53.4, 242.3; p=0.21), and a nonsignificant negative post-intervention trend change differential of 5.5 per 1000 patients per month for 12 months (95% CI: -37.2, 26.3; p=0.74). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Figure 4.6. Number of ED visits in person-months per 1000 patients enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The index visit was excluded from analysis. The intervention led to a nonsignificant negative post-intervention level change differential of 7.6 visits per 1000 patients (95% CI: -41.8, 26.6; p= 0.67), and a nonsignificant negative post-intervention trend change differential of 2.1 per 1000 patients per month for 12 months (95% CI: -9.4, 5.2; p=0.57). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Figure 4.7. Number of ED visits in person-months per 1000 patients aged under 80 enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The index visit was excluded from analysis. The intervention led to a nonsignificant positive post-intervention level change differential of 3 visits per 1000 patients aged under 80 (95% CI: -39.5, 45.0; p= 0.89), and a nonsignificant negative post-intervention trend change differential of 4 per 1000 patients per month for 12 months (95% CI: -13.0, 4.4; p=0.34). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Figure 4.8. Number of ED visits in person-months per 1000 patients aged under 80 who were discharged from the ED on their index visit, enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The index visit was excluded from analysis. The intervention led to a nonsignificant positive post-intervention level change differential of 2 visits per 1000 patients aged over 80 (95% CI: -45.1, 48.8; p = 0.94), and a nonsignificant negative post-intervention trend change differential of 5 per 1000 patients per month for 12 months (95% CI: -14.3, 3.7; p = 0.25). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Figure 4.9. Number of ED visits in person-months per 1000 patients aged over 80 enrolled in medication review or control, 12 months before and after their index ED visit (beginning at time 0). The index visit was excluded from analysis. The intervention led to a nonsignificant negative post-intervention level change differential of 30 visits per 1000 patients aged over 80 (95% CI: -61.2, 2.5; p=0.08), and a nonsignificant positive post-intervention trend change differential of 2 per 1000 patients per month for 12 months (95% CI: -4.3, 7.1; p=0.62). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
Figure 4.10. Number of ED visits in person-months per 1000 patients aged over 80 who were discharged from the ED on their index visit, 12 months before and after their index ED visit (beginning at time 0). The index visit was excluded from analysis. The intervention led to a nonsignificant negative post-intervention level change differential of 19 visits per 1000 patients aged over 80 (95% CI: -51.4, 12.8; p=0.24), and nonsignificant negative post-intervention trend change differential of 1 per 1000 patients per month for 12 months (95% CI: -6.3, 3.6; p=0.59). The green shading highlights points (at time -1 and 0) that were excluded from the model as expected outliers.
<table>
<thead>
<tr>
<th></th>
<th><strong>Number of Total Physician Visits per 1000</strong> (Units: visits/1000 patients)</th>
<th><strong>Number of GP Visits per 1000</strong> (Units: visits/1000 patients)</th>
<th><strong>Number of ED Visits per 1000</strong> (Units: visits/1000 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Existing Level</strong></td>
<td>2454.3(2129.9,2778.6; p-val: 0)</td>
<td>1056.4(913,1199.9; p-val: 0)</td>
<td>107.1(83.4,130.8; p-val: 0)</td>
</tr>
<tr>
<td><strong>Existing Trend</strong></td>
<td>61.5(17.2,105.9; p-val: 0.01)</td>
<td>21.1(1.7,40.5; p-val: 0.04)</td>
<td>3.6(0.3,6.9; p-val: 0.037)</td>
</tr>
<tr>
<td><strong>Pre-existing Difference at time 0 between Intervention and Control</strong></td>
<td>110.3(-348.4,569.1; p-val: 0.64)</td>
<td>26.2(-176.6,229.1; p-val: 0.8)</td>
<td>-5.3(-38.8,28.3; p-val: 0.76)</td>
</tr>
<tr>
<td><strong>Differential Trend for the Intervention relative to Control</strong></td>
<td>-4.4(-67.1,58.3; p-val: 0.89)</td>
<td>-1.6(-29.1,25.8; p-val: 0.908)</td>
<td>2.1(-2.6,6.7; p-val: 0.392)</td>
</tr>
<tr>
<td><strong>Level Change Post-Intervention (Control)</strong></td>
<td>1488.2(1181.3,1795; p-val: 0)</td>
<td>612.2(483.5,740.9; p-val: 0)</td>
<td>47.9(23.7,72.1; p-val: 0.004)</td>
</tr>
<tr>
<td><strong>Trend Change Post-Intervention (Control)</strong></td>
<td>-384.5(-455.5,-313.6; p-val: 0)</td>
<td>-152.3(-183.6,-121; p-val: 0)</td>
<td>-16.6(-21.7,-11.4; p-val: 0)</td>
</tr>
<tr>
<td><strong>Difference in Level Change between Intervention and Control</strong></td>
<td>163.6(-270.4,597.5; p-val: 0.46)</td>
<td>113.4(-68.6,295.4; p-val: 0.23)</td>
<td>-7.6(-41.8,26.6; p-val: 0.67)</td>
</tr>
<tr>
<td><strong>Difference in Trend Change between Intervention and Control</strong></td>
<td>7.1(-93.3,107.4; p-val: 0.89)</td>
<td>-2.2(-46.5,42.1; p-val: 0.92)</td>
<td>-2.1(-9.4,5.2; p-val: 0.57)</td>
</tr>
</tbody>
</table>
**Figure 4.11.** Number of potentially inappropriate prescriptions per 1000 patients allocated to medication review vs. control, 12 months before and after the index ED visit (beginning at time 0). The intervention led to a nonsignificant negative post-intervention level change differential of 51 potentially inappropriate prescriptions per 1000 patients (95% CI: -112.9, 11.7; p=0.12), and a nonsignificant positive post-intervention trend change differential of 1 prescription drug change per 1000 patients (95% CI: -9.4, 12.2, p=0.99). Potentially inappropriate prescriptions were identified using the 2012 version of the Beers list.7,8
Figure 4.12. Number of benzodiazepine discontinuations per 1000 patients allocated to medication review vs. control, 12 months before and after the index ED visit (beginning at time 0). The intervention led to a nonsignificant negative post-intervention level change differential of 0.9 changes per 1000 patients (95% CI: -3.5, 1.7; p=0.48), and a nonsignificant positive post-intervention trend change differential of 0.06 per 1000 patients per month for 12 months (95% CI: -0.3, 0.5; p=0.78).
### Table 4.5. Potentially Inappropriate Prescription and Benzodiazepine Model Results

<table>
<thead>
<tr>
<th></th>
<th>Number of PIPs per 1000 patients (Units: Number dispensed/1000 patients)</th>
<th>Number of Benzodiazepine Discontinuations per 1000 patients (Units: Number discontinued/1000 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Existing Level (Control)</td>
<td>543.0 (506.2, 579.8; p-val: 0.00)</td>
<td>14.7 (13.3, 16.0; p-val: 0.00)</td>
</tr>
<tr>
<td>Existing Trend (Control)</td>
<td>8.6 (3.7, 13.5; p-val: 0.00)</td>
<td>-0.2 (-0.4, 0.0; p-val: 0.13)</td>
</tr>
<tr>
<td>Pre-existing Difference at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time 0 between Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing Difference at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>time 0 between Intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and Control</td>
<td>49.3 (-2.7, 101.3; p-val: 0.07)</td>
<td>-1.4 (-3.3, 0.53; p-val: 0.17)</td>
</tr>
<tr>
<td>Differential Trend for the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention relative to Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level Change Post-Intervention</td>
<td>7.8 (0.8, 14.8; p-val: 0.03)</td>
<td>0.1 (-11.9, 3.6; p-val: 0.40)</td>
</tr>
<tr>
<td>Level Change Post-Intervention</td>
<td>92.3 (23.7, 3.9; p-val: 0.00)</td>
<td>1.7 (-0.2, -0.4; p-val: 0.08)</td>
</tr>
<tr>
<td>Trend Change Post-Intervention</td>
<td>-13.1 (-140.6, -9.4; p-val: 0.00)</td>
<td>-0.3 (-0.6, -0.0; p-val: 0.03)</td>
</tr>
<tr>
<td>Difference in Level Change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>between Intervention and Control</td>
<td>-51.0 (-112.9, 11.7; p-val: 0.12)</td>
<td>-0.9 (-3.5, 1.7; p-val: 0.48)</td>
</tr>
<tr>
<td>Difference in Trend Change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>between Intervention and Control</td>
<td>-0.9 (-9.4, 12.2; p-val: 0.99)</td>
<td>0.1 (-0.3, 0.4; p-val: 0.78)</td>
</tr>
</tbody>
</table>
Chapter 5: Discussion and Conclusion

This study presented a large longitudinal interrupted time-series evaluation of ED-based pharmacist led medication review on two-year trends of outpatient health services utilization and potentially inappropriate prescriptions including benzodiazepines.

5.1 Systematic Allocation

The lack of difference between the intervention and control in the pre-intervention level and trend for all three outcomes lessens the concern that there may have been bias introduced through the systematic allocation process. This also provides evidence for the effectiveness of the unique systematic allocation process used for this study. Future research studies unable to perform a randomized control trial may wish to consider a similar algorithm to allocate patients to two arms for a controlled quasi-randomized study.

5.2 Health Services Utilization Outcomes

These results indicate that this ED-based medication review did not significantly modify long-term trends of total physician, GP visits, or ED revisits even when stratified by age, discharge status, or by hospital site.

5.2.1 General Practitioner Visits

To my knowledge, this was the first study to present the longitudinal trends of GP visits following an ED-based pharmacist-led medication review. GP visits accounted for approximately 70% of the level change in total physician visits, more than any other physician subspecialty. This provides evidence to support the claim that GPs are likely the outpatient physician specialty most impacted by medication review and should be actively included during the intervention to encourage patient follow-up on the results of the review in order to produce the recommended medication changes.

There were no significant differences in the overall health services utilization for the entire study cohort. The lack of differences between the medication review and control group is generally well supported in the literature, with three studies indicating no effect, and only one indicating a modest increase in both GP visits, and urgent care visits, 51-53,64
While Okere et al. did see a positive differential change in GP visits among patients who received ED-based medication review, their study had a substantially younger population than other previous work (Appendix A: Table A.1). The patients included in the present study were older, with a median age of 70 years. As older patients are more likely to return to residential care or be admitted to the hospital, they may be less likely to follow up on the result of a medication review with a GP in the community. In addition, due to higher levels of multi-morbidity and frailty in older patients, it is less likely that their chief compliant to the ED was medication-related, and therefore any subsequent health services utilization may be driven by factors other than medication-related problems, leading to smaller differences between the intervention and control groups.

As there were no significant differences in GP visits by age over or under 80 years, even after stratifying by admitting status, these results cannot effectively determine whether age may be acting as an interaction term in the effect of medication review on primary care use, as previously reported. This lack of difference was surprising given more patients under age 80 (37.4%) who received medication review were suspected to have an ADE relative to patients over age 80 (32.5%; p<0.05). This was likely caused by selection bias introduced by the clinical decision rule towards enrolling more older patients without medication problems in this study than younger patients (Appendix C). Therefore, while patients under age 80 would have had more reason to follow up on their suspected ADE with their GP, no difference in follow-up was observed.

5.2.2 ED Visits
The lack of difference in 12-month trends among all subgroups following the medication review provides strong evidence to suggest that the intervention did not result in differences to the long-term number of ED revisits per 1000 patients. However, the intervention led to a nearly significant negative post-intervention level change of 30 visits per 1000 patients aged over 80 years. While this effect was attenuated when the analysis was stratified by discharge status, to control for the differential proportion of admission between the intervention and control on the index visit, the small decrease in level change
may be indicative of findings from previous studies demonstrating a small effect of medication review on ED revisits with shorter follow-up time. Santolaya-Perrín et al. found a differential decrease in the number of ED visits at three months, only at sites where uptake of pharmacist recommendations were high, however their results did not persist at their six and 12 month follow-up points. Overall, this study did not observe a significant trend change in ED revisits, suggesting that any effect of medication review does not persist long-term (beyond one to three months post-intervention.)

These findings suggest that as it is currently designed, medication review does not result in long-term changes to patient health services outcomes. One possible explanation for this, grounded in the theory of change, is that there is not enough connection between the medication review process and outcome and the community-based prescriber, or possibly that pharmacist recommendations are not accepted by physicians and therefore does not result in long-term changes to health outcomes. Of four studies which previously measured outpatient health services utilization, the percentage of pharmacist recommendations that were adopted into clinical practice ranged from 18% to 94%. Future interventions should prioritize follow-up between GPs and patients identified as suspected of having an ADE, and should measure the proportion of recommendations accepted and adopted.

5.3 Prescription Medication Outcomes

The most significant challenge associated with measuring medication optimization resulting from medication review was defining a set of medication-related outcomes relevant to the entire population under study. Unlike health services utilization which can be measured among all patients who receive the intervention or control, many of the commonly used or recommended measures of prescription medication use including overuse, underuse, drug-drug interaction, or potentially inappropriate prescriptions would not be relevant to all patients who receive the review. It is estimated that only a minority of patients who receive the medication review will require medication optimization due to a suspected ADE, and the recommendations for optimization often differ by patient. This presents two major issues for research. Firstly, it fragments the intervention so that there is no common outcome which can be assessed for all patients,
because the types of optimization required differ depending on the ADE subtype suspected. For example, measuring a decrease in the mean number of medications may be a reasonable outcome among patients suspected to have an unnecessary drug, but would not be reasonable among patients with an untreated indication (Appendix D). Secondly, it is nearly impossible to identify a population to match by ADE type from a control group, because controls cannot be identified without receiving medication review. These concerns are not often adequately addressed in studies measuring the effect of medication review on prescription optimization. Unfortunately, I was unable to measure a more precise outcome of medication optimization with the limitations given beyond the number of PIPs and number of benzodiazepine discontinuations.

5.2.1 Number of PIPs
The results in this study indicate that medication review did not influence trends of PIPs, however, this result should be interpreted cautiously. Unlike previous studies which have found an effect of medication review on PIP, the purpose of the intervention under investigation in this thesis was not to apply an explicit tool to identify and correct PIP. Instead, this intervention used the implicit knowledge of the pharmacists to determine ADEs, most of which were not associated with PIP listed in the Beers criteria. Therefore, the lack of difference in trends of PIPs may not indicate a lack of effectiveness of the medication review, but rather that drugs on the Beers criteria were not associated with the ADEs identified by the clinical pharmacists. While older editions of the Beers list have not been associated with predicting ADEs, some prospective data has shown STOPP criteria to be effective at detecting ADEs that are causal or contributory to acute hospitalization in older adults. While, the STOPP criteria can be challenging to measure administratively as it determines the appropriateness of a patient’s prescription drugs in the context of his/her concurrent diagnoses, there is currently a validation study taking place to compare and validate newer a version of the Beers list (2012) relative to the STOPP criteria for use in health administrative data. Depending on the results of this study, future evaluations could measure the effect of a medication review on rates of STOPP/ START medications.

5.2.2 Benzodiazepine Discontinuations
The lack of differences in 12-month trends following the medication review provides evidence to suggest that the intervention did not result in differences to the long-term number of benzodiazepine discontinuations nor benzodiazepine dose changes per 1000 patients. This result is generally consistent with the literature, which highlights the challenges in discontinuing potentially inappropriate prescriptions including benzodiazepines in the acute care setting.\textsuperscript{107,108} As only 27.6\% of patients had a prescription for a benzodiazepine during the two year study period, this outcome was not well representative of the entire population. Ideally, we would have only looked at the number of benzodiazepine discontinuations among older patients who presented to the ED with falls, but unfortunately, the sample size was not sufficient for these analyses. The proportion of benzodiazepines dispensed over the study period was equally balanced between groups, and age was also approximately balanced, therefore we could assume that there would be equal numbers of patients needing benzodiazepine discontinuations in both groups.

Although benzodiazepine discontinuation was acting as a proxy measure for medication appropriateness, deprescribing benzodiazepines was not the intended focus of this intervention. Unfortunately, this analysis was not able to assess the culprit drug indicated in the ADE for the patient, and therefore, it is difficult to know whether the pharmacist conducting the review would have definitively made recommendations regarding a patient’s benzodiazepine use. Interventions which focus solely on discontinuing benzodiazepines have previously been found to be effective, but many of these interventions had access to substantially more resources and time than what was available in this intervention.\textsuperscript{109}

\section*{5.4 Strengths and Limitations}

\subsection*{5.4.1 Strengths}
This large observational study was the first interrupted time series to evaluate the two-year trends of physician visits and potentially inappropriate prescriptions leading to and following medication review. Although this study was not a randomized controlled trial,
this observational setting had many advantages. Firstly, it allowed a very large sample size which provided a realistic interpretation of how medication review could be conducted outside of controlled experimental environments. In addition, the comparison between medication review to medication reconciliation also improves the external validity of these findings relative to other studies which used no medication intervention as a control. It is unlikely in any clinical setting that a control group would not receive any medication services, given medication reconciliation is the standard-of-care in Canada. The rigorous interrupted time series analysis confirmed that there were no pre-intervention differences in level or trend for any of the outcomes measured which indicates the success of the systematic allocation algorithm. Future studies hoping to conduct similar methodology at a lower cost than randomized controlled trial, or when a clinical trial is not ethically feasible may consider adapting this algorithm.

The unprecedented presentation of easily interpretable differences in health services utilization over 24 study-month time periods provides highly convincing evidence to suggest that medication review did not have an impact on the number of physician visits relative to medication reconciliation. Unlike all previous studies, the measurement of trends undertaken in this approach controlled for outliers, which, may not have been representative of a true change in the outcome. Furthermore, the clinically derived and validated high-risk criteria substantially increased the external validity of this study and allowed for subgroup analyses to examine the differences in effect in the population by age and among patients discharged on their index visit.

### 5.4.2 Limitations

Four major limitations for this thesis can be summarized by the four assumptions in the Theory of Change (Figure 2.2). Firstly, the *population assumption* states that appropriate pharmacist recommendations are communicated to and accepted by patients. This assumption requires that the pharmacist’s recommendations are appropriate, and that they are understood by patients. Several studies have previously measured the appropriateness of pharmacist recommendations and have found that generally the recommendations are appropriate and clinically relevant. This study did not use an explicit tool during the
medication review to identify potentially inappropriate medications (e.g. STOPP/START checklist), which has been found to standardize identification of inappropriate medications, standardize communication between care providers and improve the generalizability for future research to replicate the process of medication review.\textsuperscript{52,112} However, this study did enable pharmacists to use their own clinical decision making when assessing the patient which may have led to more individualized and personalized care. Research has shown that these explicit tools may not be effective at identifying all types of ADEs, and could restrict the medication review and limit its potential impact.\textsuperscript{75-77,113} More recent work has shown including both implicit and explicit criteria may capture the benefits of both approaches.\textsuperscript{54}

The second component of the population assumption requires that recommendations are effectively accepted by patients. To my knowledge, few studies have looked at patient perception and acceptance of pharmacist recommendations, however, one study found that patient knowledge of their medications improved following in-hospital medication review.\textsuperscript{114} Verifying this assumption would likely require survey data obtained from patients following medication review, and unfortunately, this information was not available for this study.

This study was the also unable to accurately assess the capacity change assumption, which assumed that medication changes made by the clinical pharmacists in the ED were successfully communicated to and accepted by GPs. The lack of differential follow-up in GP visits among all patients, and the absence of a decreasing trend of ED visits per 1000 at any point in the post intervention period point indicated that this capacity change assumption may not have been adequately met. This limitation due to communication and acceptance of pharmacist recommendations has been previously measured in other studies, and has been identified as a large threat to the potential success of medication review.\textsuperscript{51,54,101}

Specifically, the role of communication and acceptance was investigated more thoroughly in a recent study by Santolaya-Perrín et al. which trialed four different
communication techniques on the uptake of physician acceptance of pharmacist’s recommendations.\textsuperscript{54} The technique which led to the lowest acceptance of 27\% was most similar to the phone call/ fax and discharge summary forms of communication used in the present study. In contrast, the site with the highest acceptance of 53\% used a primary care pharmacist to communicate the findings from the ED pharmacists to the GP. This technique also resulted in a significant decrease in hospital admissions and ED revisits at 3 months post intervention (aRR= 0.57; 95\% CI: 0.33, 0.98). This finding could potentially be explained because GPs may have a greater expectation for collaboration and a stronger pre-existing relationship with the mediating primary care pharmacist, and therefore, may be more likely to accept the recommendations.\textsuperscript{115} In addition, the recommendations were eventually made face-to-face which has been identified as an important factor for success in the past.\textsuperscript{116} The second most effective communication technique identified by Santolaya-Perrín was the use of a common primary care electronic clinical record which resulted in a 52\% acceptance of recommendations. Recently, a separate survey found that 96.7\% of GPs stated electronic communication of medication recommendations as their preferred method of receiving prescribing information.\textsuperscript{117} The effectiveness of technological solutions for communicating between care providers may continue to improve with growing use and could provide a more cost-effective pathway for information exchange than face-to-face interactions.\textsuperscript{118}

Next, the behavior change assumption stated that increased knowledge of medications influences physician prescribing and patient’s medication use. Previous research has found that persuading physicians to change prescribing behavior can be extremely difficult.\textsuperscript{119} Also, informing patients of the potential risks of their medication use or non-adherence is rarely sufficient to change behavior, instead successful persuasion often requires multiple attempts.\textsuperscript{120,121}

Finally, the well-being change assumption stated that a decreased likelihood of experiencing an adverse drug event would lead to patients changing their health services utilization patterns. Although measuring health services utilization is essential for showing the potential economic benefits of an intervention, it is possible that it was not
sensitive enough to detect smaller changes in medication optimization, especially within a high-risk population where many patients had a high baseline usage of health services utilization which was not necessary associated with medication appropriateness. Therefore, it is important for future studies to consider alternative measures of medication optimization in addition to health services utilization in order to capture the true effectiveness of medication review. This could be accomplished by measuring changes to culprit medications which has been specifically flagged by pharmacists as being associated with ADEs. Unfortunately, this study did not have access to the culprit drug information in order to perform this analysis.

In addition to the limitations highlighted by the Theory of Change, this study was also limited by its quality improvement design. Patients in the control arm may have received assessment by clinical pharmacists if the emergency physician requested consultation for a specific medication management question. Unfortunately, these consultations were not documented and therefore, this study was unable to account for the potential benefit that additional staffing of pharmacists may have had on the outcomes for patients in the control group. This may have biased the results of the intervention towards the null.

5.5 Conclusion
This thesis provides an in-depth discussion and analysis on the effectiveness of emergency-based pharmacist-led medication review on health services utilization and medication optimization. This thesis provides several new contributions to the field. Methodologically, this work presents evidence for the effectiveness of this quality improvement initiative at creating two comparable groups for analysis using one of the strongest quasi-experimental analytic designs available, an interrupted time series, without requiring an RCT. The many time points and physician specialities evaluated in this work provide a broad overview of the effect of medication review on health services utilization.

This study found a significant bivariate difference in ED revisits at 0-30 days, among all patients, and a nonsignificant negative post-intervention level change differential in ED revisits among patients aged over 80 years. There were no long-term differences in trends
of ED revisits. Therefore, it appears that any potential effect of medication review on ED revisits may only be short-term (one to two months). This information is consistent with the literature which suggests that 55% of older patients who were previously hospitalized for an ADE are re-exposed to previously harmful medications within six months.27 This information suggests that patients who receive medication review should receive an additional follow-up with their prescribing care provider around one-month to three-months post-intervention to determine if medication recommendations have been implemented.

Unfortunately, this study was unable to evaluate the effectiveness of this intervention on the acceptance of pharmacist recommendations by prescribing care providers in the community and the literature suggests that this limitation has a significant impact on the potential of the intervention for enacting improvements in care. Unfortunately, despite interest in an electronic system that could facilitate communication of medication review results from pharmacists to GPs, no current system exists in British Columbia.112

Future research is required to determine the number of pharmacist recommendations that are effectively communicated to and accepted by both patients and providers, as well as determining which communication efforts are most sustainable and effective. New medication review interventions should prioritize communication of results between care providers, and follow-up between GPs and patients who are suspected of experiencing an ADE.
References


65. Chiu PKC, Lee AWK, See TYW, Chan FHW. Effectiveness of a pharmacist-led medication review programme on medication appropriateness and hospital readmissions among geriatric in-patients in Hong Kong. *Hong Kong medical journal = Xianggang yi xue za zhi.*


# Appendices

## Appendix A. Literature Review

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Objective</th>
<th>Population (size)</th>
<th>Analysis Method</th>
<th>Relevant Results</th>
</tr>
</thead>
</table>
| Lisby (2015)[41] | Investigated the health-related effect of systematic medication review performed by a clinical pharmacist and a clinical pharmacologist | Population: Age ≥ 65 years, orthopedic nonelective admitted to hospital, on ≥4 drugs (n=108) Setting: In-hospital | Method: RCT; \(X^2/ t\)-test Follow-up: 3 months | • Mean GP contacts were 7.6 (6.3-8.9) in the intervention and 7.7 (6.3-9.2) in the control (p=0.97)  
• Mean outpatient care visits were 1.1 (0.8-1.4) for both the intervention and control group  
• Mean time to the first unplanned contact to a physician was 14.9 days (95% CI, 8.9-21.0) in the intervention group compared with 27.3 days (95% CI, 18.9-35.7) in the control group (log-rank test, 0.05)  
• Only 18% of pharmacist recommendations were adopted |
| Okere (2015)[64] | To evaluate the effect of systematic implementation of a pharmacist-led patient-centered approach to medication therapy management and reconciliation service (MRS) in the ED on patient utilization of available health care services. | Population: Age ≥ 18 years (n= 544) Setting: Single hospital ED | Method: Prospective randomized cohort study Follow-up: 1, 2, 3 months | • Patients in the intervention were 1.9 times (95% CI:1.4, 2.6) more likely to visit their PC providers, compared to the control at 3 month follow-up  
• Intervention patients were less likely than controls to visit urgent care (OR=0.7; 95% CI: 0.4, 1.2), although the difference was not significant |
| Gallagher (2011)[52] | Evaluated pharmacist recommendations for improvements in prescribing appropriateness | Population: Age ≥ 65 years, admitted to hospital (n=382) Setting: In-hospital | Method: RCT; \(X^2/ t\)-test Follow-up: 2,4,6 months | • There was a trend toward a lower frequency of GP visits during the follow-up period in the intervention group relative to the control group (p= 0.063)  
• 94% of pharmacist recommendations adopted |
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Objective</th>
<th>Population (size)</th>
<th>Analysis Method</th>
<th>Relevant Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisby (2010)53</td>
<td>Investigate whether interdisciplinary systematic medication reviews would reduce the readmissions, mortality and contacts to primary healthcare.</td>
<td>Population: Age ≥ 70 years, admitted to internal medicine ward of hospital, on ≥1 drugs (n=99)</td>
<td>Method: RCT; (X^2) / t-test Follow-up: 3 months</td>
<td>• Mean GP contacts were 8.8 (7.0-10.6) for intervention and 7.1 (3.9-10.4) for the control&lt;br&gt;• 39% of pharmacist recommendations adopted</td>
</tr>
<tr>
<td>Santolaya-Perrin (2019)44</td>
<td>Assess the influence of an interprofessional collaboration program between ED specialists, hospital pharmacists and GPs (GPs), on the number of all-cause emergency visits and hospital admissions</td>
<td>Population: Age≥ 65 years, 1 or more outpatient drug, has a long-term chronic disease (n=665)</td>
<td>Method: RCT; adjusted multivariate negative binomial regression analysis Follow-up: 3, 6, 12 months</td>
<td>• The adjusted rate ratio of emergency visits and hospital admissions was 0.808 (95% CI 0.617 to 1.059) at 3 months, 0.888 (95% CI 0.696 to 1.134) at 6 months and 0.954 (95% CI 0.772 to 1.179) at 12 months&lt;br&gt;• ED sites with higher percentage of medication review recommendations adopted by the GP led to significant reduction in emergency visits and hospital admissions at 3 months (0.452 (95% CI 0.222 to 0.923) and 0.567 (95% CI 0.328 to 0.983))&lt;br&gt;• Percentage of recommendations adopted varied from 27% to 53% across 4 sites</td>
</tr>
<tr>
<td>Chiu (2018)65</td>
<td>Conducted a prospective controlled study to investigate the effectiveness of a comprehensive pharmacist intervention on medication use and hospital readmission among a group of geriatric inpatients in Hong Kong</td>
<td>Population: Age ≥ 65 years, who were transferred from an acute hospital (n=212)</td>
<td>Method: Prospective controlled study; (X^2) / t-test Follow-up: 1, 3 months</td>
<td>• No statistical difference in the number of ED visits between intervention and control at 1 month (17.9% vs 28.2%; p=0.079, respectively) or 3 months after discharge (43.4%, 46.6%; p=0.641)</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Population</td>
<td>Setting</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>--------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Lisby</td>
<td>2015</td>
<td>RCT; X²/ t-test</td>
<td>Age ≥ 65 years, orthopedic nonelective admitted to hospital, on ≥4 drugs (n=108)</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Okere</td>
<td>2015</td>
<td>Prospective randomized cohort study, mixed methods linear analysis</td>
<td>Age ≥ 18 years (n= 544)</td>
<td>Single hospital ED</td>
</tr>
<tr>
<td>Farris</td>
<td>2014</td>
<td>RCT, univariate logistic regression</td>
<td>Age ≥ 18, diagnosis of cardiovascular condition (n=945)</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Lisby</td>
<td>2010</td>
<td>RCT; X²/ t-test</td>
<td>Age ≥ 70 years, admitted to internal medicine ward of hospital, on ≥1 drugs (n=382)</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Gillespie</td>
<td>2009</td>
<td>RCT; X²/ t-test</td>
<td>Age ≥ 65 years, admitted to hospital (n=382)</td>
<td>In-hospital</td>
</tr>
</tbody>
</table>
To evaluate the effect of pharmaceutical care provided in addition to acute Geriatric Evaluation and Management (GEM) care on the appropriateness of prescribing.

Population: All patients admitted to acute geriatric evaluation and management unit, (n=203)
Setting: In-hospital

Method: RCT; $X^2 / t$-test
Follow-up: 1, 3, 12 months

- One year after discharge, the rate of emergency visits was lower in the intervention group than in the control group (7.9% vs 12.0%, respectively, $p=0.45$), but the difference was not statistically significant.

Table A.3. Effect of Pharmacist-led Medication Review on Potentially Inappropriate Prescriptions

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Objective</th>
<th>Population (size)</th>
<th>Analysis Method</th>
<th>Method for assessing Potentially Inappropriate Prescriptions</th>
<th>Relevant Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu (2018)</td>
<td>Conducted a prospective controlled study to investigate the effectiveness of a comprehensive pharmacist intervention on medication use and hospital readmission among a group of geriatric inpatients in Hong Kong</td>
<td>Population: Age ≥ 65 years, who were transferred from an acute hospital (n=212)</td>
<td>Method: Prospective controlled study; $X^2 / t$-test</td>
<td>MAI</td>
<td>- After the program and at discharge, the proportion of subjects with inappropriate medications in the intervention group was significantly lower than that in the control group (28.0% vs 56.4%; p&lt;0.001).</td>
</tr>
<tr>
<td>Van der Linden (2018)</td>
<td>Evaluate the effect of a pharmacist intervention, consisting of the application of the Rationalization of home medication by an Adjusted STOPP in older Patients (RASP) list and a pharmacist-led medication review on polypharmacy, the quality of prescribing, and clinical outcome in geriatric inpatients</td>
<td>Population: Dutch speaking patients admitted from home or a nursing home (n=59)</td>
<td>Method: Prospective controlled trial; $t$-test</td>
<td>RASP (modification of STOPP)</td>
<td>- More RASP PIMs were discontinued in the intervention cohort, with a mean difference of 1.49 PIMs (95% confidence interval (CI): 0.70, 2.23; p &lt; 0.001)</td>
</tr>
<tr>
<td>Marvin (2016)</td>
<td>Identify patients affected by falls, and find whether medication review in the acute setting led to deprescribing of falls-risk medicines</td>
<td>Population: Age ≥ 70 years, admitted for fall (n=45)</td>
<td>Method: prospective cohort study</td>
<td>STOPIT (modification of STOPP)</td>
<td>- The number of falls-risk medicines decreased by a mean of 0.53 per patient before and after review (not including the dose</td>
</tr>
<tr>
<td>Study</td>
<td>Title</td>
<td>Population</td>
<td>Setting</td>
<td>Method</td>
<td>Follow-up</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>------------</td>
<td>---------</td>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td>Dalleur 2014&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Evaluate the effect of STOPP criteria recommendations from an IGCT on discontinuation of PIMs in older inpatients discharged from a hospital medical ward.</td>
<td>Population: Age ≥ 75 years, frail, admitted to medical ward (n=146)</td>
<td>In-hospital</td>
<td>STOPP (clinical relevance evaluated by care providers)</td>
<td>Follow-up: 1 year (among patients with PIM)</td>
</tr>
<tr>
<td>Gallagher (2011)&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Evaluated pharmacist recommendations for improvements in prescribing appropriateness</td>
<td>Population: Age ≥ 65 years, admitted to hospital (n=400)</td>
<td>In-hospital</td>
<td>STOPP/START/MAI</td>
<td>Follow-up: 2,4,6 months</td>
</tr>
</tbody>
</table>
**Spinewine (2007)**

<table>
<thead>
<tr>
<th>Evaluate the effect of pharmaceutical care provided in addition to acute Geriatric Evaluation and Management (GEM) care on the appropriateness of prescribing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong> Age ≥ 70 years, admitted to geriatric unit (n=200)</td>
</tr>
<tr>
<td><strong>Setting:</strong> In-hospital</td>
</tr>
<tr>
<td><strong>Method:</strong> RCT; $X^2$-/t-test</td>
</tr>
<tr>
<td><strong>Follow-up:</strong> at discharge, 3 months</td>
</tr>
<tr>
<td><strong>MAI/ACOVE/ Beers 1997</strong></td>
</tr>
</tbody>
</table>

- Intervention patients significantly more likely to have an improvement in MAI, ACOVE, and Beers at discharge ((OR) 5 9.1, 95% confidence interval (CI) 5 4.2–21.6 and OR 5 6.1, 95% CI 5 2.2–17.0, respectively).
- At 3 months, found a trend toward higher appropriate maintenance rates in the intervention group for two criteria: Beers drugs (improvement maintained in 94% of intervention vs 86% of control cases) and benzodiazepines in patients with previous fall (86% vs 56%, respectively). The differences were not significant.

ACOVE: Assessing Care of Vulnerable Elders; MAI: Medication Appropriateness Index; START: Screening Tool to Alert to Right Treatment; STOPP: Screening Tool of Older People’s potentially inappropriate Prescriptions; RASP: Rationalization of home medication by an Adjusted STOPP in older Patients
Appendix B. Anatomical Therapeutic Chemical Codes to Identify Benzodiazepines

Table B.1. List of Benzodiazepine derivatives included

<table>
<thead>
<tr>
<th>ATC code</th>
<th>Name</th>
<th>DDD</th>
<th>Unit</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>N05BA01</td>
<td>diazepam</td>
<td>10</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>mg</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>mg</td>
<td>R</td>
</tr>
<tr>
<td>N05BA02</td>
<td>chlordiazepoxide</td>
<td>30</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>mg</td>
<td>P</td>
</tr>
<tr>
<td>N05BA03</td>
<td>medazepam</td>
<td>20</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA04</td>
<td>oxazepam</td>
<td>50</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA05</td>
<td>potassium clorazepate</td>
<td>20</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA06</td>
<td>lorazepam</td>
<td>2.5</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>mg</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5</td>
<td>mg</td>
<td>SL</td>
</tr>
<tr>
<td>N05BA07</td>
<td>adinazolam</td>
<td>10</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA08</td>
<td>bromazepam</td>
<td>20</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA09</td>
<td>clobazam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BA10</td>
<td>ketazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BA11</td>
<td>prazepam</td>
<td>30</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA12</td>
<td>alprazolam</td>
<td>1</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA13</td>
<td>halazepam</td>
<td>0.1</td>
<td>g</td>
<td>O</td>
</tr>
<tr>
<td>N05BA14</td>
<td>pinazepam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BA15</td>
<td>camazepan</td>
<td>30</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA16</td>
<td>nordazepam</td>
<td>15</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA17</td>
<td>fludiazepam</td>
<td>0.75</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA18</td>
<td>ethyl loflazepate</td>
<td>2</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA19</td>
<td>etizolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BA21</td>
<td>clotiazepam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BA22</td>
<td>cloxazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BA23</td>
<td>tofisopam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N05BA24</td>
<td>benzodiazepam</td>
<td>75</td>
<td>mg</td>
<td>O</td>
</tr>
<tr>
<td>N05BA56</td>
<td>lorazepam, combinations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix C. Clinical Decision Rule

Figure C.1. Clinical Decision Rule for identifying patients at high-risk of experiencing an ADE in the ED\textsuperscript{80}
Appendix D. Addressing Adverse Drug Events

Legend

- **Net Increase**: Net increase in number of prescriptions dispensed
- **No net change**: No net change in number of prescriptions dispensed/possible change in dose/frequency
- **Net decrease**: Net decrease in number of prescriptions dispensed

### Figure D.1
Hypothesized Effect of Addressing ADE on Mean Number of Medications. Percentages indicate hypothesized proportion of ADE subtypes.\(^{123}\)