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Printed educational materials directed at Ontario primary care physicians fail to improve adherence to guideline recommendations for the management of diabetes complications: a pragmatic, factorial, cluster randomized trial

Alison Howie, *The University of Western Ontario*

Supervisor: Zwarenstein, Merrick, *The University of Western Ontario*
Co-Supervisor: Klar, Neil, *The University of Western Ontario*
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Abstract

Printed educational materials (PEMs) have long been used as a tool for knowledge translation despite the conflicting evidence surrounding their effectiveness. A pragmatic, 2x2 factorial, cluster-randomized controlled trial was designed to ascertain the effectiveness of two distinct formats of a PEM (insert and outsert) at improving adherence to guideline recommendations for the management of diabetes complications among Ontario family and general practitioners. Administrative databases were used to compare patient's treatment regimens at baseline and one year following PEM mailout to determine whether prescription rates intensified in response to the PEMs. A total of 4,118 practices (4,957 physicians) and 185,454 patients were included. Intensification rates in the four groups were similar and approximately equal to 46%. In intention-to-treat analyses, no treatment effect was found with the insert (OR 0.99, 95% CI 0.96 to 1.02), nor with the outsert (OR 1.01, 95% CI 0.98 to 1.04). Thus, PEMs were not effective at improving physician's adherence to guidelines for diabetes care.

Keywords

Summary for Lay Audience

Despite numerous medical breakthroughs, the health status of Ontarians is far from perfect. This disconnect is, in part, due to the poor translation of research findings from the bench to the bedside. To address this problem, many studies have investigated different strategies to bridge the gap between researchers and front-line staff. Printed educational materials (PEMs) consist of any recommendation for clinical care, whether it be a journal article, a magazine insert, or a letter that is delivered in print format to the recipient. PEMs have long been used as a strategy to inform clinicians on evidence-based practices and to persuade them to use these treatments or interventions. However, the literature provides conflicting evidence surrounding the effectiveness of PEMs, yet they continue to be used today. Thus, the present study aimed to investigate the effectiveness of PEMs at changing provider behavior.

The Ontario Printed Educational Message (OPEM) trial was carried out in 2005, a time when the prescription rate of drugs used to prevent diabetic complications was well below guideline recommendations. PEMs were thus developed to highlight several evidence-based recommendations for drug use among individuals with diabetes, and Ontario family and general practitioners' practices were allocated at random to receive one of two formats of the resulting PEM (a post card sized message or a long article, referred to as the outsert and insert, respectively), both, or neither (as a usual situation comparison group). Health administrative databases were used to ascertain the effectiveness of PEMs by observing whether treatment intensification occurred to a greater degree among patients of physicians who received a PEM, compared to those who did not.

Neither the insert nor the outsert were successful at causing physicians to intensify their patient's treatment regimen by adding a new drug, increasing the dose of a current drug, or switching from one drug to another drug.

Thus, the use of PEMs to improve physician's adherence to guideline recommendations for diabetes care is ineffective and should not be encouraged. Further research is required to investigate other strategies to inform physicians on evidence-based recommendations, as prescriptions for diabetes care remain below standard today.

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List of Abbreviations

ACE inhibitor – Angiotensin-converting enzyme inhibitor

ARB – Angiotensin receptor blocker

BP – Blood pressure

CI – Confidence interval

CPDB – Corporate Provider Database

cRCT – Cluster randomized controlled trial

CVD – Cardiovascular disease

DIN – Drug identification number

EBM – Evidence based medicine

EBP – Evidence based practice

FP – Family practitioner

GEE – Generalized estimating equations

GP – General practitioner

IPDB – ICES Physician Database

ITT – Intention-to-treat

KT – Knowledge translation

LHIN – Local health integration network

ODB – Ontario Drug Benefit Claims

ODD – Ontario Diabetes Dataset

OHIP – Ontario Health Insurance Program

OPEM – Ontario Printed Educational Message

OR – Odds ratio

PCP – Primary care physician

PEM – Printed educational material

PRECIS – Pragmatic-explanatory continuum indicator summary

RCT – Randomized controlled trial

RPDB – Registered Persons Database

SD – Standard deviation

T1DM – Type 1 diabetes mellitus

T2DM – Type 2 diabetes mellitus

WHO – World Health Organization

Chapter 1

1 Introduction

This chapter begins with a brief introduction to the thesis and the main topics to be covered in section 1.1. The study rationale is then discussed in section 1.2, followed by the objectives and hypotheses in section 1.3. The role of the student is highlighted in section 1.4. The last section, 1.5, describes the format of the thesis.

1.1 Overview

Investing in health research alone does relatively little to improve patient outcomes unless sufficient effort and resources are allocated to ensure that the information is communicated effectively to the relevant parties and changes their practice to conform to the evidence. The Government of Canada's commitment to improving the health of their citizens through research efforts is pronounced. In fact, since 2000, the Canadian Institutes of Health Research, Canada's research investment agency, has invested over $14 billion into health research (Canadian Institute for Health Research, 2018). However, the health status of many Canadians continues to be poor. In 2017, the Canadian Institute for Health Information measured physicians' adherence to selected guidelines, and found that up to 30% of the care that Canadians received was potentially unnecessary and even harmful (Canadian Institute for Health Information, 2017). This disconnect between health research and routine clinical practice is known as the evidence-to-practice gap, or the second translational gap, and continues to pose a threat to the health of Canadians today (Lau et al., 2014).

Despite being a highly researched area for decades, the evidence-to-practice gap persists. Researchers have quantified that it takes, on average, 17 years for research to be applied to practice (Morris et al., 2011). As a result, clinicians continue to deliver care that has been proven to be outdated, unnecessary, and even harmful for many years following the emergence of research results (Grimshaw et al., 2012). Patients are therefore unable to benefit from advances in healthcare and, consequently, experience a diminished quality of life (Grimshaw et al., 2012). It is estimated that, to keep up with current medical research, general internists would be

required to read 20 papers per day (Shaneyfelt, 2001). Balancing a heavy load of reading in addition to seeing numerous patients per day is unrealistic, necessitating the development of novel strategies to bridge this gap.

1.1.1 Knowledge translation

Knowledge translation (KT) is an emerging field focused on the activities required to move research from the bench to the beside in attempts to attenuate the evidence-to-practice gap. The overall aim is to enhance communication through all stages of research, starting from the creation of knowledge to its application in routine care (Sudsawad, 2007). In essence, researchers and clinicians must collaborate, rather than operating in two unconnected fields. For a KT intervention to be successful, the following four steps must be completed: synthesis, dissemination, exchange, and ethically-sound application of knowledge (Canadian Institute for Health Research, 2016). KT interventions are classified into three categories: implementation tools, resource planning tools, and evaluation tools (Moore et al., 2017). Among the extensively researched interventions is audit and feedback. This KT strategy provides clinicians with feedback on their performance to encourage them to address any gaps in their practice (Flottorp et al., 2010). Moreover, local opinion leaders are credible, trustworthy and likeable individuals who are tasked with delivering educational material to clinicians in attempts to eliminate evidence-to-practice gaps (Flodgren et al., 2011). Another example of a commonly used KT strategy is reminder systems (Grimshaw et al., 2012). Reminders, delivered via mail or electronically, are used to prompt clinicians to engage in desirable behaviors or actions according to best practices (Grimshaw et al., 2012). Researchers generally agree that active dissemination of materials and multi-faceted interventions are superior to passive dissemination strategies. Nonetheless, printed educational materials (PEMs), a passive dissemination strategy, have been used extensively throughout the years in attempts to change physician practice. The wide-reach, convenience, and low-cost associated with PEMs has led to their widespread use (Giguère et al., 2012).

1.1.2 Printed educational materials

PEMs are defined as "the distribution of published or printed recommendations for clinical care" (Johnson & May, 2015). Clinical recommendations come in a variety of forms, including clinical

practice guidelines, email summaries, and journal articles (Grudniewicz et al., 2015a). To attract the eye of the reader, PEMs must be designed and developed with careful consideration and substantial detail. Including too much detail, or too few details, may prevent the uptake of the PEM. Researchers have suggested that many characteristics, such as font size, color, use of graphics and specificity influence the uptake of PEMs and should therefore be considered in the design phase (Grudniewicz et al., 2015b). While the development and design of PEMs may be time-consuming and costly, the costs associated with the distribution of PEMs, including printing and mailing, are small and much lower than other KT interventions which have a costly human component.

The value, convenience, and low cost of PEMs has led to their widespread use (Giguère et al., 2012). However, the overall effectiveness of PEMs continues to be debated today. Numerous systematic reviews have attempted to provide a formal recommendation for the use of PEMs as a behaviour change strategy aimed at physicians, but the flaws in the available literature compromise the quality of their conclusions (Grudniewicz et al., 2015a). A 1998 systematic review concluded that passive dissemination strategies are generally ineffective, and, when they do alter practice, the effect is negligible (Bero et al., 1998). This conclusion failed to dissuade researchers from using PEMs, as evident by the large number of primary research articles investigating the effectiveness of PEMs in recent years. A large review conducted in 2004 found a modest improvement in guideline dissemination with the use of PEMs (Grimshaw et al., 2004). With a more explicit analytical framework than previous reviews, the authors revealed that PEMs resulted in a median absolute improvement in physician performance of 8.1% (range +3.6 to +17%), much larger than previously found (Grimshaw et al., 2004). The evidence has more recently reversed again; the most recent review was undertaken in 2015 and revealed that, at present, PEMs are ineffective at changing primary care physician (PCP) behaviors (Grudniewicz et al., 2015a).

1.1.3 Diabetes mellitus

Despite being considered a "healthy nation", Canada continues to fall short in one area: chronic disease management (Government of Canada, 2019). In 2017, 89% of Canadian deaths were attributed to non-communicable diseases such as cancers, cardiovascular diseases, and diabetes

(Institute for Health Metrics and Evaluation, 2017). Diabetes mellitus, commonly referred to as diabetes, is an example of a chronic disease that poses a large threat to the health of Canadians in spite of many measures available for both the prevention and management of the disease. Diabetes, in its most basic definition, is a disease characterized by chronically high blood sugar, known as hyperglycemia. Hyperglycemia results from impairments associated with insulin secretion, with insulin being a hormone responsible for regulating blood sugar levels, as well as insulin resistance. The nature, and severity, of insulin impairment depends on the type of diabetes. According to Diabetes Canada, diabetes can be classified into four categories: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes, and "other" diabetes (Diabetes Canada, 2018b). T1DM is the most severe form, characterized by insulin deficiency due to the destruction of cells in the pancreas responsible for the production of insulin (Diabetes Canada, 2018b). Individuals with T1DM are therefore unable to produce insulin, resulting in the need for daily insulin administration (World Health Organization [WHO], 2018). T2DM is characterized by the body's inability to effectively use insulin due to insulin resistance, or the inability to produce enough insulin due to relative insulin deficiency (WHO, 2018; Diabetes Canada, 2018b). The treatment course for T2DM is less straightforward, as it depends on the severity of the disease. While some individuals with T2DM are able to manage their hyperglycemia with lifestyle changes, others require insulin therapy (WHO, 2018). Another form of diabetes characterized by the inability to produce enough insulin is gestational diabetes. Gestational diabetes is a temporary form of diabetes, characterized by glucose intolerance induced by pregnancy (Diabetes Canada, 2018b). Despite being temporary, the onset of gestational diabetes increases the likelihood of developing T2DM, and therefore represents a serious health concern (WHO, 2018). The last categorization of diabetes, "other", consists of uncommon forms of the disease, such as specific genetically defined diabetes and drug induced diabetes (Diabetes Canada, 2018b).

While diabetes manifests in different forms, the consequences are undifferentiated. Prolonged hyperglycemia is associated with numerous long-term complications, including cardiovascular disease (CVD), blindness, kidney disease, and non-traumatic amputation (Booth et al., 2012). With CVD being the leading cause of morbidity and mortality among patients with diabetes, it is essential that its risk factors be managed (Leon & Maddox, 2015). Many conditions, such as

hypertension and high cholesterol, are common in individuals with diabetes and have been shown to contribute to the development of CVD (Diabetes Canada, 2018b). The evidence for the cardiovascular risk reduction abilities of antihypertensives and cholesterol-lowering agents for individuals with diabetes is well documented (UK Prospective Diabetes Study Group, 1998b; Heart Protection Study Collaborative Group, 2003). In fact, in 1998, it was shown that aggressive blood pressure (BP) management resulted in significantly greater reductions in the vascular complications associated with diabetes than did glucose-lowering agents (UK Prospective Diabetes Study Group, 1998b). Thus, the need to adopt a multi-faceted treatment approach, managing all risks associated with diabetes, rather than treating high blood glucose alone, is clear.

As both the prevalence and the incidence of diabetes continue to increase, researchers consider diabetes to be "one of the most costly and burdensome chronic diseases of our time" (Lipscone & Hux, 2007). The WHO estimated that by 2030, the worldwide prevalence of diabetes would rise to 6.4%, corresponding to a 60% and a 39% increase from 1995 and 2000, respectively (Lipscone & Hux, 2007). This prediction was based on the assumption of a constant obesity rate over the years; however, with current lifestyle and behaviour changes, this prediction is likely to largely underestimate the true prevalence (Lipscone & Hux, 2007). In fact, between 1995 and 2005, the prevalence of diabetes in Ontario increased by 81.6%, surpassing the 39% predicted increase, suggesting that the true prevalence in 2030 is likely to be much higher than anticipated (Lipscone & Hux, 2007).

1.1.4 The Ontario printed educational messages programme

The Ontario printed educational message (OPEM) research programme consisted of a series of three factorial cluster randomized controlled trials (cRCTs) aimed at investigating the effectiveness of PEMs by addressing key gaps in primary care practice (Zwarenstein et al., 2007). The trial was designed to be pragmatic to answer the question of effectiveness: does the intervention work in real-world settings (Singal et al., 2014)? The programme was carried out between 2004 and 2006, a time when hypertension and diabetes care were below standard (Zwarenstein et al., 2007). Accordingly, the programme attempted to bridge the evidence-to-practice gap in the following areas: retinal screening for patients with diabetes, the use of

diuretics for hypertension, and prescription drug use for managing the complications associated with diabetes (Zwarenstein et al., 2007). The research programme aimed to answer the following questions: whether PEMs are effective at changing Ontario PCPs adherence to guidelines, if different sized PEMs have a varying degree of effectiveness, and the ability of PEMs to close gaps in the health care system (Zwarenstein et al., 2007). The PEMs were mailed to Ontario family and general practitioners (FP/GPs) and came in three different forms: a short message, a long message, or both (Zwarenstein et al., 2007). Administrative data held at ICES was used to obtain baseline and outcome measures, and all physician- and patient-level characteristics. A large proportion of trials conducted before the OPEM programme were small-scale and encompassed numerous methodological and analytical flaws. This programme thus represented a novel approach to studying the effectiveness of PEMs on a large scale by utilizing administrative data to study multiple interventions at dramatically lower costs.

1.2   Rationale

The rising prevalence and incidence of diabetes in Ontario is worrisome to both individuals and to public health officials. The lifestyle and behavioral trends that have contributed to the increase in incidence do not appear to be changing, necessitating the development of strategies targeted at improving the course of disease among those who are suffering. Despite numerous efforts, both at the national and provincial level, the adherence to guidelines for diabetes management continues to be poor (Canadian Diabetes Association | Diabète Quèbec, 2011; Diabetes Canada, 2018b). While self-management plays a large role in the disease course, treatment recommendations originate in the hands of the family physician (Diabetes Canada, 2018b). Studies have shown that prescription rates for medications to control diabetes-associated complications are below national guidelines, providing an opportunity for intervention (Braga et al., 2010). While many strategies exist for changing physician behaviour, PEMs have seen the most widespread use despite having inconclusive evidence for their effectiveness. The most recent systematic review revealed that PEMs are ineffective at changing provider behaviour (Grudniewicz et al., 2015a). However, rather than dissuading researchers from using PEMs, the authors provide direction for future research on PEMs (Grudniewicz et al., 2015a). They recommend that researchers provide a clear description of the intervention and how it was

developed to determine whether the PEM was optimized, as well as powering the study to be able to detect the intended effects (Grudniewicz et al., 2015a).

The OPEM programme offers a means for evaluating the effectiveness of PEMs through large scale, pragmatic RCTs. The first two trials in the OPEM series have been analyzed and published (Zwarenstein et al., 2014; Zwarenstein et al., 2016); however, the trial investigating the effectiveness of PEMs in terms of improving adherence to guideline recommendations for managing the cardiovascular risks associated with diabetes has not yet been analyzed due to a shortage of resources. At the time of the trial, antihypertensives and cholesterol-lowering agents were proven to effectively manage cardiovascular risks, and a substantial number of patients required more than one antihypertensive to reach target BP levels (UK Prospective Diabetes Study Group, 1998b; Heart Protection Study Collaborative Group, 2003; Diabetes Canada, 2018b). Accordingly, the trial aimed to increase prescribing rates of antihypertensives (including, specifically, angiotensin converting enzyme (ACE) inhibitors and "other" antihypertensives, such as angiotensin II receptor blockers (ARBs), beta-blockers, calcium channel blockers, and diuretics) and cholesterol-lowering agents (Zwarenstein et al., 2007). Research has since revealed that antihyperglycemic agents can also be effective at reducing the cardiovascular risks associated with diabetes (Diabetes Canada, 2018b). Nevertheless, BP and cholesterol-lowering agents remain important therapies to mitigate the risk factors associated with CVD, a disease that continues to be prevalent among diabetes patients (Diabetes Canada, 2018b). Accordingly, analyzing the results from this trial will still provide valuable information today. By including a large proportion of Ontario FP/GPs in the study population, the study was adequately powered to detect the intended effect. Furthermore, detailed information about the intervention was provided, including an image of the original PEMs, allowing researchers to determine whether the PEM was optimized. Adhering to the recommendations outlined in the latest systematic review, this trial has the capacity to significantly contribute to the debate surrounding the effectiveness of PEMs.

1.3   Objectives and Hypotheses

1. What is the effectiveness of a two-page (insert) PEM at intensifying FP/GP prescribing rates for diabetes treatment?

   Hypothesis: It is expected that prescribing practices among physicians who receive the two-page insert will be superior to those who do not receive the insert.

2. What is the effectiveness of a short, directive (outsert) PEM at intensifying FP/GP prescribing rates for diabetes treatment?

   Hypothesis: It is expected that prescribing practices among physicians who receive the short, directive outsert will be superior to those who do not receive the outsert.

3. Does the effect of the two-page (insert) PEM differ based on the presence of the short, directive (outsert) PEM (test of interaction)?

   Hypothesis: It is expected that the effect of the insert is independent of the effect of the outsert.

4. A subgroup analysis will be carried out to determine whether newly diagnosed diabetes patients are more likely to receive treatment intensification compared to those who have had diabetes for many years.

   Hypothesis: It is expected that patients who have been diagnosed with diabetes for extended periods of time may be on a stable treatment regimen and are thus less likely to alter this regimen in response to PEMs.

1.4   Role of the student

I had no involvement in the design or the implementation of the OPEM programme. Trial data were obtained, cleaned, and converted to level 4 student access by an analyst at ICES Western. Since the trial was conducted a number of years ago and the protocol lacked specific information on the trial, I worked with a team at ICES Western to develop a detailed dataset creation plan from the raw data. Although the basic analysis plan is traditional for an RCT and follows the original broad OPEM protocol, the specifics of these analyses and a number of additional analyses were planned by myself, together with my supervisors. I conducted all analyses and interpreted the results with the help of my thesis committee. I was responsible for writing all chapters of the final thesis.

1.5   Format

This thesis consists of five chapters, beginning with the introduction in chapter 1. Chapter 2 presents a review of the literature, including the current understanding of the effectiveness of printed educational materials and the present state of diabetes in Ontario. The following chapter, chapter 3, provides a description of the research methodology and the data sources. The study results, including multiple logistic regression models, are outlined in chapter 4. The final chapter, chapter 5, draws conclusions based on the results, lists the strengths and limitations of this research, integrates it with recent literature, and provides direction for future research.

Chapter 2

2 Literature Review

This chapter is composed of five sections and provides an overview of the current literature, beginning with the evidence-to-practice gap and the barriers to implementing evidence-based practices in primary care in section 2.1. The following section, 2.2, introduces knowledge translation and the common strategies used to mitigate the evidence-to-practice gap. The predictors of clinical behaviour are outlined in section 2.3. Printed educational materials, a frequently used knowledge translation intervention, are discussed in section 2.4 in terms of both their ability to influence practice and their cost-effectiveness. A general overview of diabetes and diabetes epidemiology is then provided in section 2.5, followed by a section on the complications associated with diabetes and treatment strategies. This section will also discuss the barriers to optimal management.

2.1 The evidence-to-practice gap

Evidence based medicine (EBM) is defined as the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al., 1996). Integrating the findings from the nearly 2.5 million scientific articles published each year into routine practice does not itself generate EBM; rather, health care providers must combine the relevant scientific evidence with their clinical expertise regarding their patients symptom profile, their history, and their values to deliver the highest quality of care (Sackett et al., 1996; Ware & Mabe, 2015). As a result, medical decisions should not follow a "cookbook approach", but instead require that health care providers exercise their best judgment to reconcile the available evidence and the individual patient's unique needs on all decisions made for each individual patient (Sacket et al., 1996). This requirement for both evidence-based and individualized care poses a challenge to health care providers, who already experience substantial demands on their time (Dugdale et al., 1999). Consequently, the evidence-to-practice gap emerges.

As discussed in section 1.1, the evidence-to-practice gap reflects the disconnect between what researchers know about what works, and what clinicians actually decide and recommend in their daily clinical decision making. These gaps emerge as a result of both clinicians not knowing what the guidelines are due to a lack of knowledge, and due to clinicians being aware of the guidelines, but choosing not to follow them. There are many examples of evidence-to-practice gaps in the medical literature (Grol & Grimshaw, 2003; Morales et al., 2013; Tan et al., 2008). For example, despite decades of well-established evidence for the benefits of thorough handwashing, compliance to handwashing procedures among health care providers continues to be poor (Grol & Grimshaw, 2003). For a second example, in family medicine practice, a significant proportion of Bell's Palsy patients are not receiving treatment with corticosteroids in spite of high-quality evidence demonstrating the effectiveness of this drug class (Morales et al., 2013). Moreover, extensive evidence exists to contest the use of antibiotics for the treatment of most acute respiratory tract infections; nonetheless, antibiotics continue to be widely prescribed (Tan et al., 2008). The consequences associated with these gaps are marked. Patients failing to receive effective care, and, in some cases, receiving harmful treatments, health care providers wasting their time and social resources applying outdated and ineffective guidelines, and medical advances with proven efficacy being ignored, among many more.

Studies addressing the evidence-to-practice gap have only recently become prominent in the clinical research community. In the past, researchers have mainly focused on conducting studies in specific patient groups to yield novel findings that merit publication in prestigious journals with the assumption that widespread uptake of effective treatments would follow naturally (Bauer et al., 2015). RCT researchers have typically not been concerned with the application of their findings to routine practice and to diverse patient groups (Bauer et al., 2015). However, with increasing concerns about the applicability of such trials, and decreasing funding for research globally, funding agencies have had to prioritize the type of studies they can support and have thus gained a deeper appreciation for studies with potential public health impact (Bauer et al., 2015). As a result, more applicable studies, and more studies focused on KT and implementation research, have emerged.

2.1.1 Evidence-to-practice gaps in primary care

Evidence-to-practice gaps are especially common in primary care practices (Lau et al., 2014). According to Lau and colleagues, "primary care has its own distinctive research and implementation culture", which has been described as contributing to the evidence-to-practice gap (Lau et al., 2014). The integration of new interventions in primary care is challenged by the diversity of the practices. Each practice is unique in terms of its team composition, culture, and working practices (Lau et al., 2014). While the complexity of teams is beneficial in terms of providing a more comprehensive approach to care, it can heighten the evidence-to-practice gap. Furthermore, it has been argued that achieving change in primary care practice often requires complex interventions that necessitate change at multiple levels, making the implementation process more challenging (Lau et al., 2014).

PCPs face many barriers to implementing EBPs and their resistance to integrating new knowledge has been extensively researched. PCPs have been known to consider general practice and research as two separate entities, reasoning that research is so far from patient centered care that it cannot be effectively incorporated into routine practice (Salmon et al., 2007). Reasons for disregarding EBPs are multifaceted and depend on the type of behaviour change that the intervention aims to target (Carleson et al., 2007). Interventions that attempt to eliminate a physician behavior (proscriptive interventions) are more challenging to implement than are interventions encouraging a new behaviour (prescriptive interventions), as the physician risks compromising a positive relationship they've maintained with their patients by eliminating common practices (Carleson et al., 2007). The integration of EBPs, especially those that require services to be rationed, threaten to compromise this relationship and therefore become less of a priority for PCPs (Carleson et al., 2007). Among the reasons for PCP resistance to EBPs includes the broad nature of conditions they treat (Hannes et al., 2005). PCPs are confronted with a wide range of patients each day who often present with vague symptoms and pose general questions relating to their health (Hannes et al., 2005). As a result, PCPs must possess a broad understanding of all symptoms and conditions. For this reason, they express that staying informed on current knowledge in all areas of general medicine is challenging (Hannes et al., 2005). Similarly, what PCPs experience in primary care is different from that of clinicians providing secondary care (Freeman & Sweeney, 2001). In a qualitative study, PCPs reported that

specialists treated "diseases rather than patients", making it easier to stay up to date on new advancements compared to their obligation to treat the patient as a whole, taking into account family and social context rather than simply treating a series of diseases (Freeman & Sweeney, 2001). PCPs also attribute their resistance to EBPs to the complexity of consultations in primary care (Carleson et al., 2007). The relative simplicity of guidelines often overlooks the struggles of treating complex individual circumstances, including patient preference, co-morbidities, and adverse events (Carleson et al., 2007). Lastly, PCPs' personal and professional experiences, including both successes and failures, dictate how they treat their patients (Freeman & Sweeney, 2001; Carleson et al., 2007).

2.2   Translating research into practice

Despite only recently gaining a formal definition, the concept of KT dates back to the early 1900s (Tarde, 1903). Sociologist Gabriel Tarde recognized that certain innovations were not being adopted in society and offered insight into factors that may affect implementation (Grimshaw et al., 2012). Several years later, in 1983, Everett Rogers developed the diffusion of innovation theory in attempts to better understand how new ideas are spread (Rogers, 1983). His theory suggests that the following four elements determine how effectively a new idea is spread: the innovation, communication, time, and social system (Rogers, 1983). However, a commitment to studying KT strategies to address the evidence-to-practice gap has only recently become widespread. In 2000, the Canadian Institute for Health Research released the first official definition of KT as the "exchange, synthesis and ethically-sound application of knowledge— within a complex system of interactions among researchers and users—to accelerate the capture of the benefits of research for Canadians through improved health, more effective services and products, and a strengthened health care system" (Canadian Institute for Health Research, 2004). Since then, many modifications to the definition have been released; however, the fundamental concept remains the same: KT strategies aim to facilitate the exchange of information between researchers and users. A main point highlighted by the Canadian Institute for Health Research is the need for continuous dialogue and interaction between researchers and users throughout the entirety of the process (Sudsawad, 2007). Researchers have compiled a list of desirable features of KT interventions, including, but not limited to, a clear statement of the tool's objectives, providing instructions to users, including users in the development process, and collecting user

feedback (Moore et al., 2017). While Canada has adopted the term "knowledge translation", many terms exist that are used interchangeably globally (Graham et al., 2006). A study revealed that 29 different terms exist to describe the concept of translating research into practice, including knowledge exchange, research utilization, implementation and dissemination (Graham et al., 2006).

To promote the successful uptake of KT interventions, knowledge producers are encouraged to answer five questions before implementing their intervention (see table 1.1) (Lavis et al., 2003). These questions are intended to force researchers to consider key design elements to ensure that the effect of their intervention is optimized.

Table 1.1: Questions to consider during the development process of a new intervention

Question	Considerations
What should be transferred to decision makers?	▪ Transfer "actionable messages" from multiple studies, rather than a single study
To whom should research knowledge be transferred?	▪ Primary target audience depends on the nature of the information to be transferred (see Appendix 1)
By whom should research knowledge be transferred?	▪ Choose credible messengers ▪ Endorsement by professional organizations and respected colleagues influences knowledge uptake
How should research knowledge be transferred?	▪ Weigh the facilitators and barriers to specific intervention strategies
With what effect should research knowledge be transferred?	▪ Select performance indicators to measure *whether* knowledge is used ▪ Measure *how* knowledge is used (i.e. in instrumental, symbolic, conceptual ways)

Data sources: Lavis et al (2003); Grimshaw et al (2012).

2.2.1 Knowledge translation interventions in the health care field

KT interventions are frequently utilized in the health care field and exist in many different forms. Interventions are classified into the following 3 categories based on the nature of their objective: resource planning, implementation, and evaluation (Moore et al., 2017). Interventions focused on resource planning include strategies to assess costs, equipment and technology requirements, and staff education and training, among many more (Gagliardi et al., 2014). Implementation tools

focus on the assessment of barriers and enablers to intervention adoption and point-of-care tools that determine how the clinician practices (Gagliardi et al., 2014). Evaluation tools include quality indicators, performance measures, and relevant benchmarks (Gagliardi et al., 2014).

Since interventions characterized by implementation tools are frequently used in the health care field, and are the main topic of this thesis, they will be discussed in greater detail (Moore et al., 2017). Educational materials and decision aids are among the most commonly used intervention tools due to their adaptability to a wide variety of scenarios (Moore et al., 2017). Educational materials exist in many forms, such as infographics, clinical practice guidelines and frequently asked questions (Moore et al., 2017). While traditionally delivered in print, the increased use of electronic systems in the medical field has allowed for educational materials to also be delivered electronically (Moore et al., 2017).

Decision aids share many characteristics with educational materials; however, their explicitness in terms of the decision in question sets them apart (Moore et al., 2017). Common formats of decision aids include decision trees, infographics, and algorithms (Moore et al., 2017). Despite being a valid tool to inform all of clinicians, patients, and caregivers, decision aids are most frequently used as a tool to inform patients (Moore et al., 2017).

Among the other KT interventions that have seen widespread use is audit and feedback. Audit and feedback systems are used to improve the quality of care delivered by clinicians by providing them with feedback on their routine clinical performance (Flottorp et al., 2010). Audit and feedback interventions are often paired with other tools, such as educational materials, to promote intervention uptake by highlighting the most effective approaches to care (Flottorp et al., 2010). By comparing clinicians' current practices with best practices, the evidence-to-practice gap is highlighted and may prompt change.

Another KT strategy commonly used is reminders. Reminders may be delivered on paper or electronically, and are used to prompt desired behaviours or actions (Grimshaw et al., 2012).

Local opinion leaders have also been used in attempts to promote intervention uptake in the health care field. Researchers hypothesize that individuals who are credible, trustworthy, and likeable have a greater ability to drive behaviour change (Flodgren et al., 2011). As a result, local opinion leaders have often been tasked with delivering educational messages to clinicians in attempts to emphasize the evidence-to-practice gap and to prompt behaviour change (Flodgren et al., 2011).

Similarly, educational outreach visits have been postulated to evoke change in health care settings. Outreach visits are mainly used to inform clinicians on a one-on-one basis on topics relevant to their specific practice, delivered by knowledgeable experts in the field (Centre for Effective Practice, 2018).

Furthermore, educational meetings have been suggested as a tool for KT. The nature of educational meetings can be didactic, addressing knowledge barriers, or interactive, addressing attitudes, skills and knowledge (Grimshaw et al., 2012).

Patient-mediated interventions have also been used as a KT strategy to enact change among clinicians. These interventions attempt to change clinician performance through patient education and appear in many forms, such as patient decision aids, the inclusion of patients on committees and boards, and patient-led training of health care providers (Fønhus et al., 2018).

Lastly, local consensus processes enable shared decision-making to assist groups of people in attaining agreement on issues in the health care field (Nasser et al., 2017). It is hypothesized that including people in the decision-making process evokes a sense of ownership and commitment to adhering to the proposed change; therefore, local consensus processes are thought to be a means of bridging the evidence-to-practice gap (Nasser et al., 2017).

2.2.2 The effectiveness of knowledge translation interventions

Despite the multitude of tools available for KT in the health care field, evidence-to-practice gaps remain widespread, prompting researchers to investigate the effectiveness of the available strategies. The development of the diverse array of KT strategies arose partly due to the

discovery that traditional continuing medical education activities, such as lectures and case methods, were generally ineffective at stimulating change in clinical decision making and practice among clinicians (Davis et al., 1999; Sandelowsky et al. 2018).

In early systematic reviews on KT interventions, researchers discovered that passive interventions, such as educational materials and didactic lectures, are less effective at initiating change compared to active interventions, such as outreach visits and interactive educational meetings (Bero et al., 1998). However, passive dissemination strategies continue to be used extensively today and their effects appear to be mixed (Grimshaw et al., 2012; LaRocca et al., 2012). Educational materials and reminders, both passive interventions, were found to improve care by 4.3% and 4.2%, respectively (Grimshaw et al., 2012). Educational outreach and educational meetings, two active interventions, resulted in absolute improvements in care of 4.8% and 6%, respectively (Grimshaw et al., 2012). Though the active strategies did yield greater improvements than the passive strategies, the magnitude of the difference is not large enough to discount passive interventions as effective KT tools. Furthermore, certain single component interventions have performed as well as their multi-component counterparts, indicating that simple interventions have the potential to induce change (Grol & Grimshaw, 2003; LaRocca et al., 2012). Researchers have suggested that overly complex interventions may even be less likely to be integrated into practice, as the excess information may dilute the key messages (Dobbins et al., 2009).

The inconsistency in findings has led to the continued use of KT strategies despite uncertainties about their true effectiveness. Most well-designed interventions have some effect, but there is not one "gold-standard" intervention that successfully promotes change in all settings (Grol & Grimshaw, 2003).

2.3   Predictors of clinical behaviour

To understand the inconsistencies in the provision of care, researchers have attempted to quantify the factors that influence physician performance. These characteristics can be grouped into three categories: physician factors, organizational factors, and systemic factors (Wenghofer et al., 2009). Among the frequently studied physician factors include physician age and sex. Studies

have shown that increasing age is correlated with poorer adherence to therapeutic standards, increased rates of inappropriate prescribing, and increased patient mortality (Anderson et al., 1997; Tsugawa et al., 2017). Similarly, as the number of years in practice increase, physician performance tends to decline (Choudhry et al., 2005; Cadieux et al., 2007). As physicians gain years of experience, they begin to accumulate a personal drug formulary from which they routinely prescribe, making it challenging to integrate new therapeutics when they are recommended in clinical guidelines (Carthy et al., 2000). The differences between males and females are less pronounced. Nevertheless, it has been reported that higher patient mortality rates are linked to male physicians (Davidson et al., 1995). Furthermore, another study revealed that female physicians perform better in the following areas: acute care, health maintenance, and managing patient records (Wenghofer et al., 2009). The impact of physician certification has also been studied. Physicians who are certified by the College of Family Physicians of Canada have been shown to deliver enhanced care in terms of health maintenance and managing patient records (Wenghofer et al., 2009). Physicians with a speciality certification were also found to provide enhanced patient care, as they are more likely to prescribe the most appropriate and effective drugs (Anderson et al., 1997). Lastly, the physician's place of training has been proposed to influence their performance (Cadieux et al., 2007; Wenghofer et al., 2009). It was determined that internationally trained physicians are more likely to prescribe inappropriate antibiotics compared to their Canadian trained counterparts (Cadieux et al., 2007). However, Wenghofer et al. (2009) showed that there is no significant difference in performance between physicians trained in North America and those trained elsewhere. The following physician characteristics have been investigated but failed to demonstrate a significant effect on performance: years practising with *current* patient population, and whether the physician has undergone peer assessment by the College of Physicians and Surgeons of Ontario (Wenghofer et al., 2009).

Organizational factors comprise the characteristics of the physicians working practice (Wenghofer et al., 2009). The number of patients seen per week has been shown to significantly influence physician performance (Wenghofer et al., 2009). Those who see fewer patients per week perform better in the following key dimensions: acute care, chronic care, continuity of care, health maintenance, and record management (Wenghofer et al., 2009). Furthermore, larger

patient volumes have been associated with increased rates of inappropriate antibiotic prescribing and higher patient mortality (Davidson et al., 1995; Cadieux et al., 2007). The effect of the number of yearly billings on physician performance has also been a variable of interest. Patients of physicians who bill larger amounts per year experience higher mortality rates than those who bill smaller amounts (Davidson et al., 1995). Lastly, physicians who hold active hospital privileges have been shown to outperform those who work solely as a GP (Wenghofer et al., 2009). Factors of interest that have not been proven to be significant include the number of staff per practice (including both clinical and administrative staff), number of hours worked per week, and whether the physician works in solo or group practice (Wenghofer et al., 2009).

Systemic factors are those associated with the broader context in which the physician works (Wenghofer et al., 2009). Practice location significantly impacts performance due to resource availability. In a study among Ontario physicians, those working in Southern communities significantly outperformed those practicing in Northern areas in acute care, health maintenance, and records management (Wenghofer et al., 2009). Moreover, it has been shown that Canadian physicians working in rural areas are less likely to comply with diabetes guideline recommendations than are physicians working in urban areas (Worrall et al., 1997). A factor that is often related to practice location is the physician-to-population ratio (Wenghofer et al., 2009). Physicians with higher physician-to-population ratios perform better in terms of acute care, chronic care, and continuity of care compared to those with smaller ratios (Wenghofer et al., 2009). Lastly, practices with a greater abundance of resources have enhanced performance (Wenghofer et al., 2009). The availability to order basic diagnostic tests improves chronic care, continuity of care, and health maintenance (Wenghofer et al., 2009). The effect of 911 service accessibility and time to emergency medical services have both been studied but have failed to show significant effects on physician performance (Wenghofer et al., 2009).

While the aforementioned studies have provided insight into the factors associated with physician performance, they are equipped with a limitation that cannot be overcome. Since neither patient symptoms, nor their disease course, are taken into consideration in these studies, the authors are unable to conclusively confirm that variations in performance are solely due to

physician characteristics, rather than the nature of their patient population. Nonetheless, the characteristics that have been proven to influence performance will be studied in our population.

2.4   Defining printed educational materials

According to the Cochrane Effective Practice and Organisation of Care Review Group (2019), PEMs are defined as the "distribution of published or printed recommendations for clinical care, including clinical practice guidelines, audio-visual materials and electronic publications. The materials may have been delivered personally or through mass mailings". PEMs are a common form of passive dissemination strategy that aim to mitigate the evidence-to-practice gaps prevalent in the health care field to enhance patient care (Farmer et al., 2003). While PEMs can be developed to target all members of the health care system, from patients to health care organizations, they have been frequently used to address knowledge and skill gaps among health care providers (Giguère et al., 2012).

The sole criteria required to be classified as a PEM is to provide a printed recommendation for clinical care; thus, the characteristics of PEMs vary extensively. PEMs can differ based on format, content, information source, and mode and timing of delivery, all of which contribute to the effectiveness of the PEM (Farmer et al., 2003). The format of PEMs includes the appearance and the length of the recommendation (Farmer et al., 2003). PEMs may be colorful or black and white, written in traditional or creative fonts, and printed on glossy or matte paper (Farmer et al., 2003). The length of PEMs is often determined by the context in which the recommendation is delivered, and can range from brief messages to multi-page journal articles (Farmer et al., 2003). For example, multi-page PEMs may be embedded in journals sent to providers, whereas short updates may be delivered on their own. The minimal criteria for PEMs also allows them to vary greatly in terms of content. The topic of PEMs may cover any clinical area, particularly focusing on areas in which care is below standard. Furthermore, PEMs may be tailored to specific audiences, such as PCPs, or may be generic, targeting diverse groups of individuals (Farmer et al., 2003). Lastly, the source of information used to develop recommendations determines the credibility of a PEM. PEMs may be developed by a variety of sources, including official organizations, such as the College of Physicians and Surgeons of Ontario, corporate sources, and governmental agencies (Farmer et al., 2003).

2.4.1 Do printed educational materials change provider behavior?

PEMs have a long history of use to address evidence-to-practice gaps (Farmer et al., 2008). However, despite their prominence in the health research community, the effectiveness of PEMs is still poorly understood. Bero et al. (1998) were the first to question effectiveness of PEMs. The authors provided strong evidence suggesting that the effect of educational materials on changing provider behaviour is little to none, and instead recommended that more intensive interventions should be utilized to alter practice (Bero et al., 1998). However, this revelation failed to dissuade trialists from delivering PEMs to health care providers to promote the uptake of research findings. A 2003 review similarly found that educational materials are generally ineffective at changing provider behaviour (Grol & Grimshaw, 2003). However, the authors note that inadequately powered and poorly analyzed studies dominate the literature (Grol & Grimshaw, 2003); therefore, to ascertain the true effectiveness of PEMs, studies of higher quality are required. The succeeding systematic review was published in 2004 and suggested that PEMs modestly improve guideline implementation (Grimshaw et al., 2004). The authors reported that PEMs resulted in absolute improvements in performance ranging from 3.6% to 17%, with a median absolute improvement of 8.1% (Grimshaw et al., 2004). Despite also making reference the poor quality of studies, Grimshaw et al. (2004) concluded that PEMs should not be disregarded as a strategy to change provider behaviour. They alluded to the fact that in many situations, resources for behaviour change interventions are scarce; therefore, policy makers should carefully estimate the benefits and costs of the desired intervention (Grimshaw et al., 2004). These promising results were the catalyst for the development of the OPEM programme to further investigate the effect of PEMs. The OPEM programme is discussed in greater detail in section 3.3.

Several reviews have been published since the OPEM programme was conducted. In 2008, a review by Farmer et al. supported the claim of effectiveness made by Grimshaw et al. (2004). While PEMs were generally shown to be ineffective when compared to other intervention types, when compared to no intervention, they led to statistically significant improvements in care (Farmer et al., 2008). The authors concluded that, while small, the benefits of PEMs are apparent and merit further study (Farmer et al., 2008). Two additional reviews were conducted in 2012. Ho & Venci (2012) investigated the effect of mailed letters on the prescribing behaviours of

physicians and found that mailed letter interventions, when well-orchestrated, have the potential to influence physician behaviour. Of the RCTs included in the review, 53.3% found that PEMs successfully impacted prescribing habits (Ho & Venci, 2012). Observational studies yielded larger effects, with 85.7% finding a positive association between mailed letters and physician prescribing patterns (Ho & Venci, 2012). However, the authors again concluded that, while it appears that prescribers are open to change in response to a mailed letter, definitive conclusions could not be drawn due to the heterogeneity of the articles in the literature (Ho & Venci, 2012). The second review conducted in 2012 revealed similar results (Giguère et al., 2012). While it was determined that PEMs have a small positive effect on provider behaviour when compared to no intervention, the authors concluded that the poor quality of the current evidence takes away from the strength of their conclusions (Giguère et al., 2012). The most recent review on the effectiveness of PEMs was undertaken in 2015 (Grudniewicz et al., 2015a). The authors acknowledged that the nature of the health care setting likely impacts the effectiveness of PEMs and thus focused their review on primary care practices specifically (Grudniewicz et al., 2015a). This review concluded that, at present, PEMs do not improve outcomes, neither at the PCP level, nor at the patient level (Grudniewicz et al., 2015a). The authors suggest that the positive results identified in previous reviews may be due to the inclusion of specialist physicians, as they are likely to respond differently to PEMs than are PCPs (Grudniewicz et al., 2015a). Instead of dissuading researchers from studying the effects of PEMs, the authors provide direction for future research that is required before ruling out this widely used dissemination strategy (Grudniewicz et al., 2015a). Some of the characteristics of the desired future studies include the improved design of PEMs, more detailed descriptions of the intervention, and sufficiently powered analyses (Grudniewicz et al., 2015a).

Today, the effect of PEMs continues to be researched. A study published in 2019 investigated the effect of PEMs on guideline adherence among PCPs and found that PEMs had a beneficial effect on providers compliance to clinical recommendations (Boltin et al., 2019). The odds of PCP behaviour change were 64% higher (p=0.04) among those who were exposed to PEMs compared to those who received no intervention (Boltin et al., 2019).

The effectiveness of PEMs warrants further investigation. Throughout the years, researchers have drawn repeatedly changing conclusions surrounding their effectiveness, and, to this day,

their ability to influence practice remains unknown. As a result, more trials investigating PEMs are needed. The present thesis analyses the results from an unreported trial from the OPEM programme. The conclusions drawn from the most recent systematic review were influenced by the first OPEM trial that was published, as it was a large-scale, pragmatic trial with a low risk of bias (Grudniewicz et al., 2015a). Accordingly, the results from the OPEM trial analyzed in this thesis are likely to be influential.

2.4.2 Cost-effectiveness of printed educational materials

The most commonly cited reason for using PEMs as a KT strategy despite understanding that their effectiveness has been repeatedly doubted is the low costs associated with implementation. In reviews that found PEMs to be relatively ineffective at changing provider behaviour, the authors often concluded that PEMs should not be disregarded due to their low cost and the ease with which wide coverage could be achieved (Grimshaw et al., 2004; Farmer et al., 2008). However, concrete evidence surrounding the cost effectiveness of PEMs is lacking.

A recent European study attempted to establish the implementation strategies that are the most effective given their costs (Mewes et al., 2017). It was determined that the costs associated with PEMs were substantially lower than other intervention strategies (Mewes et al., 2017). The total cost to mail a PEM, on three occasions, to a single provider, was €18 (Mewes et al., 2017). Compared to reminder systems and audit and feedback, which incurred costs of €77 and €1,075 per provider, respectively, PEMs are a relatively inexpensive intervention strategy (Mewes et al., 2017). A study by Padwal et al. (2017) confirmed this claim. In their study, three interventions that aimed to improve self-management strategies for bariatric care were compared in terms of effectiveness and cost (Padwal et al., 2017). The cost of mailing a single PEM to each individual was $1.33 (Padwal et al., 2017). In comparison, an in-person educational strategy and a web-based educational strategy cost $273.40 and $5.54, respectively (Padwal et al., 2017). Given that there was no significant difference between patient outcomes in the three intervention groups, the authors concluded that more intensive and costly strategies are not necessarily superior to cheaper, less effective options (Padwal et al., 2017).

The cost-effectiveness of PEMs was quantified in a 2004 study by Paul et al. PEMs were developed to provide women with information on a Pap Test Reminder Service (Paul et al., 2004). The authors compared the following three PEMs in terms of their cost to implement: a pamphlet incorporating literature characteristics only ('C'), a pamphlet incorporating both literature characteristics and behavioural strategies ('C + B'), and a pamphlet incorporating all of literature characteristics, behavioural strategies, and marketing strategies ('C + B + M') (Paul et al., 2004). Total costs were calculated by summing staffing costs (i.e. draft development and graphic designers), printing costs, and consumables costs (i.e. postage and supply costs) (Paul et al., 2004). The cost-effectiveness of each PEM was ascertained by dividing the costs by the number of women who joined the program in response to the PEM (Paul et al., 2004). The cost per women enrolled in the program for 'C', 'C + B', and 'C + B + M' was (AUD) $34.55, $21.33, and $22.78, respectively (Paul et al., 2004). Accordingly, the authors concluded that the pamphlet that incorporated both literature characteristics and behavioural strategies was the most cost-effective (Paul et al., 2004). More recently, Hallsworth et al. (2016) completed a similar cost effectiveness analysis on printed materials. Their study aimed to reduce inappropriate antibiotic prescribing among GPs by sending letters outlining their prescribing patterns relative to their peers (Hallsworth et al., 2016). They found that the cost per prescription prevented was £0.06, and, given the interventions success, concluded that these letters substantially reduce inappropriate prescribing at low costs (Hallsworth et al., 2016).

While the literature on the cost-effectiveness of PEMs is sparse, the available studies have revealed that the implementation of PEMs requires dramatically lower costs than other intervention strategies. Until we have strong evidence to suggest that PEMs are not effective, and given their low cost and apparent absence of harm, there is value in continuing to evaluate the cost-effectiveness of this KT strategy.

2.5   Diabetes mellitus

Diabetes mellitus, referred to as diabetes hereafter, is defined as a "heterogenous metabolic disorder characterized by the presence of hyperglycemia due to impairment of insulin secretion, defective insulin action, or both" (Diabetes Canada, 2018b). Insulin is a hormone used to regulate blood sugar levels. In diseased states, the body is unable to properly use insulin and thus

develops abnormal blood sugar levels, known as hyperglycemia. The mechanism by which hyperglycemia develops determines the nature of the diabetes diagnosis. Diabetes is classified into 4 categories: T1DM, T2DM, gestational diabetes, and other specific types. The majority of individuals with diabetes are diagnosed with either T1DM or T2DM; therefore, these disorders will be discussed in further detail in sections 2.5.1 and 2.5.2, respectively. Diagnosing diabetes is done through a variety of blood samples and laboratory tests, including a fasting plasma glucose test, a two-hour plasma glucose test, and a hemoglobin A1C test (Diabetes Canada, 2018b).

The symptom profile of individuals with diabetes differs based on the specific type of diabetes. However, common symptoms experienced by individuals with diabetes include increased thirst (polydipsia), frequent urination (polyuria), fatigue, weight change, and recurring infections (Diabetes Canada, 2019f). These symptoms, if improperly managed or left untreated, can give rise to numerous serious, and sometimes fatal, complications. These will be discussed in section 2.5.4.

2.5.1 Type 1 diabetes mellitus

T1DM, also known as insulin-dependent diabetes, is an autoimmune disease characterized by the inability to produce insulin (Diabetes Canada, 2018b). Though the underlying mechanism of T1DM remains unknown, researchers suspect that it results from the destruction of pancreatic beta cells, the cells responsible for producing insulin (Diabetes Canada, 2018b). Without insulin, sugars from ingested foods are unable to be used for energy and instead accumulate in the blood. Consequently, those with T1DM often require daily insulin injections to fill this void to maintain healthy blood sugar levels (Diabetes Canada, 2019f). Inadequate insulin supplementation can lead to diabetic ketoacidosis, a condition that is particularly concerning among individuals with T1DM (Diabetes Canada, 2018b). Without insulin, the body is unable to use glucose as fuel and thus compromises by burning fats (American Diabetes Association, 2019). The breakdown of fat produces a chemical called ketones, which increase the acidity of the blood and leads to several dangerous symptoms, including diabetic coma and death (American Diabetes Association, 2019).

While the majority (80-90%) of diabetes cases that develop during childhood or adolescence are T1DM, the onset of this disease can also occur in adulthood, complicating the ability to accurately diagnose this disease (Kharroubi & Darwish, 2015). Numerous factors have been hypothesized to give rise to beta cell destruction, such as genetic predisposition, exposure to viruses, and exposure to environmental factors (Kharroubi & Darwish, 2015). That being said, T1DM is not preventable. The onset of T1DM is often sudden, causing immediate symptoms such as polydipsia, polyuria, extreme hunger (polyphagia), sudden weight loss, and blurred vision (Kharroubi & Darwish, 2015). While unfortunate and troublesome, the sudden onset of symptoms can allow for a quicker diagnosis and improved prognosis. Aside from the general complications associated with diabetes (see section 2.5.4), individuals with T1DM are at a greater risk of developing other autoimmune disorders, such as Addison's disease, celiac disease, and Grave's disease (Kharroubi & Darwish, 2015).

2.5.2 Type 2 diabetes mellitus

T2DM is characterized by insulin resistance. While the beta cells of the pancreas *are* able to produce insulin, in contrast with T1DM, often not enough insulin is produced, or the body is unable to make proper use of it (Diabetes Canada, 2018b). As a result, blood sugar levels begin to rise. The insulin secretion, albeit small, usually allows individuals with T2DM to cope without the need for daily insulin supplementation (Kharroubi & Darawish, 2015). However, over time, the increased demand for insulin production can damage beta cells, resulting in insulin depletion that may eventually require daily insulin supplementation (Kharroubi & Darawish, 2015).

Unlike T1DM, T2DM can, in some cases, be prevented. Researchers believe that the worldwide obesity epidemic has contributed substantially to the rise in T2DM diagnoses (Kharroubi & Darawish, 2015). Accordingly, by maintaining a heathy body weight, engaging in regular physical activity, and eating a well-balanced, nutritious diet, individuals are able to reduce their likelihood of developing obesity and subsequently diabetes. However, like T1DM, genetic factors are also predicted to play a role in the development of T2DM (Wu et al., 2014). While the role of many genes has been studied, the *TCF7L2* gene has been identified as the largest contributor to T2DM susceptibility (Gloyn et al., 2009). Moreover, individual characteristics such as age, sex, and ethnicity have been shown to play a role in the development of T2DM

(Khan et al., 2010). While the onset of symptoms in T1DM is sudden, individuals with T2DM experience a more gradual development of symptoms. In fact, individuals can live with T2DM for many years before presenting any symptoms. As a result, diagnosing T2DM is challenging, and delayed diagnoses can lead to heightened long-term complications (Kharroubi & Darawish, 2015).

2.5.3 Diabetes epidemiology

According to the WHO (2016), "diabetes is one of the biggest global health crises of the 21st century". In 1980, the estimated worldwide prevalence of diabetes was 108 million, or 2,436 cases per 100,000 individuals (WHO, 2016; The World Bank, 2018). Over 30 years later, in 2014, the prevalence was reported to be 422 million, corresponding to 5,816 cases per 100,000 individuals (WHO, 2016; The World Bank, 2018). This alarming rise is largely fuelled by an increase in the incidence of T2DM risk factors, mainly obesity and sedentary lifestyles (WHO, 2016). In 2016, approximately 1.6 million individuals died due to diabetes, making diabetes the seventh leading cause of death worldwide (WHO, 2018). While the prevalence of diabetes has seen the greatest increase in low- and middle-income countries, high-income countries, like Canada, have not been spared (WHO, 2018).

Canadian statistics

Recent estimates suggest that one in three Canadians are either diagnosed with T1DM or T2DM, or have elevated blood sugars indicative of a "pre-diabetes" state (Diabetes Canada, 2019e). This corresponds to roughly 11 million Canadians directly affected by diabetes (Diabetes Canada, 2019d). Among Canadian individuals diagnosed with diabetes, 90-95% of them have T2DM (Diabetes Canada, 2019e). While this disease can affect individuals of all ages, the majority of cases are diagnosed among those 40 years or older (Doucet & Beatty, 2010). With an aging population, experts predict that the prevalence of T2DM will continue to rise (Doucet & Beatty, 2010). That being said, some studies suggest that, while the incidence of diabetes rose between 1995 and 2005 in Canada, it has since begun to level off (Magliano et al., 2019). Along with the increasing prevalence, the annual economic impact of diabetes has risen dramatically over the years (Diabetes Canada, 2019d). From $6.3 billion in 2000, to $14 billion in 2008, to almost $30 billion in 2019, diabetes presents a large burden on health care systems (Doucet & Beatty, 2010;

Diabetes Canada, 2019d). Estimates from the International Diabetes Federation (2019) suggest that in 2019, 7.4% of the total health expenditure in Canada was attributable to diabetes.

Though diabetes can affect virtually anyone, certain individuals are at a greater risk of developing this disease. In 2018, the prevalence of diabetes was greater in males than in females, with 8.1% of males being affected and 6.2% of females (Statistics Canada, 2019). Furthermore, among males, the highest prevalence of diabetes is reported in those aged 75 years and older (Statistics Canada, 2018). In females, however, the prevalence of diabetes increases steadily until the age of 74, after which the percentage of reported diabetes cases does not significantly increase (Statistics Canada, 2018). Moreover, ethnicity has been reported to influence an individual's risk of developing T2DM due to a combination of biological and behavioural differences (Government of Canada, 2011). Individuals of South Asian, Hispanic American, Chinese, and African descent are more prone to developing T2DM than are individuals of European descent (Government of Canada, 2011). While Caucasians reportedly engage in higher levels of physical activity, they are also more likely to smoke (Government of Canada, 2011).

Ontario statistics

It is estimated that, among the 10,991,000 Canadians currently living with diabetes or pre-diabetes, 4,424,000 are Ontarians (Diabetes Canada, 2019d). Ontario's high burden is, in part, due to evolving immigration patterns, with Toronto being a common city for new residents (Canadian Diabetes Association, 2011). The prevalence of diabetes in Ontario continues to rise, placing a significant burden on the health care system.

A 2012 ICES study attempted to determine the spread of diabetes and its associated complications across the 14 Local Health Integration Networks (LHINs) in Ontario (see Appendix 2) (Booth et al., 2012). The highest prevalence of diabetes was reported in Central West regions of Ontario, with a prevalence of 12.39% (Booth et al., 2012). The lowest prevalence was seen in the following LHINs: South West, Waterloo Wellington, Toronto Central, and North Simcoe Muskoka (Booth et al., 2012). In terms of hospital visits for hyper- or hypoglycemia, the provincial rates varied two-fold, but averaged at 486 per 10,000 individuals with diabetes (Booth et al., 2012). Individuals who experienced the greatest number of

hospitalizations were concentrated in Southwestern, Southeastern, Central and Northern Ontario regions (Booth et al., 2012). Furthermore, hospitalizations for cardiovascular events were recorded, averaging at 888 per 10,000 Ontarians with diabetes (Booth et al., 2012). Northern regions experienced hospitalizations as high as 1,376 per 10,000 individuals, whereas regions such as Central and Mississauga Halton experienced as few at 705 hospitalizations (Booth et al., 2012). The provincial average of lower extremity amputations was 74 per 10,000, but this number varied by 3.5-fold across regions (Booth et al., 2012). While individuals in Northern regions experienced rates as high as 148 per 10,000, those residing in Central areas experienced as few as 42 lower limb amputations (Booth et al., 2012). Lastly, the rate of additional chronic illnesses experienced by individuals with diabetes was measured (Booth et al., 2012). The provincial average was 54.84%, and varied little between regions (Booth et al., 2012). Despite this high prevalence of concomitant illnesses, only approximately one in three individuals paid a visit to their health care provider for a psychotic or non-psychotic illness (Booth et al., 2012).

While the majority of health care is covered for Ontarians enrolled in the Ontario Health Insurance Plan (OHIP), individuals are still required to pay out-of-pocket costs to effectively manage their disease. These costs include, but are not limited to, medications, devices and supplies (Canadian Diabetes Association | Diabète Quèbec, 2011). These out-of-pocket costs vary significantly throughout Canada, with Ontario ranking well above the national average for personal expenses for both T1DM and T2DM (Canadian Diabetes Association | Diabète Quèbec, 2011). Ontarian's with T1DM are required to spend nearly $950 annually to manage their diabetes, while those with T2DM are spending, on average, $2,173 per year (Canadian Diabetes Association | Diabète Quèbec, 2011). Accordingly, in 2011, 57% of individuals living with diabetes revealed that they do not fully comply with their treatment regimen as a result of the associated costs (Canadian Diabetes Association | Diabète Quèbec, 2011).

2.5.4 Complications associated with diabetes

Apart from the usual symptoms of diabetes discussed above, there are numerous complications that manifest in response to hyperglycemic states. These complications can be grouped into two main categories: macrovascular complications, and microvascular complications.

Macrovascular complications

The macrovascular complications associated with diabetes refer to conditions that arise in response to damage to the large blood vessels. This damage is largely due to atherosclerosis, the process of plaque build-up in the arterial walls that eventually leads to the narrowing and blockage of arteries (Fowler, 2008). As a result, individuals with diabetes are at an increased risk of numerous adverse cardiovascular events (Diabetes Canada, 2018b). The blockage of arteries results in reduced blood flow to all areas of the body. Without adequate blood supply to the heart, individuals with diabetes can experience chest pain and shortness of breath, both symptoms of coronary artery disease (Diabetes Canada, 2018b). Furthermore, limited blood supply to the brain can result in cerebrovascular disease and ischemic stroke (Fowler, 2008). Once an individual with diabetes experiences a stroke, they are more likely to experience another one and are at a greater risk of dying from the injury (Fowler, 2008). Lastly, reduced blood supply to the limbs can result in peripheral artery disease. This disease causes patients to experience pain in their lower extremities, and, in advanced states, can require amputation to deal with the resulting pain and infection (American Diabetes Association, 2003).

While there is substantial evidence to suggest that these complications can be avoided with appropriate therapy, CDV continues to be the main driver behind the devastating disability and premature death experienced by individuals with diabetes (Diabetes Canada, 2018b). In fact, according to Diabetes Canada, "diabetes confers a CVD event risk that is equivalent to aging approximately 15 years" (Diabetes Canada, 2018b).

Microvascular complications

Microvascular complications arise in response to damage to the small blood vessels. While less common than macrovascular complications, these conditions are severe, and, if improperly managed, can be fatal. Retinopathy has been hypothesized to be the most common microvascular complication experienced by individuals with diabetes (Fowler, 2008). This condition is caused by damage to the retina and results in visual impairments, including blindness (Fowler, 2008; WHO, 2019). Signs of retinopathy may be apparent before a definitive diabetes diagnosis is made; however, the majority of cases begin to manifest as the number of years lived with diabetes increases and if poor glycemic control is present (Fowler, 2008). Unfortunately,

retinopathy is often completely asymptomatic and therefore requires routine yearly eye examinations. Diabetes related nephropathy is another microvascular complication associated with diabetes that results from injury to the small blood vessels of the kidney (WHO, 2019). This condition is characterized by high levels of protein in the urine and usually causes patients to be asymptomatic in its early stages (WHO, 2019). However, if left untreated, nephropathy can lead to kidney failure and eventually death (WHO, 2019). Lastly, diabetes related neuropathy results from hyperglycemic-induced nerve damage and causes a wide variety of symptoms that differ according to the type of affected nerves (WHO, 2019). Symptoms can vary from numbness in extremities, to foot ulceration, to impotence in men (Fowler, 2008; WHO, 2019). Neuropathy, if untreated, can result in lower-limb amputation (WHO, 2019). In fact, it is estimated that greater than 80% of all amputations result from symptoms associated with diabetes related neuropathy (Fowler, 2008).

2.5.5 Treating diabetes

To standardize the treatment of diabetes across Canada, Diabetes Canada has published six sets of guidelines to provide a comprehensive summary of the current literature to guide care (Diabetes Canada, 2018b). These documents were designed as a tool to educate health care providers to close the gap between what is known and what is done in terms of caring for individuals with diabetes (Diabetes Canada, 2018b). The guidelines provide recommendations for, and an in-depth explanation of, the treatment of diabetes, addressing the direct effects of diabetes, and mitigating the risk factors for other complications. As referenced in section 2.5.4, cardiovascular complications associated with diabetes are responsible for the greatest symptom burden experienced by individuals with diabetes, with their ability to cause substantial disability and premature death (Diabetes Canada, 2018b). Accordingly, Diabetes Canada has put the management of cardiovascular risk factors at the forefront of their care plan (Diabetes Canada, 2018b). They believe that aggressive management of CVD risk factors is necessary for all individuals living with diabetes, and summarize their treatment recommendations into the "ABCDES of diabetes care" (Diabetes Canada, 2018b). These recommendations incorporate both pharmacologic and lifestyle management strategies to address the most serious complications associated with diabetes (Diabetes Canada, 2018b). There is no particular order in which these

targets should be addressed. Rather, the health care provider must make a plan for each individual patient, with the eventual goal of reaching as many targets as possible.

The first guideline involves controlling blood glucose levels (Diabetes Canada, 2018b). The "A" refers to hemoglobin A1C levels, which represent the amount of sugar in the blood (Diabetes Canada, 2018b). The target is A1C levels less than 7%, which may be managed differently based on the type of diabetes (Diabetes Canada, 2018b). While it is recommended that individuals with T1DM maintain their blood glucose levels by taking daily insulin injections, the first-line therapy for individuals with T2DM is oral doses of metformin (Diabetes Canada, 2018b). In instances in which the combination of metformin and lifestyle changes is unable to adequately manage T2DM, then second-line therapies, such as dipeptidyl peptidase-4 inhibitors and insulin secretagogues, are recommended (Diabetes Canada, 2018b).

The second guideline involves the management of high blood pressure, "B" (Diabetes Canada, 2018b). The BP target for individuals with both T1DM and T2DM is the same: less than 130/80 mmHg (Diabetes Canada, 2018b). This target can be achieved with a variety of antihypertensive medications; however, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) is generally recommended as first-line therapy for individuals with diabetes presenting with elevated BP and cardiovascular risk factors (Diabetes Canada, 2018b). In addition to their BP lowering abilities, ACE inhibitors and ARBs have additional renal protective effects, giving them the title of first choice agents (Diabetes Canada, 2018b). If BP is unable to be controlled with one of the aforementioned agents along with lifestyle management, combination therapy involving two or more antihypertensives may be recommended (Diabetes Canada, 2018b). Studies by the UK Prospective Diabetes Study Group (1998) suggest that more than one antihypertensive agent is often required. Additional therapies include thiazides, thiazide-like diuretics, and dihydropyridine calcium channel blockers (Diabetes Canada, 2018b).

The "C" represents controlling cholesterol levels to treat dyslipidemia, a condition that affects numerous individuals with diabetes (Diabetes Canada, 2018b). While the risk of CVD is elevated in all individuals living with diabetes, irrespective of their cholesterol levels, those with elevated cholesterol levels are at an even greater risk of complications (Diabetes Canada, 2018b). Experts

recommend that levels of low-density lipoprotein cholesterol, known as the "bad cholesterol", be less than 2.0 mmol/L (Diabetes Canada, 2018b). To achieve this target, treatment with statins is generally recommended (Diabetes Canada, 2018b). When low-density lipoprotein cholesterol is not lowered to target with statin therapy, second-line agents, such as ezetimibe and evolocumab, may be added to the individual's treatment regimen (Diabetes Canada, 2018b).

The "D" in the ABCDES approach represents "**D**rugs to protect your heart", and provides a comprehensive summary of the pharmacologic management of the CVD risk factors mentioned above (Diabetes Canada, 2018b). A combination of blood glucose-lowering medications, BP-lowering drugs, and cholesterol-lowering agents is recommended to prevent cardiovascular events (Diabetes Canada, 2018b). This step highlights the common need for pharmacologic agents in addition to lifestyle changes.

The next guideline, the "E", outlines two lifestyle management strategies that can have a considerable impact on the course of the disease: exercise and eating (Diabetes Canada, 2018b). Maintaining a healthy body weight by engaging in regular exercise and consuming a healthy diet are vital to adequate diabetes management (Diabetes Canada, 2018b). The current literature recommends that, to achieve health benefits, a weekly plan of 150 minutes of aerobic activity plus two sessions of resistance training per week is required (Diabetes Canada, 2018b). In terms of diet, researchers strongly recommend that individuals with diabetes consult a registered dietician to determine the most appropriate dietary changes to mitigate their individual risk factors (Diabetes Canada, 2018b).

The "S" encompasses two habits that can negatively impact diabetes management: stress and smoking (Diabetes Canada, 2018b). It has been reported that individuals who smoke have poorer glycemic control, as well as an increased risk of myocardial infarction, stroke, and end stage renal disease (Diabetes Canada, 2018b). Accordingly, Diabetes Canada recommends that individuals with diabetes quit smoking to reduce their risk of complications (Diabetes Canada, 2018b). Furthermore, individuals experiencing high levels of stress may be unable to adhere to their care plan and thus are more likely to experience poor glycemic control (Diabetes Canada,

2018b). Engaging in regular exercise and calming activities, such as yoga, are therefore recommended (Diabetes Canada, 2018b).

2.5.6 Barriers to optimal diabetes management

While the ABCDEs approach to caring for diabetes seems straightforward, the evidence suggests that numerous factors prevent individuals from achieving optimal care. Researchers have attempted to quantify these barriers to care, both in terms of barriers at the patient level as well as barriers to optimal physician performance. Since the present study is addresses a physician-controlled behavior, the discussion will be limited to barriers at the physician level. However, numerous barriers exist at the patient level, including misconceptions about perceived side-effects, missed medication doses due to illness or a change in routine, and non-compliance with diet and lifestyle modifications (Harris et al., 2005; Grover et al., 2014).

Therapeutic or clinical inertia, defined as the "failure of providers to begin new medications or to increase dosages of existing medications when an abnormal clinical parameter is recorded", has been proposed as a barrier to achieving proper diabetes management (Okonofua et al., 2006). Practitioners caring for individuals with diabetes often adopt a "treat to failure" strategy, rather than "treating to success" strategy, meaning they are often reluctant to alter treatment regimens until the patient presents with advanced symptoms (Brunton, 2019). A study among physicians treating patients with elevated blood glucose (A1C>7.5%) revealed the following results: "it took [physicians] an average of 1.9 years to intensify treatment by one agent, 7.2 years to add a second agent, and 6.1 years to intensify with a third oral antidiabetic drug" (Brunton, 2019). The causes of therapeutic inertia are widespread and vary based on the individual health care provider. However, researchers believe that overestimating the quality of care that they provide to their own patients, as well as finding justifications to avoid treatment intensification (i.e. assuming that their patient will have poor adherence to the new drug), and a lack of knowledge of changing scientific understandings of best care likely all contribute to the commonality of this barrier to care (Harris et al., 2005). The slow integration of guidelines into practice prevents patients from benefiting from novel therapies and treatments.

Concomitant medical and mental health concerns challenge a physician's ability to provide adequate diabetes care (Booth et al., 2012). The relationship between diabetes and mental health disorders is well documented (Diabetes Canada, 2018b). Accepting a diabetes diagnosis can be challenging, as the proper management requires a lifelong commitment. The burden of continuous monitoring and treatment can give rise to numerous negative feelings, such as anger, frustration, guilt, and depression (Diabetes Canada, 2019a). Individuals who experience these feelings for prolonged periods are at a greater risk of developing psychiatric disorders. In fact, individuals with diabetes experience mental health disorders, specifically depression, at a higher rate than the general population (Canadian Diabetes Association, 2008; Booth et al., 2012). It is estimated that the prevalence of depressive symptoms and major depression among individuals with diabetes is 30% and 10%, respectively (Diabetes Canada, 2018b). Apart from the burden associated with the symptoms of psychiatric disorders, studies have shown that pharmacological treatments for mental health disorders can pose a threat to the health of individuals with diabetes (Diabetes Canada, 2018b). Weight gain, poor glycemic control, and changes to lipid profile have been associated with certain medications (Diabetes Canada, 2018b). As a result, caring for these competing medical concerns becomes challenging. A study among diabetes patients in Ontario revealed that these competing concerns pose a challenge to both individuals and their health care providers (Booth et al., 2012). While individuals living with diabetes and a mental health disorder have greater difficulty managing their symptoms and adhering to treatments, their practitioners are confronted with competing issues that makes designing appropriate diabetes and CVD treatment plans challenging (Booth et al., 2018).

Chapter 3

3   Methodology

This chapter provides an overview of the research methodology, starting with the study design in section 3.1. Section 3.2 discusses the advantages and disadvantages of using administrative data to conduct health research. The following section, 3.3, provides an overview of the OPEM programme, focusing specifically on the first trial replicate. Participant selection is then discussed in section 3.4, followed by the data sources in section 3.5. Section 3.6 describes the study variables, and the last section, 3.7, covers the statistical analyses.

3.1   Randomized controlled trials

It has long been accepted that the RCT is the "gold-standard" for clinical research evaluating the effect of an intervention. This design, in its simplest form, involves following two groups of participants over time to observe whether outcomes differ between groups. By employing randomization techniques to assign participants to experimental and control groups, all factors besides the intervention itself tend to be balanced across groups. Many of the biases inherent in other study designs are minimized by the randomization process; thus, RCTs provide strong grounds on which causal mechanisms can be established.

3.1.1 Pragmatic randomized controlled trials

Historically, most RCTs have not been designed with an awareness that they can serve either one of two purposes, and that a trial is best designed with an awareness of these two alternative purposes (Schwartz & Lellouch, 1967). "Explanatory" trials aim to optimize their ability to detect a mechanism of action and often require controlled conditions to ensure that the outcome is a direct result of the exposure of interest (Schwartz & Lellouch, 1967). "Pragmatic" trials, on the other hand, aim to generate results that will assist in decision making processes and are therefore conducted in routine, "real-world", settings (Schwartz & Lellouch, 1967). Other researchers have used the concepts of efficacy and effectiveness as a parallel to explanatory and pragmatic trials (Singal et al., 2014).

The answer to the question "what makes a trial pragmatic?" is neither simple nor succinct. To aid in trialists' understanding of the correlates of pragmatism, Thorpe et al. (2009) designed the Pragmatic-Explanatory Continuum Indicator Summary wheel, commonly referred to as PRECIS. This tool highlights 10 key domains to consider while designing a trial to ensure that the design matches its intended purpose (Thorpe et al., 2009). Elements to consider when designing a pragmatic trial include the selection of a wide range of participants, selecting outcomes that are clinically relevant to participants, and using "usual practice" as a comparison group, among many more (Thorpe et al., 2009). The authors of this tool agree with the assertion by Schwartz and Lellouch that the design of a trial is rarely purely pragmatic or purely explanatory; as the tools name suggests, trials instead lie on a continuum (Thorpe et al., 2009). As a result, trialists must optimize design choices that will facilitate the application of results to their intended setting.

PRECIS became a widely recognized tool for designing trials that match their intended purpose, and thus was referenced in numerous papers (Loudon et al., 2015). With this awareness came feedback from trial investigators to improve the tools function (Loudon et al., 2015). Accordingly, in 2015, the authors published a revised version of the tool, named PRECIS-2, that was designed to address the identified weaknesses (see figure 3.1) (Loudon et al., 2015). While maintaining the original wheel format, the updated form revised its components to include the following nine domains: eligibility criteria, recruitment, setting, organization, flexibility (delivery), flexibility (adherence), follow-up, primary outcome, primary analysis (Loudon et al., 2015). Furthermore, a scoring system was introduced whereby domains that are very explanatory receive a score of 1, while those that are very pragmatic are given a score of 5 (Loudon et al., 2015).

Figure 3.1: The PRECIS-2 wheel.
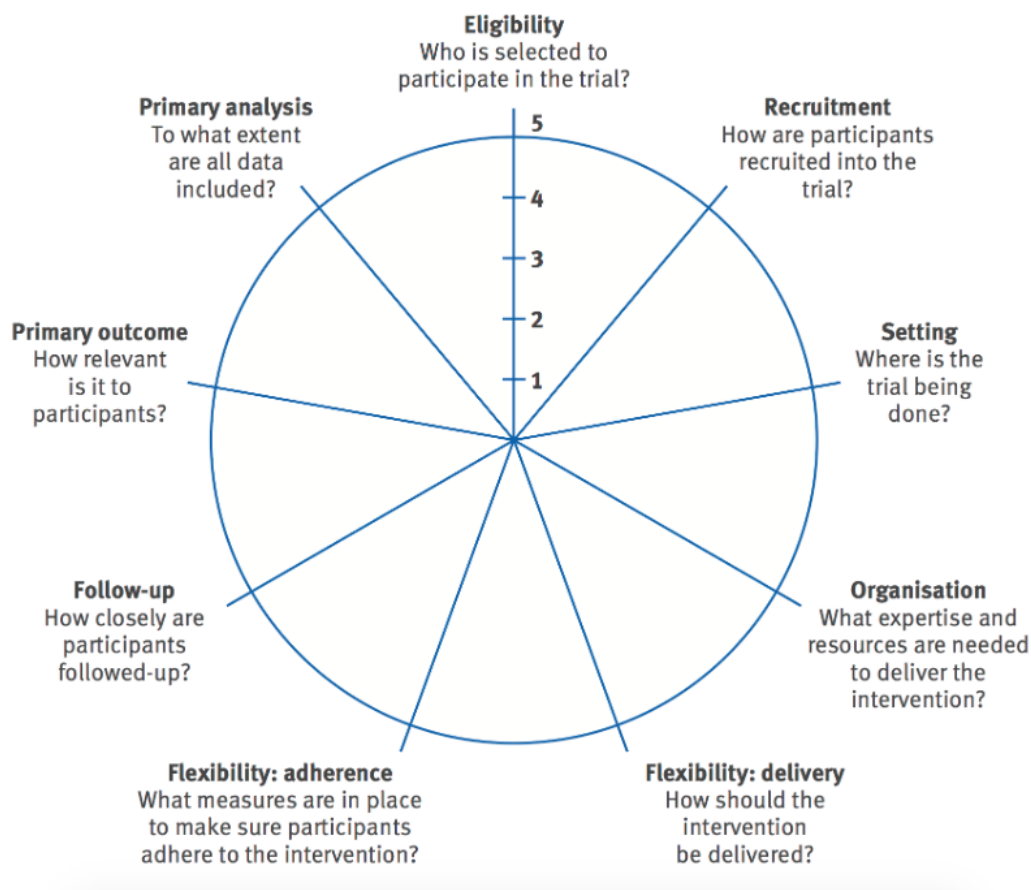
Data source: Loudon et al. (2015)

The value in designing pragmatic trials to conduct health-related research is clear. While all well-conducted RCTs generally achieve high internal validity, traditional RCTs have been criticized as lacking in external validity (Patsopoulos, 2011). Strict inclusion and exclusion criteria, blinding, and optimized conditions, which enable the trial to focus on a mechanism of action, make the trial so different from the usual care in the setting in which the trial was actually conducted, let alone from the settings in which the results are intended to be applied, that using its findings to make decisions in a real-world setting is challenging (Patsopoulos, 2011). Pragmatic trials attempt to overcome this barrier by designing trial conditions that mirror everyday practice. As a result, the direct application of findings from pragmatic trials to decision-making processes by clinicians, policymakers, or patients in usual care in the setting in which the trial was conducted and other similar settings is facilitated. Health care policy makers

are increasingly demanding that researchers provide high-quality, generalizable evidence to inform decision making processes (Patsopoulos, 2011). Pragmatic trials aim to do just this.

3.1.2 Cluster randomized controlled trials

Cluster randomized controlled trials (cRCTs) are a form of RCT where random assignment is at the "cluster" and not the individual level. Clusters may be families, physician practices or even entire communities. Reasons for using cRCTs include avoiding contamination between intervention groups, factors related to how the interventions are applied (e.g. physician education programs are naturally applied at the practice level) or out of ethical concerns. cRCTs are typically more pragmatic in nature than are traditional, individual-RCTs, as they are equipped to study different approaches to patient care and, as a result, generate results of importance to healthcare decision makers (Cook et al., 2016; Ford & Norrie, 2016). To account for clustered data, more advanced statistical methods are required (see section 3.7.3).

3.1.3 Factorial randomized controlled trials

While traditional RCTs are designed to study a single intervention, factorial RCTs are designed to study two or more interventions simultaneously. In a trial investigating two unique interventions (referred to as a 2x2 factorial trial), participants are randomized to one of four groups: intervention A alone, intervention B alone, intervention A and intervention B, or neither. The goal of factorial trials is to achieve "two [or more] trials for the price of one"; thus, one must assume that the effect of intervention A is unchanged in the presence of intervention B (no interaction) (Cipriani & Barbui, 2013). Results are therefore reported as if they were obtained through two independent trials investigating the effect of intervention A and intervention B (Cipriani & Barbui, 2013). Section 3.7.2 discusses the analysis of factorial RCTs.

3.2 Implications of using administrative data in health research

Health administrative databases capture all information gathered during routine care visits, including, but not limited to, vital statistics, demographic information, claims, and clinical documentation (Cowie et al., 2017). As health administrative databases have become increasingly common in the medical community, they have been utilized as the primary data

source for many clinical studies. Health administrative databases have particularly facilitated the conduct of studies on large populations, and among hard-to-reach individuals (Harron et al., 2017). However, these studies do not replace traditional studies that employ primary data collection techniques (Harron et al., 2017). As a result, the benefits of using health administrative data as the basis of a research study must be weighed against the drawbacks before carrying out the study (see table 3.1).

Table 3.1: The potential advantages and disadvantages to using health administrative data as the main data source for research.

Advantages	Cost and ease[1] ▪ No recruitment and follow-up procedures
	Reduced participant burden ▪ Participants do not have to repeat information previously shared
	Near-universal coverage[1] ▪ Captures individuals normally hesitant to participate in research ▪ Prevents differential non-response and attrition bias
	Long-term availability[1] ▪ Regularly collected data allows for outcome measurement over long periods of time
	Accuracy[1] ▪ Detailed information available on complex and difficult to remember events
Disadvantages	Data quality[2] ▪ Coding errors
	Data validation[2] ▪ Lack of validated and generalized tools for measuring data quality
	Data privacy and security[2] ▪ Consent and ethics approval
	Timeliness of data access[2] ▪ May be a delay between when data is collected and when data is approved for research purposes
	Missing data[3] ▪ Occurs when reporting is incomplete and when subjects choose not to interact with the health care system
	Problems with data linkage[3] ▪ Insufficient identifying information can prevent databases from being linked to ascertain exposure and outcome variables

Data sources: [1] Finkelstein A & Taubman (2015); [2] Cowie et al. (2017); [3] Harron et al. (2017)

3.3 The OPEM programme

The OPEM research programme consisted of three individual trials (replicates) that shared a common objective: to investigate the ability of printed educational materials (PEMs), referred to in the OPEM protocol as "printed educational messages", to addresses evidence-to-practice gaps pertaining to diabetes and hypertension care delivered in primary care settings (Zwarenstein et al., 2007). The three replicates were designed as pragmatic, 2x2 factorial, cRCTs. The protocol is registered under ISRCTN72772651.

The ultimate goal of the OPEM programme was to improve patient outcomes by reducing complications associated with diabetes and hypertension (Zwarenstein et al., 2007). To achieve this goal, health care providers must be well educated and informed on the most current, and relevant, guideline recommendations. Accordingly, the interventions were directed at FP/GPs. To prevent contamination, physicians who work in group or shared practices were identified by common address and were randomized using a random number generator, omitting stratification, to receive the same intervention (Zwarenstein et al., 2007). As a result, randomization occurred by cluster at the group practice level, rather than at the individual FP/GP level. Group practices also allow for patients to be seen by more than one physician; therefore, patients who received a prescription written by any Ontario FP/GP throughout the study period qualified for inclusion, even if the physician wasn't their primary care provider (Zwarenstein et al., 2007). Since administrative data was used to ascertain all baseline and outcome measurements, both FP/GPs and patients were blinded to the conduct of the trial.

The programme spanned a nine-month period, with the first replicate delivered in January of 2005 and the second and third replicates delivered three and six months later, respectively. The replicate that pertains to this study is the first replicate, focusing on treatment intensification for diabetes care. The objectives of this replicate, as discussed in section 1.3, were to evaluate the effect of two separate versions of a PEM (insert, and outsert) and their interaction on physician adherence to guidelines for the prescription of drugs used to reduce the risk of cardiovascular complications associated with diabetes. Namely, the PEMs recommended that at least two antihypertensives, one of which is an ACE inhibitor and another that is considered, in this study, to be an "other" antihypertensive (i.e. ARB, beta-blockers, calcium channel blockers, diuretics),

and a cholesterol-lowering agent, be prescribed. Moreover, we aimed to determine whether the recency of diabetes diagnosis impacted the likelihood of adhering to guidelines, as well as the physician characteristics that are associated with engaging in treatment intensification.

Figure 3.2 provides a timeline of events for the study. To determine whether the intervention was effective, a baseline look at prescribing habits was required to be able to compare treatment regimens pre-intervention and post-intervention. All of the information required to answer the research questions was available in administrative databases held at ICES; therefore, primary data collection techniques were not employed. The details of the data collected are provided in section 3.5.

Figure 3.2: Timeline for the OPEM trial focusing on diabetes treatment intensification.

PEM mailing date: January 15th, 2005

Pre-intervention period:
January 15th, 2004 – January 14th, 2005

Follow-up period:
January 16th, 2005 – January 15th, 2006
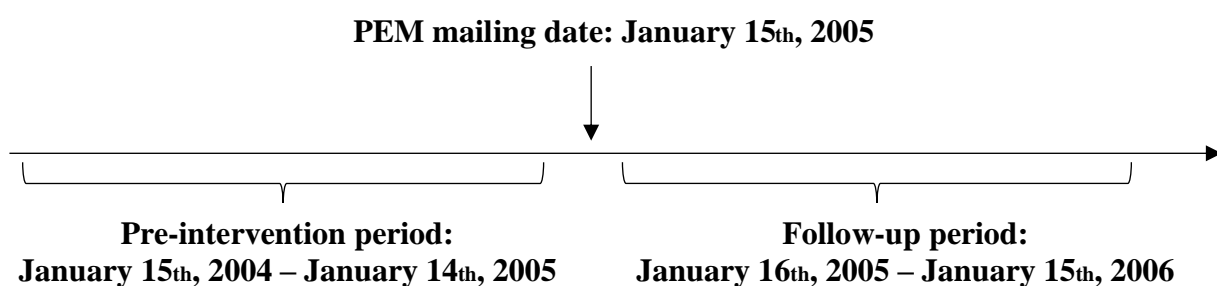
3.3.1 Ethics

The OPEM programme was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre and the Women's College Health Sciences Centre in Toronto, Ontario (Zwarenstein et al., 2007). ICES is approved by Ontario's Information and Privacy Commissioner under section 45 of Ontario's Personal Health Information Protection Act to analyze routinely collected health data while insuring the privacy of the individual patients (ICES, 2020). Because all study outcomes were measured using ICES data, informed consent from the physicians and the patients was not required. The decision to waive informed consent would be now supported by The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials on the grounds of posing no more than minimal risk to study participants (Weijer et al., 2012). All data is encrypted; therefore, neither individual patients, nor physicians,

can be directly or indirectly identified provided that small cells (<6) are suppressed. Since this project involves the analysis of data from several years ago, we sought and received approval from the College of Physicians and Surgeons of Ontario to re-link their data on physician identifiers to the administrative databases held at ICES.

3.3.2 Setting

The study was carried out in Ontario, Canada. All FP/GPs practicing within the province who met the inclusion criteria (see section 3.4.1) were included in the study. Ontario residents are eligible to access the majority of health care services at no cost as a result of a publicly funded health care system, OHIP. Among the list of qualifying services is visits to a family doctor. Accordingly, all Ontario residents who meet the criteria for OHIP are permitted to seek care from a family doctor, irrespective of their financial status, and were therefore eligible to participate in the study.

3.3.3 *informed*

informed was a peer-reviewed practice synopsis that provided an overview of the latest research findings to promote EBM (Zwarenstein et al., 2007). The 8-page issues were developed using expertise from both clinical and research staff at ICES (Zwarenstein et al., 2007). The first edition of *informed* was released in 1994, and publication continued quarterly until ceasing in 2007 (Zwarenstein et al., 2016). Subscription to *informed* was free and voluntary for all PCPs in Ontario, and approximately 15,000 PCPs subscribed throughout the 13-year period (Zwarenstein et al., 2007).

Despite the large list of subscribers, the effectiveness of *informed* remained unknown until a sample of 500 Ontario physicians were surveyed in 1997 (Kelsall, 2005). The results revealed that 71% of the physicians had received *informed*, and, among these, 89% reported that the information was useful and 53% reported reading at least the majority of the issues (Kelsall, 2005). Additional surveys revealed that physicians considered *informed* to be a "respected and valued source of information" (Kelsall, 2005).

The OPEM programme utilized the reach of *informed*, and its reputation, to deliver the intervention. A communications consultant assisted in the design of the PEMs, while a diverse team of physicians was consulted to ascertain the barriers to implementing new evidence in their practice (Zwarenstein et al., 2007). The PEMs came in two different forms: a short, directive message (outsert), and a long, detailed message (insert) (see Appendix 3, 4A, and 4B). The outsert was printed on a postcard sized paper, and was attached to the front page of *informed* in the bottom left corner (Zwarenstein et al., 2007). Bright colors and large font sizes were used to attract the eye of the reader. The main recommendations to prescribe more than one antihypertensive, one of which is an ACE inhibitor, and a cholesterol-lowering agent are clearly highlighted on front side of the outsert, while the back side provides a brief explanation for the recommendations, as well as a link to obtain more information. The alternative intervention against which the insert was compared was a two-page, more traditional narrative review article that was designed to look like the rest of the articles in that edition of the newsletter, but covered a topic (intensification of treatment for diabetes) that was not covered elsewhere in the edition (Zwarenstein et al., 2007). Similar to the outsert, the insert also made use of bright colors and graphics to attract readers. The article guides readers through the "A-B-Cs" of diabetes treatment, with one section for each of the three recommendations. Each section highlights the recommendation and gives an in-depth explanation for the evidence behind this recommendation. The article ends with a section entitled "The Bottom Line" that summarizes the main points, similar to the outsert.

3.3.4 Pragmatism of the trial

The design elements of the OPEM trial for diabetes treatment intensification were assessed using the PRECIS-2 tool (see table 3.2 and figure 3.3). The extent to which the trial mimics routine practice suggests that the design elements are highly pragmatic, chosen to maximize the trials applicability. The one design element that may raise doubt among readers is the choice to exclude patients under the age of 66 despite being eligible for the medications in usual care. This decision was made in response to the availability of data at ICES, as prescriptions for those under 66 are generally not covered by the Ontario Drug Benefit (ODB) program and are thus not captured in the databases. Moreover, since the primary objective of the study was to measure the

effectiveness of an intervention aimed at physicians, and not patients, this choice is justified.

Therefore, overall, the design elements of the trial agree with its intended purpose.

Table 3.2: PRECIS-2 components of the OPEM trial for diabetes treatment intensification.

PRECIS-2 domain	Score	Explanation
Eligibility	4	- Physicians: Almost all Ontario FP/GPs in active practice during the trial period - Almost all individuals 66 and above with type 1 and type 2 diabetes in Ontario
Recruitment	5	Physicians and patients identified from administrative databases held at ICES - no consent required, zero impact on behavior
Setting	5	FP/GP practices across Ontario, Canada – no exclusions based on geography, staffing levels, patient population, etc.
Organization	5	No additional staff or training required to deliver the intervention – unobtrusive and feasible to do unchanged in usual Ontario setting, provided the ministry or other organization develops and mails the intervention
Flexibility: delivery	5	Guideline recommendations are provided to physicians in the PEMs, but the choice to prescribe is ultimately up to the physician – a naturalistic approach with no restrictions on behavior so would be identical if implemented as policy
Flexibility: adherence	5	No measures in place to monitor whether physicians receive, open, and read the PEM
Follow-up	5	One-year post intervention mailout by means of administrative databases - no contact at all with individual physicians or patients
Primary outcome	4	Behavior change among physicians (manifested through intensification of prescriptions for ACE inhibitors, "other" antihypertensives, and cholesterol-lowering agents) – more important to physicians than to patients
Primary analysis	5	Intention-to-treat analysis; no physicians or patients lost to follow-up

Figure 3.3 PRECIS-2 wheel for the OPEM diabetes trial.
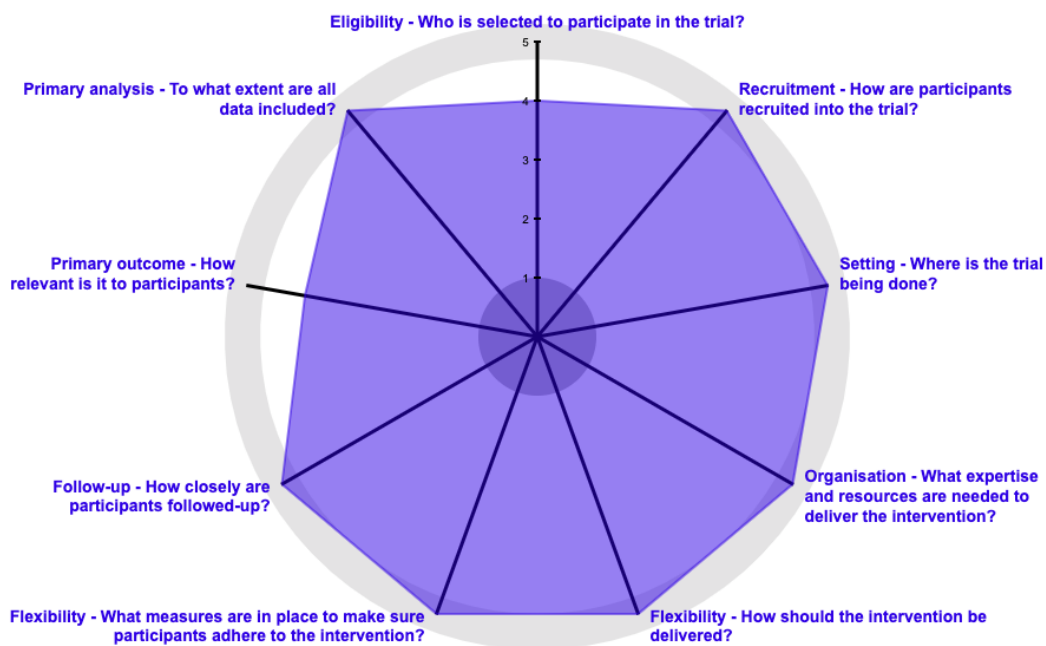
3.4 Participant selection

Both physicians and their individual patients were included in the study population; as a result, separate inclusion and exclusion criteria were developed for each group.

3.4.1 Physician selection

Inclusion criteria:

To be eligible to participate, physicians must have been practicing as a fee-for-service FP or GP in Ontario between August 1st, 2003 and July 31st, 2004 (Zwarenstein et al., 2007). Fee-for-service is a compensation model characterized by the billing of all services to OHIP based on a standard fee system (ICES, 2006). Both individual physicians and those practicing in group settings are eligible to be compensated using the fee-for-service model (Ministry of Health & Long-Term Care, 2020). FP/GPs were chosen to comprise the physician population as they are responsible for delivering nearly 80% of care for patients with diabetes (Diabetes Canada, 2018b). In 2019, there were only 231 Endocrinologists working in Ontario, compared to the

14,962 practicing FP/GPs (Canadian Medical Association, 2019b). Accordingly, FP/GPs continue to take on the primary role in caring for individuals with diabetes.

Exclusion criteria:

Physicians who submitted an additional claim under a different specialty code between August 1st, 2003 and July 31st, 2004 were excluded. In addition, physicians who were not considered to be in "active" practice in 2004 were excluded. This included those who accumulated less than $50,000 in fee-for-service billings in 2004, those who prescribed medications to fewer than 100 patients aged 66 and above in 2004, and those who did not prescribe medication to an individual 66 or older in at least 10 of the 12 months in 2004 (Zwarenstein et al., 2016). The latter two exclusion criteria were used to ensure that the physicians had adequate experience with elderly patients. Furthermore, physicians who submitted a claim under a speciality other than FP/GP between January 16th, 2005 and January 15th, 2006, and those who were no longer practicing during this period, were excluded. Physicians who were not matched to a diabetes patient were excluded, as were physicians who were missing information on personal identifiers. Lastly, physicians working in shared practices that were mistakenly sent multiple versions of the PEM were excluded.

3.4.2 Patient selection

Inclusion criteria:

Patients were considered for inclusion if they had a diabetes diagnosis on or before January 15th, 2004.

Exclusion criteria:

Individuals who were younger than 66 years, had an invalid ICES key number, or were non-Ontario residents were excluded. Individuals who did not see an OPEM physician one year prior to the PEM mailout, or who received an equal amount of services from more than one physician, were also excluded. Moreover, individuals who did not see a study FP/GP between February 1st, 2005 and January 31st, 2006 were excluded. Those who filled a prescription for one of the study drugs (ACE inhibitor, "other" antihypertensive, or cholesterol-lowering agent) that was prescribed by a non-OPEM physician between January 16th, 2005 and January 15th, 2006 were

excluded from the analyses. Individuals who died before the intervention was delivered were also excluded. Lastly, individuals who were matched to a physician with missing data were excluded.

3.4.3 Linking patients to physicians

All individuals who received a prescription for an ACE inhibitor, "other" antihypertensive agent, or cholesterol-lowering agent during the lookback period were identified by DIN in ODB. The prescription(s) closet to January 15th, 2005 (PEM mailout) were identified and the OPEM physician/physician group that prescribed these drugs was flagged. The patient was then linked to this physician/physician group. If a patient was not prescribed an ACE inhibitor, "other" antihypertensive agent, or cholesterol-lowering agent by an OPEM physician during the lookback period, this patient was linked to the OPEM physician/physician group that provided the majority of visits for that patient in the lookback year. If more than one physician/physician group tied for the majority of visits, the patient was excluded from the study.

3.5   Data sources

Seven administrative databases were linked at ICES to ascertain patient and physician characteristics, treatment regimens for diabetes medications, and the overall effectiveness of the intervention. To ensure confidentiality, patients were stripped of personal identifiers and were assigned a unique 10-digit ICES Key Number that was used to connect the patient's demographic information to the health services they received. Similarly, physicians were identified by an encrypted physician number that was used to link information about the individual care provider with the services they provided.

Ontario Drug Benefit Claims (ODB):

The ODB program is a publicly funded system that provides a wide range of prescription drugs to qualifying individuals in Ontario, including those 65 years and older. This database was used to quantify prescriptions of ACE inhibitors, "other" antihypertensives, and cholesterol-lowering agents to those 66 and older during the pre-intervention period, and throughout follow-up.

Ontario Health Insurance Plan Claims Database (OHIP):

The OHIP database contains information on the inpatient and outpatient services that are publicly funded for Ontario residents. This database was used for cohort creation by identifying individuals who were eligible for inclusion. The OHIP database was used to identify patients who did not see a FP/GP during the pre-intervention period, as well as those who did not attend an appointment during follow up. Moreover, physicians who did not submit at least one claim as a FP/GP during the pre-intervention period, or during follow-up, were identified and excluded.

Corporate Provider Database (CPDB):

The CPDB contains demographic, specialty, eligibility, and practice location information for all physicians funded by the Ministry of Health. This database was used to identify physician characteristics at baseline to produce descriptive statistics. The characteristics that were obtained from CPDB were physician age, sex, and years in practice. Furthermore, CPDB was used to identify and exclude physicians no longer practicing in the pre-intervention and follow-up periods.

ICES Physician Database (IPDB):

The IPDB contains information on both demographic and professional characteristics of all Ontario physicians. The characteristics that were obtained from IPDB were practice location (Northern/Southern, and rural/non-rural), visits per year, total billings per year, and location of medical school. This database was also used to ensure that the physicians included in our study practiced in office-based care; FPs working in areas such as sports medicine or psychotherapy were excluded.

Registered Persons Database (RPDB):

The RPDB houses information on basic patient demographics, received from the Ministry of Health, for all Ontarians with a health card number. This database was used to obtain information on patients age and sex at baseline. In addition, RPDB was used to exclude non-Ontario residents, and those who died during the pre-intervention period.

Drugs List - Drug Identification Number (DIN):

The DIN database was used to characterize the prescription drugs identified through ODB. Each prescription drug that has been approved for use in Canada has an 8-digit drug identification number (DIN). The DIN database was used to obtain information on each medications DIN, drug name, drug group, route of administration, and strength.

Ontario Diabetes Database (ODD):

The ODD contains information on incident and prevalent cases of diabetes in Ontario. This dataset was used to build our cohort of patients. Only those with a diagnosis date on or before the beginning of the pre-intervention period (August 1_{st}, 2003) were included. In addition, the diagnosis date available in the ODD was used to create the variable "years since diagnosis" to guide a subgroup analysis.

3.6   Study variables

3.6.1 Intervention

The intervention variable is the PEM delivered with *informed*, discussed in detail in section 3.3.3. We were interested in determining whether the ability of a PEM to influence physicians to intensify their patient's treatment regimens depended on the format of the message, and therefore studied two distinct PEMs: an insert, and an outsert. Thus, due to the 2x2 factorial design, FP/GP groups had the opportunity to be assigned to one of four intervention groups: *informed* alone (control), *informed* + insert, *informed* + outsert, *informed* + insert + outsert. The rationale for choosing this intervention is clearly highlighted in section 2.4.1: the conflicting, and poor quality, evidence for the effectiveness of PEMs has caused researchers to question the use of this common KT strategy within the health care field.

3.6.2 Outcomes

The goal of the study was to determine whether PEMs are effective at prompting FP/GPs to intensify their patient's treatment regimens. Thus, the outcome was measured at the patient level. In the context of diabetes care, one of the ways in which this behaviour change manifests is through treatment intensification efforts. The literature suggests that a single definition for

treatment intensification, even within the realm of diabetes care, does not exist. However, one characteristic of treatment intensification that appears to be consistently incorporated in all definitions is the addition of a new (i.e. not previously prescribed) antidiabetic agent to the patient's treatment regimen (Fu & Sheehan, 2016; Desai et al., 2018; Arnold et al., 2018; Canivell et al., 2019). Moreover, any increase in the dose of antidiabetic medications was also considered by Arnold et al. (2018) to qualify as treatment intensification. Canivell et al. (2019) listed the lack of medication dose information in their data as a limitation to their study, as they were unable to identify and include in the treatment intensification group patients who experienced a dose titration of their current medication.

Our definition of treatment intensification was developed based on a combination of criteria available in the literature and will be discussed in further detail below. The decision to focus on ACE inhibitors, "other" antihypertensives (i.e. ARBs, beta-blockers, calcium channel blockers, diuretics, etc.), and cholesterol-lowering agents stemmed from preliminary research that revealed that prescription rates for each of these drug classes was below standard by at least 30% (Zwarenstein et al., 2007). Moreover, the Clinical Practice Guidelines that were available at the time of the trial recommended all of ACE inhibitors, "other" antihypertensives, and cholesterol-lowering agents to promote vascular protection in all individuals with diabetes (Canadian Diabetes Association, 2003). Lastly, we focused solely on antihypertensives and cholesterol-lowering agents since, at the time of the trial, these drug classes had been shown to significantly reduce CVD complications and death among diabetes patients (UK Prospective Diabetes Study Group, 1998; Heart Protection Study Collaborative Group, 2003).

All outcome definitions included only ACE inhibitors, "other" antihypertensives, and cholesterol-lowering agents that are administered orally. Since our study aimed to target prescription rates among PCPs, we excluded intravenous therapies, as these are likely to be administered in hospital by a non-FP/GP. Moreover, ophthalmic solutions were excluded, as these medications are often prescribed to treat conditions other than the ones of interest in our study. Glucose-lowering therapies, such as insulin, were also excluded since the study aimed to target therapies used to prevent complications associated with diabetes, rather than those used to treat hyperglycemia. All doses were recorded in milligrams.

Primary outcome:

Objectives one through three are described by the primary outcome. We defined the primary outcome as the treatment intensification of medications used for controlling the cardiovascular complications associated with diabetes. The outcome is a composite outcome due to the fact that intensification could have occurred in any one of the drug classes. A FP/GP is considered to have intensified their patients treatment regimen if they engaged in one of the following behavior changes: added a new drug, either an ACE inhibitor, "other" antihypertensive agent, or cholesterol-lowering agent to their patients treatment regimen, or increased the dose of a current ACE inhibitor, "other" antihypertensive agent, or cholesterol-lowering agent. An individual's baseline treatment regimen was defined as all of the drugs prescribed within the three drug classes (ACE inhibitor, "other" antihypertensive agents, and cholesterol-lowering agents) during the lookback period that the individual was *still* taking at the end of the lookback period. All drugs prescribed during the follow-up period were recorded. A drug addition occurred when the number of drugs prescribed was greater in follow-up than at baseline. A dose increase occurred when the dose of a drug prescribed during the follow-up period was higher than the dose of the same drug prescribed at baseline.

Our decision to only include drug additions and dose increases as intensification came from both the definitions used in previous studies, as well as our personal judgement. We believe that any drug addition or titration that was captured in our study had a high probability of occurring in response to our intervention, as opposed to other reasons, such as patient side effects.

Secondary outcomes:

We developed a broader definition of treatment intensification as a secondary outcome to explore objectives one and two (insert and outsert effect) further. While we were confident that drug additions and titrations observed within our study population likely occurred in response to our intervention, we approached drug switches with less certainty. Since our PEMs focused on additions in certain drug classes, but did not directly recommend specific drug names, we had less confidence in concluding that physicians who switched their patients' medications did so in response to the PEM. Drug switches can occur for many reasons, such as patient preference, physician preference, pharmaceutical company influence, and patient side-effects. However,

since our PEM specifically recommended that all patients receive an ACE inhibitor, those who were taking "other" antihypertensives at baseline may have been switched to an ACE inhibitor in response to the PEM. As a result, we have included medication switches in our composite secondary outcome measurement to capture FP/GPs who intensified their patient's treatment regimen by making a drug switch. The secondary outcome is thus defined as the addition of an ACE inhibitor, "other" antihypertensive agent, or cholesterol-lowering agent, an increase in the dose of a current ACE inhibitor, "other" antihypertensive agent, or cholesterol-lowering agent, or the switch from one drug to another drug across all drug classes. Drug additions and dose increases were defined previously (see primary outcome). A switch occurred if the total number of drugs prescribed at baseline was less than or equal to the number of drugs prescribed during follow up, but at least one drug name differed between the two time periods. Switches were captured across the three drug classes.

While the primary outcome focused on the intensification of medications across three drug classes, we were also interested in determining whether this intensification occurred to a greater extent in certain drug classes. Accordingly, we repeated the primary outcome measurement for individual drug classes, specifically ACE inhibitors, "other" antihypertensive drugs, and cholesterol-lowering agents.

3.7 Statistical Analysis

All statistical analyses were conducted using SAS Enterprise Guide 7.1. Analyses followed the recommendations set forth by the CONSORT extension for cRCTs (Campbell et al., 2012). We deemed two-tailed p-values less than or equal to 0.05 to be statistically significant. Following standard practice for the analysis of pragmatic RCTs, the primary analysis attempted to follow intention-to-treat (ITT) guidelines.

3.7.1 Descriptive statistics

Descriptive statistics were generated to obtain an overall understanding of drug use among individuals with diabetes in Ontario. The number, and percent, of individuals taking an ACE inhibitor, "other" antihypertensive, cholesterol-lowering agent, and all three, were calculated

both at baseline and at the end of follow-up. Moreover, characteristics of the patients and the physicians were explored at baseline. Patient characteristics of interest included age, sex, years since diabetes diagnosis, and recency of diabetes diagnosis. Due to ICES constraints on student data access, it was required that patient age be categorized. Thus, the following three categories were chosen to classify patients by age: 66-74, 75-84, 85+. These categories were selected to reflect a commonly used grouping of seniors as the "young-old", "middle old", and "old-old", which has previously been used in studies (Koo et al., 2017; Kingston et al., 2018). Physician characteristics of interest included age, sex, billings per year, total visits per year, years in practice, practice location (Northern/Southern, and rural/non-rural), and whether the physician graduated from a Canadian medical school. To categorize practice location as Northern or Southern, we used the forward sortation area of the practices' postal code. Forward sortation areas beginning with the letter P were considered to be Northern, while all other Ontario postal codes (beginning with K, L, M, N) were classified as Southern (Wenghofer et al., 2011; Gauthier et al., 2012).

3.7.2 Analyzing factorial randomized controlled trials

The primary analysis of a 2x2 factorial trial is conducted "at-the-margins" of the table. In the present study, we were interested in testing the main effects of the insert and the outsert. Thus, patients who received the insert (irrespective of whether or not they received the outsert) were compared to patients who received no insert (objective one). Likewise, patients who received the outsert (irrespective of whether or not they received the insert) were compared to patients who did not receive the outsert (objective two). However, intensification rates were calculated and presented for each of the four intervention groups, allowing readers to summarize the data in their desired format.

While factorial RCTs are typically underpowered to detect an interaction effect, it is common practice to evaluate and report on the interaction between the interventions (Kahan et al., 2020). Thus, a model incorporating the interaction between the insert and outsert was fit and the estimated size of the interaction, confidence interval, and p-value were reported, as per Kahan et al. (2020) (objective three). Moreover, interactions were also explored for the secondary outcomes (Kahan et al., 2020).

3.7.3 Accounting for clustered data

The statistical methods for analyzing conventional RCTs cannot be applied to cRCTs directly (Austin, 2007). When subjects are grouped into clusters, the outcomes within clusters may be more highly correlated than the outcomes between clusters (Austin, 2007). The grouping of patients within a physician's practice is a common example of clustered data, and clearly highlights the need to consider correlated data in the analysis (Austin, 2007). Despite receiving similar formal training, physicians develop unique styles of patient management. Accordingly, individuals who are treated by the same physician are likely to receive similar diagnoses and treatment plans, and, as a result, their outcomes are likely to be correlated. Moreover, since physicians are known to seek answers to their clinical queries from their colleagues (Coumou & Meijman, 2006), outcomes among patients within group practices are likely to be correlated. Thus, the OPEM programme randomized at the group practice level. The similarity between responses within a cluster is termed within-cluster homogeneity, and complicates the analysis of cRCTs (Austin, 2007).

Several methods have been proposed for analyzing cRCTs with binary outcomes. The choice of method depends on whether the unit of analysis is at the subject- or cluster-level (Austin, 2007). In the present study, treatment regimens were measured at the individual patient level; as a result, the unit of analysis is subjects. One method for analyzing subject-level data is generalized estimating equations (GEE) (Austin, 2007).

The GEE method for accounting for clustered data was developed by Liang and Zeger in 1986 and has since seen extensive use in the literature (Liang & Zeger, 1986; Wang, 2014). The premise is that GEE utilizes correlation matrices to estimate the model's population-averaged parameters (Wang, 2014). Examples of correlation structures include the exchangeable structure, autoregressive structure, stationary structure, and unstructured (Vittinghoff et al., 2012). According to Vittinghoff et al. (2012), it is appropriate to apply the exchangeable structure to studies in which patients are clustered to their physician, as the patients themselves are exchangeable, meaning that they cannot be distinguished from one another within a practice. The exchangeable structure assumes that the correlations within each cluster share a common value (Vittinghoff et al., 2012).

The specification of the appropriate correlation structure improves efficiency (Shults et al., 2009); however, there are methods to account for misspecified correlation structures. While the estimates of treatment effect are generally fairly accurate, irrespective of the specified model, the standard errors can be largely inaccurate (Vittinghoff et al., 2012). The consequences associated with the failure to account for within-cluster correlation in standard error calculations are vast, including small standard errors, narrow confidence intervals (CIs), and low p-values (Cameron & Miller, 2015). Robust, or "sandwich", standard errors are often used in conjunction with GEE to estimate proper standard errors (Vittinghoff et al., 2012).

Applying the recommendations of Vittinghoff et al. (2012) to cRCTs, we fit logistic regression models estimated using GEE, with robust standard errors, to ascertain the effectiveness of PEMs. SAS can accommodate both GEE and robust standard errors in a single command: proc genmod; thus, this command was used to conduct all analyses.

3.7.4 Primary outcome

Objectives one and two are similar in that they both aim to determine whether a PEM is effective at intensifying prescribing habits for diabetes treatment; however, objective one focuses on the outsert, while objective two focuses on the insert. Since we were only interested in determining whether or not prescription rates intensified, the dependent variable was binary: the physician either intensified the treatment regimen, or they did not. Accordingly, a logistic regression model estimated using GEE was fit (see equation 3.1), where p represents the probability of intensifying the treatment regimen. This model is referred to as the "main effects model" for the remainder of the thesis. Separate hypotheses were developed for objectives one and two. The null hypothesis for objective one was that $\beta_1=0$; in other words, the odds of treatment intensification among physicians who received the insert were no different than among those who did not receive the insert. Similarly, the null hypothesis for objective two was $\beta_2=0$, meaning that the odds of treatment intensification did not differ between physicians who received the outsert and those who did not.

$$\text{logit}(p) = \beta_0 + \beta_1 \text{insert} + \beta_2 \text{outsert} \qquad (3.1)$$

$$\begin{cases} \text{insert} = 1 \text{ if a physician reieved the insert PEM} \\ \text{insert} = 0 \text{ otherwise} \\ \text{outsert} = 1 \text{ if a physician received the outsert PEM} \\ \text{outsert} = 0 \text{ otherwise} \end{cases}$$

Testing for an interaction between the insert and the outsert

While the study was not primarily designed to test for interaction, we evaluated the effectiveness of the insert in the presence of the outsert for exploratory purposes in objective three. A logistic regression model was fit (see equation 3.2) to test the null hypothesis that γ_3 is equal to zero, where p represents the probability of intensifying a treatment regimen.

$$\text{logit}(p) = \gamma_0 + \gamma_1 \text{insert} + \gamma_2 \text{outsert} + \gamma_3 \text{insert} \bullet \text{outsert} \qquad (3.2)$$

$$\begin{cases} \text{insert} = 1 \text{ if a physician reieved the insert PEM} \\ \text{insert} = 0 \text{ otherwise} \\ \text{outsert} = 1 \text{ if a physician received the outsert PEM} \\ \text{outsert} = 0 \text{ otherwise} \end{cases}$$

Adjusted analysis

To account for any imbalance in baseline predictors on the estimated effect of the insert and the outsert, an adjusted analysis was carried out. The main effects model (equation 3.1) was adjusted for the following variables: physician age, sex, years in practice, practice location (Northern vs. Southern, and rural vs. non-rural), country of training, billings per year, and visits per year. This analysis simultaneously allowed us to determine the effect of each of the aforementioned variables on the likelihood of treatment intensification.

Subgroup analysis

The fourth objective was to determine whether the intervention effect differed based on the stability of a patient's treatment regimen. We hypothesized that among individuals who have reached clinical stability, both the patient and the physician may be less inclined to alter their therapeutic regimen to avoid complications. Since the only patient-level data we had available from the administrative datasets was on the prescription of drugs rather than on actual consumption, or response to drugs in the form of side effects, we had no indication of how well

tolerated the medications were. As a result, we used years since diabetes diagnosis as a proxy measure of the stability of a patient's treatment regimen. Since there is no established time to a stable treatment regimen, we combined evidence from the literature with clinical expertise to predict the amount of time it takes to attain clinical stability. The three- to six-month period is consistently referenced when treating an individual with diabetes (Diabetes Canada, 2018b). When treating a newly diagnosed patient, the goal is to have their A1C, BP, and lipid levels at target within 3-6 months (Diabetes Canada, 2018b). While these targets are achievable with commonly prescribed medications, achieving target does not equate to achieving clinical stability. Antihypertensives are, for the most part, fast-acting drugs, and, as a result, patients generally achieve a stable BP after three to six months (The PROGRESS Collaborative Group, 2001; Patel et al., 2007; Liu et al., 2005). However, attaining a stable lipid profile is a lengthier process. Colhoun et al. (2004) showed that, while total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol tend to stabilize after 6 months on statin therapy, triglycerides don't reach a stable level until two years. As a result, we predict that clinical stability in terms of diabetes treatment is most likely achieved after two years of therapy. Thus, we classified individuals who had been diagnosed with diabetes for two years or less at PEM mailout as "recent diagnoses", while those who had been living with diabetes for more than two years were considered "non-recent diagnoses". This classification assumes that therapy is initiated immediately upon diabetes diagnosis. To determine whether the recently diagnosed cases were more likely to have their treatment regimen intensified, we first measured the interaction between the interventions and the recency of diabetes diagnoses. A subgroup analysis was only carried out if the interaction terms were significant.

Sensitivity analyses

It was of interest to determine whether the effectiveness of the PEMs was altered by patients who switched providers throughout the study period. For reference, the trial had two arms (intervention, and control) and four groups (control, insert, outsert, and insert+outsert). Patients who were linked to a physician receiving the intervention (any of insert, outsert, or insert+outsert) at the beginning of the study but were prescribed a medication from a physician randomized to the control arm during follow-up, or vice versa, were flagged as switching between treatment arms (switcharm). A logistic regression model was fit to measure the primary

outcome in patients who remained in their original treatment arms (per-protocol analysis). The process outlined above was repeated for patients who switched between intervention groups (switchgroup). A patient was said to have switched between groups if they saw a physician randomized to a different treatment group than the one to which their original physician was assigned.

3.7.5 Secondary outcomes

The logistic regression model 3.1 was used to explore the secondary outcome definition that includes switches, and for each of the individual drug classes.

3.7.6 Missing data

A number of variables in IPDB are not mandatory; thus, certain physician characteristics of interest were not available for all OPEM physicians. Information on two physician personal identifiers, age and sex, were missing for a small number of physicians (<6). To maintain confidentiality, it was required that these physicians (and their corresponding patients) be removed from the dataset. Moreover, less than six physicians had missing data for total yearly billings and patient visits. These physicians were included in the primary and secondary ITT analyses; however, they were excluded from the adjusted analysis.

Chapter 4

4 Results

This chapter summarizes the results of the study, beginning with a description of the physician and patient selection in section 4.1. Descriptive baseline statistics are provided for both physicians and patients in section 4.2. The primary and secondary outcomes are presented in sections 4.3 and 4.4, respectively.

Tables presenting outcomes provide odds ratios (ORs), 95% confidence intervals (95% CIs), and two-tailed p-values for all comparisons. Attention is limited to ORs and CIs in the main text.

4.1 Physician and patient selection

Among the 10,863 FP/GPs practicing in Ontario between August 1_{st}, 2003 and July 31_{st}, 2004, 5,685 were excluded for reasons outlined in figure 4.1. While 5,178 FP/GPs were randomized to receive the intervention, a further 221 were excluded; thus, 4,957 FP/GPs were included in the study, operating in 4,118 unique practices (clusters). There were 946,853 Ontarians living with diabetes as of January 15_{th}, 2004. After exclusions, 185,526 individuals were retained in the sample. Seventy-two patients were matched to a physician with missing data; therefore, 185,454 patients were analyzed.

Figure 4.1: Participant flow chart: physicians and patients

Physicians assessed for inclusion:
10,863 general and family practitioners in Ontario between August 1st, 2003 and July 31st, 2004 who submitted at least one OHIP claim during this period.

Patients assessed for inclusion:
946,853 individuals with a diabetes diagnosis on or before January 15th, 2004.

Excluded (physicians):
- 3,051 prescribed medications to fewer than 100 patients ≥66 years old between August 1st, 2003 and July 31st, 2004, or did not prescribe medication to an individual ≥66 years old in at least 10 months
- 2,357 total fee-for-service billings <$50,000 in 2004
- 277 physicians submitted a claim under a different specialty code between August 1st, 2003 and July 31st, 2004 or failed to be randomized

Excluded (patients):
- 637,625 <66 years old, missing or invalid IKN, or non-Ontario residents
- 3,254 did not see an OPEM physician one year prior to index or could not be assigned to a physician group due to equal number of services provided by another physician group
- 63,618 did not see one of the study FP/GPs between January 16th, 2005 and January 15th, 2006
- 56,817 filled a prescription for an ACE inhibitor, hypertension drug, or cholesterol-lowering agent that was prescribed by a non-OPEM physician between January 16th, 2005 and January 15th, 2006
- 13 died on or before January 15th, 2005

Randomized: 4,231 practices and 5,178 FP/GPs in active practice

Retained: 185,526 patients ≥ 66 years old who saw an OPEM physician between January 16th, 2005 and January 15th, 2006

- 33 physicians submitted a claim under a specialty other than FP/GP or no longer practicing between January 16th, 2005 and January 15th, 2006
- 147 physicians in groups with multiple interventions
- 41 physicians not matched to diabetes patients and physicians missing personal identifiers

- 72 patients matched to a physician with missing personal identifiers

Analyzed: 4,957 physicians working in 4,118 practices serving 185,454 patients with diabetes.

4.2   Descriptive statistics

Characteristics of the physicians and the patients at baseline are provided in tables 4.1 and 4.2, respectively. No clinically meaningful differences were observed for any of these characteristics across the four groups as a consequence of randomization. Of note, the mean age of physicians in the study was approximately 52 years. The percent of female physicians was less than 25% in each group, and approximately 75% of physicians graduated from Canadian medical schools. Less than 10% of practices were located in Northern Ontario, and approximately 12% of practices were considered rural. Nearly half of the patients were between 66 and 74 years and approximately 41% were between 75 and 84; few patients (~10%) were older than 85. Patients received their diabetes diagnosis, on average, seven years prior to the study; thus, few were considered "recent cases".

Each FP/GP group (cluster) had, on average, 1.2 working FP/GPs (standard deviation (SD)=0.62). Among the 4,118 practices, 3,548 physicians worked in solo-practice and 570 physicians worked in group practices. Based on the final patient cohort, the number of patients per FP/GP group was, on average, 45 (SD=38), and individual physicians treated an average of 37 patients (SD=26).

Baseline drug use

Baseline use of ACE inhibitors, "other" antihypertensives (i.e. ARBs, beta-blockers, calcium channel blockers, diuretics) and cholesterol-lowering agents was similar among the intervention groups (see table 4.2). "Other" antihypertensives were the most commonly prescribed drug class, with approximately 81% of individuals taking at least one prior to the study. ACE inhibitors and cholesterol-lowering agents were prescribed to approximately 61% and 63% of patients, respectively. A treatment regimen consisting of an ACE inhibitor, "other" antihypertensive, and cholesterol-lowering agent was rather uncommon at baseline, with only one third of patients receiving prescriptions for all three drug classes.

Drug use at the end of follow-up

One year following PEM mailout, drug use among intervention groups was similar across arms (see table 4.3). Approximately 84%, 66%, and 61% of individuals were prescribed "other"

antihypertensives, cholesterol-lowering agents, and ACE inhibitors, respectively. The combination of an ACE inhibitor, "other" antihypertensive, and cholesterol-lowering agent was prescribed to approximately 35% of patients.

Table 4.1: Baseline characteristics of physicians in the OPEM diabetes trial.

Variable	Statistic	*informed only* N(%)= 1254 (25.3)	*informed +* insert N(%)= 1228 (24.8)	*informed +* outsert N(%)= 1255 (25.3)	*informed +* insert + outsert N(%)= 1220 (24.6)
Age (years)	Mean ± SD	52.1 (10.0)	51.9 (10.1)	52.2 (9.9)	52.3 (10.3)
Sex	Female (%)	260 (20.7)	257 (20.9)	283 (22.5)	300 (24.6)
Canadian Medical Graduate	Yes (%)	951 (75.8)	951 (77.4)	945 (75.3)	941 (77.1)
Years in practice	Mean ± SD	22.0 (9.2)	21.7 (8.8)	22.0 (9.2)	22.2 (9.1)
Visits per year	Mean ± SD	7,142.4 (3,391.6)	7,096.0 (3,217.0)	7,229.0 (3,335.8)	7,075.7 (3,239.0)
Billings per year (per CAD $10^5)	Mean ± SD	2.2 (1.0)	2.2 (1.0)	2.3 (1.1)	2.2 (1.0)
Practice location	Northern Ontario[a] (%)	77 (6.1)	99 (8.1)	117 (9.3)	105 (8.6)
Rural practice	Yes[b] (%)	151 (12.0)	150 (12.2)	150 (12.0)	169 (13.9)

SD = standard deviation; "N" is used to denote the total number of individuals in each intervention group.

Brackets within the table represent either SD or an overall percent (see "Statistic" column).

a: Northern Ontario practices defined by a postal code with a forward sortation area beginning with "P".

b: Rural practices defined by practices in locations with a population of less than 10,000.

Table 4.2: Baseline characteristics of patients in the OPEM diabetes trial.

Variable	Statistic	*informed* only N(%)= 47,499 (25.6)	*informed* + insert N(%)= 44,845 (24.2)	*informed* + outsert N(%)= 47,602 (25.7)	*informed* + insert + outsert N(%)= 45,508 (24.5)
Age (years)	66-74 (%)	22,895 (48.4)	21,469 (47.9)	22,909 (48.1)	22,096 (48.6)
	75-84 (%)	19,603 (41.3)	18,599 (41.5)	19,790 (41.6)	18,914 (41.6)
	85+ (%)	4,911 (10.3)	4,777 (10.7)	4,903 (10.3)	4,498 (9.9)
Sex	Female (%)	24,615 (51.8)	23,364 (52.1)	24,879 (52.3)	23,695 (52.1)
Years since diabetes diagnosis	Mean ± SD	7.8 (4.1)	7.8 (4.1)	7.8 (4.1)	7.8 (4.1)
Recent diabetes diagnosis (≤2 years)	Yes (%)	3,411 (7.2)	3,126 (7.0)	3,488 (7.3)	3,178 (7.0)
ACE inhibitor use	Yes (%)	28,836 (60.7)	27,114 (60.5)	28,916 (60.8)	27,568 (60.6)
"Other" antihypertensive use	Yes (%)	38,474 (81.0)	36,224 (80.8)	38,452 (80.8)	36,807 (80.9)
Cholesterol-lowering agent use	Yes (%)	30,476 (64.2)	28,381 (63.3)	30,213 (63.5)	28,801 (63.3)
All three drug classes	Yes (%)	16,065 (33.8)	14,828 (33.1)	15,871 (33.3)	15,161 (33.3)

SD = standard deviation; ACE inhibitor = angiotensin-converting enzyme inhibitor; "N" is used to denote the total number of individuals in each intervention group. Brackets within the table represent either SD or an overall percent (see "Statistic" column).

Table 4.3: Drug use among patients in the OPEM diabetes trial at the end of follow-up.

Variable	Statistic	*informed only*	*informed + insert*	*informed + outsert*	*informed + insert + outsert*
ACE inhibitor use	Yes (%)	29,026 (61.1)	27,453 (61.2)	29,113 (61.2)	27,783 (61.1)
"Other" antihypertensive use	Yes (%)	39,998 (84.2)	37,634 (83.9)	39,973 (84.0)	38,277 (84.1)
Cholesterol-lowering agent use	Yes (%)	31,789 (66.9)	29,723 (66.3)	31,561 (66.3)	30,186 (66.3)
All three drug classes	Yes (%)	16,758 (35.3)	15,662 (34.9)	16,561 (34.8)	15,857 (34.8)

ACE inhibitor = angiotensin-converting enzyme inhibitor

Table 4.4: Death rates during follow-up.

Variable	Statistic	*informed only*	*informed + insert*	*informed + outsert*	*informed + insert + outsert*
Died during follow-up	N (%)	2,500 (5.3)	2,375 (5.3)	2,485 (5.2)	2,444 (5.4)

Death rates

Approximately 5% of patients died during follow-up; no meaningful differences were observed between intervention groups (see table 4.4).

4.3 Primary outcome

The primary outcome is defined as intensification, by drug addition or dose increase, of medications (ACE inhibitors, "other" antihypertensives (i.e. ARBs, beta-blockers, calcium channel blockers, diuretics, etc.), and cholesterol-lowering agents) used to control the cardiovascular complications associated with diabetes.

Intensification rates

Treatment intensification rates were computed for each intervention group by dividing the number of patients whose treatment regimen intensified (n) by the total number of individuals in the intervention group (N). Intensification rates were similar across groups, with approximately 46% of patients having experienced a treatment intensification by adding a drug or increasing the dose of a current drug in all four groups (see table 4.5).

Unadjusted analysis

In the main effects model, the OR for the insert effect was 0.99 (95% CI 0.96 to 1.02), and the OR for the outsert effect was 1.01 (95% CI 0.98 to 1.04) (see table 4.6).

A model was also fit to include the interaction between the insert and the outsert. The OR for the interaction was 1.01 (95% CI 0.98 to 1.11), indicating that the effect of the insert was unchanged by the presence of the outsert (p=0.17). Interaction effects were explored for the remaining outcomes as per Kahan et al. (2020); however, none of the interactions were statistically significant with p-values ranging from 0.19 to 0.94. Further analyses are therefore limited to models with only the main effects of the insert and the outsert.

The intra-cluster correlation coefficient for both the main effects model, and the model including the interaction term, was 0.023. The variance inflation factor was 2.01, highlighting the need to account for clustered data in the analyses.

Table 4.5: Intensification rates based on drug additions and dose increases.

		INSERT	
		No	Yes
OUTSERT	No	**46.4%** N=47,499 (1,025 clusters)	**45.5%** N=44,845 (1,025 clusters)
	Yes	**46.0%** N=47,602 (1,037 clusters)	**46.2%** N=45,508 (1,031 clusters)

N denotes the total number of patients in each intervention group

Table 4.6: Unadjusted main effect of the insert and outsert on intensification by drug addition or dose increase.

Intervention	OR (95% CI)	p value
insert	0.99 (0.96,1.02)	0.50
outsert	1.01 (0.98,1.04)	0.74

Adjusted analysis

Neither a statistically significant insert effect, nor an outsert effect, were observed after adjusting for the following physician characteristics: physician age, sex, Canadian medical graduate, practice location, rural practice, total general patient visits per year, total billings per year, and years in practice (see table 4.7). Female physicians were more likely to intensify their patient's treatment regimens than were male physicians (OR 1.08, 95% CI 1.03 to 1.12). Moreover, physicians who graduated from Canadian medical schools were less likely to intensify their patient's treatment regimens compared to those who graduated from international medical schools (OR 0.93, 95% CI 0.89 to 0.97). For every ten additional years that a physician had been in practice, their likelihood of complying with guideline recommendations decreased (OR 0.96, 95% CI 0.91 to 0.99).

Table 4.7: Main effects model adjusted for physician characteristics.

Variable	OR (95% CI)	p value
Insert	0.99 (0.96, 1.02)	0.58
Outsert	1.00 (0.97, 1.03)	0.77
Physician age (per 10 years)	1.00 (0.97, 1.04)	0.94
Sex (reference is male)	1.08 (1.03, 1.12)	<0.0001
Canadian medical graduate (reference is no)	0.93 (0.89, 0.97)	<0.0001
Years in practice (per 10 years)	0.96 (0.91, 0.99)	0.03
Total visits (per 100 visits)	1.00 (1.00, 1.00)	0.23
Total billings (per $10,000)	1.00 (1.00, 1.00)	0.10
Practice location (reference is Southern)	0.97 (0.91, 1.03)	0.32
Rural practice (reference is no)	0.99 (0.94, 1.03)	0.55

4.3.1 Subgroup analysis

<u>Intensification rates</u>

Intensification rates among patients with recent diabetes diagnoses were similar to those observed in patients with non-recent diagnoses (see tables 4.8 and 4.9, respectively). Approximately 46% of patients in each of the four treatment groups experienced an intensification of their treatment regimen; this rate did not appear to be affected by the recency of diabetes diagnosis.

<u>Interaction effect</u>

Neither the interaction between the insert and the recency of diabetes diagnosis, nor the interaction between the outsert and the recency of diabetes diagnosis, were statistically significant (p=0.77 and p=0.82, respectively). Thus, a logistic regression analysis was not justified.

Table 4.8: Intensification rates among patients diagnosed with diabetes on January 14th, 2003 or later (recent diagnoses).

		INSERT	
		No	Yes
OUTSERT	No	46.1% N=3,411	45.4% N=3,126
	Yes	46.0% N=3,488	46.5% N=3,178

Table 4.9: Intensification rates among patients diagnosed with diabetes prior to January 14th, 2003 (non-recent diagnoses).

		INSERT	
		No	Yes
OUTSERT	No	46.4% N=44,088	45.5% N=41,719
	Yes	46.0% N=44,114	46.2% N=42,330

4.3.2 Sensitivity analyses

The trial had two arms (intervention, and control) and four groups (control, insert, outsert, and insert+outsert). The first sensitivity analysis identified patients who switched from the control arm to any intervention arm (or vice versa), and the second sensitivity analysis identified patients who made any type of switch between groups (i.e. from insert to outsert group, from outsert to insert+outsert group, from control group to insert group, etc.).

Switching between arms

Throughout the follow-up period, 4,430 patients (9.3%) in the control group switched physicians and moved to a physician in an intervention arm of the trial. Conversely, 1,554 patients (3.5%) in the insert group, 1,665 patients (3.5%) in the outsert group, and 1,518 patients (3.3%) in the insert+outsert group were seen by a control physician during the follow-up period. A total of 176,287 patients stayed in their original intervention group and thus remained in the per-protocol analysis.

Intensification rates among patients who stayed in their original treatment arm differed slightly across intervention groups, with the control group seeing a marginally higher rate of intensification than did the intervention groups (see table 4.10). The OR for the insert effect was 0.97 (95% CI 0.94 to 0.99), and the OR for the outsert effect was 0.98 (95% CI 0.96 to 1.01) (see table 4.11).

Table 4.10: Intensification rates among patients who remained in their original treatment arm.

		INSERT	
		No	Yes
OUTSERT	No	**47.8%** N=43,069	**46.0%** N=43,291
	Yes	**46.6%** N=45,937	**46.7%** N=43,990

Table 4.11: Unadjusted effect of the insert and outsert on intensification rates among patients who stayed in their original intervention arm.

Intervention	OR (95% CI)	p value
insert	0.97 (0.94,0.99)	0.03
outsert	0.98 (0.96,1.01)	0.29

Switching between groups

Throughout the follow-up period, 23,455 patients (12.7%) saw a physician who belonged to a different treatment group than the group to which they were assigned. The frequency of switches was similar among intervention groups; 5,821 patients (12.3%) in the control group, 5,719 patients (12.8%) in the insert group, 6,244 patients (13.1%) in the outsert group, and 5,671 patients (12.5%) in the insert+outsert group switched to a new group in the one year following the PEM mailout. Thus, 161,999 patients were included in the per-protocol analysis.

Treatment intensification rates among the patients who remained in their original intervention group were similar across groups (see table 4.12). The frequency of intensification was lowest in the insert only group, but the difference was trivial. The ORs for the insert and outsert effects were 0.99 (95% CI 0.96 to 1.02) and 1.01 (95% CI 0.98 to 1.04), respectively (see table 4.13).

Table 4.12: Intensification rates among patients who remained in their original treatment group.

		INSERT	
		No	Yes
OUTSERT	No	**48.4%** N=41,678	**47.4%** N=39,126
	Yes	**48.2%** N=41,358	**48.1%** N=39,837

Table 4.13: Unadjusted effect of the insert and outsert on intensification rates among patients who stayed in their original intervention group.

Intervention	OR (95% CI)	p value
insert	0.99 (0.96,1.02)	0.36
outsert	1.01 (0.98,1.04)	0.63

4.4   Secondary outcomes

4.4.1 Including drug switches in the definition of treatment intensification

Intensification rates

The frequency of patients who experienced a treatment intensification based on drug additions, dose increases, or drug switches was comparable across intervention groups (see table 4.14). Intensification rates based on additions, dose increases, and switches (secondary outcome) were, on average, slightly higher (approximately 2%) than those based on additions and dose increases alone (primary outcome) (see table 4.5).

Unadjusted analysis

The OR for the insert effect was 0.99 (95% CI 0.96 to 1.02), and the OR for the outsert effect was 1.01 (95% CI 0.98 to 1.04) (see table 4.15).

Table 4.14: Intensification rates based on drug additions, dose increases, and drug switches.

		INSERT	
		No	Yes
OUTSERT	No	**48.7%** N=47,499	**47.9%** N=44,845
	Yes	**48.4%** N=47,602	**48.7%** N=45,508

Table 4.15: Unadjusted effect of the insert and outsert on intensification by addition, dose increase, or switch.

Intervention	OR (95% CI)	p value
insert	0.99 (0.96,1.02)	0.64
outsert	1.01 (0.98,1.04)	0.60

4.4.2 Intensification within individual drug classes

ACE inhibitors

Approximately 12% of patients experienced treatment intensification by the addition of an ACE inhibitor, or the increase in dose of a current ACE inhibitor; no substantial differences were observed across intervention groups (see table 4.16). There was no difference in the odds of intensification by ACE inhibitor between those who received the insert and those who did not (OR 1.00, 95% CI 0.96 to 1.04) (see table 4.17). Similarly, the odds of intensification by ACE inhibitor were the same for those who received the outsert and those who did not (OR 1.00, 95% CI 0.96 to 1.04), suggesting no effect.

Table 4.16: Intensification rates for the addition or dose increase of ACE inhibitors.

		INSERT	
		No	Yes
OUTSERT	No	11.9% N=47,499	12.0% N=44,845
	Yes	12.1% N=47,602	11.9% N=45,508

Table 4.17: Unadjusted effect of the insert and outsert on intensification by the addition of a new ACE inhibitor, or the increase in dose of a current ACE inhibitor.

Intervention	OR (95% CI)	p value
insert	1.00 (0.96,1.04)	0.99
outsert	1.00 (0.96,1.04)	0.97

"Other" antihypertensives

Approximately 32% of patients in all four intervention groups experienced treatment intensification by the addition of a new antihypertensive (excluding ACE inhibitors), or the increase in dose of a current antihypertensive (see table 4.18). The ORs for the insert effect and the outsert effect on prescriptions of "other" antihypertensives were 0.99 (95% CI 0.97 to 1.02) and 1.01 (95% CI 0.99 to 1.04), respectively (see table 4.19), again suggesting no effect.

Table 4.18: Intensification rates for the addition or dose increase of antihypertensives.

		INSERT	
		No	Yes
OUTSERT	No	**32.0%** N=47,499	**31.6%** N=44,845
	Yes	**32.1%** N=47,602	**32.2%** N=45,508

Table 4.19: Unadjusted effect of the insert and outsert on intensification by the addition of a new antihypertensive agent, or the increase in dose of a current antihypertensive agent.

Intervention	OR (95% CI)	p value
insert	0.99 (0.97,1.02)	0.68
outsert	1.01 (0.99,1.04)	0.35

Cholesterol-lowering agents

Treatment intensification by the addition of a new cholesterol-lowering agent or the increase in dose of a current cholesterol-lowering agent occurred, on average, in 13% of patients; no meaningful differences were observed between intervention groups (see table 4.20). The ORs for the effect of the insert and outsert on intensification by cholesterol-lowering agents were 0.99 (95% CI 0.95 to 1.03) and 1.01 (95% CI 0.97 to 1.06), respectively (see table 4.21), suggesting no effect.

Table 4.20: Intensification rates for the addition or dose increase of cholesterol-lowering agents.

		INSERT	
		No	Yes
OUTSERT	No	**13.0%** N=47,499	**12.8%** N=44,845
	Yes	**13.0%** N=47,602	**13.0%** N=45,508

Table 4.21: Unadjusted effect of the insert and outsert on intensification by the addition of a new cholesterol-lowering agent, or the increase in dose of a current cholesterol-lowering agent.

Intervention	OR (95% CI)	p value
insert	0.99 (0.95,1.03)	0.66
outsert	1.01 (0.97,1.06)	0.56

Chapter 5

5 Discussion

This chapter begins with a discussion of the key findings in section 5.1, including both a summary and interpretation of the results. The strengths and the limitations of the study are discussed in sections 5.2 and 5.3, respectively. Directions for future research are provided in section 5.4, followed by the conclusions in section 5.5.

5.1 Key Findings

5.1.1 Summary of findings

The aim of the OPEM trial was to determine whether PEMs can successfully influence physicians to improve adherence to guideline recommendations for diabetes care through treatment intensification. Owing to the factorial design, the trial was able to simultaneously evaluate the effectiveness of two distinct PEMs: a two-page insert, and a short, directive outsert. Based on previous studies, it was determined that an absolute improvement as small as 5% is clinically significant (Zwarenstein et al., 2007). Considering the large sample size, a 5% improvement in prescribing rates would mean that a substantial number of Ontarians would, in theory, live healthier lives due to their improved treatment regimens.

Baseline characteristics of both patients and physicians were well balanced among the four groups. Moreover, there were no meaningful differences in baseline use of ACE inhibitors, "other" antihypertensives (i.e. ARBs, beta-blockers, calcium channel blockers, diuretics, etc.), and cholesterol-lowering agents among patients in all four groups. Death rates were also balanced between the groups and approximately equal to 5%, which is consistent with death rates among Ontarians aged 66 and above between 2004 and 2006 (Statistics Canada, 2020). During this time, death rates for Ontarians aged 66-74 and 75-84, the two most common age groups for trial patients, were between 1.2-2.6%, and 2.9-7.4%, respectively (Statistics Canada, 2020).

Intensification rates during the one-year follow-up were approximately 46%; these rates did not meaningfully differ (neither statistically, nor clinically) between groups. In regression analyses,

it was found that the OR for the insert effect was 0.99 (95% CI 0.96 to 1.02), while the OR for the outsert effect was 1.01 (95% CI 0.98 to 1.04). In light of the statistically not significant findings, we had insufficient evidence to conclude that intensification rates among physicians who received the insert or outsert were any different than among those who did not.

While the trial was not powered to study the interaction between the insert and the outsert, we completed this analysis for exploratory purposes. It was determined that the effect of the insert was not significantly altered by the presence of the outsert, and vice-versa (p=0.17).

We were interested in testing whether the intervention effect differed in patients with recent diabetes diagnoses (≤ 2 years) compared to patients who had been living with the disease for a number of years. Thus, a subgroup analysis was planned. Neither the interaction between the insert and the recency of diagnosis, nor the interaction between the outsert and recency of diabetes, were statistically significant (p=0.77 and p=0.82, respectively). A subgroup analysis using a logistic regression model was therefore not carried out, as it would not provide any meaningful information. Accordingly, it is reasonable to report the main effects of the insert and the outsert without considering the recency of diabetes diagnosis.

The characteristics of physicians that influenced their likelihood of changing practice were explored. Three variables were found to have small, but statistically significant effects on intensification among physicians. Female physicians were more likely to intensify their patient's treatment regimens than were male physicians (OR 1.08, 95% CI 1.03 to 1.12). Moreover, a physician's likelihood of adhering to guideline recommendations in response to PEMs decreased for every ten years that they were in practice (OR 0.96, 95% CI 0.92 to 0.99). Lastly, Canadian-trained physicians were less likely to intensify their patient's treatment regimens than were internationally trained physicians (OR 0.93, 95% CI 0.89 to 0.97). Nevertheless, all three ORs were very close to one, suggesting that, while statistically significant, the effect of the aforementioned physician characteristics on treatment intensification is minimal and is unlikely to translate into clinically meaningful effects. We note that the relationship between these physician characteristics and the likelihood of engaging in behavior change (specifically,

treatment intensification) are fixed phenomena and it is difficult to see how an intervention, such as a PEM, could target them.

Two sensitivity analyses were run. First, the primary outcome was analyzed in the 176,287 patients who did not switch between arms throughout the study period. Intensification rates were higher in the per-protocol population, albeit marginally so, than in the ITT population. The OR for the insert effect was 0.97 (95% CI 0.94 to 0.99), suggesting that physicians who received the insert were less likely to intensify than were those who did not receive the insert, a result opposite to the one we intended to find. However, while this result was statistically significant (p=0.03), it was of little clinical significance since it was less than the smallest effect size (5%) that we regarded as clinically important. Moreover, the OR for the outsert effect was 0.98 (95% CI 0.96 to 1.01), again suggesting that the effect of the outsert was to decrease intensification rates; however, this result was neither of statistical significance (p=0.29), nor of clinical significance. The second sensitivity analysis was conducted to ascertain whether the results of the primary outcome were significantly altered by patients who switched between groups. Among the 161,999 patients who remained in their original treatment group, neither a statistically significant insert effect (OR 0.99, 95% CI 0.96 to 1.02), nor a statistically significant outsert effect (OR 1.01, 95% CI 0.98 to 1.04), were detected.

The results, taken together, suggest that PEMs do not lead to statistically significant, nor clinically important, improvements in adherence to guideline recommendations for diabetes care by way of treatment intensification. Moreover, the absolute effect of both the insert and outsert were near zero and thus well below the 5% minimally clinically important improvement that we intended to find.

5.1.2 Interpretation of findings

The finding that PEMs do not successfully influence provider behavior is not unusual. In fact, this result has been reported by many researchers previously, although never in as large a trial (Bero et al., 1998; Grol & Grimshaw, 2003). Moreover, these results are not surprising in light of the findings from the previously published OPEM trials (Zwarenstein et al., 2014; Zwarenstein et al., 2016).

While the exact reason for the failure of the PEMs to lead to intensification remains unclear, we offer several hypotheses below.

Pre-intervention prescribing rates

The rate of ACE inhibitor use among Ontarian's with diabetes was measured around the time the OPEM programme was developed (Zwarenstein et al., 2007). Pilot data revealed that only 36% of individuals were taking an ACE inhibitor (Zwarenstein et al., 2007). However, the rate of ACE inhibitor use among the trial patients was measured one year prior to the PEM mailout and was found to be approximately 60% across all groups (see table 4.2). The reason for this marked increase in prescribing rates is unclear, but may offer an explanation for the failure of PEMs to lead to treatment intensification. While a substantial number of individuals were still not prescribed an ACE inhibitor at baseline, the number requiring treatment intensification using an ACE inhibitor was much lower than anticipated and may have reached its ceiling. Moreover, baseline prescribing rates of "other" antihypertensives was over 80% (see table 4.2), offering little room for improvement. Thus, it is possible that, between the time when the pilot research was conducted and baseline data were collected, physicians were encouraged, by other sources, to increase prescribing of the study drugs. As a result, when the PEMs were mailed, physicians may have assumed that they already intensified their patient's treatment regimens enough, and that the recommendations outlined in the PEMs no longer applied to them.

informed

A survey conducted in 1997 revealed that Ontario physicians considered *informed* to be a useful source of clinical information (Kelsall, 2005). However, eight years later, when the PEMs were delivered, *informed* readership may have declined and the way in which *informed* was mailed to the entire FP/GP group for the OPEM programme may simply not have engaged these doctors as readers. Thus, the failure of PEMs to lead to treatment intensification may not be attributed to the PEMs themselves, but rather to the failure of physicians to open and read the journal.

Information seeking behaviors of physicians

Despite widely available clinical practice guidelines, the evidence-to-practice gaps suggest that health care providers do not uniformly follow these recommendations. Accordingly, researchers have attempted to study the information-seeking behaviours of health care providers to determine the most efficient ways to deliver educational materials. Numerous studies have revealed that health care providers do not pursue answers to many of their clinical queries (Ely et al., 1999; Dawes & Sampson, 2003; Coumou & Meijman, 2006; Clarke et al., 2013). While the percentage of questions that providers sought answers to varied in each of the studies, it ranged from 23% to 57% of all potential questions (Ely et al., 1999; Dawes & Sampson, 2003; Coumou & Meijman, 2006; Clarke et al., 2013). Factors that prompted information seeking behaviors included the convenience of access, reliability of sources, urgency of the problem, habit, and whether or not the provider believed a definitive answer existed (Ely et al, 1999; Dawes & Sampson, 2003). The most commonly cited reasons for not seeking answers were a shortage of time and information overflow (Dawes & Sampson, 2003; Coumou & Meijman, 2006; Davies, 2007; Clarke et al., 2013).

Near the time of the OPEM programme, research showed that primary care providers continued to seek answers to their clinical queries by consulting with colleagues and searching in textbooks (Coumou & Meijman, 2006). Paper sources have been known to provide readily available and applicable information, thus providing a solution to the barrier of time (Dawes & Sampson, 2003). Accordingly, in 2003, researchers predicted that the proportion of physicians who utilized paper sources was between 50-80% (Dawes & Sampson, 2003). As a result, one might expect that the OPEM physicians would be inclined to read a PEM. However, paper sources have also been criticized for being outdated and for not providing the most appropriate answer to clinical queries (Clarke et al., 2013). With the increased availability of computers and internet access, electronic sources may have been a more trusted information source for OPEM physicians. While studies on information seeking behavior of Ontario physicians is lacking, research in other countries suggests that, at the time of the trial, electronic databases, namely MEDLINE, were gaining prominence (Dawes & Sampson, 2003; Coumou & Meijman, 2006). Thus, it is possible that PEMs were not well received by OPEM physicians due to the shift towards consuming electronic information for clinical decision making.

The struggle of unlearning

To change clinical practice, physicians must replace routine, outdated operations with new, evidence-based practices. While adding to their knowledge base can be a simpler undertaking, dismissing current practices has been consistently found to be challenging (Rushmer & Davies, 2004; Gupta et al., 2017). The process of change disrupts the status quo equilibrium, causing physicians to be uncertain about practices they considered to be "certain" (Gupta et al., 2017). Physicians included in the study had been practicing as a FP/GP for, on average, 22 years (see table 4.1). As a result, they may have adopted standard prescribing practices for individuals with diabetes over the years and were thus unwilling to implement a change to multiple drug classes in response to the PEM.

Failure to account for specialist physicians

We focused solely on prescriptions that were written by FP/GPs, despite knowing that a subset of patients received care from diabetes specialists. In 2005, there were 128 Endocrinologists practicing in Ontario (Canadian Medical Association, 2005). Many of these physicians also treat patients with non-diabetes endocrine disorders; thus, the number of individuals who had their diabetes managed solely by an Endocrinologist was likely very low. Accordingly, the inclusion of individuals whose diabetes was managed by an Endocrinologist, rather than a FP/GP, is unlikely to have largely influenced our intervention effect.

5.2   Strengths

Study design

The 2x2 factorial design allowed us to test two versions of a PEM at once: an insert, and an outsert. This allowed us to make recommendations about PEMs in general, but also about specific design choices. Moreover, random assignment ensured that baseline characteristics of the physicians and patients were well-balanced, on average, among the intervention groups (see tables 4.1 and 4.2).

All study data came from databases held at ICES. Without the need for primary data collection, the costs associated with this study were low (in fact, all three OPEM trials, randomizing hundreds of thousands of patients and thousands of physicians were completed on a budget of

less than $300,000 CAD). Moreover, though the costs associated with developing, printing, and mailing the PEMs were not recorded, previous research suggests that the costs to develop and implement PEMs are significantly lower than other KT intervention strategies (Mewes et al., 2017).

Directly answers literature demands

The debate surrounding the effectiveness of PEMs is ongoing. The most recent systematic review suggests that, to determine the true benefit of PEMs, high-quality studies must be undertaken that clearly describe the intervention and are adequately powered to detect small treatment effects (Grudniewicz et al., 2015a). Our study directly meets these requirements. We clearly outlined the professionals who contributed to the design of the PEMs, provided a detailed description of the PEM layout, and included pictures of the exact PEMs that were mailed (see Appendix figures 3-4). Moreover, our large sample size ensured that we had adequate power to detect an effect as small as 5% (see Zwarenstein et al., 2007 for more details). Accordingly, our study provides concrete evidence for the effectiveness of PEMs, and the findings may be included in future systematic reviews investigating the benefit of PEMs.

5.3 Limitations

The use of administrative data

The reliance on administrative data to build our cohort and to ascertain outcomes presented as a limitation to this study for three reasons. Firstly, the only database available to monitor prescription patterns is ODB, a program that, at the time of the trial, covered prescription drugs for the following individuals: those 65 and older, on social assistance, receiving benefits from Ontario's Assistance for Children with Severe Disabilities program, receiving care under the Home Care Program, eligible under the Trillium Drug Program, and residing in Long-Term Care facilities and in Homes for Special Care (HIV & AIDS Legal Clinic Ontario, 2020). Since the majority of individuals eligible for ODB are 65 and older, we chose to limit our study population to those 66 and older (an additional year to allow for baseline measurements). However, the recommendations outlined in the PEMs are not unique to seniors, but rather apply to all individuals above 50 living with diabetes. As a result, we are unable to ascertain whether the

intervention effects are consistent across all age groups; thus, the generalizability of our results are limited to populations of individuals with diabetes aged 66 and above.

Moreover, without access to any clinical documentation on the actual wellbeing and BP and cholesterol levels of individual patients, we were unable to differentiate between those who had well-controlled diabetes, and those who required treatment intensification. Despite national and provincial statistics that suggest that diabetes is, on average, poorly managed, we should expect that some patients are taking the appropriate medications to manage their disease and/or that their clinicians consider it unwise to intensify their treatment because of reasons other than their diabetes. Obtaining BP and cholesterol measurements would have allowed us to exclude those patients who would not benefit from treatment intensification. Instead, those who did not undergo treatment intensification throughout the study period were classified as "failures". Furthermore, we were unable to identify patients who had allergies or contraindications to any of the study drugs; therefore, they were regarded as "failures" in our study, despite being ineligible to receive the drugs in routine practice. However, as a consequence of randomization, we expect that individuals who were not in need of intensification by the study drugs were equally distributed between trial arms; thus, this is unlikely to have meaningfully distorted our findings.

Lastly, relying solely on administrative data necessitated that a large assumption be made about our population. We assumed that all FP/GPs received the PEMs, read them, and subsequently decided whether or not to implement the guideline recommendations in their practice. As a result, all FP/GPs who were mailed a PEM and who met our inclusion criteria were included in our analysis. However, it is possible that the PEM was not delivered to the proper address, or that the FP/GP discarded the journal without reading the PEM. Additionally, we are unable to distinguish between a FP/GPs decision to ignore the PEM from a patient's resistance to implementing the change. Another assumption was that the patients were taking the drugs they were prescribed.

Generalizability
While the trial was designed with a pragmatic intention, the eligibility criteria proved to be rather strict. According to the Canadian Medical Association (2005), there were 10,545 family

physicians practicing in Ontario in 2005. After excluding those not deemed to be in "active practice", our intervention was delivered to 5,178 physicians (see figure 4.1). Thus, while the sample size was still remarkably high, the intervention did not reach as many physicians, and thus patients, as anticipated. The results are therefore generalizable to Ontario FP/GPs who billed at least $50,000 in 2004, and who prescribed medications to at least 100 seniors (≥66 years old) in at least 10 months between August 2003 and July 2004. Over 3,000 physicians were excluded on the basis of not treating an adequate number of individuals aged 66 and above (see figure 4.1). It is possible that physicians who treat a smaller number of individuals 66 and above have less experience with diabetes care and would therefore benefit from the receipt of PEMs. However, these physicians were not included in the study population and, as a result, the findings may not be generalizable to all Ontario FP/GPs.

Use of the ODB database to ascertain outcome status

The ODB database only contains prescriptions that have been dispensed. Thus, since our intervention is targeting physician behavior change, it is possible that the intervention effect was diluted by patients who received a prescription for one of the study drugs, but failed to get it dispensed. Nevertheless, we expect that the proportion of patients who failed to fill their prescriptions would be balanced among the four groups as a consequence of randomization; thus, the intervention effect is unlikely to biased.

Time period

A discussion of the limitations would not be complete without acknowledging the timeframe in which the study was carried out. The PEMs were mailed in January of 2005, and the outcome measurement took place between 2005 and 2006. Estimates at the time of the trial suggested that prescriptions for all of ACE inhibitors, "other" antihypertensives, and cholesterol-lowering agents were at least 30% below guideline recommendations (Zwarenstein et al., 2007). There is wonder whether or not the results from the present study are generalizable to today's environment. Despite a lack of recent Canadian statistics, we have reason to believe that care for diabetes remains below standard. The 2018 Diabetes Clinical Practice Guidelines still declare that diabetes-related cardiovascular complications are responsible for the greatest burden of disability and death among individuals with diabetes (Diabetes Canada, 2018b). Accordingly,

Diabetes Canada strongly recommends that individuals are treated with appropriate medications to manage these risks, including antihypertensives and cholesterol-lowering agents (Diabetes Canada, 2018b). Moreover, recent estimates from the U.S. revealed that care has not improved in spite of major advances and standardized treatment strategies (Kazemian et al., 2019). It has been previously shown that diabetes treatment targets are comparable in Canada and the U.S. despite different methods of care delivery, suggesting that this poor treatment is likely also observable in Canada (Booth et al., 2002). Thus, while we have several reasons to believe that care for diabetes continues to be poor in Ontario, we do not have concrete evidence that the prescription rates for the study drugs are as poor today, and in need of intensification, as they were at the time of the trial.

Fifteen years later, we might expect that healthcare providers use alternate sources to seek answers to their clinical queries. While the shift from paper-based medical records to electronic-based systems has been gradual, in 2019, 94.3% of FP/GP's in Ontario reported using some form of electronic tool for tasks such as specialist referrals, ordering lab tests, or accessing patient information systems, in their practice (Canadian Medical Association, 2019a). Simultaneously, physicians have increasingly relied on internet sources, such as MEDLINE, the Cochrane Library, and Google, to assist in decision-making (Clarke et al., 2013). PEMs continue to be utilized as a knowledge translation tool today; however, one wonders whether electronic sources have a greater capacity to alter physician prescribing practices than do printed materials.

Primary outcome definition

The primary outcome definition, as described in section 3.6.2, considers either a drug addition or a dose increase as treatment intensification. While we expect that the majority of individuals re-filled their prescription once their previous one was complete, it is possible that some individuals received a new prescription before finishing their previous one. For example, an individual may have seen their FP/GP for reasons other than diabetes management shortly before their diabetes prescription was to run out. The FP/GP may have, for convenience's sake, written a new prescription for that individual to be taken once the previous course was complete. In these situations, it will appear that the physician intensified the individual's treatment regimen by adding a drug, even though the two drugs were never taken simultaneously. Even if the FP/GP

made a medication switch, which we chose to exclude from the primary outcome, this was erroneously captured as a medication addition in the primary outcome definition in these scenarios. That being said, we expect the individuals who re-filled their prescriptions early, if there were any, to be balanced across the four groups due to randomization; therefore, the treatment effect is unlikely to be biased.

Competing risks challenges

All analyses were carried out using logistic regression models estimated using GEE, as described in the OPEM protocol (Zwarenstein et al., 2007). While this model accounts for clustered data, it fails to take into account the competing risk of death. The model assumes that patients can experience one of two outcomes after one year of follow-up: a treatment intensification, or no intensification. Thus, patients who died during the follow-up period without experiencing a treatment intensification were placed in the "no intensification" group. However, once these patients died, for the remainder of the follow-up period they had no opportunity to experience a treatment intensification. A more complex analysis of the cumulative incidence of intensification while taking into account the competing risk of death may have been more appropriate (Anderson et al., 2012). That being said, the death rates among patients in the trial were low (see table 4.4). Moreover, death rates were balanced across groups, and appear to be representative of death rates among Ontario seniors at the time of the trial. Accordingly, the models used in the analyses are reasonable and the estimates of the intervention effect are likely valid.

5.4   Direction for future research

Despite notable efforts to attenuate the evidence-to-practice gap, prescription drug use for diabetes care continues to fall short of guideline recommendations today. This study revealed that PEMs did not successfully influence FP/GP physicians to intensify their patients' treatment regimens. However, a limitation of the study, as discussed in section 5.3, is the absence of any clinical information on the individual patients. Future studies could link a larger number of databases to include clinical data, such as BP and cholesterol measurements, to limit the patient sample to only those in need of treatment intensification. In addition, since the vast majority of physicians have shifted to the use of electronic medical records, it is of interest to explore whether an electronic version of a PEM would lead to greater improvements in adherence to

guideline recommendations than did the mailed PEM. The electronic recommendations would presumably be sent via email or through online portals, and would need to be designed with meticulous detail to overcome the barriers associated with electronic information sharing. Lastly, Primary Care Practice Reports have the potential to influence physician prescribing practices. These confidential reports, developed by Ontario Health Quality and ICES, are designed to encourage physicians to provide high-quality care according to guideline recommendations by providing them with an overview of their current care patterns in relation to their peers (Health Quality Ontario, 2019). At present, the diabetes section of the report provides information on HbA1c testing, retinal screening, and statin prescriptions (Health Quality Ontario, 2019). These reports could be updated to provide additional information on prescribing patterns of ACE inhibitors and "other" antihypertensives. While the receipt of these reports is currently voluntary, future studies may consider sending these reports, either by mail or electronically, to all Ontario FP/GPs to investigate whether this KT strategy is effective at attenuating the evidence-to-practice gap. The PEMs delivered in this study provided broad recommendations for prescribing patterns for all physicians. A tailored report, like the Primary Care Practice Report, may encourage physician compliance, as they are provided with clear examples of areas that need improvement in their individual practice.

5.5 Conclusion

Overall, it was found that PEMs alone, whether long and narrative and inside a journal (insert) or whether brief and action focused attached to the cover (outsert), are not effective at changing physician prescribing behaviours for individuals with diabetes aged 66 and above. Despite their low costs and wide reach, PEMs, in their present form, are not an effective KT strategy in primary care in Ontario for diabetes intensification and should not be utilized as a knowledge translation strategy. Given the context of multiple studies of a range of PEM interventions for a number of evidence-to-practice gaps, this may be a generalized failure of PEMs. Further research is warranted to investigate the effect of other knowledge translation strategies targeted at physicians to narrow the evidence-to-practice gap for the management of diabetes complications. In this modern era of electronic health records, one might think of electronic interventions such as point of care reminders, on screen prompts, and electronic audit and feedback (Shojania et al., 2009; Tuti et al., 2017).

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Appendices

Appendix 1: Target audiences (stakeholders) for the various types of research

| Potential stakeholder	Type of research			
	Basic	Clinical	Health Services	Population Health
Consumers	-	+++	+++	-
Professionals	-	+++	+++	-
Local Administrators	-	++	+++	+++
National Policy Makers	-	+++	+++	+++
Regulatory Bodies	+++	+++	+++	+++
Industry	+++	+++	++	+
Research Funder	+++	+++	+++	+++
Researchers	+++	+++	+++	+++

Table Legend:
- Not Relevant.
+ Low Relevance to +++ High Relevance.

Data source: Grimshaw et al. (2012)

Appendix 2: Map of the Local Health Integration Networks in Ontario
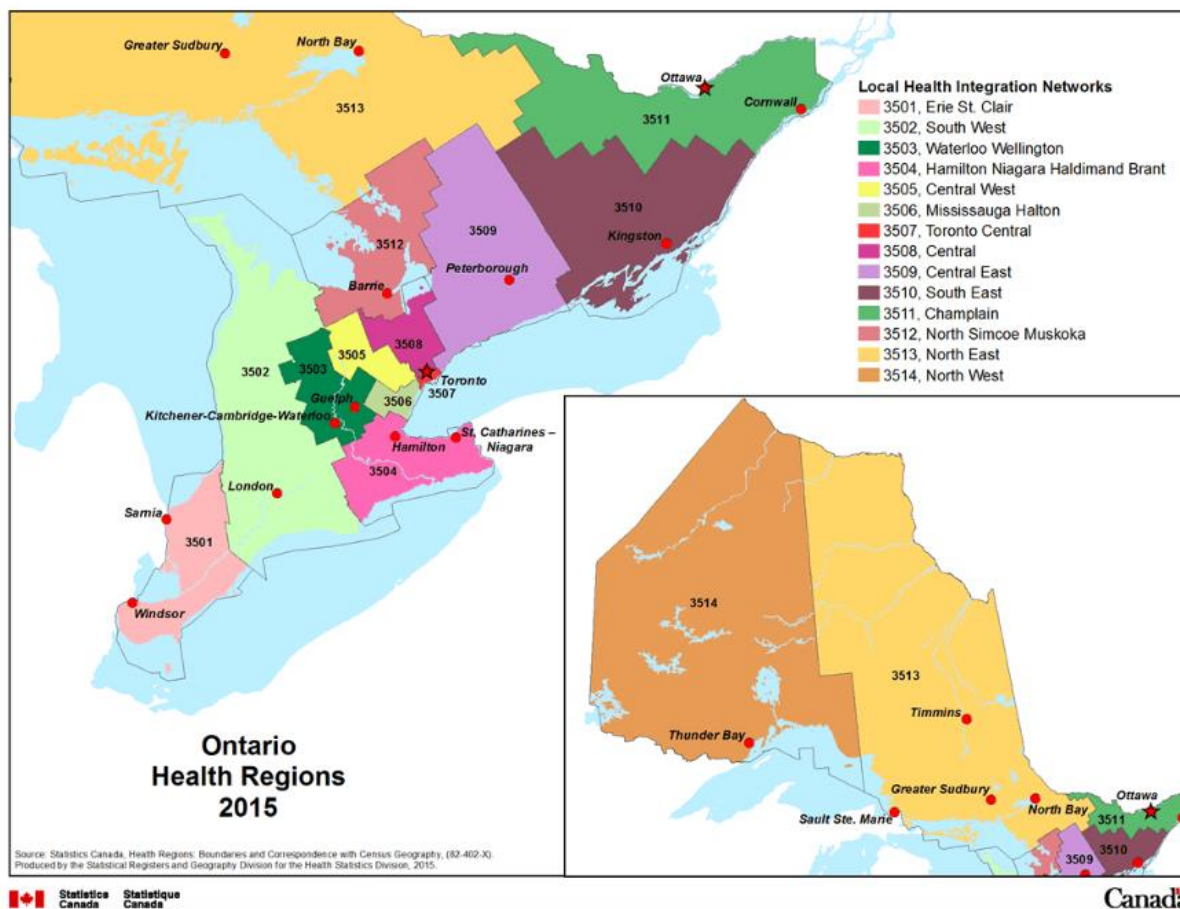
Data source: Statistics Canada (2015)

Appendix 3: Front and back side of the outsert

Front

You Can Help Prevent 75% of Diabetes Deaths
Cut the risk of heart attack and stroke for your diabetic patients

Lower BP all the way down to 130/80.
▼
You may need two or three drugs. One should be an ACE Inhibitor‡
‡See reverse side

Treat cholesterol even if it's normal
▼
Give a STATIN to all diabetic patients over 50 years of age*
*See reverse side

informed

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Back

‡ Additional benefit of lowering blood pressure, with agents like ACE inhibitors, includes protection of renal function.

Adverse reactions to ACE inhibitor use may include: angioedema, cough and elevated creatinine/potassium.

* Adverse reactions to statin use may include: myalgias, myositis and rhabdomyolysis. Avoid concomitant use of statins with macrolides, some antifungals, niacin, fibrates and grapefruit juice.

For further information see http:/www.diabetes.ca/cpg2003 and *Lancet* 2003; 361:2005–16.

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Data source: Zwarenstein et al. (2007)

Appendix 4A: First page of the insert

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A–B–C in Diabetes

Cardiovascular (CV) disease is an important cause of morbidity and mortality in persons with diabetes mellitus (DM). One study found that the risk of myocardial infarction (MI) and cardiac death in patients with type 2 DM and no history of MI is the *same* as patients without DM who have had a prior MI (*NEJM* 1998; 339:229–234). Other studies have reported smaller effects, but the message remains the same: patients with DM are at high risk of cardiovascular events. How can their long-term outcomes be improved? Research has shown that a multi-pronged management strategy *(the ABCs)* is central in managing vascular risk factors in DM.

Clinical options to manage common adverse reactions to ACE inhibitor use

Adverse reactions	Clinical options
✔ Angioedema	▸ Stop the drug.
✔ Cough	▸ Consider: 1) Stopping the drug. 2) Continuing if cough tolerable. 3) Switching to ARB.
✔ Elevated creatinine	▸ If the creatinine is elevated but <250 µmol/L, a trial of an ACEI is appropriate. • Start low and go slow (⅓ to ½ of usual dose). • Check creatinine and electrolytes two weeks after start, and monthly while increasing the dose. • Check creatinine and electrolytes every three months thereafter. • If creatinine rises, treatment may still be beneficial. If the rise is <15% and not progressive, the ACEI can still be continued. • Consult a specialist as needed. ▸ If the creatinine is > 250 µmol/L, ACEI may still be beneficial, but consider consultation with a specialist.
✔ Elevated potassium	▸ Check other sources (salt substitutes and potassium sparing diuretics, such as spironolactone). ▸ In patients with hypertension, concomitant treatment with a thiazide diuretic will reduce both BP and potassium. (Thiazide diuretics are not effective with a serum creatinine > 200 µmol/L.)

Angiotension converting enzyme inhibitors (ACEI) are medications that can provide benefits to persons with DM on several levels:

❶ Cardiovascular disease
Research supports the use of ACEIs to reduce cardiovascular events in persons with DM *and* a vascular risk factor, hypertension or stable coronary artery disease, even without evidence of heart failure.

Evidence: The **HOPE** Study (*Lancet* 2000; 355:253–259) looked at the use of an ACEI in patients who were at high risk for cardiovascular events (had at least one CV risk factor), but did not have either left ventricular dysfunction or heart failure. In the large subset of patients with DM, the use of an ACEI led to significant reductions in death, MI or stroke. Similar findings were reported in the **LIFE** trial (*Lancet* 2002; 359:995–1003) which studied angiotension receptor blockers (ARBs) in patients with DM and hypertension. The **EUROPA** trial looked at the effects of an ACEI plus optimal therapy on preventing cardiac events in patients with stable

coronary artery disease and no heart failure (*Lancet* 2003; 362:782–788). Analysis of the subgroup of patients with DM revealed that the number needed to treat (NNT) to prevent one CV death or non-fatal MI was just 27 patients over four years.

❷ Renal disease
Kidney disease is a major complication in DM. Thirty percent of patients with type 2 DM will have evidence of kidney disease within four years of diagnosis. Research supports the use of ACEI to prevent progression of nephropathy.

Evidence: ACEI use in patients with type 1 DM and microalbuminuria (the earliest warning sign of diabetic nephropathy) has been shown to slow the progression of proteinuria and creatinine rise in several large clinical trials (*NEJM* 1993; 329:1456–1462). In type 2 DM, ACEIs and ARBs have been shown to decrease albuminuria and prevent worsening of nephropathy (*Ann Int Med* 1993; 118:577–581; *NEJM* 2001; 345:870-878).

Using ACEI: Three common adverse reactions to ACEIs are angioedema, cough, and elevated creatinine/potassium (see box above). Declining renal function is part of the long term disease process in DM. Finding the balance is sometimes difficult in those who already have some renal impairment but who can still benefit from ACEIs.

Just to complicate matters...
The **ALLHAT** trial (*JAMA* 2002; 288:2981–2997) demonstrated that diuretics were as good or even better than ACEIs and calcium channel blockers in preventing CV events, even in the subgroup with DM. This result muddies the waters less than you might think, because most patients with DM will require at least two antihypertensive agents to reach the benchmark BP of 130/80 (see section on **Blood Pressure Reduction**). The combination of a diuretic *plus* an ACEI is attractive, because diuretics are potent, effective and inexpensive, and ACEIs offer the additional benefits of renal protection.

Blood pressure reduction has been targeted even lower in your patients with both DM and hypertension. Aim for a blood pressure (BP) less than 130/80 mm Hg.

Evidence: A series of large, long-term trials in Great Britain (the **UKPDS** trials) tested treatments used to prevent complications and mortality in persons with type 2 DM. One of the unexpected findings was that controlling blood pressure produced greater benefits than controlling blood glucose in terms of preventing the vascular complications of diabetes (**UKPDS** 38 in *BMJ* 1998; 317:703–713). In the **HOT**

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Data source: Zwarenstein et al. (2007)

Appendix 4B: Second page of the insert

trial, the risk of cardiovascular events was reduced by 50% in a large subset of patients with DM by lowering diastolic BP by 10 mm Hg (from 90 mm Hg to 80 mm Hg) (*Lancet* 1998; 351:1755–1762).

Meeting the target: Non-pharmacologic approaches, such as modest weight loss (even 4–5 kg leads to substantial improvement), restricting salt intake, avoiding excess alcohol, and exercising regularly can produce important benefits.

Most older patients with DM will need medication to reach the target BP, and the majority of these will require several drugs to do so. More than 60% of patients required two or more medications and 30% required three or more to reach BP target levels in the **UKPDS** trial. Thiazide diuretics, ACEIs, ARBs and beta-blockers all show evidence of benefit in patients with DM who have concomitant hypertension. Which to start first? Experts disagree, and we think it's moot, given that most patients won't be controlled with monotherapy (*Ann Int Med* 2003; 138:587–602).

Check points for blood pressure management in persons with DM

✔ Aim for BP <130/80 mm Hg.

✔ Consider non-pharmacologic approaches.

✔ Thiazides, ACEIs, ARBs and β-blockers all have been shown to provide benefit.

✔ Multi-drug therapy may be needed (e.g. diuretic with an ACEI or ARB).

✔ Keep it simple (e.g. combination tablets, once daily dosing).

✔ Tailor therapy to patient's daily routine.

✔ Consider BP self-measurement.

Cholesterol-lowering agents have an important role in reducing morbidity and mortality in DM. The Canadian Diabetes Association 2003 guideline (http://www.diabetes.ca/cpg2003/) recommends that the goals of treatment for adults with DM are:

✔ LDL <2.5 mmol/L.

✔ Total/HDL ratio <4.

✔ Total triglycerides <2 mmol/L.

More recently, some experts are suggesting that those with DM at sufficiently high risk of vascular events (e.g. over the age of 50, secondary prevention) will benefit from lipid-lowering therapy *regardless* of the initial cholesterol levels.

Evidence: The Heart Protection study (*Lancet* 2003; 361:2005–2016) looked at the effects of statin therapy in persons with DM or occlusive vascular disease on preventing major coronary events, strokes and revascularizations over a five-year treatment period. There were highly significant reductions of about a quarter overall in both groups. The study also found that there was a 27% reduction in adverse events among those with DM whose pretreatment LDL was *below* 3.0 mmol/L.

Meeting the targets: Non-pharmacologic strategies such as a low fat/high fibre diet and exercise should be encouraged in all patients with DM. Most, however, will need medication to reach the recommended lipid levels.

Which drug to choose? The statins remain the best agents to lower LDL cholesterol. They are believed to have other protective effects that target atherosclerosis, as well as lowering the risk of MI and stroke in patients with or without DM. Fibrates are effective in lowering triglycerides (see table upper-right).

Complications of statin therapy? Up to 10% of patients will experience myalgias. Myositis can occur in about 0.5% and rhabdomyolysis in less than 0.1%. The risk of these complications is potentiated when patients are being treated concomitantly with macrolides (e.g. erythromycin), some antifungals,

Effects of Lipid-lowering Drugs

	LDL	HDL	TGs
Statins	▼▼▼	▲	▼
Fibrates	▼	▲	▼▼
Nicotinic Acid	▼	▲▲	▼▼
Resins	▼▼	⊙	⊙
Cholesterol absorption inhibitors	▼▼	⊙	⊙

▼ decreases ▲ increases ⊙ does not change

TGs: triglycerides;
Resins: bile acid sequestrants
(i.e. cholestyramine)

niacin, fibrates and grapefruit juice. Careful history-taking is important.

Up to 3% of patients will develop elevated transaminase levels within the first three months of statin therapy. Do serum levels at baseline and at three months after initiating therapy. Stop the drug if levels are more than two or three times the upper limit. ■

The Bottom Line

A Use ACEIs in patients with DM who have no contraindications:

✔ As part of a multi-level hypertension regimen in combination with a diuretic.

✔ In patients with microalbuminuria to prevent progression of nephropathy.

✔ To reduce the risk of MI, stroke and death.

B Target BP <130/80 to reduce the risk of vascular complications of DM. BP control may be at least as important as tight glycemic control in DM.

C Tight cholesterol/lipid control will reduce cardiovascular risks in DM. In your patients with DM over the age of 50 years, consider starting a statin, even if the cholesterol is normal.

Article
Peer-reviewed

Data source: Zwarenstein et al. (2007)

Curriculum Vitae

ALISON HOWIE

EDUCATION

Master of Science, epidemiology and biostatistics   2018-2020 (anticipated)
Western University, London, ON
- Supervisors: Dr. Merrick Zwarenstein, Dr. Neil Klar
- Thesis: Printed educational materials directed at Ontario primary care physicians fail to improve adherence to guideline recommendations for the management of diabetes complications: a pragmatic, factorial, cluster randomized trial

Bachelor of Science, life sciences (Honours)   2014-2018
Queen's University, Kingston, ON
- Relevant coursework: Principles of Epidemiology, Biostatistical Data Analysis for Life Science Students, Global and Population Health, Foundations of Health Policy

SCHOLARSHIPS AND ACADEMIC HONOURS

Western Graduate Research Scholarship, Western University   2018-2020
- Entrance scholarship valued at $3000 annually

Dean's Honour List, Queen's University   2018
- Recognition for an average grade of 80% or above

RELEVANT EXPERIENCE

MSc Thesis, Western University   2019-2020
- Focus: knowledge translation and clinical trials
- Developed several multivariable logistic regression models to evaluate the effectiveness of printed educational materials on prescribing patterns for diabetes care among primary care practitioners in Ontario
- Utilized information stored in health services databases (Ontario Drug Benefit Claims, Ontario Health Insurance Plan Claims Database), ICES-derived databases (Ontario Diabetes Database), population and demographic databases (Registered Persons Database), and care provider databases (Corporate Provider Database) held at ICES to answer all research questions

Graduate Research Assistant, Western University   June 2019-Present
- Assisting in the literature search for a textbook on pragmatic clinical trials by managing the compilation of over 400 articles in the reference manager Mendeley on topics related to ethics, generalizability, bias, analysis, design, confounding, etc.

Writing Associate, Health Science Inquiry   2019-Present
- Selected to be part of a team of Canadian graduate students who collaborate to publish high-quality, student-reviewed articles on topics relevant to health science

- Researched local health science graduates working in areas related to the journals theme, "Our Environment = Our Health", to include in the Spotlight on Careers section of the journal
- Led Q&A style interviews with two epidemiologists – one in academia, one in industry – and captured key quotations to be included in a final report for publication

Science Awareness and Communication, Strong Bones Strong Minds Strong Muscles 2019-Present
- Committee mandate: to deliver science and research awareness to the community, bridging the gap between researchers and the public
- Delivered science-related activities to pediatric patients and their families at the Children's Hospital to increase science awareness and to support families through stressful times

Reviewer, Diabetic Medicine and Endocrinology, Diabetes & Metabolism   2020
- Reviewed an article describing a peer support intervention for type 2 diabetes by considering the trial design, analysis, and content in terms of diabetes and knowledge translation

Reviewer, Journal of Clinical Epidemiology   2019
- Applied my knowledge of pragmatic trials, PRECIS-2, statistical methods, and the English language to conduct 3 rigorous evaluations of an article investigating the nature of nursing trials

Research Assistant, The Ottawa Hospital Research Institute   2018
- Updated and corrected errors in a clinical HIV database by extracting demographic information, treatment rounds, and laboratory data from the medical records of new and existing HIV patients
- Utilized knowledge and skills acquired from my undergraduate epidemiology and microbiology courses, and gained new knowledge in relation to HIV detection, transmission and treatment

GRADUATE COURSEWORK

Foundations of Epidemiology	Principles of Biostatistics
Clinical Epidemiology	Multivariable Methods
Analytic Epidemiology	Randomized Trials – Design
Health Services Research	Randomized Trials – Analysis
Questionnaire Design and Survey Implementation	

LANGUAGES

English (fluent)   **French** (intermediate, DELF B2)

TECHNICAL AND ANALYTICAL SKILLS

MS Office Software (advanced)   **Stata** (beginner)
SAS (intermediate)   **SPSS** (beginner)