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Assessing potentially inappropriate prescribing (PIP) and predicting patient outcomes in Ontario's older population: a population-based cohort study applying subsets of the STOPP/START and Beers' criteria in large health administrative databases

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ABSTRACT

Introduction: Adverse drug events (ADEs) are common in older people and contribute significantly to emergency department (ED) visits, unplanned hospitalisations, healthcare costs, morbidity and mortality. Many ADEs are avoidable if attention is directed towards identifying and preventing inappropriate drug use and undesirable drug combinations. Tools exist to identify potentially inappropriate prescribing (PIP) in clinical settings, but they are underused. Applying PIP assessment tools to population-wide health administrative data could provide an opportunity to assess the impact of PIP on individual patients as well as on the healthcare system. This would open new possibilities for interventions to monitor and optimise medication management on a broader, population-level scale.

Methods and analysis: The aim of this study is to describe the occurrence of PIP in Ontario's older population (aged 65 years and older), and to assess the health outcomes and health system costs associated with PIP—more specifically, the association between PIP and the occurrence of ED visits, hospitalisations and death, and their related costs. This will be done within the framework of a population-based retrospective cohort study using Ontario's large health administrative and population databases. Eligible patients aged 66 years and older who were issued at least 1 prescription between 1 April 2003 and 31 March 2014 (approximately 2 million patients) will be included.

Ethics and dissemination: Ethical approval was obtained from the Ottawa Health Services Network Ethical Review Board and from the Bruyère Research Institute Ethics Review Board. Dissemination will occur via publication, presentation at national and international conferences, and ongoing exchanges with regional, provincial and national stakeholders, including

Strengths and limitations of this study

- The application of medication appropriateness criteria (such as the STOPP/START and Beers' criteria) to health administrative data provides a unique opportunity to estimate the prevalence of potentially inappropriate prescribing (PIP) at the population level, with near-complete coverage (our study population will comprise approximately 97% of Ontario's seniors) and to assess its impact, both human and economic, at the individual and societal level.
- This study is expected to identify patient and prescriber characteristics associated with a higher likelihood of PIP, which could become the target of interventions aimed at improving the quality of prescribing.
- The use of health administrative data provides high power to detect relevant associations at comparatively lower cost than would be possible using clinical data collected at the bedside.
- Several limitations may be encountered that are inherent to studies relying on health administrative data, including uncertainty surrounding patient adherence to dispensed medications, the unavailability of some clinical or diagnostic data, and the absence of data for over-the-counter or non-formulary medications. Each of these could impact the estimate of true PIP in the population.
- Adverse effects of medication are known to be broadly under-recognised and under-reported, particularly in health administrative data, which may limit this study's ability to detect medication-specific patient outcomes; for this reason, more reliable outcome measures, such as the occurrence of emergency department visits, hospitalisation and mortality, will be used as main outcomes for this study.

the Ontario Drug Policy Research Network and the Ontario Ministry of Health and Long-Term Care.

Trial registration number: Registered with clinicaltrials.gov (registration number: NCT02555891).

INTRODUCTION

Background

Older people consume a disproportionate share of medication compared with younger people. According to a recent report from the Canadian Institute for Health Information (CIHI) released in May 2014, patients aged 65 years and older currently represent 15% of the Canadian population, yet their spending on prescription medications accounts for over 40% of all retail prescription drug sales and 60% of public drug programme spending,[1] three times the Canadian average. Furthermore, nearly two-thirds (65.9%) of Canadian patients aged 65 years and over had claims for 5 or more drug classes, and more than one-quarter (27.2%) of seniors had claims for 10 or more drug classes.[2] Finally, older people are at higher risk of adverse drug events (ADEs) than the rest of the population.[3 4] This elevated risk of ADE is due to various factors, including higher numbers of medications prescribed per person, increasing numbers of prescribers, greater sensitivity to medication effects secondary to natural age-related and disease-related changes in pharmacokinetics, as well as higher baseline risk of disease including higher likelihood of multimorbidity.[3 4]

The occurrence of ADE contribute significantly to more frequent emergency department (ED) visits, unplanned hospitalisations,[5] high healthcare costs,[6] morbidity and mortality in older populations.[7] A recent study showed that, of 600 older patients admitted to hospital for an acute illness, 25% of them had one or more ADEs prior to hospitalisation, of which two-thirds had contributed to the hospitalisations.[8] Of these events, 69% were deemed avoidable.

Potentially inappropriate prescribing (PIP), which includes errors of co-mission as well as of omission, is common in older people. Its likelihood increases with the number of medications prescribed and it is often associated with increased costs.[9–11] A number of medication assessment tools exist to identify PIP that can lead to ADE.[9–19] Unfortunately, few of these tools have been shown to reliably predict ADE,[17 19] and although there are a few studies showing associations between PIP and adverse outcomes, their predictive validity needs to be assessed further, particularly using large-scale national health databases.

STOPP/START criteria

The STOPP/START criteria[20 21] were developed by a multidisciplinary team of geriatricians, pharmacists, pharmacologists and primary care physicians and consist, in the updated 2014 version, of 81 STOPP and 34 START criteria organised by physiological organ system; STOPP criteria target errors of commission, whereas START are concerned with errors of omission.

STOPP lists instances of PIP that should be avoided, drug interactions and drugs that increase risk of falls, while START lists instances of potential prescribing omissions, where clinically indicated medicines are not prescribed. The STOPP/START criteria were successfully applied, with good inter-rater reliability, in a number of settings, revealing rates of PIP of 22% in primary care clinics, 35% in acute hospital settings and 60% in nursing homes.[12 16 20 22] In a validation study, screening medications with the STOPP/START criteria was associated with the subsequent use of fewer medications, fewer incorrect doses and lower potential interactions.[23]

Beers' criteria

The Beers' criteria were the first explicit criteria to be published and have become widely used, particularly in the USA where they originated.[17 24] These criteria were originally developed for use in nursing home patients; they were modified three times, in 1997,[25] 2003[15] and 2012,[26] and are now intended for use in all patients above 65 years of age. Despite their popularity, the Beers' criteria have been criticised for including obsolete medications, as well as medications no longer available outside the USA, particularly in Europe,[8 10] though some of these issues have been addressed in the 2012 revision.[26–29] They have also been criticised for not being sufficiently inclusive of a number of common instances of PIP.[8 17] In particular, Beers only lists drugs to avoid, but does not include other categories of PIP, such as drug–drug and drug–disease interactions, drug duplications or underuse and overuse of medications.[17] Finally, Beers' criteria have not been shown to be associated with experiencing an ADE, discharge to a higher level of care or in-hospital mortality.[30]

In a review of medication review tools performed before the 2012 Beers' update and the 2014 STOPP/START update, STOPP/START were deemed 'most promising', and were thought to have international applicability.[31]

Assessing PIP at the population level

There are relatively few studies looking at the appropriateness of prescribing at the population level. However, population-level approaches using health administrative data have the potential to assess the impact of inappropriate prescribing on large numbers of individual patients as well as on healthcare systems.[9]

STOPP/START criteria were designed for use in conjunction with patients' clinical records; therefore, access to patients' full medical records and biochemical (laboratory) data are necessary in order to deploy the full set of criteria. As this information is usually not available in health administrative databases, a subset of STOPP criteria (26 out of the 65 original STOPP criteria) that did not require patient-level clinical data were

identified by Cahir *et al*;[9] START criteria could not be used because they all require clinical data. The subset of STOPP criteria was applied to population-level health administrative prescription data to identify instances of PIP, and to estimate their cost.[9] The authors concluded that the total healthcare expenditures on PIP amounted to 9% of the overall drug expenditures of Ireland.[9] They were not able to assess the association of inappropriate prescribing with patient outcomes (ED visits, hospitalisations or mortality) and their associated costs, as these data were not available in their database.

Ontario possesses a comprehensive collection of linked health administrative databases containing drug, health services, socioeconomic and patients' health outcome data such as ED visits, hospitalisations and deaths. These data sets offer opportunities to prospectively assess the frequency of PIP, as well as associated outcomes and costs for a whole population. In the present study, we will apply a subset of the 2014 STOPP, START[21] and 2012 Beers' criteria[26] to Ontario's population-wide health administrative data to describe the occurrence of PIP in Ontario's older population, and assess the health outcomes and health system costs associated with it.

Evidence gaps to be filled

Using subsets of STOPP/START and, possibly, Beers' criteria applicable to health administrative data is a promising approach for the identification of PIP in older patients. Nonetheless, although PIP identified using STOPP/START criteria have been shown to be associated with ADEs and hospitalisations in clinical cohort studies,[8 32 33] a number of questions remain unanswered, particularly with respect to their application to population-wide health administrative data. In this context, it remains to be established whether a subset of STOPP/START and/or Beers' criteria are predictive of relevant patient outcomes, such as the incidence of ADE, ED visits, hospitalisations, composite healthcare utilisation and mortality. Furthermore, it is not clear whether such a subset of criteria could help identify patient and prescriber characteristics associated with a high likelihood of PIP, which could become the target of interventions aimed at improving the quality of prescribing.

To address these knowledge gaps, we will test three hypotheses pertaining to the effects of PIP on Canada's senior population:

1. Instances of PIP are frequent and costly.
2. ED visits and hospitalisations are significantly associated with PIP.
3. The likelihood of PIP is associated with patient and physician characteristics.

Identifying significant associations for some or all of the aforementioned hypotheses could provide evidence to support important policy measures aimed at effectively reducing PIP and its consequences on patients and the healthcare system on a broader, population-level scale.

METHODS AND ANALYSIS

Study design

We will conduct a population-based, retrospective, dynamic (open) cohort study.

Definition of observation periods

The *study period* will span from 1 April 2002 to 31 March 2014. These dates were chosen based on availability for all the required databases at the projected time of study initiation (fall 2015); should recent data be available at the time the study is conducted, the end of the study period will be adjusted to allow inclusion of these data. The *accrual period* is defined at the period for ascertainment of exposure (the occurrence of PIP); it starts 1 year *after* the start of the study period (ie, on 1 April 2003), and ends 1 year *before* the end of the study period (ie, on 31 March 2013). This will allow a 1-year look-back period preceding the first included PIP, to describe prior health services utilisation, medication use and comorbidities (baseline risks), as well as a 1-year follow-up period after the last possible PIP, to allow for adequate follow-up of patient outcomes (see figure 1 for a graphical illustration of study period, accrual period and time frame for ascertainment of baseline risks, exposures and outcomes).

Participants

Inclusion/exclusion criteria

Individuals eligible for participation in the study will include all patients who were: (1) continuously eligible for Ontario Health Insurance Plan (OHIP) coverage, (2) issued at least one prescription (of any type) during the *accrual period* (between 1 April 2003 and 31 March 2013), and (3) 66 years of age or older at the date of first dispensation during the accrual period; this is necessary to ensure the availability of 1 year of background information on medication and health services use for all patients. Instances of PIP will be identified and catalogued during the accrual period.

The index date of a patient's recruitment into the study cohort will be the date of the first prescription dispensed following the beginning of the accrual period (1 April 2003). Patients will be excluded if they do not have a valid OHIP number. This includes individuals whose healthcare is provided by other plans (eg, First Nations people living on reserves, members of the Canadian Armed Forces and refugee claimants) and is therefore not captured by Institute for Clinical Evaluative Sciences (ICES) data. Patients will also be excluded if they were not OHIP-eligible for at least 1 year prior to the index date, or 1 year after the index date, or if they do not have continuous OHIP coverage between these two dates; this is necessary to ensure that predictors and outcomes of PIP can be adequately captured. Patients not dispensed any prescription medication will not be included in the study. The selection of the study cohort is shown graphically in figure 2. Based on these criteria, we estimate that in excess of two

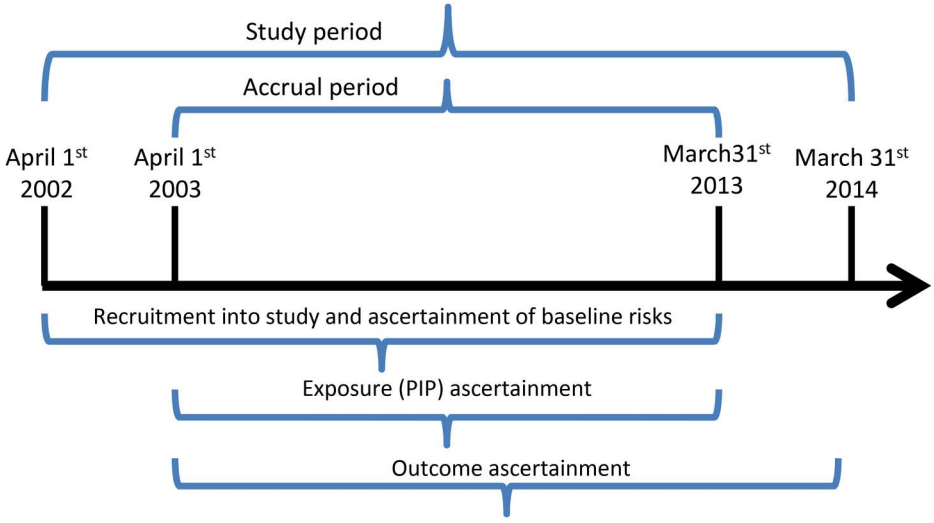

Figure 1 Definition of observation period (OHIP, Ontario Health Insurance Plan).

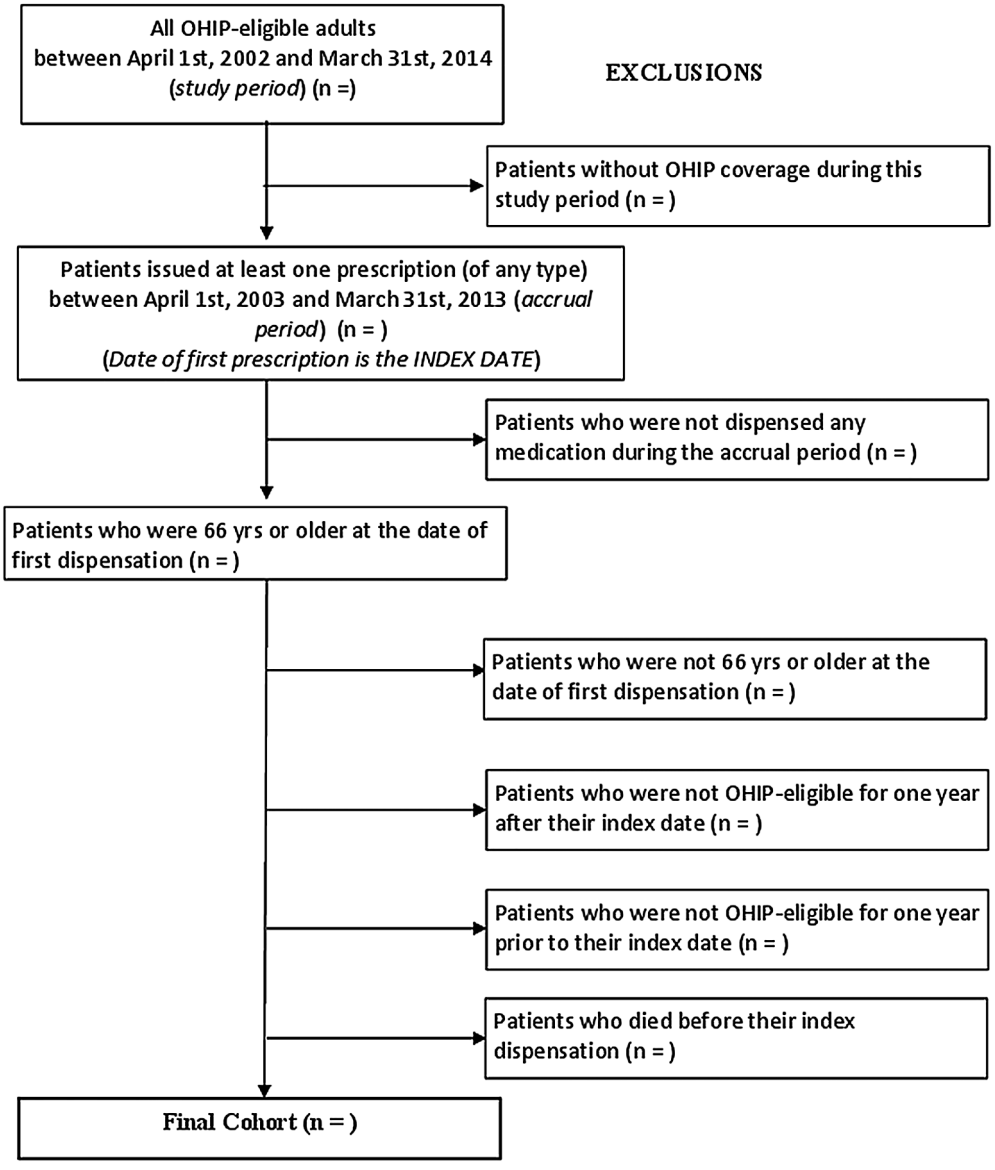

Figure 2 Description of study cohort creation (PIP, potentially inappropriate prescribing).

million patients will contribute data to our study (see Methods section, 'Validation and power', for calculations leading to this estimate).

Data sets

Patient data will be drawn from linked and de-identified health administrative data sets housed at the ICES, which will be accessed from the ICES@uOttawa site. ICES is an independent, non-profit organisation funded by the Canadian province of Ontario's Ministry of Health and Long-Term Care (MOHLTC). ICES databases contain information on hospital and outpatient use of health services, demographic data and socioeconomic data for over 13 million Ontarians. All of these data sets are linked using a patient-specific encrypted identifier. This study will use five general use health services data sets.[34 35]

Ontario Drug Benefits Claims Database

The Ontario Drug Benefit (ODB) programme provides drug benefits for all Ontario residents aged 65 and older and those with disability/social assistance benefits. The Ontario Drug Benefits Claims Database (ODBD) contains a number of data related to prescription drugs, including drug identification number (DIN), quantity of drugs provided, number of days supplied (which can be used to compute the daily dose), itemised cost, dispensing fee, long-term care indicators, the plan affiliated with the prescription (eg, Seniors, Trillium, Ontario Works, etc), the date the drug was dispensed, and patient and prescriber identifiers (encrypted). Additionally, ICES maintains a list linking DINs to their associated drug and product names, subclass information, pharmacological-therapeutic classification group codes, drug strength, route of administration, and first and last dispensing dates from the ODB.[35]

Discharge Abstract Database

The Discharge Abstract Database (DAD) captures all acute care hospitalisations in Ontario dating back to 1988. Each row in the DAD records demographic, diagnostic, procedural and treatment information for a given hospitalisation.[35]

Same Day Surgery Database

The Same Day Surgery Database (SDS) contains patient-level data for day surgery institutions in Ontario. Every record corresponds to one same-day surgery or procedure stay.

National Ambulatory Care Reporting System

The National Ambulatory Care Reporting System (NACRS) captures all visits to hospital EDs beginning in 2002. As with the DAD, each row of the NACRS contains demographic, diagnostic, procedural and treatment information for each emergency room visit.[35]

OHIP database

The OHIP database captures health services billing claims paid by the OHIP to providers. Each row in the OHIP database records the patient, provider and diagnosis/procedure being claimed for remuneration.

Care provider data will be obtained from the *ICES Physician Database (IPDP)*, which contains yearly information about all physicians in Ontario, including physician demographics (age, sex); specialty (functional and certified); location; and measures of physician activity (billings, workload, types or services provided). The *Client Agency Program Enrolment (CAPE)* database will be used to determine the enrolment of an individual in a programme with a specific practitioner and group. Birth date and death date of every individual eligible for Ontario health service will be obtained from the *Registered Persons Database (RPDB)*.[35] In addition, we will utilise five ICES-derived cohorts for case ascertainment of diseases specified in the STOPP/START and Beers' criteria: asthma, diabetes, hypertension, chronic obstructive pulmonary disease and congestive heart failure.

Exposure and outcomes

An overview of all variable definitions and units is presented in table form (table 1) and the variables are expanded on in the following paragraphs.

Exposure variable

The main exposure variable will be the occurrence of the first PIP ever during the accrual period (see figure 3). This will be used to quantify the association of a first PIP with an outcome (see 'Primary outcome' below).

A secondary exposure variable will be defined to assess the overall impact of PIP burden on patient outcomes: we define this secondary outcome as the annualised number of first PIPs for any STOPP/START or Beers' criterion experienced by each patient during his or her accrual period, a quantity which we term the 'first (criterion-specific) PIP incidence density'. PIP incidence density will be calculated separately for STOPP/START and for Beers' criteria. Since different patients will have different accrual periods, this variable will be expressed on an annualised basis, where the numerator is the total number of first criterion-specific PIPs experienced by the patient, and the denominator is the person-time contributed by the patient during his or her accrual period. Since patients can only experience one first PIP per criterion, subsequent PIPs for the same criterion will not be considered. This approach is made necessary because the risk of outcome is likely to change with habituation and prolonged exposure to a given PIP, and to reduce the impact of patients with a large number of PIPs for a given medication, or combination of medications.

To identify PIP, we will apply a subset of STOPP/START and Beers' criteria applicable to health administrative data by assessing both the patient's drug history, as recorded in the ODBD, and disease history as obtained from linking DAD, SDS, NACRS, OHIP and

Table 1 Variable definitions and units

Category	Variable name	Definition	Scale	Valid range/levels	Units
Main exposure variable	First PIP ever	Occurrence of the first PIP ever experienced by a patient during his/her study eligibility period	Dichotomous	Yes or no	1 if PIP 0 if no PIP
Secondary exposure variable	First criterion-specific PIP incidence density	Number of instances of first PIP for each criterion experienced by a patient during his/her eligibility period divided by the duration of the study eligibility period in years (will be calculated separately for STOPP/START and Beers' criteria).	Continuous	0 to unlimited	Counts/year
Primary outcome variable	Time to any outcome	Time between first PIP and first of ER visit, hospitalisation or death, occurring within the time window for 'PIP relevant outcomes' (usually up to 3 months after an instance of PIP, but may be longer for some criteria—see text for examples)	Ordinal	0–90	Days
Secondary outcome variables	Time to ER visit	Time between first PIP and first ER visit	Ordinal	0–90	Days
	Time to hospitalisation	Time between first PIP and first hospitalisation	Ordinal	0–90	Days
	Time to ADE	Time to any diagnostic code for an ADE	Ordinal	0–90	Days
Covariates	Patient age	Patient's age at time of first PIP	Continuous	66–116	Years
	Patient sex	Patient's biological gender	Dichotomous	Male or female	Male or female
	Patient location	Type of setting a patient lives in at time of PIP	Dichotomous	Long-term care vs community setting	Long-term care vs community setting
	Number of prescribers	Number of prescribers who have issued prescriptions for a patient in year prior to the first PIP	Continuous	1 to unlimited	Count
	Number of dispensing pharmacists	Number of pharmacists from whom a patient obtained medication in the year prior to the first PIP	Continuous	1 to unlimited	Count
	Polypharmacy	Number of medications concurrently in use at time of prescription of a PIP	Continuous	1 to unlimited	Count
	SES	Socioeconomic quintile attributed to patient on the basis of his/her census data and postal code	Ordinal	Very low SES, low SES, middle SES, high SES, very high SES	Quintile
	Prior hospitalisations	Number of hospital admissions experienced by a patient in the 12 months preceding a PIP	Continuous	0 to unlimited	Count
	ER visit in past 6 months	Number of visits made to the emergency room by a patient in the 6 months preceding a PIP	Continuous	0 to unlimited	Count
	Comorbidities	Deyo modification of Charlson Comorbidity Index for a patient calculated at the time of first PIP, if patient was hospitalised in the year prior to the first PIP; for patients who were not hospitalised, we will use the Johns Hopkins ADG score	Continuous	0–32	NA

Continued

Table 1 Continued

Category	Variable name	Definition	Scale	Valid range/levels	Units
	Acuity of prior hospitalisations	Whether a hospitalisation occurring in the 12 months preceding a PIP was coded as 'acute' or not in the Discharge Abstract Database	Dichotomous	Acute vs other	1 if acute 0 if other
	Discharge diagnosis	Most responsible diagnosis for a hospitalisation occurring in the 12 months preceding a PIP as recorded in the Discharge Abstract Database	Categorical	ICD groups	Diagnostic groups
	Prescribing physician age	Physician age	Continuous	20 to ??	years
	Prescribing physician sex	Physician's biological gender	Dichotomous	Male or female	Male or female
	Prescribing physician year of graduation	Physician year of graduation	Ordinal	1945 to ??	Year (date)
	Prescribing physician location	Physician location of practice (rural vs urban)	Dichotomous	Rural vs urban	0 rural, 1 urban
	Type of prescribing physician	Type of physician prescribing a PIP for a given patient	Dichotomous	Specialist vs family physician	Specialist or family MD

ADE, adverse drug event; ADG, Aggregated Diagnostic Group; ER, emergency room; ICD, International Classification of Disease; NA, not available; PIP, potentially inappropriate prescribing; SES, socioeconomic status.

ICES-derived cohorts as appropriate. Three members of our team (a pharmacist (RH), a physician/epidemiologist (LMB) and a data analyst (ChC)) will identify this subset of criteria using an iterative process. They will assess the updated 2014 STOPP/START and 2012 Beers' criteria for applicability to Ontario/ICES health administrative data, codify them using appropriate diagnostic (ICD—International Classification of Disease) and medication (DIN) codes, and convert them to SAS code for use with ICES data. The resultant criterion selection and coding will be reviewed by all co-authors and approved by an iterative discussion and consensus process.

Primary outcome

Because ADEs are frequently under-recognised during ED visits and hospitalisations,[36 37] our study cohort is also subject to substantial underestimation of ADEs. We have therefore chosen to focus on reliably documented clinical events, namely ED visits, hospitalisation and death as our main outcome events, even though we recognise that not all will be causally related to a PIP. We will control for this using multivariate methods. The primary study end point is the time from the first PIP ever (during the accrual period) for any STOPP/START or Beers' criterion to the first PIP-related event, which is defined as the first all-cause ED visit, hospitalisation or death occurring within 3 months after this PIP.

In secondary analyses, we will look at time to outcomes following first PIPs for individual criteria, which means that patients can have more than one PIP-related event (one for each criterion they fulfil; see figure 3). Each type of PIP-related event (ie, ED visits, hospitalisations and deaths) will also be considered as a separate outcome and ADEs-related outcomes will be identified using diagnostic codes. ED visits will be determined from the NACRS database, hospitalisations from the DAD database and death will be determined from the RPDB. The relationship between these events and time intervals is illustrated in figure 3, together with a few examples of possible patient scenarios.

If the PIP includes a time-dependent definition (eg, 'NSAID use >3 months'), the observation window will be extended by 3 months beyond the specified minimum exposure (thus, the outcome observation window would be 6 months in the above example).

Censoring

Patients will be censored if they die or move out of the province without experiencing an event, and their move is captured by the RPDB. For the observation window following an instance of PIP, we have chosen a 3-month cut-off since we anticipate that the potential influence of an instance of PIP would not likely last longer than this, and probably would be shorter. If a patient experiences an event other than death (ie, an ED visit or hospitalisation), that patient will be censored for the duration of that event, but will remain in the study cohort after discharge from the ED or hospital, as he/she may contribute further instances of PIP to the study base.

Covariates

Our analyses will control for the following covariates, which are either known or perceived to be associated with PIP and subject to their availability in the provincial

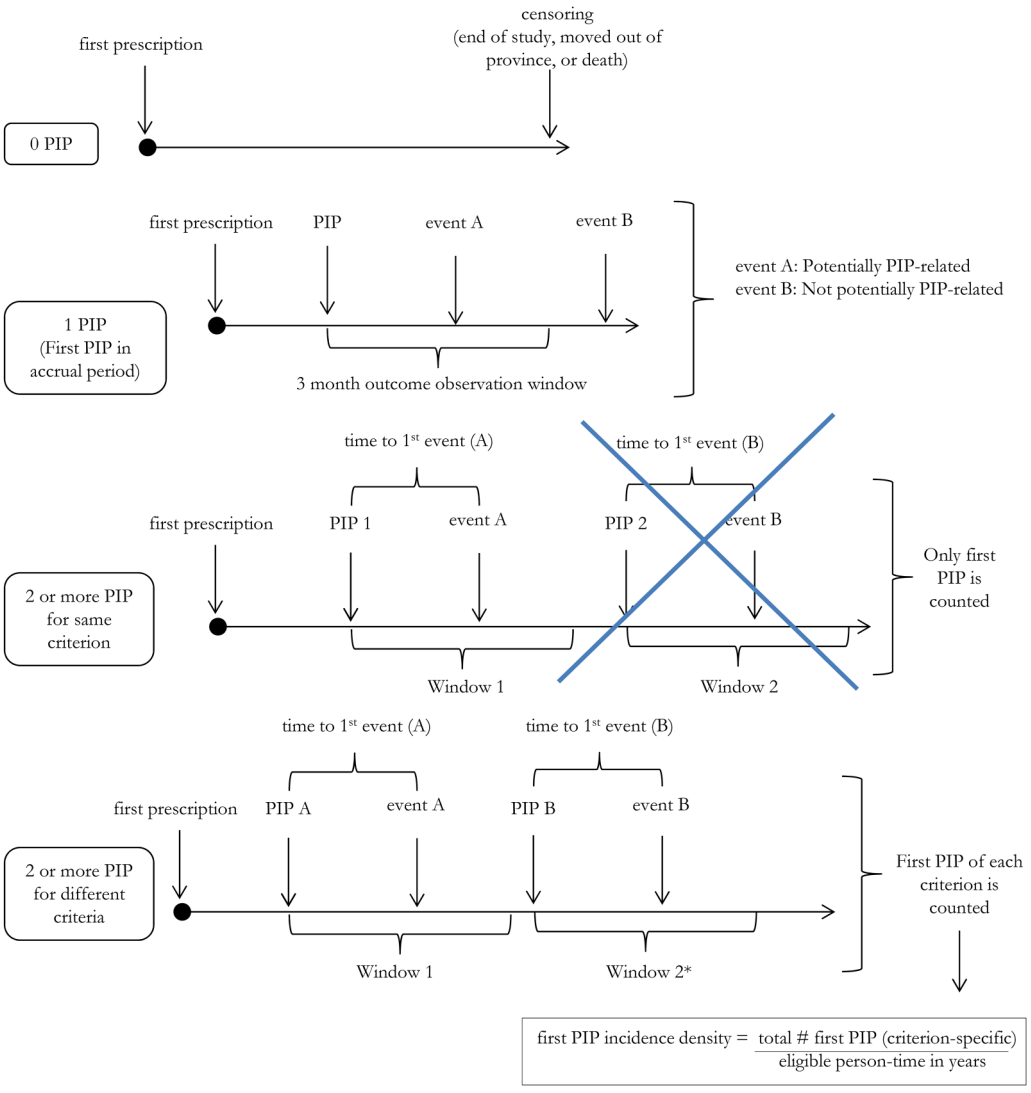

Figure 3 Time-to-event as a function of potentially inappropriate prescribing (PIP): possible patient scenarios, definition of eligible exposure and of outcome observation time window.

health administrative databases (table 1 for a full list of variable definitions): patient age, prescribing physician sex, type of physician (specialist vs family physician), physician year of graduation, practice location (urban vs rural), whether a patient has a regular family physician, number of prescribers in the year prior to a PIP,[13] number of dispensing pharmacists during study eligibility period, patient location (long-term care vs community setting)[16] and polypharmacy (number of drugs used concurrently by one patient at the time of prescription of a PIP).[38–42] Other patient-level factors known or suspected of being associated with unplanned hospital admissions and ED visits will also be included in the analyses as covariates: age,[43 44] sex,[44] socioeconomic status (SES),[44 45] rurality, comorbidity[44 46 47] (calculated using the Deyo modification[48] of the Charlson's Comorbidity Index (CCI)[49]), Johns Hopkins Adjusted Clinical Groups (ACG) system,[50] number of ED visits in 6 months prior to a PIP, number of prior hospitalisations in the 12 months preceding a PIP,[43 44 46 51–55] and whether a patient has had a MedsCheck or Pharmaceutical Opinion assessment performed in year prior to first PIP. We will use the postal code conversion file to link the patient's postal code to the dissemination area, which is the smallest geographical census unit that exists across all of Canada. We will then use census data to determine the median household income of each dissemination area, which we will use as a proxy for individual SES. Linear interpolation will be used to infer income for non-census years.

Statistical analyses

In order to address each of our three hypotheses, we will fit multivariable regression models. We will retain all of the prespecified covariates in the model regardless of statistical significance, and we will validate our fitted models using modern bootstrap validation methods to assess predictive performance and protect against overfitting.[56]

The 'skeleton' tables of expected results for each of the three hypotheses are shown in online supplementary appendices A–C, respectively. In accordance with standard ICES procedures, data cell sizes containing fewer than five counts will not be reported to protect confidentiality.

Hypothesis 1: Instances of PIP are frequent and costly.

We will describe the characteristics of the study cohort using the parameters described in online supplementary table 1A. To test hypothesis 1, we will first apply the STOPP/START and Beers' criteria subset (as defined in the 'Exposure variable' section above) to our data by identifying the occurrence of the first PIP ever, and also, in secondary analyses, by calculating the first criterion-specific PIP incidence density (see online supplementary table 1B), and make comparisons to other studies that used STOPP/START and Beers. Subgroup analyses will be conducted to estimate PIP incidence density in long-term care and ambulatory patients (see online supplementary table 1B), as these individuals are particularly vulnerable to PIP.[57]

We will estimate the annual attributable risk[58] of adverse events by grouping patients' first PIP incidence density (no PIP (reference), ≤1 PIP/year, 1≤2 PIP/year, 2≤3 PIP/year, 2≤3 PIP/year), and calculate HRs for each group (see online supplementary table 1C). Patients who did not experience a PIP will serve as the reference category. We will apply the HRs for each group to the proportion of the population attributable to that group, using the frequency of events in the reference category as a baseline. This will yield an estimate of the frequency of adverse events attributable to PIP, a quantity that can also be expressed as an annual number of adverse potential PIP-related events experienced by Ontario seniors. We will conduct this calculation using all primary and secondary outcomes.

To estimate the overall cost of PIPs, we will combine direct medication-related and direct non-medication (healthcare utilisation)-related costs (see online supplementary table 1D). Medication-related costs will be calculated by aggregating all medications costs (including medication costs and dispensing fees) associated with each PIP in the study cohort. In instances where a PIP involves more than one drug, only the cost of the cheaper drug will be included, yielding a conservative estimate; if a PIP involves the use of a high-dose drug (with low-dose not considered a PIP), then we will consider only the difference in price between high and low dose as a potential saving. Healthcare utilisation costs (direct non-medication costs) will include the costs of ED visits and hospitalisations that are attributable to each PIP, as defined above by the attributable risk.

Hypothesis 2: ED visits and hospitalisations are significantly associated with PIP.

To test this hypothesis, we will use two complementary approaches. First, a logistic regression will be performed to assess the association between the occurrence of a first PIP ever and the likelihood of PIP-related events. The reference category for this step will be '0 PIP'. Second, a time-to-event analysis will be carried out to address the following question: among patients experiencing PIP, does the likelihood of a PIP-related events depend on the total number of first PIPs by criteria occurring before a given event? We will use '1' as a reference category for this step. We will control for covariates known or suspected of being associated with PIP (see Covariates section above) by including them in our models. Additional analyses that may be conducted, if applicable (tables not shown): instrumental variables regressions to adjust for potential unmeasured confounders, hierarchical models to address clustering, and sensitivity analyses with different suboutcomes (time to ED visit, time to hospitalisation, time to death, time to ADE).

Hypothesis 3: The likelihood of inappropriate prescribing is associated with patient and physician characteristics.

To test this hypothesis, we will identify each physician's PIP incidence density, calculated by dividing the number of first PIP per patient they issued by the total number of first prescriptions they provided over the study period and then use a multilevel model to explore the association of patient-level and physician-level covariates with incidents. We will use intracluster correlation coefficients to estimate the variation in PIP prescribing across prescribers and to identify which covariates may explain this variation (see online supplementary table 3A).[59]

Next, we will perform a multivariate linear regression to describe provider and patient characteristics associated with first PIP incidence density (see online supplementary table 3B), which will be ranked and categorised into deciles and will act as the dependent variable, with prescriber and patient characteristics serving as independent variables. We expect to find that certain patient characteristics (eg, age, number of prescribers) and prescriber characteristics (eg, rurality, sex, age) are significantly associated with PIP density, as identified in previous studies.[13]

Finally, we will describe the distribution of first PIP incidence density and then use a multilevel model to explore the association of patient-level and physician-level covariates and patient outcomes (ED visits, hospitalisations and mortality).

Cohort size and power

Dispensation of a first prescription represents a patient's point of entry into our study population. Every year in

Ontario, over 50 million prescriptions are dispensed and recorded in the ODBD.[35] The Ontario population in 2006 (mid-way through our study period) was approximately 12 600 000,[60] of which about 14% were seniors,[2] corresponding to 1 680 000 seniors. Given that this is a dynamic population, with additions through ageing of the population and patients moving into the province, and losses through deaths and emigration, the actual number of seniors in the database can be expected to be higher, around 2–2.5 million patients. Given an average annual number of medications per senior of 6.7,[2] this would translate into approximately 13 million medications being prescribed under ODB per year (with more prescriptions, since there may be more than one prescription for the same medication). Given our 10-year accrual period (1 April 2003 to 31 March 2013), we could expect to have access to a total of over 130 million different instances of medications dispensed to individual patients, and even more prescriptions.

As for event rates, applying a rate of PIP of 22% in primary care found in earlier studies[16] would result in about 500 000 elderly patients experiencing PIPs per year in Ontario (based on an estimated seniors population of about 1.6 million). Since some patients will experience more than one type of PIP during the study accrual period, the number of eligible observations will be greater.

This large cohort size, in terms of patients, number of prescriptions and PIPs, ensures high statistical power to detect any effect of even minor clinical importance. However, we are in fact conducting a census of all eligible patients—as opposed to sampling a population—rendering a power calculation of little value. Nonetheless, even if this represented a population sample, we would have more than 90% power for the vast majority of our planned analyses.

ETHICS AND DISSEMINATION

Registration

This cohort study is registered with clinicaltrials.gov (registration number: NCT02555891)

Dissemination

Dissemination will occur via publication, presentations at national and international conferences, professional networks, and ongoing exchanges with regional, provincial and national stakeholders, including the Ontario Drug Policy Research Network and the Ontario MOHLTC.

Statement of originality

To the best of our knowledge, the association of PIP with patient outcomes, prescriber characteristics and healthcare utilisation has not been studied in such a large population-based study in any jurisdiction. Ontario's extensive holdings of linked health administrative databases provide a unique opportunity to examine the effects of PIP on a large scale.

Anticipated limitations

Our study is subject to several limitations inherent in studies relying on health administrative data. We cannot guarantee that patients regularly took the medications dispensed to them, or that they adhered to the guidelines for their use. Adherence to treatment can only be assessed by comparing the date when an original prescription was scheduled to expire with the dispensation date of the renewal prescription. Some over-the-counter medications included in the STOPP criteria subset (eg, low-dose acetylsalicylic acid (ASA)) as well as medication not covered by ODB plan (eg, sildenafil—Viagra) are not recorded in the ODBD and thus cannot be included. It is also possible that some PIP identified by the STOPP criteria subset in our database would actually be considered appropriate were clinical or diagnostic data available to support their use.[61] That said, we anticipate that some laboratory values housed in Ontario's Laboratory Integration System (OLIS) will become available to researchers using ICES data within the coming year or two. We expect that this will enable us to expand the subset of STOPP/START and Beers' criteria applicable to health administrative data.[62] Despite these limitations, we are confident that our study will produce useful estimates of the occurrence of PIP in Ontario's senior population, enable us to assess the health outcomes and health system costs associated with PIP, and help evaluate an existing measure aimed at mitigating its effects.

Safety and confidentiality considerations

Our study will make use of previously collected data, and will not require any additional intervention or data collection at the patient level. This study will be conducted using Ontario health administrative databases housed at the ICES, accessed from the ICES@uOttawa site. ICES is an independent, non-profit organisation whose infrastructure funding and access to Ontario's large administrative databases is provided by the Ontario MOHLTC. ICES links de-identified population-based health information at the patient level in a way that ensures privacy and confidentiality of patients. ICES is named as a section 45(1) Prescribed Entity in Ontario's Personal Health Information Protection Act (PHIPA). Review, audit and approval of ICES' policies, practices and procedures related to data privacy and security are performed triannually by the Information and Privacy Commissioner of Ontario (IPC). This approval/review document is available at http://www.ipc.on.ca. All of these data sets are linked using a patient-specific encrypted identifier. This linkage is deterministic and does not require any probabilistic methods. As per usual ICES procedures, cell sizes <5 will not be reported to address concerns about possible breaches in confidentiality.

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Contributors LMB conceived of the idea for this project, wrote the original grant application (see online supplementary appendix E), updated and adapted it to fit the requirements of the present protocol; she also generated all the tables in the present manuscript, as well as in the online supplementary material appendices. TR, CaC, CR, RH, BF, KT, ChC, SH, UG and DGM provided expertise in their respective fields, all reviewed the manuscript for important intellectual content and made suggestions for improvement as appropriate; furthermore, they all approved the final version of the manuscript for submission.

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Competing interests CaC is the author of the study that applied a subset of the 2008 STOPP criteria to an Irish prescription database.[9] CR is a co-author of the original STOPP/START criteria.[20 21]

Competing interests None declared.

Ethics approval Ottawa Health Services Network Ethical Review Board and BruyereBruyère Research Institute Ethics Review Board (see online supplementary appendix D).

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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Online appendix A. Skeleton tables for hypothesis 1

Table 1a. Characteristics of study cohort

CHARACTERISTIC	Had at least 1 PIP during accrual period (N=)	Had no PIP during accrual period (N=)	OVERALL cohort (N=)
PREDICTORS/COVARIATES			
Patient characteristics:			
Mean age (SD)			
Sex (reference: female)			
Charlson Comorbidity Index >1 or ADG			
Number of concurrent meds at time			
≥1 acute admissions in year prior to 1st PIP			
≥1 elective admissions in year prior to 1st PIP			
≥1 ED visits in 6 months prior to 1st PIP			
Income quintile			
1			
2			
3			
4			
5			
Missing			
Place of residence (reference: rural)			
Number of prescribers in the year prior to first PIP			
Number of dispensing pharmacists in the year prior to first PIP			
Prescriber characteristics:			
Prescribing physician age (mean; range)			
Prescribing physician sex (reference: female)			
Prescribing physician year of graduation			
Prescribing physician location (reference: rural)			
Type of prescribing physician (reference: family physician)			
EXPOSURE			
First criterion-specific PIP counts per patient for all criteria			
• STOPP/START			
• Beers			
Average annualized first PIP counts by criteria per patient per year (also known as "First criterion-specific PIP incidence density") (n total per year)			
OUTCOME			
Any outcome			
>1 ER visit after 1st PIP			
>1 hospitalization after 1st PIP			
Number of ADE diagnostic codes after 1st PIP			
Death after 1st PIP			

SD = standard deviation, IQR = interquartile range, ED = emergency department

* Not used as an outcome in the analyses

Table 1b. Average annual incidence density by patient characteristics (crude rates)

		Number of first criterion-specific PIP experienced by all patients in cohort	Total person-time in cohort	First criterion-specific PIP incidence density (n total per year)
Total cohort (number of patients)				
Ambulatory patients				
Long-Term Care patients*				
Sex	Males			
	Females			
Income	Q1 (lowest -reference)			
	Q2			
	Q3			
	Q4			
	Q5 (highest)			
Age	66-70 years			
	71-75 years			
	76-80 years			
	81-85 years			
	86-90 years			
	>90 years			

Key: PIP: Potentially inappropriate prescribing

* The same patient may contribute person-time to both ambulatory and long-term groups if they were admitted to a long-term care facility during the study.

Table 1c. Calculation of attributable risk due to PIP (unit of analysis is the patient, each patient appears in only one exposure category)

Exposure category (PIP incidence density)	**Person-years per exposure category**	**Hazard ratio for dependent variable, transcribed from Table 2a (column B)**	**Frequency (%) of patient outcomes (ED visits, hospitalizations and deaths/patient-year)**	**Estimated frequency of adverse events potentially attributable to PIP/year**
No PIP (ref)			()	
<=1 PIP/year			()	
1<=2 PIP/year			()	
2<=3 PIP/year			()	
3>PIP/year			()	
Total person-time				
Total frequency of potentially PIP-related ADEs (n)				

Table 1d. Direct cost attributable to PIP, based on an attributable risk approach.

	Total costs over the study period (in 2015 Canadian dollars)	Proportion attributable to PIP (from Table 1c, column 5) (=weighted average of risk of all four PIP categories)	Study period (person-time)	PIP-attributable cost/person-year
Medication related costs (direct medication costs)				
Health care utilization costs (non-direct medication costs)				
ED visits				
Hospitalizations				
Total costs (direct + non-direct)				

Online appendix B. Skeleton tables for hypothesis 2

Table 2a. Skeleton table of planned analyses for Hypothesis 2

	A. Cox proportional hazards model of the association between first PIP and adverse patient outcomes (unit of analysis is the PIP, patients may contribute more than one PIP)	**B. Multivariable models with exposure expressed as number of PIP during total patient eligibility period, annualized; unit of analysis is the patient, each patient is attributed to one single stratum)**				
		No PIP (ref)	<=1 PIP/yr	1<=2 PIP/yr	2<=3 PIP/yr	3>PIP/yr
Number of patients on which each model is based	n=	n=	n=	n=	n=	n=
	Hazard ratio (HR) (95% confidence interval)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Dependent variable: Time from first PIP to any potentially PIP-related patient outcome (ED visit, hospitalization or death) (days)		1 (or indeterminate)				
Independent variables:						
Physician Characteristics						
Physician age (years)						
Physician sex (male or female (ref=female))						
Physician year of graduation (date)						
Physician location (rural (ref = 0) vs urban)						
Patient has a regular family physician (ref = no)						
Type of physician						

prescribing a PIP for a given patient (specialist or family MD (ref=family MD))						
Patient Characteristics						
Patient age (years)						
Patient sex (male or female (ref=female))						
Patient location (Long-term care vs community setting (ref=community))						
Number of prescribers in 12 months preceding first PIP (n)						
Number of dispensing pharmacists in 12 months preceding first PIP (n)						
Polypharmacy (Number of medications concurrently in use at time of prescription of a first PIP)						
Socioeconomic status (Socioeconomic quintile attributed to pt. on the basis of his/her census data and postal code; ref= highest quintile)						
Prior hospitalizations (number of hospital admissions experienced by a patient in the 12 months preceding first PIP)						
Number of ED visit in past six months preceding first PIP						
Comorbidities (Deyo modification of Charlson comorbidity index for a patient						

calculated at the time of first PIP)						
Acuity of prior hospitalizations (whether a hospitalization occurring in the 12 months preceding first PIP was coded as "acute" or not in the Discharge Abstract Database; 1 if acute, 0 if other; ref=0)						
Diagnosis of a hospitalization occurring in the 12 months preceding first PIP as recorded in the Discharge Abstract database (dummy variable)						
Patient has seen a geriatrician in year prior to first PIP (no=0 (ref), yes=1)						
Patient has had MedsCheck or Pharmaceutical Opinion performed in year prior to first PIP (no=0 (ref), yes=1)						

Online appendix C. Skeleton tables for hypothesis 3

Table 3a. Assessing PIP Clustering

	Physician PIP density range (PIP/100 prescriptions) in deciles	**Number of physicians per decile**	**Proportion of physicians per decile**
Decile 1 (lowest PIP density -- best prescribing)	0 to unlimited		
Decile 2			
Decile 3			
Decile 4			
Decile 5			
Decile 6			
Decile 7			
Decile 8			
Decile 9			
Decile 10 (highest PIP density -- worst prescribing)			

Table 3b. Multivariable regression to describe provider and patient characteristics associated with physician PIP density

Variables	**Relative risk (95% confidence interval)**
Dependent variable:	
Physician PIP density (no. PIP/100 prescriptions /physician)	
Independent variables:	
Physician characteristics	
Physician age (years)	
Physician sex (male or female (ref=female))	
Physician year of graduation (date)	
Physician location (rural (ref = 0) vs urban)	
Type of physician prescribing a PIP for a given patient (specialist or family MD (ref=family MD))	
Patient characteristics	
Patient age (years)	
Patient sex (male or female (ref=female)	

Patient location (Long-term care vs community setting (ref=community))	
Number of prescribers in the year prior to first PIP	
Number of dispensing pharmacists in the year prior to first PIP	
Polypharmacy (Number of medications concurrently in use at time of prescription of a PIP)	
Socioeconomic status (Socioeconomic quintile attributed to pt. on the basis of his/her census data and postal code; ref=highest income quintile)	
Prior hospitalizations (number of hospital admissions experience by a patient in the 12 months preceding a PIP)	
Number of ED visit in past six months preceding first PIP	
Comorbidities (Deyo modification of Charlson comorbidity index for a patient calculated at the time of first PIP)	
Acuity of prior hospitalizations (whether a hospitalization occurring in the 12 months preceding first PIP was coded as "acute" or not in the Discharge Abstract Database; 1 if acute, 0 if other (ref))	
Diagnosis of a hospitalization occurring in the 12 months preceding first PIP as recorded in the Discharge Abstract database (dummy variables)	

Online appendix D: Ethical approval letters

Ottawa Hospital Research Institute
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April 10, 2015

Dr. Lise Bjerre
Elisabeth Bruyere Research Institute
CT Lamont Primary Health Care Research Centre
43 Bruyere St
Ottawa, ON K1N 5C8

Dear Dr. Bjerre:

RE: Protocol# - 20130161-01H **Assessing Potentially Inappropriate Prescribing (PIP) and predicting patients outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)**

Renewal Expiry Date - April 9, 2016

Thank you for your e-mail of April 10, 2015I am pleased to inform you that your Annual Renewal Request was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the protocol without the OHSN-REB's review and approval.

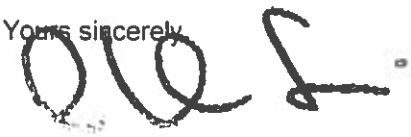
The projected date of study completion was extended to March 31, 2017.

Kednapa Thavorn and Steven Hawken have been added as Co-Investigators.

Renewal is valid for a period of one year. Approximately one month prior to that time, a single renewal form should be sent to the REB office.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,



Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board
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Affilié à / Affiliated with

uOttawa

March 26, 2015

Dr. Lise Bjerre
Clinical Investigator, Assistant Professor
Bruyère Research Institute
CT Lamont Primary Health Care Research Centre

RE: Assessing Potentially Inappropriate Prescribing (PIP) and predicting patients outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study).
(Bruyère Continuing Care REB Project # M16-13-020)

Renewal/Extension Approval

Dear Dr. Bjerre,

Thank-you for submitting the Annual Project Update form for the above named study.

The Bruyère Continuing Care Research Ethics Board is pleased to extend ethical approval for the above-named project as requested from April 24, 2015 to April 24, 2016.

We wish you best of luck as you proceed with this study.

Sincerely,

Dorothy Kessler, M.Sc., O.T. Reg (Ont), PhD Student
Chair
Research Ethics Board
Bruyère Continuing Care
(613) 562-6262 ext 1420
dkessler@bruyere.org

cc: Cody Black

Online appendix F: CIHR Grant application and funding confirmation

This work was supported by the Canadian Institutes of Health Research (CHIR), grant number 287245-HPM-BRUY-46830. The original grant application as well as the notice of funding are included in this appendix.

Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

AUTHORIZATION FOR FUNDING

CIHR (Canadian Institutes of Health Research) has approved funding as detailed below. Subject to the approbation of funding by Parliament, these funds will be made available to the business officer at the indicated institution for disbursement.

AUTORISATION DE FINANCEMENT

IRSC (Instituts de recherche en santé du Canada) vous accorde les fonds tel qu'indiqué ci-dessous. Suivant l'affectation des crédits par le Parlement du Canada, les fonds seront mis à la disposition du trésorier de l'établissement indiqué qui s'occupera des versements.

201209MOP-287245-HPM-BRUY-46830

12/02/2013

Institution Paid/Établissement chargé d'administrer les fonds: Bruyère Research Institute

Recipient(s)/Bénéficiaire(s): BJERRE, Lise

Bruyère Research Institute

Program/Programme: Operating Grant
Grant New

Primary Institute/Institut principal: Health Services and Policy Research

Project Title/Titre du projet:

Assessing Potentially Inappropriate Prescribing (PIP) and predicting patient outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)

Co-investigator(s) & Associates/Supervisor(s)/Host/Co-chercheur(s)/Directeur(s) de recherche/Hôte:

Dr. Roland HALIL, Dr. Timothy Owen RAMSAY, Dr. Douglas G. MANUEL, Dr. Caitriona CAHIR

PAYMENT DETAILS/DÉTAILS DES VERSEMENTS

Funding Reference Number/
No. de Référence du financement: **MOP — 125861**

Period / Période	Type	Amount by Type / Montant par type	Total by Fiscal Year / Total par exercice	
01/01/2013 to 31/03/2013	Operating	$12,000	$12,000	2012-13
01/04/2013 to 31/03/2014	Operating	$48,000	$48,000	2013-14
01/04/2014 to 31/03/2015	Operating	$72,451	$72,451	2014-15
01/04/2015 to 31/03/2016	Operating	$60,000	$60,000	2015-16

Progress Report Required:
Rapport des progrès réalisés requis: **Not Applicable**

Application to Renew Funding Required:
Demande de renouvellement des fonds requis: **15/09/2015**

NOTES:

Operating funds approved for payment in fiscal year 2012-13 represent 3/15 of the first year of approved Operating funding - the balance of the Operating funds of the first year of approved funding (12/15) will be paid in fiscal year 2013-14.

If you are in receipt or become eligible to receive any funding from another source for any part of this project you must advise CIHR immediately by following the instructions outlined in the "Funding Overlap Declaration" form http://www.cihr-irsc.gc.ca/e/797.html. Failure to self-declare overlap could lead to CIHR cancelling all funding related to this grant.

CIHR requires that its contribution to your research project be acknowledged in all written and oral presentations of your research results, including scientific articles, news releases, news conferences, public lectures and media interviews. Please see CIHR's Guidelines on Public Communication which are enclosed for more information on public communication and acknowledgement requirements.

You received this funding because your colleagues volunteered their time to assist CIHR with the review of your application. We ask that, as a recipient of CIHR funding, you will participate in CIHR peer review activities if invited.

By drawing on the funds provided through this grant/award you agree to the terms and conditions set out in the attached "Conditions of Funding", any breach of which may result in CIHR taking remedial action as described therein.

Following CIHR's implementation of the Research Reporting System, you will be required to submit an electronic Final Report on ResearchNet for this grant. You will be provided with instructions through an email notification from the ResearchNet system once the activity becomes available.

Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

PROTECTED WHEN COMPLETED

Appl. # 287245

Application Details

Funding Opportunity:
Operating Grant: 2012-2013 (2012-09-17)

Proposed Start Date:

Proposed End Date:

Nominated Principal Applicant/Candidate:

Surname: BJERRE

Given Names: Lise

Institution: Bruyère Research Institute/Institut de recherche Bruyère

Faculty:

Department:

Telephone: 613-562-6262 ext.1284

Fax:

E-mail: lbjerre@bruyere.org

Project Title:
Assessing Potentially Inappropriate Prescribing (PIP) and predicting patient outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)

Primary location where research to be conducted: Bruyère Research Institute/Institut de recherche Bruyère

Faculty:

Department:

Institution which will administer project funds (Institution Paid):
Bruyère Research Institute/Institut de recherche Bruyère

Location of proposed Activity:

Period of support requested: 3 **Year(s)** _____ **Month(s)**

THE FOLLOWING SECTIONS ARE NOT APPLICABLE TO ALL PROGRAMS

Budget section - Amounts Requested from CIHR in the First Full Year:
Operating: 63354 Equipment: 0 Total Amount Requested: 63354

☑ New ☐ Renewal Funding Reference Number (FRN):

Is this application a resubmission of a previously unsuccessful new application? ☑ Yes ☐ No

Is this application a resubmission of a previously unsuccessful renewal application? ☐ Yes ☑ No FRN #:

Have you applied to this program in the last two years? ☐ Yes ☐ No

Is this a multi-center study? ☐ Yes ☑ No

*** For Administrative Purposes Only**

RN #: 173076

Certification Requirements:

☐ Human subjects ☐ Human stem cells ☐ Animals ☐ Biohazards

☐ Environmental Impact ☐ Containment Level _____

☐ Clinical Trial

☐ Contains a randomized trial

☐ In order to carry out the proposed research in this application, an exemption from Health Canada under Section 56 of the Controlled Drugs and Substances Act is required. Should my application be approved, I understand that I will need to seek an exemption from Health Canada and provide this exemption to CIHR before any funding will be released for this application.

Other Project Information:

☐ For statistical purposes, does this application propose research involving Aboriginal people?

☑ Are sex (biological) considerations taken into account in this study?

☑ Are gender (socio-cultural) considerations taken into account in this study?

Please describe how sex and/or gender considerations will be considered in your research proposal:

The sex of the patient will be entered as a variable in all our analyses. We will examine the combined effects of sex, socio-economic status, and age, which, in combination, can be a proxy for gender effects in administrative data. This will enable us to assess whether sex and gender are associated with differences in the frequency of adverse drug events.

Request to be considered for the following Priority Announcements/Funding Pools*:

Relevant Research Area:	Title of the Priority Announcement/Funding Pool:
Aging (Bridge Funding)	Aging (Bridge Funding)

Linked Programs:

RELEVANCE FORM | FORMULAIRE DE PERTINENCE

Title of Research Proposal l Titre de la proposition de recherche :

Assessing Potentially Inappropriate Prescribing (PIP) and predicting patient outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)

Relevant Research Area |Thème de recherche pertinent *:*	**Title of Priority Announcement/Funding Pool | Titre de la demande d'Annonce de priorités/Classe de financement :**
Aging (Bridge Funding)	Aging (Bridge Funding)

Description | Description :

Adverse drug events (ADE) are common in the elderly, who are particularly vulnerable to them due to changes in their physiology that occur with aging and disease. Many of these adverse drug events are avoidable if due attention is directed toward identifying and preventing inappropriate drugs and undesirable drug combinations. The PIP/STOPP study will use the modified Screening Tool of Older Persons' for potentially inappropriate Prescriptions (STOPP) criteria and Ontario health administrative databases to assess the impact of inappropriate prescribing on individual patients as well as on the health care system.

The study will describe the occurrence of potentially inappropriate prescribing (PIP) in Ontario's elderly (>65 years) population, assess the health and economic burden associated with it, and evaluate a measure aimed at mitigating its effects. Identifying significant associations could provide evidence to support important policy interventions aimed at effectively reducing PIP and its consequences.

By pursuing research designed to reduce inappropriate prescribing in elderly populations, this study is particularly relevant to promoting healthy and successful aging, health services and policy relating to older people, as well as aging and maintenance of functional autonomy. With better prescribing and fewer adverse drug events, elderly people are more likely to spend more time in good health.

Other Applicants

Surname	Given Names	Role
CAHIR	Caitriona	Co-Applicant
Institution	**Department**	**Faculty**
Royal College of Surgeons in Ireland (UK)		

Surname	Given Names	Role
HALIL	Roland	Co-Applicant
Institution	**Department**	**Faculty**
Élisabeth Bruyère Health Centre (Ottawa)/Centre de santé Élisabeth-Bruyère		

Surname	Given Names	Role
MANUEL	Douglas	Co-Applicant
Institution	**Department**	**Faculty**
Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa		

Surname	Given Names	Role
RAMSAY	Timothy	Co-Applicant
Institution	**Department**	**Faculty**
Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa		

Surname	Given Names	Role
Institution	**Department**	**Faculty**

Surname	Given Names	Role
Institution	**Department**	**Faculty**

Surname	Given Names	Role
Institution	**Department**	**Faculty**

Surname	Given Names	Role
Institution	**Department**	**Faculty**

Lay title of the research
Estimating the health and economic effects of potentially inappropriate prescribing in Ontario's elderly population

Abstract suitable for preparation of a press release
The elderly are at a higher risk than the rest of the population for adverse drug reactions. This is due to high numbers of medications prescribed per person, increasing numbers of prescribers as well as the elderly's greater sensitivity to medication effects due to natural age-related changes in the way the body deals with medication. Emergency room visits and unplanned hospital readmissions amongst the elderly are commonly due to adverse drug reactions. Many of these are avoidable and a number of tools have been developed to identify potentially inappropriate medications, with varying degrees of success. This study will apply a novel and promising tool to health data kept by the Ontario Ministry of Health and Long Term Care. It is hoped this tool will identify instances where patients were prescribed inappropriate medications and will show links between inappropriate prescriptions and patient outcomes, such as ER visits and hospitalizations. This tool is usually used by looking at individual patient charts in family physician clinics, so it is hoped that by applying it to provincial data, the rates and costs of inappropriate prescribing can be estimated for the whole elderly population of Ontario.

Project Descriptors *
Inappropriate prescribing, Elderly patients, Health administrative data, Adverse drug events, Emergency room visits, Hospitalizations, Mortality, Medication cost, Health care resource use, Screening tool

Areas of Research *	**Classification Codes ***
Primary DRUG RESEARCH	Primary DRUGS- PHARMACEUTICAL SCIENCE/CHEMISTRY & NON MEDICAL USE OF DRUGS
Secondary AGING	Secondary AGING

Themes *	**Categories ***
1st Health systems/services	1st Health Services and Policy Research
2nd Clinical	2nd Aging
3rd Social/Cultural/Environmental/Population Health	3rd Population and Public Health
4th	4th

Suggested Peer Review Committees:

1st Health Policy & Systems Management Research	2nd

Suggested External Referee(s)*

Name	E-mail
Area of Expertise	
Name	E-mail
Area of Expertise	
Name	E-mail
Area of Expertise	
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Area of Expertise	

Background:

Adverse drug events are common in the elderly, and contribute significantly to emergency room (ER) visits and unplanned hospitalizations. Patients aged sixty-five and over currently represent over 14% of the Canadian population, yet spending on prescription medications by seniors accounts for over 40% of all retail prescription drug sales. This is equivalent to a per capita spending on prescription drugs by seniors that is three times the Canadian average. A recent Irish study showed that, of 600 elderly patients admitted to hospital for an acute illness, 25% of them had one or more adverse drug events, of which two thirds had contributed to the hospitalizations. Of these adverse events contributing to hospitalizations, 69% were deemed avoidable. A number of tools and strategies have been developed to identify potentially inappropriate prescribing (PIP), however, until recently, none of the commonly used tools had been shown to reliably predict adverse events. The STOPP/START criteria (Screening Tool of Older Persons' potentially inappropriate Prescriptions / Screening Tool to Alert doctors to Right Treatment)was recently compared to the long-standing Beers criteria, and found to detect adverse drug effects that are causal or contribute to hospitalization in elderly patients with acute illness 2.8 times more often than the Beers criteria.

The application of these criteria is usually done in a clinical context, which involves time-intensive and expensive chart reviews. There are relatively few studies looking at appropriateness of prescribing at the population level, using health administrative data. Applying tools to assess appropriateness of prescribing, such as the modified STOPP criteria, to health administrative data can provide a unique opportunity to assess both the frequency of potentially inappropriate prescribing and its associated costs, in terms of both medication and health services use at the population level.

Proposed Objective:

The overall objective of the present study will be to describe the occurrence of Potentially Inappropriate Prescribing (PIP) in Ontario's elderly (>65 yrs) population, assess the health and economic burden associated with it, and evaluate interventions aimed at mitigating its effects. To attain this objective, we will test four specific hypotheses: **Hypothesis 1**: *Instances of Potentially Inappropriate Prescribing are frequent and costly.* To test this hypothesis, we will apply the modified STOPP criteria to Ontario health administrative data to identify instances of potentially inappropriate prescribing, and estimate potential savings, both direct and indirect, that could be achieved by reducing inappropriate prescribing. **Hypothesis 2:** *An important proportion of ER visits and hospitalizations are associated with Potentially Inappropriate Prescribing*. To test this hypothesis, we will estimate the attributable fraction of ER visits and hospitalizations associated with different frequencies of PIP using multivariate methods and survival analysis. **Hypothesis 3:** *Inappropriate prescribing is attributable to a small number of prescribers.* To test this hypothesis, we will describe how frequently PIP instances occur for each prescriber, adjusted for prescribing volume. **Hypothesis 4:** *Interventions aimed at improving prescribing in primary care are effective in reducing Potentially Inappropriate Prescribing.* To test this hypothesis, we will compare the frequency of PIP instances for prescribers who have access to the services of a pharmacist with that of those who do not.

We will test these hypotheses in the framework a retrospective cohort study which we will conduct using Ontario's large health administrative and population databases. These are housed at the Institute for Clinical Evaluative Sciences (ICES) and contain information on both hospital and outpatient use of health services, as well as demographic and socioeconomic data. Patients included in the study will be all OHIP (Ontario Health Insurance Plan) eligible patients aged 65 yrs of age and older who have been issued at least one prescription between July 1st 2003 and December 31st 2010.

Our team, housed at ICES@uOttawa, has extensive experience and expertise with the analysis of these databases, and has the support and resources necessary to successfully carry out this study.

Assessing Potentially Inappropriate Prescribing (PIP) and predicting patient outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)

1. Introduction:

Patients aged sixty-five and over currently represent 14% of the Canadian population, yet spending on prescription medications by seniors accounts for over 40% of all retail prescription drug sales – three times the Canadian average[1]. Adverse drug events (ADE) are common in the elderly, who are particularly vulnerable to them due to changes in their physiology that occur with aging and disease[2], and ADE contribute significantly to emergency room (ER) visits, unplanned hospitalizations[3] and in-hospital morbidity and mortality[4]. A recent study showed that, of 600 elderly patients admitted to hospital for an acute illness, 25% of them had one or more ADE prior to hospitalization, of which two thirds had contributed to the hospitalizations[5]. Of these events, 69% were deemed avoidable.

Potentially inappropriate prescribing (PIP) is common in the elderly; its likelihood increases as patients are prescribed more drugs (polypharmacy) and it is often associated with increased costs[6-8]. A number of tools and strategies have been developed to identify PIP in clinical settings, however, until recently, none of the commonly used tools had been shown to reliably predict adverse events[9;10]. The STOPP/START criteria[11] (Screening Tool of Older Persons' potentially inappropriate Prescriptions / Screening Tool to Alert doctors to Right Treatment), which were recently developed by a multidisciplinary team of geriatricians, pharmacists, pharmacologists and primary care physicians, were compared to the long-standing Beers criteria[12;12-14], and found to detect adverse drug effects that are causal or contribute to hospitalization in elderly patients with acute illness 2.8 times more often than the Beers criteria[15].

There are relatively few studies looking at appropriateness of prescribing at the population level, yet population-level approaches using health administrative data have the potential of providing powerful tools to assess the impact of inappropriate prescribing on individual patients as well as on the health care system[6]. One study, published in 2002, applied the Beers criteria to Ontario health administrative data to assess the prevalence of PIP in patients newly admitted to nursing homes[15;16]. More recently, a study applied a modified version of the STOPP criteria to population-level health administrative prescription data to identify instances of potentially inappropriate prescribing (PIP), and estimate its cost[17]. The authors concluded that the total expenditures on PIP amounted to 9% of the overall drug expenditures of Ireland, yet the authors were not able to assess the association of inappropriate prescribing with patient outcomes (hospitalizations, mortality) and their associated costs, as these data were not available in their database.

Ontario possesses a unique set of linked health administrative databases containing drug, health services, socioeconomic and patient outcome data such as ER visits, hospitalizations, and death; these datasets offer unparalleled opportunities to prospectively assess both the frequency of inappropriate prescribing and its associated outcomes and costs for a whole population. In the present study, we will apply the modified STOPP criteria[17] to Ontario's population-wide health administrative data to **describe the occurrence of potentially inappropriate prescribing (PIP) in Ontario's elderly (>65 years) population, assess the health and economic burden associated with it, and evaluate a measure aimed at mitigating its effects.** Identifying significant associations could provide evidence to support important policy measures aimed at effectively reducing PIP and its consequences.

2. Background:

Validated drug utilization review tools:

A number of drug utilization review tools have been developed to assist pharmacists and physicians in assessing the appropriateness of a patient's drug regimen in the clinical context: the Beers criteria[12-14], the Improved Prescribing in the Elderly Tool (IPET)[18], the STOPP/START criteria[11], the HEDIS (based on the Beers criteria)[19], the Medication Appropriateness Index (MAI)[20], and the Assessment of Underutilization of Medication (AUM) index[21], as well as a number of adaptations of these tools[22]. These tools can be broadly categorized into two categories, "explicit" and "implicit"[23]. Explicit tools, such as the Beers, IPET, STOPP/START and HEDIS tools, employ clearly defined criteria in the form of drug lists, drug classes and prescribing indicators that enable an efficient drug review process and rely relatively little on clinical judgment and experience. Implicit criteria, such as the Medication Appropriateness Index (MAI) and Assessment of Underutilization of Medication (AUM), call for much more clinical judgment and therefore can be very time-consuming in their application[9], however, due to their thorough nature they are often considered the gold standard in drug reviews[24]. Because of their ease of use and objective approach, there has been a clear preference for explicit criteria in recent years. In the next paragraphs, we will review the main characteristics of drug utilization review tools relevant to this proposal.

Beers' criteria:

The Beers' criteria were the first explicit criteria to be published[12] and have become widely used, particularly in the United States, where they originated[9]. Originally developed for use in nursing home patients, the criteria were modified three times, in 1997[13], 2003[14] and 2012[25] and are now intended for use in all patients above 65 years of age. Despite their popularity, the Beers' criteria have been criticized for including obsolete medications, as well as medications no longer available outside the United States, particularly in Europe[5;8], though some of these issues have been addressed in the 2012 revision[25-28]. They have also been criticized for not being sufficiently inclusive of a number of common instances of PIP[5;9]. In particular, Beers only lists drugs to avoid, but does not include other categories of PIP, such as drug-drug and drug-disease interactions, drug duplications or under and over-use of medications[9]. Finally, Beers' criteria have not been shown to be associated with experiencing an adverse drug event (ADE), discharge to a higher level of care, or in-hospital mortality[29].

STOPP/START criteria:

Developed by a multidisciplinary team of geriatricians, pharmacists, pharmacologists and primary care physicians using a modified Delphi process, the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) / Screening Tool to Alert doctors to Right Treatment (START) criteria is a promising tool that includes not only drugs to avoid in the elderly, but also drug-drug and drug-disease interactions, drugs that increase risks of falls, as well as duplicate drug class prescriptions that should be avoided[9;24;30]. Furthermore, the 65 STOPP and 22 START criteria are grouped by physiological system (cardiovascular system, central nervous system, etc.), and each criterion is accompanied by a brief rationale as to why a particular medication or combination of medications is considered potentially inappropriate[30] (see appendix A for the full list of STOPP/START criteria).

The authors of the STOPP/START criteria conducted a study[5] to compare the ability of the STOPP/START and Beers criteria to identify PIP (as defined by the STOPP/START criteria – see Appendix A for the complete list) associated with serious, avoidable ADE (as defined by the WHO-Uppsala Monitoring Center Criteria[31]). They conducted a prospective study of 600 elderly patients admitted to hospital for an acute illness. They applied both the STOPP/START criteria and the Beers criteria to assess the patients' medication at admission for PIP, and evaluated whether ADE were causal or contributory to the admission. They found that ADE that were definitely or possibly avoidable and

simultaneously considered causal to the admission were 2.8 times more likely to be identified when the patient's medications were assessed than using the STOPP/START criteria than when using Beers criteria. Expressed in other terms, the STOPP/START criteria were shown to be significantly predictive of "serious avoidable drug events that cause or contribute to urgent hospitalizations"; the odds ratio (OR) for this association was 1.85 (95% confidence interval: 1.5 - 2.3)[5]. Furthermore, they found that, even after adjusting for a number of possible confounders, the likelihood of patients experiencing an ADE was almost 85% higher if they were prescribed a PIP listed in the STOPP criteria than if they were not, which was a significant difference. On the other hand, receiving PIPs listed in the Beers criteria did not increase a patient's chance of experiencing an ADE. The authors conclude that the STOPP/START criteria are significantly more sensitive than the Beers criteria to PIP resulting in ADE, and that the STOPP/START criteria are therefore more clinically relevant.

The STOPP/START criteria were also validated as an intervention tool to improve prescribing in hospitalized elderly (>=65 yrs) patients[30]. This was done in the context of a randomized controlled trial where 400 elderly hospitalized patients were randomized to receiving either "usual pharmaceutical care" while in hospital, or screening with the STOPP/START criteria followed by recommendations for modifications of their drug regimen made to their attending physician. Prescribing appropriateness was assessed at discharge and 6 months after discharge using the Medication Appropriateness Index (MAI) and the Assessment of Underutilization (AUM) Index, both implicit drug review tools that are considered gold standards. Both at discharge and at 6-month follow-up, the intervention group, whose medication had been screened using STOPP/START criteria, had significantly less polypharmacy, use of drugs at incorrect doses, and potiential drug-drug and drug-disease interactions than the control group. The "number needed to screen" to yield improvement was 2.8 for the MAI and 4.7 for the AUM, both being statistically significant.

The STOPP/START criteria have been applied in a variety of settings, and recent studies have shown that the proportion of patients with at least one PIP identified using the STOPP/START criteria varies from 22% in the primary care setting, to 35% in the acute care hospital and 60% in the nursing home setting[15].

In a comparative overview of recent developments in explicit drug review tools in the post-2003 Beers criteria era[23], Barenholtz-Levy and colleagues state that the STOPP/START criteria stand out among the explicit criteria "because, indeed, they are comprehensive, purposefully organized, and have greater potential for international applicability." They conclude their review by stating that "STOPP/START criteria are beginning to define their role in identifying and preventing inappropriate prescribing in older adults [...] continued research […] will help establish their role for clinicians worldwide and in various practice settings."[23]

Adapting drug utilization review tools for use with large health administrative databases:
Because they consist of a list of drugs, and do not rely on additional clinical data, such as indication or patient characteristics, the Beers criteria can be used with health administrative data relatively easily. This has been done in a number of studies[16;32-35], most of them focusing on nursing home patients.

More recently, the STOPP/START criteria were adapted for use with a health administrative prescription database in Ireland[17]. Because many of the criteria rely on clinical information, such as indication and co-morbidities, not all original STOPP/START criteria could be applied to health administrative data. An expert panel consisting of five members with expertise in geriatric pharmacotherapy, clinical pharmacology, pharmacoepidemiology and academic general practice determined which of the original STOPP/START criteria could be applied to pharmacy claims data

without the need to rely on diagnostic information[17]. This resulted in a short list of thirty criteria, which we thereafter refer to as the "modified STOPP criteria" (see Appendix B for full list of modified STOPP criteria). Except for one, none of the START criteria can be applied to health administrative data because they all require diagnostic information to be available (see Appendix A). For the purposes of the present study, PIP is defined as any one of the modified STOPP criteria[17] listed in Appendix B.

3. Deficiencies in our knowledge about the association of potentially inappropriate prescribing and patient outcomes assessed using large health administrative databases:

The START/STOPP criteria and the modified STOPP criteria are promising tools for the identification of PIP in elderly patients. Nonetheless, a number of questions remain unanswered, particularly with respect to their application to health administrative data. In this context, it remains to be established whether the modified STOPP criteria are predictive of relevant patient outcomes, such as the incidence of ADE, ER visits, hospitalizations, composite health care utilization, and mortality. Furthermore, it is not clear whether the modified STOPP criteria could help identify patient and prescriber characteristics associated with a high likelihood of PIP, which could become the target of interventions aimed at improving the quality of prescribing. Finally, it remains to be seen whether the modified STOPP criteria can be used to evaluate the effectiveness of existing measures aimed at improving prescribing quality.

4. Research Plan:

Overall objective and specific aims:

The overall objective of the present study will be to describe the occurrence of Potentially Inappropriate Prescribing (PIP) in Ontario's elderly (>65 yrs) population, assess the health and economic burden associated with it, and evaluate a measure aimed at mitigating its effects.

To attain this objective, we will test four specific hypotheses. A brief description of the analytic approach is provided after each hypothesis, with full details provided below in the "Analysis" section:

Hypothesis 1: *Instances of Potentially Inappropriate Prescribing are frequent.*
To test this hypothesis, we will apply the modified STOPP criteria[17] to Ontario health administrative data to identify instances of PIP.

Hypothesis 2: *An important proportion of ER visits and hospitalizations are associated with Potentially Inappropriate Prescribing, which leads to high costs.*
To test this hypothesis, we will estimate the attributable fraction of ER visits, hospitalizations and deaths associated with different frequencies of PIP using multivariate methods and survival analysis. We will also estimate potential savings, both direct and indirect, that could be achieved by reducing inappropriate prescribing.

Hypothesis 3: *Inappropriate prescribing is attributable to a small number of prescribers.*
To test this hypothesis, we will describe how frequently PIP instances occur for each prescriber, adjusted for prescribing volume.

Hypothesis 4: *An existing measure aimed at improving prescribing in primary care is effective in reducing Potentially Inappropriate Prescribing.*
To test this hypothesis, we will compare the frequency of PIP instances for prescribers who have access to the services of a clinical pharmacist within their practice setting with that of those who do not.

Proposed research:

Study design:
To achieve these aims, we will conduct a retrospective cohort study using Ontario's large health administrative and population databases, that contain information on both hospital and outpatient use of health services, as well as demographic and socioeconomic data.

Study setting:
The study is set in Ontario. The study period will span from July 1, 2002 to December 31, 2011. This start date was selected because the National Ambulatory Care Reporting System (NACRS) dataset for ER visits is available only after that date. This end date was selected because, when this study is conducted, the Ontario Health Insurance Plan (OHIP) and NACRS databases will be complete up to (at least) December 31, 2011. The accrual period, during which new patients can enter the study cohort, will start one year after the start of the NACRS database to ensure that we have adequate data on emergency room utilization prior to a patient's entry into the cohort, which will be used as a co-variate to control for confounding. The accrual period for recruitment into the study cohort will end one year prior to the latest available OHIP data (i.e., on Dec. 31, 2010) to ensure sufficient follow-up data for outcomes.

Inclusion Criteria:
The index date of recruitment of a patient into the study cohort will be the date of first prescription following the beginning of the accrual period (July 1, 2003). Patients included in the study will be all OHIP (Ontario Health Insurance Plan) eligible patients aged 65 years of age and older who were issued at least one prescription between July 1st 2003 and December 31st 2010. We expect to have approximately 2 million patients above 65 years of age who will be eligible for inclusion into our study (see Appendix C for details of how this estimate was calculated).

Exclusion Criteria:
Patients will be excluded if they do not have a valid Ontario provincial health care (OHIP) number. Patients residing in Ontario whose health care is covered through other plans, and are therefore not captured through ICES data, such as First Nations people living on reserve, members of the Armed Forces, and refugee claimants, will also be excluded.

Datasets to be used for the study:
This study will be conducted using Ontario administrative health databases housed at the Institute for Clinical Evaluative Sciences (ICES), which will be accessed from the ICES@uOttawa site. ICES is an independent, non-profit organization whose infrastructure funding and access to Ontario's large administrative databases is provided by the Ontario Ministry of Health and Long Term Care. ICES links de-identified population-based health information at the patient level in a way that ensures privacy and confidentiality of patients. ICES is named as a section 45(1) Prescribed Entity in Ontario's Personal Health Information Protection Act (PHIPA). Review, audit and approval of ICES' policies, practices and procedures related to data privacy and security are performed tri-annually by the Information and Privacy Commissioner of Ontario (IPC). This approval/review document is available at www.ipc.on.ca. All of these datasets are linked using a patient-specific encrypted identifier. This

linkage is deterministic and does not require any probabilistic methods. This study will use the following five datasets[36;37].

Ontario Drug Benefits Claims Database (ODBD):
The Ontario Drug Benefit (ODB) program provides drug benefits for all adults aged 65 and over and those receiving social assistance in Ontario. There are well over fifty million drug claims per year. The main data elements of the Ontario Drug Benefits Database include: ICES Key Number (IKN - anonymously linkable to other individual-level data holdings), Drug Identification Number (DIN); drug quantity, number of days supplied (can be used to compute daily dose), cost (split into its elements), long-term care indicator, the plan that prescription falls under (such as Seniors, Trillium, Ontario Works etc.), dispensing date, patient and prescriber identifiers (encrypted). ICES also maintains a list of drug identification numbers and the associated drug and product names, subclass information, Pharmacologic-therapeutic Classification Group (PCG) codes, drug strength, route of administration, first and last dispensing dates from ODB[37].

Discharge Abstract Database (DAD):
The DAD captures all acute-care hospitalizations in Ontario back to 1988. Each row in the DAD records demographic, diagnostic, procedural, and treatment information for a single hospitalization[37].

National Ambulatory Care Reporting System (NACRS):
NACRS captures all hospital emergency department visits back to 2002. Similar to DAD, each row records demographic, diagnostic, procedural, and treatment information for a single emergency room visit[37].

Ontario Health Insurance Plan (OHIP) database:
The OHIP database captures most claims paid by the Ontario Health Insurance Plan. Each row in the OHIP database records the patient, physician, and diagnosis/procedure being claimed for remuneration[37].

Registered Persons Database (RPDB): The RPDB records the birth date and death date (if applicable) of every person eligible for Ontario health services[37].

Creation of the analytical data set:
An overview of all variable definitions and units is presented in table form in Appendix D, and the variables are expanded upon in the following paragraphs.

Exposure variable:
The main "exposure" will be the **number of instances of potentially inappropriate prescribing** that a patient experiences during his or her study eligibility period. A secondary exposure variable will be that number of PIP instances divided by the duration of the patient's study eligibility expressed in years. This will yield an **average annual number of potentially inappropriate prescribing (PIP) instances per patient,** which corresponds to the annual PIP incidence per patient. Potentially inappropriate prescriptions will be determined by applying the modified STOPP criteria[17] to the Ontario Drug Benefits Database (ODBD). The variables included in the modified STOPP criteria are shown in Appendix B.

Outcome variables:
The primary study end-point is **the time between the most recent PIP and the first PIP-related event,** which is defined as the first **ER visit, hospitalization or death** occurring after a PIP**.** We have chosen to focus on reliably documented clinical events, namely ER visits, hospitalization and death as our main outcomes. ER visits will be determined from the NACRS database, hospitalizations from the DAD database, and death will be determined from the Registered Persons Database (RPDB). Our outcome definition using the "most recent PIP" is necessary in order to enable the inclusion of patients

experiencing more than one PIP. If a patient experiences more than one PIP due to the exact same medication(s), each instance of PIP will be counted individually. This is necessary in order to account for the longer exposure periods and higher risk of events to which patients receiving multiple prescriptions of a single PIP are exposed. If a patient experiences an event other than death (i.e. an ER visit or hospitalization), that patient will remain in the study cohort, as he/she may contribute further instances of PIP to the study base; patients who die are of course censored and can no longer contribute to the study base. In order to assess for possible colinearity in our data due to patients contributing more than one PIP, we will conduct a sensitivity analysis in which the outcome will be the time to first PIP only (i.e. subsequent PIPs will not be taken into account). The relationship between these events and time intervals is illustrated in Appendix E, together with a few examples of possible patient scenarios.

For our secondary analyses, our main end-points will be the time between the most recent PIP and the first of each one of these outcomes considered separately, i.e. **time to first ER visit, time to first hospitalization, or time to death**. Due to unreliable diagnostic coding of clinical data related to ADE, we have decided against using specific diagnostic codes indicative of ADE as one of our main outcomes, as we suspect this would largely underestimate the ADE rate in our population. We will, however, include these codes as outcomes in a secondary analysis, where the end-point will be **time to ADE**.

Censoring:

Patients will be part of the study population and will be observed for the occurrence of PIP from first dispensed prescription (whether PIP or not) to the first of either loss of OHIP eligibility or patient death, whichever comes first; observation will be censored if patients move out of the province and their move is captured by the RPDB. As for the observation window following an instance of PIP, we have chosen a 3-month cut-off since we anticipate that the potential influence of an instance of PIP would not likely last longer than this, and probably would be shorter. If a patient experiences a second PIP during the observation window of a first PIP, the observation time window for the first PIP will be censored (i.e. terminated) when the second PIP occurs (see Appendix E). If a PIP itself has a time-dependent definition, such as "NSAID use >3 months" (see Appendix B for full list of modified STOPP criteria), then the observation window will start at the dispensation of the PIP, include the specified minimum duration of exposure (in this case, 3 months), and extend for 3 months beyond the end of the specified duration of exposure. In the present example, this will amount to a total observation window of 6 months. We feel this approach is necessary, as PIP-related events may occur both during a time-defined exposure as well as after, since the risk period for adverse outcomes can extend beyond the actual exposure to a PIP.

Covariates:

The following covariates, which are either known or suspected of being associated with PIP, will be included in the analyses: Patient age, physician sex, type of physician (specialist vs family physician), physician location (urban vs rural), whether a patient has a regular family physician, number of prescribers[16], number of dispensing pharmacists, patient location (long-term care vs community setting)[15] and polypharmacy (number of drugs used concurrently by one patient)[38-42]. Other factors known or suspected of being associated with unplanned hospital admissions and ER visits will also be included in the analyses as covariates: patient's age[43;44] and sex[44], patient socioeconomic status[45], rurality, comorbidity[44;46;47] (will be calculated using the Deyo modification[48] of the Charlson comorbidity index[49]), Johns Hopkins Adjusted Clinical Groups (ACG) system[50], and prior hospitalization[43;44;46;51-55] will also be included as a covariate. We will use the postal code conversion file (PCCF) to link the patient's postal code to the dissemination area, which is the smallest

geographical census unit that exists across all of Canada. We will then use census data to determine the median household income of each dissemination area. For non-census years, we will use linear interpolation to infer income.

Analysis:

In the following paragraphs, we will expand on the analytic approaches we plan on using to test each one of our hypotheses.

Hypothesis 1: *Instances of Potentially Inappropriate Prescribing are frequent.*

Analytic approach:

We will assess the modified criteria proposed by Cahir[17] for appropriateness and applicability to our particular set of Ontario health administrative databases. Preliminary screening of the criteria indicates that these should all be applicable to Ontario data. Dr. Cahir, who modified the original STOPP/START criteria for use with the Irish prescription claims database[17], has agreed to be a co-investigator for this study and has offered to provide support with the application of the criteria to our database.

We will calculate the annual incidence of PIP as described in the "exposure" section above. We will compare this with data from the original Cahir study, where the annual incidence of PIP was 36%[17]. We will also compare our findings with those of a clinical study that used the full set of STOPP/START criteria; in this study, the point prevalence of PIPs in hospitalized patients was 35%[15]. We will also conduct a sub-group analysis to estimate the incidence of PIP in Long-Term Care (LTC) patients, as these patients are plagued by polypharmacy, and particularly vulnerable to mediation errors and adverse drug reactions[56;57]. Finally, we will examine the combined effects of sex, socio-economic status, and age, which, in combination, can be a proxy for gender effects in administrative data.

Hypothesis 2: *An important proportion of ER visits and hospitalizations are associated with Potentially Inappropriate Prescribing, which leads to high costs.*

Analytic approach:

To test this hypothesis, we will conduct a Cox proportional-hazards model analysis[58], controlling for potential confounders, to find the best fitting model that will enable us to estimate the association between PIP and adverse patient outcomes, as expressed by the time to first event. The reference category will be patients experiencing no PIPs. We expect to demonstrate that, as the number of instances of PIP a patient experience increases, the number of adverse events also increases, and we expect this association to be significant, even after controlling for potential confounders, in particular for co-morbidities and severity of indication, as well as for polypharmacy (number of drugs used concurrently).

In our analyses, we will control for potential confounding by disease severity and co-morbidities using multivariate survival analysis (Cox proportional-hazards modeling)[58]. We will include appropriate covariates, known or suspected of being associated with adverse outcomes, into our regression models, as detailed in the covariates section above. We will examine our data for PIP clustering patterns; if we find significant clustering, we will use hierarchical (multi-level) models to address this issue[61;62].

We will then estimate the attributable fraction (also known as *attributable risk, etiologic fraction,* and *population attributable risk*[58]) of adverse patient events associated with PIP, which is the number of additional adverse events that is due to, or attributable, to PIPs. We will do this by calculating hazard ratios using multivariate survival analysis (Cox proportional-hazards modeling)[58] for patients grouped by the number of PIPs they experienced (i.e. by PIP frequency). The reference category will be patients

experiencing no PIPs (PIP=0). We will then use the estimated hazard ratios for each PIP frequency category above the reference category (1, 2, 3, … PIPs) and apply it to the proportion of the population at risk for each frequency (proportion of population that experiences 1, 2, 3, … PIPs), using the frequency of events in the reference category as the baseline event rate. This will yield an overall estimate of event frequency attributable to PIPs. This will represent the proportion of all events occurring during the study period that are attributable to PIPs, a quantity that can also be expressed as an annual number of adverse patient events experienced by Ontario seniors that are due to PIP. We will do this calculation for all events combined (ER visits, hospitalizations and deaths), as well as for each type of event separately; we will also estimate the attributable fraction separately using ADE-related diagnostic codes as the outcome.

To estimate the costs associated with PIPs, we will calculate the actual number of PIPs per calendar year for the whole cohort. Using cost data from the ODBD, we will calculate the direct costs of the medications involved in instances of PIP. If more than one drug is involved in a PIP, then we will include only the cheaper of the two drugs, which will yield a conservative estimate of PIP-associated costs. We will also estimate the indirect costs of PIP by calculating the excess costs associated with ER visits and hospitalizations attributable to PIP (as described under "attributable fraction" in the previous paragraph), and we will term this the "health care utilization costs attributable to PIP".

Hypothesis 3: *Inappropriate prescribing is attributable to a small number of prescribers.*

Analytic approach:

To test this hypothesis, we will describe how frequently PIP instances occur for each prescriber, adjusted for prescribing volume. In order to do this, we will ascribe each instance of PIP to the physician who issued the implicated prescription(s). We will divide the number of PIPs ascribed to each physician by the total number of prescriptions issued by this physician over the course of the study period. This will yield the average number of instances of PIP expressed as a proportion of all prescriptions written by a physician, a quantity which we term the "PIP density"; this will be an indirect measure of poor prescribing. We will then rank physicians by PIP density, divide the range of PIP density into ten equal deciles, and calculate the percentage of physicians per decile as a proportion of the total number of physicians. If PIP densities were uniformly distributed, we would expect that each decile of PIP density would contain 10% of all physicians. If a decile contains more than 10% of physicians, then there is an over-representation of physicians in this decile; conversely, if a decile contains less than 10% of physicians, then physicians are under-represented in this decile. We expect that the upper deciles of PIP density (associated with poorer quality of prescribing) will contain fewer than 10% of physicians per decile, which would support our hypothesis that a proportionally higher number of PIPs are attributable to a small number of prescribers. As per usual ICES procedures, cell sizes < 5 will not be reported to address concerns about possible breaches in confidentiality.

To describe provider and patient characteristics associated with PIP, we will perform a multivariate regression, where the dependent variable will be the PIP density, and both prescriber and patient characteristics will be entered into the model. We expect that certain patient characteristics (such as age, number of prescribers) and prescriber characteristics (rural vs urban, sex, age) will be significantly associated with PIP density, as these have been shown in previous work to be associated with PIP[16].

Hypothesis 4: *A measure aimed at improving prescribing in primary care is effective in reducing Potentially Inappropriate Prescribing.*

Analytic approach:

To test this hypothesis, we will compare the frequency of PIP instances for prescribers who have access to the services of a pharmacist within their practice settings (usually Family Health Teams (FHTs))

with that of those who do not. We have contacted the Association of Family Health Teams of Ontario (AFHTO) to obtain a list of Family Health Teams and their characteristics, including the presence or absence of a pharmacist. We will supplement this with information from the Ontario Ministry of Health and Long-Term care, and will link it to our ODB prescribing data. We will then calculate a FHT-level "PIP density" for each FHT in a fashion analogous to the physician-level PIP density described in the analytic section under Hypothesis 3 above. We will then model whether FHT level PIP density is related to the presence or absence of a pharmacist by fitting multivariate linear regression models to the data while controlling for possible confounders, such as FHT size, number of physicians in the FHT, as well as other patient and physician-level co-variates described in the "Covariate" section above. The reference category will be FHTs without a pharmacist. We will include FHTs into our modeling exercise from the time of inception of each FHT; for the most part, this will be starting around 2005, so that earlier data will not be used for this sub-analysis.

As pharmacists do not bill OHIP directly for patient services provided in the context of multidisciplinary family health teams (FHTs), it is not possible to know which patient in a FHT had his or her medication reviewed by the FHT pharmacist. Therefore, it will be necessary to look at the effect of "access" to a pharmacist, which can be done by comparing PIP densities for prescribers working within Family Health Teams who do and do not have access to a pharmacist. Because there is often one pharmacist for approximately 12 000 to 15 000 patients in a Family Health Team, the fact that not all patients are seen by the pharmacist may seem problematic and may be thought to "dilute" the effect of this potentially useful resource. However, it is usually patients with many medications, i.e. those who stand to benefit most from a drug review, who are referred to the FHT pharmacist; therefore, the potential pool of patients who would benefit most from access to a pharmacist is in fact much smaller than the total FHT patient population. Because these are the patients who are most at risk for experiencing adverse outcomes, and because there will be a "learning effect" on the part of the physician from getting feedback from the pharmacist on their prescribing that will be carried over to subsequent patients, we expect that the effect of having a pharmacist in a FHT will be significant and that it will be possible to demonstrate this effect on the PIP density of physicians working in FHT with versus those without a pharmacist. This would be consistent with evidence from the clinical literature that shows that the inclusion of pharmacists in multidisciplinary primary care teams leads to improvements in quality of prescribing, reductions in cost and health resource utilization[63-67].

General approach to the control of confounding

Due to some concerns about the limits of classical Cox proportional hazards modeling to adequately control for confounding, we will conduct a secondary analysis using instrumental variables (IV). Instrumental variables, originally developed in econometrics and social sciences to deal with unmeasured confounding, have been adapted for use with prescription data[60]. This method tries to reduce bias through the use of a variable (the so-called "instrument") that is related to treatment but unrelated to the unobserved patient risk factors that act as confounders in conventional statistical approaches[60]. The instrumental variable approach has been shown to produce practically un-biased estimates of treatment effect even when strong un-measured confounders are present[59;68]. Because of this feature, we decided to use the IV approach in our secondary analyses. We have experience with and considered using propensity score matching, but elected not to, because in the context of our study, this approach would not offer much beyond what a well-built multivariate model can do[69].

In order to strengthen our case for a possible causal link between PIP and adverse patient outcomes such as ER visits and hospitalizations, we will conduct sub-group analyses focusing on specific PIP-outcome pairs which are known to be causally related, such as prolonged NSAID use and GI bleeds, combined warfarin and NSAID use and GI bleed, and long-acting benzodiazepine use and falls. In

order to assess the specificity of our PIP-outcome associations, we will also assess the association of PIP with outcomes we expect will be unrelated to PIPs, so-called "tracer outcomes", such as admissions for elective surgery.

Because our dataset is so large, for all model-generating analyses, we will, without loss of power, randomly split the dataset in two and use one half of our cohort to derive our models and the other half to validate them.

Study power:

Dispensation of a first prescription represents a patient's point of entry into our study population. A conservative estimate of the number of medications prescribed during our study period would be about 100 million medications and at least as many prescriptions (assuming annual renewal of stable medications) (see Appendix C for details of estimation). As for event rates, applying a rate of PIP of 22% in primary of care found in earlier studies[11] would result in about 500 000 elderly patients experiencing PIPs per year in Ontario (based on an estimated seniors population of about 1.6 million). Since some patients will experience more than one PIP during the study accrual period, the number of eligible observations will be greater.

This huge sample size, in terms of patients, number of prescriptions, and PIPs, ensures very high statistical power to detect any effect of even minor clinical importance. Consequently, a formal power calculation is unnecessary given the large size and population-based nature of this study.

5. Potential limitations of this study:

This study will not be able to directly account for people who move out of province: Our study design requires that we censor observations when patients move out of province; however, if a person notifies the Ministry of Health (MoH) that they are moving out of province, their move is – ironically – not captured by the RPDB. In order to ensure that this problem does not affect the validity of our results, we will do a sensitivity analysis in which we censor patients at their last contact with the health care system.

Our study is subject to many of the limitations inherent to pharmacy claims data studies, however, all of these limitations will likely result in a conservative estimate of PIP incidence and of the association of PIP and adverse outcomes (i.e. an underestimate): prescriptions recorded in the ODB database were dispensed to patients, however, it is not certain that patients actually took the medication dispensed, or were adherent to treatment on an ongoing basis. We will assess adherence to treatment by following patients through time to see if repeat prescriptions for the same medication were dispensed around the time when the previous prescription would be expected to have run out. Another limitation of this study is that over-the-counter medication which may be associated with adverse patient outcomes and are listed in the original STOPP/START criteria (such as low-dose ASA, for example) are not included in this database. It is also possible that some instances of PIP identified by the modified STOPP criteria in our database may actually be considered appropriate should clinical or diagnostic data have been available.

Nonetheless, were are confident that, overall, our study will produce useful estimates of the occurrence of Potentially Inappropriate Prescribing (PIP) in Ontario's elderly (>65 yrs) population and will enable us to assess the health and economic burden associated with PIP as well as to evaluate an existing measure aimed at mitigating its effects.

6. Knowledge translation plans:

In order to produce deliverables that have high potential for implementation, we have already started engaging decision makers at an early stage in the conception of this project. Through the CEO of her home institution (Bruyère Research Institute), the principal investigator (Dr. Bjerre) has already established contact with Diane MacArthur, the Assistant Deputy Minister (ADM) Health and Long Term Care and Executive Officer, Ontario Public Drug Programs Division. The Assistant Deputy Minister has shown interest in the project, and a face-to-face meeting will be planned to explore areas of mutual interest, particularly with respect to concrete deliverables potentially arising from this project. Dr. Bjerre has also contacted and met with Dr. Sam Shortt, Director of Knowledge Transfer and Practice Policy at the Canadian Medical Association and representative of the Optimal Prescribing Working Group[70]; Dr. Shortt expressed great interest in the potential of this project to improve our understanding of sup-optimal prescribing, which is key to developing specific approaches to enhance prescribing. (See appended letter of support.)

We expect that the results of this study will be of interest to a wide range of individuals and groups, including health care policy makers, national and provincial professional associations and licensing bodies, clinicians, health care consumer organizations, and members of the public. Several avenues of dissemination will be followed. For **end-of-grant KT**, we intend to publish in medical, health services research, and/or public health journals. More importantly, we plan to present and discuss the results of our study with relevant stakeholders, such as the Ontario Ministry of Health and Long-Term Care, the Ontario College of Physicians and Surgeons, local integrated health networks (LIHN) and lead physicians in Ontario's 150 family health teams (FHTs). We will encourage presentation of our work at health care and discipline-based, particularly drug safety and primary care conferences. We will use our informal networks to disseminate our findings nationally and internationally. As for **integrated KT**, both the principal investigator (Dr. Bjerre) and two of the co-investigators (Drs. Manuel and Halil) are knowledge users, in addition to being researchers: Dr. Bjerre and Manuel are practicing family physicians, and Dr. Halil is a pharmacist practicing in a Family Health Team. This is a strong advantage that will help us produce research findings that are relevant to end-users, and more likely to be used by them[61]. Finally, in order to support us in maximizing the dissemination and use of the results of this study, we are budgeting for a Knowledge Translation specialist to assist us in this process.

7. Study timeline:

The proposed study timeline can be seen in Appendix F. We expect to be able to complete the study in approximately 30 months, with 6 months to continue dissemination. The principal investigator (Dr. Bjerre) will meet the analyst in person weekly. A teleconference or face-to-face meeting with the four investigators and/or the whole team will occur monthly, or as needed.

8. Research team and environment:

Our team members have experience with successfully conducting analyses using large administrative databases (Dr. Bjerre, Dr. Manuel), have expertise and many years of experience in statistics (Dr. Ramsay), as well as formal training in epidemiology (Drs. Bjerre, Manuel and Ramsay) and biostatistics (Drs. Bjerre, Manuel and Ramsay), and are also active clinicians practicing as family physicians (Dr. Bjerre, Dr. Manuel) and as clinical pharmacist in primary care (Dr. Halil). The ICES@uOttawa site provides us with an ideal environment to conduct this study, providing us with both high quality data and infrastructure. Additionally, through ICES, we will have access to scientists

and data analysts who have years of practical, hands-on experience with large health databases in general, and with those housed at ICES in particular.

9. Feasibility:

We believe our team has the ability and resources necessary to complete this study within the specified timeline and proposed budget for the following reasons: a) our team has extensive experience in the field of health administrative database analysis and programming; b) the principal investigator (Dr. Bjerre) and the ICES Scientist co-investigator (Dr. Manuel) have time to dedicate to the study (Dr. Bjerre: 0.6 full-time equivalent, i.e., 3.0 days/week protected time for research); and finally, c) our team has a strong track record of productivity and of completing projects on time. Although the Principal Investigator is a junior researcher, she has gained significant experience in the use of large administrative health databases in the course of her PhD in Epidemiology (McGill University, Montreal) during which she applied newly developed methods to the Quebec RAMQ (Régie de l'Assurance Maladie du Québec) database using the SAS software. She is currently Principal Investigator (PI) on a CIHR-funded study which she is conducting at ICES@uOttawa; this study is well under way, and expected to be completed by the end of 2012. More importantly for the current project, she has the support of a very experienced team of co-investigators, backed up by qualified and experienced support staff. In short, we are ready and eager to take up the challenge of conducting this study, and we are equipped to succeed in this endeavour.

10. Study relevance:

In closing, we would like to summarize and highlight why we feel strongly that this study is important and should be carried out:

The topic is important:

Errors in prescribing are frequent and costly, and it is important to quantify their magnitude and understand the factors associated with them. Modifiable factors, such as those related to prescriber and patient characteristics, warrant particular attention. This is because even relatively small changes in practice or policy aimed at improving the quality of prescribing may lead to important reductions in morbidity and mortality as well as unnecessary expenses associated with PIP.

This study is unique:

To our knowledge, and according to our review of the literature, the association of PIP with patient outcomes, prescriber characteristics and health care utilization has not been studied in such a large population-based study in any jurisdiction, including the Canadian health care context. We will be able to do so because Ontario possesses an extensive set of linked population and health databases that is unique and not found elsewhere in the world. Furthermore, our study will enable us to, at least in part, contribute to the validation of the modified STOPP criteria and potentially test causal relationships between potentially inappropriate drug use and adverse outcomes in a population-wide context.

The problem can be addressed:

We expect to identify factors, both at the patient and prescriber levels, that are associated with poor prescribing, and to show that a measure already in place in some practice settings is effective at improving not only the quality of prescribing, but also at reducing adverse outcomes associated with poor prescribing. This evidence can provide the basis for targeted policy measures aimed at improving prescribing quality and outcomes for Ontario seniors, and reducing costs.

Appendix A: Original STOPP/START criteria (obtained from Gallagher 2011)[22]

STOPP: (Screening Tool of Older People's potentially inappropriate Prescriptions).

The following prescriptions are potentially inappropriate in persons aged ≥ 65 years of age

A. Cardiovascular System

1. Digoxin at a long-term dose > 125µg/day with impaired renal function* *(increased risk of toxicity).*
2. Loop diuretic for dependent ankle oedema only i.e. no clinical signs of heart failure *(no evidence of efficacy, compression hosiery usually more appropriate).*
3. Loop diuretic as first-line monotherapy for hypertension *(safer, more effective alternatives available).*
4. Thiazide diuretic with a history of gout *(may exacerbate gout).*
5. Non-cardioselective beta-blocker with Chronic Obstructive Pulmonary Disease (COPD) *(risk of bronchospasm).*
6. Beta-blocker in combination with verapamil *(risk of symptomatic heart block).*
7. Use of diltiazem or verapamil with NYHA Class III or IV heart failure *(may worsen heart failure).*
8. Calcium channel blockers with chronic constipation *(may exacerbate constipation).*
9. Use of aspirin and warfarin in combination without histamine H2 receptor antagonist (except cimetidine because of interaction with warfarin) or proton pump inhibitor *(high risk of gastrointestinal bleeding).*
10. Dipyridamole as monotherapy for cardiovascular secondary prevention *(no evidence for efficacy).*
11. Aspirin with a past history of peptic ulcer disease without histamine H2 receptor antagonist or Proton Pump Inhibitor *(risk of bleeding).*
12. Aspirin at dose > 150mg day *(increased bleeding risk, no evidence for increased efficacy).*
13. Aspirin with no history of coronary, cerebral or peripheral arterial symptoms or occlusive arterial event *(not indicated).*
14. Aspirin to treat dizziness not clearly attributable to cerebrovascular disease *(not indicated).*
15. Warfarin for first, uncomplicated deep venous thrombosis for longer than 6 months duration *(no proven added benefit).*
16. Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration *(no proven benefit).*
17. Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder *(high risk of bleeding).*

∗ estimated GFR <50ml/min.

B. Central Nervous System and Psychotropic Drugs

1. Tricyclic antidepressants (TCA's) with dementia *(risk of worsening cognitive impairment).*
2. TCA's with glaucoma *(likely to exacerbate glaucoma).*
3. TCA's with cardiac conductive abnormalities *(pro-arrhythmic effects).*
4. TCA's with constipation *(likely to worsen constipation).*
5. TCA's with an opiate or calcium channel blocker *(risk of severe constipation).*

6. TCA's with prostatism or prior history of urinary retention *(risk of urinary retention).*
7. Long-term (i.e. > 1 month), long-acting benzodiazepines e.g. chlordiazepoxide, fluazepam, nitrazepam, chlorazepate and benzodiazepines with long-acting metabolites e.g. diazepam *(risk of prolonged sedation, confusion, impaired balance, falls).*
8. Long-term (i.e. > 1 month) neuroleptics as long-term hypnotics *(risk of confusion, hypotension, extra-pyramidal side effects, falls).*
9. Long-term neuroleptics (> 1 month) in those with parkinsonism *(likely to worsen extra-pyramidal symptoms)*
10. Phenothiazines in patients with epilepsy *(may lower seizure threshold).*
11. Anticholinergics to treat extra-pyramidal side-effects of neuroleptic medications *(risk of anticholinergic toxicity).*
12. Selective serotonin re-uptake inhibitors (SSRI's) with a history of clinically significant hyponatraemia *(non-iatrogenic hyponatraemia <130mmol/l within the previous 2 months).*
13. Prolonged use (> 1 week) of first generation antihistamines i.e. diphenydramine, chlorpheniramine, cyclizine, promethazine *(risk of sedation and anti-cholinergic side effects).*

C. Gastrointestinal System

1. Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhoea of unknown cause *(risk of delayed diagnosis, may exacerbate constipation with overflow diarrhoea, may precipitate toxic megacolon in inflammatory bowel disease, may delay recovery in unrecognised gastroenteritis).*
2. Diphenoxylate, loperamide or codeine phosphate for treatment of severe infective gastroenteritis i.e. bloody diarrhoea, high fever or severe systemic toxicity *(risk of exacerbation or protraction of infection)*
3. Prochlorperazine (Stemetil) or metoclopramide with Parkinsonism *(risk of exacerbating Parkinsonism).*
4. PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks *(earlier discontinuation or dose reduction for maintenance/prophylactic treatment of peptic ulcer disease, oesophagitis or GORD indicated).*
5. Anticholinergic antispasmodic drugs with chronic constipation *(risk of exacerbation of constipation).*

D. Respiratory System

1. Theophylline as monotherapy for COPD. *(safer, more effective alternative; risk of adverse effects due to narrow therapeutic index)*
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD *(unnecessary exposure to long-term side-effects of systemic steroids).*
3. Nebulised ipratropium with glaucoma *(may exacerbate glaucoma).*

E. Musculoskeletal System

1. Non-steroidal anti-inflammatory drug (NSAID) with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H2 receptor antagonist, PPI or misoprostol *(risk of peptic ulcer relapse).*
2. NSAID with moderate-severe hypertension (moderate: 160/100mmHg – 179/109mmHg; severe: ≥180/110mmHg) *(risk of exacerbation of hypertension).*
3. NSAID with heart failure *(risk of exacerbation of heart failure).*
4. Long-term use of NSAID (>3 months) for relief of mild joint pain in osteoarthtitis *(simple analgesics preferable and usually as effective for pain relief)*
5. Warfarin and NSAID together *(risk of gastrointestinal bleeding).*

6. NSAID with chronic renal failure* *(risk of deterioration in renal function).* * estimated GFR 20-50ml/min.
7. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthrtitis or osterarthritis *(risk of major systemic corticosteroid side-effects).*
8. Long-term NSAID or colchicine for chronic treatment of gout where there is no contraindication to allopurinol *(allopurinol first choice prophylactic drug in gout)*

F. Urogenital System

1. Bladder antimuscarinic drugs with dementia *(risk of increased confusion, agitation).*
2. Bladder antimuscarinic drugs with chronic glaucoma *(risk of acute exacerbation of glaucoma).*
3. Bladder antimuscarinic drugs with chronic constipation *(risk of exacerbation of constipation).*
4. Bladder antimuscarinic drugs with chronic prostatism *(risk of urinary retention).*
5. Alpha-blockers in males with frequent incontinence i.e. one or more episodes of incontinence daily *(risk of urinary frequency and worsening of incontinence).*
6. Alpha-blockers with long-term urinary catheter *in situ* i.e. more than 2 months *(drug not indicated).*

G. Endocrine System

1. Glibenclamide or chlorpropamide with type 2 diabetes mellitus *(risk of prolonged hypoglycaemia).*
2. Beta-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes i.e. ≥ 1 episode per month *(risk of masking hypoglycaemic symptoms).*
3. Oestrogens with a history of breast cancer or venous thromboembolism *(increased risk of recurrence)*
4. Oestrogens without progestogen in patients with intact uterus *(risk of endometrial cancer).*

H. Drugs that adversely affect those prone to falls (≥ 1 fall in past three months)

1. Benzodiazepines *(sedative, may cause reduced sensorium, impair balance).*
2. Neuroleptic drugs *(may cause gait dyspraxia, Parkinsonism).*
3. First generation antihistamines *(sedative, may impair sensorium).*
4. Vasodilator drugs known to cause hypotension in those with persistent postural hypotension i.e. recurrent > 20mmHg drop in systolic blood pressure *(risk of syncope, falls).*
5. Long-term opiates in those with recurrent falls *(risk of drowsiness, postural hypotension, vertigo).*

I. Analgesic Drugs

1. Use of long-term powerful opiates e.g. morphine or fentanyl as first line therapy for mild-moderate pain *(WHO analgesic ladder not observed).*
2. Regular opiates for more than 2 weeks in those with chronic constipation without concurrent use of laxatives *(risk of severe constipation).*
3. Long-term opiates in those with dementia unless indicted for palliative care or management of moderate/severe chronic pain syndrome *(risk of exacerbation of cognitive impairment).*

J. Duplicate Drug Classes

Any regular duplicate drug class prescription e.g. two concurrent opiates, NSAID's, SSRI's, loop diuretics, ACE inhibitors *(optimisation of monotherapy within a single drug class should be observed prior to considering a new class of drug).* This excludes duplicate prescribing of drugs that may be required on a prn basis e.g. inhaled beta2 agonists (long and short acting) for asthma or COPD, and opiates for management of breakthrough pain.

START: Screening Tool to Alert doctors to Right i.e. appropriate, indicated Treatments.

The following medications should be considered for people ≥ 65 years of age with the following conditions, where no contraindication to prescription exists.

A. Cardiovascular System

1. Warfarin in the presence of chronic atrial fibrillation.
2. Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin.
3. Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm.
4. Antihypertensive therapy where systolic blood pressure consistently >160 mmHg.
5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is > 5 years.
6. Angiotensin Converting Enzyme (ACE) inhibitor with chronic heart failure.
7. ACE inhibitor following acute myocardial infarction.
8. Beta-blocker with chronic stable angina.

B. Respiratory System

1. Regular inhaled beta 2 agonist or anticholinergic agent for mild to moderate asthma or COPD.
2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where predicted FEV1 <50%.
3. Home continuous oxygen with documented chronic type 1 respiratory failure (pO2 < 8.0kPa, pCO2 <6.5kPa) or type 2 respiratory failure (pO2 < 8.0kPa, pCO2 > 6.5kPa).

C. Central Nervous System

1. L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability.
2. Antidepressant drug in the presence of moderate-severe depressive symptoms lasting at least three months.

D. Gastrointestinal System

1. Proton Pump Inhibitor with severe gastro-oesophageal acid reflux disease or peptic stricture requiring dilatation.
2. Fibre supplement for chronic, symptomatic diverticular disease with constipation.

E. Musculoskeletal System

1. Disease-modifying anti-rheumatic drug (DMARD) with active moderate-severe rheumatoid disease lasting > 12 weeks.
2. Bisphosphonates in patients taking maintenance oral corticosteroid therapy.
3. Calcium and Vitamin D supplement in patients with known osteoporosis (radiological evidence or previous fragility fracture or acquired dorsal kyphosis).

F. Endocrine System

1. Metformin with type 2 diabetes +/- metabolic syndrome (in the absence of renal impairment*).

2. ACE inhibitor or Angiotensin Receptor Blocker in diabetes with nephropathy i.e. overt urinalysis proteinuria or micoralbuminuria (>30mg/24 hours) +/- serum biochemical renal impairment* .
3. Antiplatelet therapy in diabetes mellitus if one or more co-existing major cardiovascular risk factor present (hypertension, hypercholesterolaemia, smoking history).
4. Statin therapy in diabetes mellitus if one or more co-existing major cardiovascular risk factor present.

∗ estimated GFR <50ml/min.

Appendix B: Variables used in the modified STOPP criteria (Cahir 2010)[13]

STOPP criteria applied to prescription claims data for all those aged ≥ 70 years in Ireland in 2007.

STOPP Criteria Description
Cardiovascular System
Digoxin > 125μmg/day (increased risk of toxicity)
Thiazide diuretic with gout (exacerbate gout)
Beta-blocker with COPD* (risk of increased bronchospasm)
Beta-blocker with verapamil (risk of symptomatic heart block)
Aspirin and warfarin without histamine H2 receptor antagonist (except cimetidine) or proton pump inhibitor (high risk of gastrointestinal bleeding)
Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence of efficacy)
Aspirin >150mg/day (increased bleeding risk)
Central Nervous System and psychotropic drugs
TCA* with dementia (worsening cognitive impairment)
TCA and glaucoma (exacerbate glaucoma)
TCA and opiate or calcium channel blockers (risk of severe constipation)
Long-term (i.e. >1 month), long-acting benzodiazepines (risk of prolonged sedation, confusion, impaired balance, falls)

Long-term (i.e. >1 month) neuroleptics (risk of confusion, hypotension, extrapyramidal side-effects, falls)

Long-term (i.e. >1 month) neuroleptics with parkinsonism (worsen extrapyramidal symptoms)

Anticholinergics to treat extrapyramidal side effects of neuroleptic medications (risk of anticholinergic toxicity)

Phenothiazines with epilepsy (may lower seizure threshold)

Prolonged use (i.e. >1 week) of first-generation antihistamines (risk of sedation and anti-cholinergic side-effects)

Gastrointestinal System

Prochlorperazine or metoclopramide with parkinsonism (risk of exacerbating parkinsonism)

PPI for peptic ulcer disease at maximumfull therapeutic dosage† for >8 weeks

(dose reduction or earlier discontinuation indicated)

Respiratory System

Theophylline with COPD (risk of adverse effects due to narrow therapeutic index)

Nebulised ipratropium with glaucoma (exacerbate glaucoma)

Musculoskeletal System

Long-term use of NSAID* (i.e. > 3 months) for pain relief (simple analgesics preferable)

Warfarin and NSAID (risk of gastrointestinal bleeding)

Urogenital System

Antimuscarinic drugs with dementia (risk of increased confusion, agitation)

Antimuscarinic drugs with chronic glaucoma (> 3 months) (risk of acute exacerbation of glaucoma)

Endocrine System

Glibenclamide or chlorpropamide with type 2 diabetes mellitus (risk of prolonged hypoglycemia)

Duplicate Drug Class Prescription

(optimization of monotherapy within a single drug class)

Two concurrent opiates

Two concurrent NSAIDs

Two concurrent SSRIs*

Two concurrent antidepressants

Two concurrent loop diuretics

Two concurrent ACE inhibitors*

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*COPD= chronic obstructive pulmonary disease, TCA= tricyclic antidepressant, NSAID= non-steroidal anti-inflammatory drug, SSRI= selective serotonin reuptake inhibitor, ACE inhibitors= Angiotensin converting enzyme inhibitors.

‡ Proton pump inhibitor (PPI) at maximum therapeutic dose= 40mg/daily omeprazole, pantoprazole and esomeprazole. 30mg/daily lansoprazole and 20mg/daily rabeprazole.

Appendix C: Calculation of expected number of prescriptions during study period

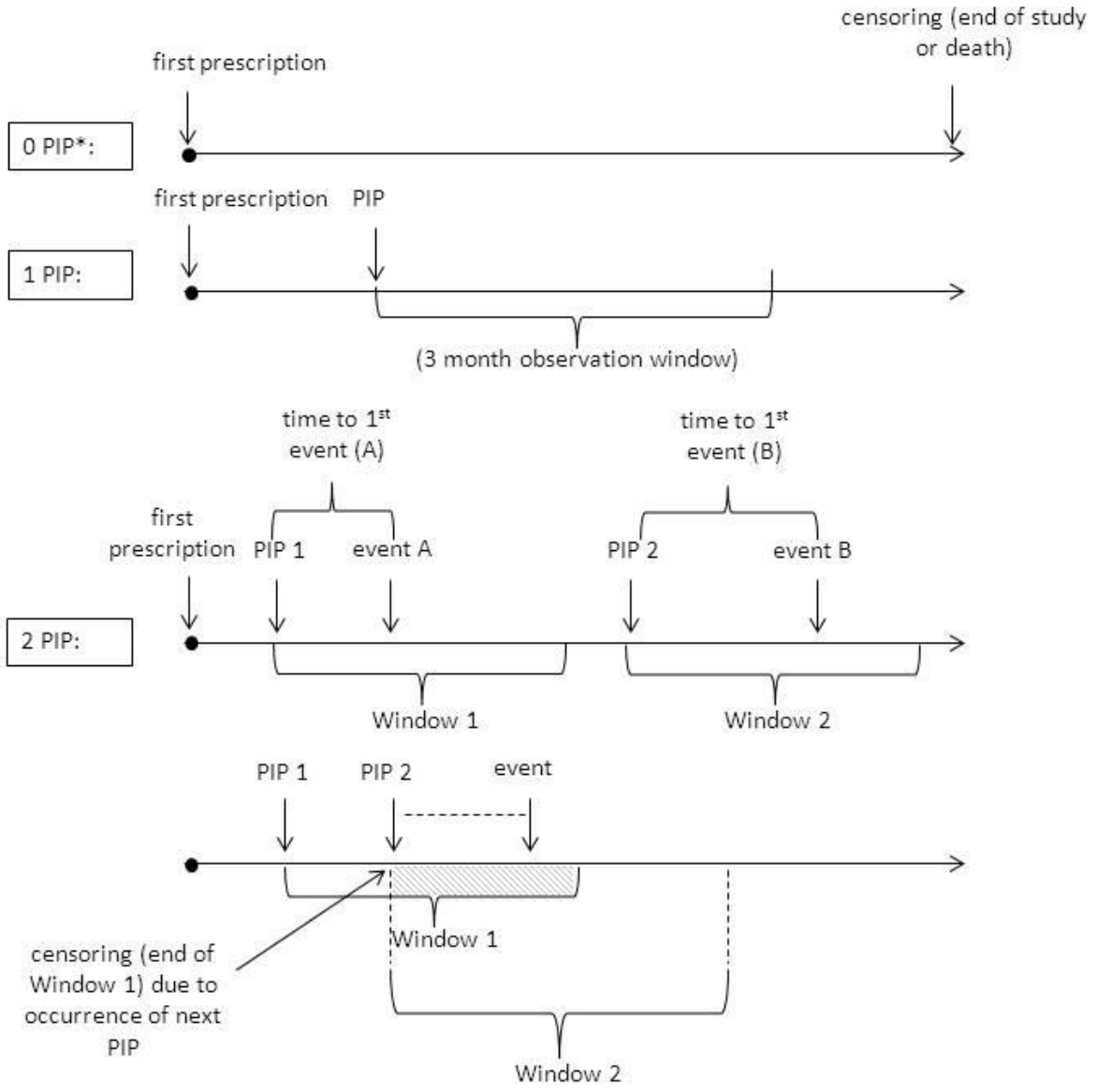
Every year in Ontario, over 50 million prescriptions are dispensed and recorded in the ODBD (Institute for Clinical Evaluative Sciences)[37]. The Ontario population in 2006 (mid-way through our study period) was approximately 12 600 000[71], of which about 14% were seniors[1], corresponding to 1, 680 000 seniors. Given that this is a dynamic populations, with additions through aging of the population and patients moving into the province, and losses such as deaths and emigration, the actual number of seniors in the database can be expected to be higher, around 2 to 2.5 million patients. Given an average annual number of medications per senior of 6.7[1], this would translate into approximately 13 million medications being prescribed under ODB per year (with more prescriptions, since there may be more than one prescription for the same medication). Given our study accrual period of seven-and-a-half years (July 1, 2003 to Dec. 31, 2010), we could expect to have access to a total of almost 100 million different instances of medications dispensed to individual patients, and even more prescriptions.

Appendix D: Variable definitions and units

Category	Variable name	Definition	Units
Main exposure variable	PIP counts per patient	Number of instances of potentially inappropriate prescribing (PIP) experienced by a patient during his/her study eligibility period	counts
Secondary exposure variable	Average annual PIP counts per patient	Number of instances of potentially inappropriate prescribing experienced by a patient during his/her eligibility period divided by the duration of the study eligibility period in years	counts/year
Primary outcome variable	Time to any outcome	Time between most recent PIP and first of ER visit, hospitalization or death	days
Secondary outcome variable	Time to ER visit	Time between most recent PIP and first ER visit	days
	Time to hospitalization	Time between most recent PIP and first hospitalization	days
	Time to death	Time between most recent PIP and death	days
Covariates	Patient age	Patient's age	years
	Patient sex	Patient's biological gender	male or female
	Patient location	Type of setting a patient lives in	Long-term care vs community setting
	Number of prescribers	Number of prescribers who have issued prescriptions for a patient during the patient's study eligibility period	count
	Number of dispensing pharmacists	Number of pharmacists from whom a patient obtained medication	count
	Polypharmacy	Number of medications concurrently in use at time of prescription of a PIP	count
	Socioeconomic status	Socioeconomic quintile attributed to patient on the basis of his/her census data and postal code	quintile
	Prior hospitalizations	Number of hospital admissions experienced by a patient in the 12 months preceding a PIP	count

Category	Variable name	Definition	Units
	ER visit in past six months	Number of visits made to the emergency room by a patient in the six months preceding a PIP	count
	Comorbidities	Deyo modification of Charlson comorbidity index for a patient calculated at the time of a PIP	N/A
	Acuity of prior hospitalizations	Whether a hospitalization occurring in the 12 months preceding a PIP was coded as "acute" or not in the Discharge Abstract Database	1 if acute 0 if other
	Discharge diagnosis	Diagnosis of a hospitalization occurring in the 12 months preceding a PIP as recorded in the Discharge Abstract Database	diagnostic groups
	Physician age	Physician age	years
	Physician sex	Physician's biological gender	male or female
	Physician year of graduation	Physician year of graduation	year (date)
	Physician location	Physician location of practice (rural vs urban)	0 rural, 1 urban
	Type of physician	Type of physician prescribing a PIP for a given patient	specialist or family MD

Appendix E: Time-to-event as a function of potentially inappropriate prescribing: possible patient scenarios



* PIP: potentially inappropriate prescribing

- **Time to event:**
  Time between **most recent** PIP and first event
- Level of exposure (PIP 0, 1, 2, 3): Number of PIPs during study eligibility
- Censoring: If event is emergency room or hospitalization, the patient remains in study, to enable inclusion of patients with multiple PIPs

Appendix F: Study timeline

Dates	Duration	Action
April 1st – June 30th, 2013	10-12 weeks	Get expedited Research Ethics Board approval for study
July 1st, 2012 - September 30st, 2013	10-12 weeks	Assess applicability of modified STOPP criteria to Ontario Drug Benefits Database
October 1st - December 31th, 2013	10-12 weeks	Create analytic dataset
January 1st - April 30st, 2014	14-16 weeks	Conduct initial analysis
May 1st - July 31th, 2014	12 weeks	Collate feedback from investigators
August 1st - November 30th, 2014	16 weeks	Conduct secondary analyses
December 1st, 2014 - February 28th, 2015	10-12 weeks	Draft initial study report
March 1st – May 31, 2015	10-12 weeks	Collate feedback from investigators
June 1st to August 31st, 2015	12 weeks	Generate final report
Dissemination of study results	September 2015 to spring 2016	Manuscript preparation/publication, communication with stakeholders and end-users, and conference presentations

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Response to Reviewers' comments

(from previous submission to CIHR, March 2012 Operating Grant competition; score 4.05, rank 12th out of 50, first 9 were funded)

Note: The reviewer's comments are *italicized* and our responses are in regular print.

Reviewer 1

Sex and gender: *Given the link in other literature of sex to specific types of inappropriate prescribing and to specific adverse events, additional detail on sex and gender analysis could have been included – very relevant. The covariates included in the analysis would allow more in-depth examination of for example not only if sex is associated with PIP and adverse events, but also combined effects of sex, socio-economic status, and age (in combination can be a proxy for gender effects in administrative data).*

Answer: The review has a good point, and we have more robustly expanded on the analyses to assess for possible gender effects; multivariate analyses of the available data will enable us to assess the combined effect of sex, socio-economic status, age and their association with PIP and adverse outcome.

Hypothesis 1: *Frequency of specific types of PIP, and also patient and physician characteristics associated with these events are also important. The unit of analysis should be patients, rather than prescribing events, if the aim is to look at PIPs within a population and public health perspective.*

Answer: We have changed our outcomes to include provider-, patient- and prescription-level frequencies of potentially inappropriate prescribing (PIP). Fortunately, the hierarchical (multi-level) model is well-suited to looking at various levels of analysis and accounting for the influence of different prescribing practices. This allows us to report adverse events at the level of the population (Ontario), according to practice- (ex: group vs solo), provider- (ex: time since graduation, sex) and patient-specific (ex: gender, polypharmacy, co-morbidities) characteristics.

Hypothesis 2: *Confounding is a key issue, as patients with the most co-morbidities at baseline may also receive more of the PIP. The authors include both sensitivity analyses, looking at the link between specific PIP and specific associated outcomes, and use of instrumental variables as a means to address confounding. This seems appropriate and necessary. One issue to flag is the strong association of PIP with polypharmacy in the Irish administration data.*

Answer: Polypharmacy is indeed strongly associated with PIPs, and polypharmacy is an important confounder for which we will control in our analyses. We have further expanded and described how we will control for polypharmacy and co-morbidity (Deyo modification of the Charlson co-morbidity index, and Johns Hopkins Adjusted Clinical Groups (ACG) system), which is also associated with polypharmacy.

Hypothesis 3*: The percent PIP per number of prescriptions per physician is used as a measure of 'PIP density' per physician. I would question this denominator, as a physician who is a heavy prescriber in general (more prescriptions per patient) would be allowed more PIP on average than a more conservative prescriber. It is especially problematic given that polypharmacy alone has been shown to be so strongly correlated with PIP in the Irish study. Shouldn't the numerator be # of patients with one or more PIPs and/or mean frequency of PIPs per patient (rather than total # of PIPs, independent of the patients who experience them), and the denominator # of patients over 65 with 1 or more prescriptions in the study period, with some sort of adjustment for the age and co-morbidity distribution of patients in the physicians' population? I realize that this is a more complex measure than PIPs per physician/total prescriptions per physician, but it seems the denominator should be patients. On page 9, the "PIP density" approach could also be used for hypothesis 1 (describing frequency and characteristics of PIP in the population, and helping to inform further hypotheses). Also I assume this is a typo – that this is being described as the dependent variable.*

Answer: As previously stated, we have expanded our discussion of how hierarchical models will enable us to consider different levels of analysis (prescribing events, patients and prescribers). Furthermore, it may well be that the prescribers we identify as having high 'PIP density' are the ones who are, for one reason or another, writing more prescriptions per patient. Most importantly, we have designed the analytic approach to identify and characterize prescribers, since our knowledge users have identified prescribers as an important target for intervention to improve PIP. As the reviewer correctly pointed out, there was a typo, which has been corrected.

Hypothesis 4: *There may be baseline differences between physicians in these teams and others that may affect prescribing quality, independent of the existence of a pharmacist in the team. Are these being considered or controlled for in the analysis?*

Answer: Yes. We will be using these differences as potential predictors in the analyses. The Ontario Health Administrative Databases contain information on the physicians sex, gender, type of physician (specialist vs. family physician), year of graduation, practice setting (rural vs. urban, socio-economic neighbourhood, type of remuneration, family health team/practice model).

Research team: *I would question was why Dr Cahir, in Ireland, has not been included as a co-investigator rather than a collaborator, given the degree of integration into the project. I realize that for non-Canadian researchers the Common CV can be onerous, but Dr Cahir appears to be playing the role of a co-investigator, based on the plans to situate part of the research assistant position in Ireland.*

Answer: As stated, there are some administrative barriers to Dr. Cahir being involved, but she has agreed to join the study as a co-investigator.

Budget: *My only concern about the budget would be that it is on the tight side, particularly in terms of the time of the research coordinator (1 day/week), analyst, and knowledge broker. I am especially concerned that if this budget is cut down further it may not be possible to complete the work with the amount of available staff time.*

Answer: Following the reviewer's comments, we have increased the budget and extended the timeline from two years to three years.

Reviewer 2: No comments warranting a reply (all positive)

Scientific Officer's summary: (including only comments that were not addressed above)

Some concern raised regarding discussion of use of IV which was not sufficiently described.

Answer: We have expanded on the IV methodology.

Question whether propensity score approach with appropriate matching could be considered

Answer: We have experience with and have considered using propensity score matching. At this time, we think propensity score matching does not offer any obvious advantages over multivariate proportional hazard modelling, however, we will explore this in more detail as we perform the analyses.

Unclear whether it will be possible to obtain list of Family Health Teams with pharmacist participation.

Answer: In addition to information available from the Ministry of Health and Long-Term Care, we have contacted the Association of Family Health Teams of Ontario (AFHTO) to obtain a list of Family Health Teams (FHT) and their characteristics, including the presence or absence of a pharmacist, as well as other characteristics such as FHT size, number of physicians in the FHT, and other patient and physician-level co-variates.

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PROTECTED WHEN COMPLETED

Appl. # 287245

Application for Funding – Budget

Funding Opportunity

Operating Grant 2012-09-17

Nominated Principal Applicant/Candidate

Last Name	First Name	Institution
BJERRE	Lise	Bruyère Research Institute/Institut de recherche Bruyère

Financial Assistance Requested **Year** 1

Research Staff (excluding trainees)	**No.**	**Salary**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Research Assistants	0.3	$17,550	$4,212	$21,762	$0	$0	$21,762
Technicians	0.0	$0	$0	$0	$0	$0	$0
Other personnel (as specified in Employment History)	0.0	$0	$0	$0	$0	$0	$0

Research Trainees	**No.**	**Stipend**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Postdoctoral Fellows (post PHD, MD, etc.)	0.0	$0	$0	$0	$0	$0	$0
Graduate Students	0.0	$0	$0	$0	$0	$0	$0
Summer Students	0.0	$0	$0	$0	$0	$0	$0

Materials, Supplies and Services	**CIHR**	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Animals	$0	$0	$0	$0
Expendables	$2,399	$0	$0	$2,399
Services	$38,772	$0	$0	$38,772
Other (as specified in the Details of Financial Assistance Requested)	$421	$0	$0	$421

	CIHR	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Travel	$0	$0	$0	$0
Total Operating	$63,354	$0	$0	$63,354
Total Equipment	$0	$0	$0	$0
Total Request	$63,354	$0	$0	$63,354

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PROTECTED WHEN COMPLETED

Appl. # 287245

Application for Funding – Budget

Funding Opportunity

Operating Grant 2012-09-17

Nominated Principal Applicant/Candidate

Last Name	First Name	Institution
BJERRE	Lise	Bruyère Research Institute/Institut de recherche Bruyère

Financial Assistance Required **Year** 2

Research Staff (excluding trainees)	**No.**	**Salary**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Research Assistants	0.3	$17,989	$4,317	$22,306	$0	$0	$22,306
Technicians	0.0	$0	$0	$0	$0	$0	$0
Other personnel (as specified in Employment History)	0.0	$0	$0	$0	$0	$0	$0

Research Trainees	**No.**	**Stipend**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Postdoctoral Fellows (post PHD, MD, etc.)	0.0	$0	$0	$0	$0	$0	$0
Graduate Students	0.0	$0	$0	$0	$0	$0	$0
Summer Students	0.0	$0	$0	$0	$0	$0	$0

Materials, Supplies and Services	**CIHR**	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Animals	$0	$0	$0	$0
Expendables	$400	$0	$0	$400
Services	$61,685	$0	$0	$61,685
Other (as specified in the Details of Financial Assistance Requested)	$4,924	$0	$0	$4,924

	CIHR	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Travel	$6,015	$0	$0	$6,015
Total Operating	$95,330	$0	$0	$95,330
Total Equipment	$0	$0	$0	$0
Total Request	$95,330	$0	$0	$95,330

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PROTECTED WHEN COMPLETED

Appl. # 287245

Application for Funding – Budget

Funding Opportunity

Operating Grant 2012-09-17

Nominated Principal Applicant/Candidate

Last Name	First Name	Institution
BJERRE	Lise	Bruyère Research Institute/Institut de recherche Bruyère

Financial Assistance Requested **Year** 3

Research Staff (excluding trainees)	**No.**	**Salary**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Research Assistants	0.3	$18,438	$4,425	$22,863	$0	$0	$22,863
Technicians	0.0	$0	$0	$0	$0	$0	$0
Other personnel (as specified in Employment History)	0.0	$0	$0	$0	$0	$0	$0

Research Trainees	**No.**	**Stipend**	**Benefits**	**CIHR**	**Other Funding Sources**		**Total**
					Cash*	**In-Kind***	
Postdoctoral Fellows (post PHD, MD, etc.)	0.0	$0	$0	$0	$0	$0	$0
Graduate Students	0.0	$0	$0	$0	$0	$0	$0
Summer Students	0.0	$0	$0	$0	$0	$0	$0

Materials, Supplies and Services	**CIHR**	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Animals	$0	$0	$0	$0
Expendables	$400	$0	$0	$400
Services	$37,268	$0	$0	$37,268
Other (as specified in the Details of Financial Assistance Requested)	$5,171	$0	$0	$5,171

	CIHR	**Other Funding Sources**		**Total**
		Cash*	**In-Kind***	
Travel	$2,220	$0	$0	$2,220
Total Operating	$67,922	$0	$0	$67,922
Total Equipment	$0	$0	$0	$0
Total Request	$67,922	$0	$0	$67,922

Human Resources

Surname	Given Names	Role	Hours / week
BJERRE	Lise	Nominated Principal Applicant/Ca	4
CAHIR	Caitriona	Co-Applicant	1
HALIL	Roland	Co-Applicant	1
MANUEL	Douglas	Co-Applicant	1
RAMSAY	Timothy	Co-Applicant	1

BUDGET JUSTIFICATION: OVERVIEW

We have developed the budget based on considerable experience with similar projects (LMB, DM, TR). Our total budget request for the three year PIP-STOPP study is $226,606.83, of which $134,575.00 will be for ICES-related expenses. The balance of $92,031.83 (non ICES-related expenses) will be to cover expenses related to hiring a research coordinator, and to cover grant submission support, ethics approval support, meeting coordination, knowledge translation and travel expenses.

RESEARCH STAFF

CIHR Request:
Year 1: $**21,762.00**
Year 2: $**22,306.05**
Year 3: **$22,863.70**

Research Coordinator– Year 1: $21,762.00/ Year 2: $22,306.05/ Year3: $22,863.70

Year 1: 0.3 FTE
Year 2: 0.3 FTE
Year 3: 0.3 FTE

The 0.3 FTE Research Coordinator will be responsible for the management and timelines of the study. The research coordinator position will be based at the Bruyère Research Institute. Tasks will include:

- Detailed planning, execution and monitoring of programmatic issues including schedules, progress, coordination, deliverables, milestones, financial/budget reports, and project status.
- Assisting with quantitative analysis
- Obtaining articles
- Maintaining a reference database
- Assisting with the writing, designing, presenting and editing of manuscripts, reports, and abstracts.
- Assisting with the application process to obtain institutional ethics approval

Up to half of the hours allocated for this position may be worked by a Research Coordinator in Ireland, in assistance to Dr. Cahir, a Co-Investigator on this Canadian project.

Based on pay rates at the CT Lamont Primary Health Care Research Centre and the Bruyère Research Institute, an individual performing these duties would expect to earn $30/hr +14% in lieu of benefits + 10% employer tax (amounting, together, to 24%). A 2.5% per year increase is included after Year 1 for increased cost of living.

Year 1 Total Salary: $30/hr * 11.25 hr/wk * 52 wks/yr * 1.24 = $21,762.00
Year 2 Total Salary: $30/hr * 11.25 hr/wk * 52 wks/yr * 1.24 * 1.025 = $22,306.05
Year 3 Total Salary: $30/hr * 11.25 hr/wk * 52 wks/yr * 1.24 * 1.025 * 1.025 = $22,863.70

MATERIALS, SUPPLIES AND SERVICES

CIHR Request:
Year 1: $41,171.00
Year 2: $62,085.00
Year 3: $37,668.00

Expendables– Year 1: $2,399.00 / Year 2: $400.00 / year 3: $400.00

$2,399.00 has been allocated for Year 1, and $400.00 for each of Years 2 and 3. Part of this amount is budgeted to cover the cost of general office supplies ($100.00), and the printing and photocopying of research materials for analysis ($300.00). Of this annual allotment of $400.00, half is designated for supplies at BRI, while the other half is to go to ICES to cover the office supply, photocopying and printing expenses there. The other $1,999.00 has been budgeted to cover the cost of a desktop computer on which the Research Coordinator will work.

Services– Year 1: $38,772.00/ Year 2: $59,585.00/ Year 3: $36,218.00

ICES Contracted Data Services

ICES is a non-affiliated non-profit corporation and maintains a data repository for the province of Ontario of linked administrative, population health, clinical and other data files, including electronic medical records and registries. The infrastructure costs for the work described in this application are not covered by CIHR funding to universities or other research institutions in Ontario.
ICES data and ICES contracted data services will be required for completion of this project. The costs of ICES data services enumerated here include pro rata charges for the following : ICES staff time for data linkage, de-identification, documentation, quality assurance, maintenance and storage; technology services and infrastructure, including software and technology controls that are required to ensure the privacy of the data and to meet ICES prescribed entity legislative requirements; technology and network infrastructure required to store and support access to the data holdings for scientists, including servers, software licenses, applications, network connection, maintenance and support services and off-site back-up storage and disaster recovery. The charges have been calculated proportional to the staff time for the data analyst working on the project.
In addition to the above data services, this project will require the following ICES staff time:

ICES Analyst:
Year 1: 0.3 FTE/ Year 2: 0.45 FTE/ Year 3: 0.15 FTE
Year 1: $34,171/ Year 2: $52,538/ Year 3: $34,071
Data storage services– Year 1: $4,601.00/ Year 2: $7,047.00/ Year 3: $2,147.00

Total ICES data contracted costs: $134,575.00

Knowledge brokerage services–Year 2: $2,100.00/ Year 3: $1,050.00

We have budgeted $3,150.00 for a knowledge broker's time to develop the KT products outlined in our grant proposal. This includes drafting plain language summaries and consulting on manuscripts and other KT products. We expect this to amount to a total of 15 days of work at $28 per hour.

Other– Year 1: $420.90 / Year 2: $4,924.28 / Year 3: $5,170.90

Telephone costs– Year 1: $420.90 / Year 2: $420.90 / Year 3: $420.90

Telephone costs will be required for calls for monthly teleconferences with the investigators and research coordinators to discuss project progression (5 participants local, 2 international). We estimate $31.80 plus tax/month for 36 months. This calculation is based on rates provided by A.C.T. Teleconferencing:

($ 0.05 per minute (within Canada) x 60 minutes (per month) x 5 lines) + ($0.14 per minute (from Ireland) x 60 minutes (per month) x 2 lines) = $31.80 per month x 12 months per year = $381.60, plus post-rebate tax amount (10.3%) of $39.30 = $420.90 per year

Publishing- Year 3: $4,000.00
We are requesting $4,000 for the publication of two open access peer-reviewed articles related to our study.

Poster printing- Year 2: $1,600.00
We are requesting $1,600 for the printing of 4 posters on the study, to be presented at conferences and meetings to disseminate results.

Conference Registration- Year 2: $2,903.38 / Year 3: $750.00
We are requesting a total of $3,653.38 to cover the cost to register one investigator at four conferences, for the purpose of knowledge dissemination. The conferences we would like to attend, their dates, locations and their registration fees are as follows:

Table 1. Conference Registration Fees

Conference	Location	Dates	Registration fee
29 ICPE (2014) (International Conference on Pharmacoepidemiology and Therapeutic Risk Management)	location TBD	August 2014	**Estimated at $1,000**
FMF 2014 (Family Medicine Forum)	Quebec city, QC	November 2014	**$1166.81** (cost estimate based on the 2011 fee, estimated 3% price increase per year and post-rebate tax amount of 10.3%)
42nd NAPCRG (2014) Annual Meeting (North American Primary Care Research Group)	New York, NY	22-11-2014 to 25-11-2014	**$736.57** (cost estimate based on the 2011 fee, estimated 5% price increase and 10.3% post-rebate tax amount.
CAHSPR 2015 (Canadian Association for Health Services and Policy Research)	Location TBD	TBD, likely May 2015	**Estimated at $750.00**

TRAVEL

CIHR Request:
Year 2: $6,015.00
Year 3: $2,220.00

In order to complete and disseminate the results of this project, the investigators will incur some travel-related expenses. The travel funds requested are to cover the travel expenses incurred by having one investigator attend each of the four conferences outlined above (with no travel costs budgeted for the conference local to Ottawa).

Flight costs are best estimates based on internet searches. Meals are budgeted as per the BRI travel policy, which is $15 for breakfast, $25 for lunch, and $40 for dinner.

Travel to conferences– Year 2: $6,015.00 / Year 3: $2,220.00

We are requesting a total of $8,235.00 (excluding conference registration fees, which are budgeted for separately) for one of the investigators to travel to the four conferences we would like him or her to attend for knowledge translation. Details such as date and registration fees for the conferences can be seen in Table 1. Costs for the conferences are outlined in Table 2, below.

Table 2. Conference travel expenses.

Conferences	Expenses				
	Flight/train (roundtrip from Ottawa)	Taxi (roundtrip from airport/train station to hotel)	Hotel	Meals	Total travel costs
ICPE 2014 (TBD)	$850.00	$50.00 (estimate, do not yet know location)	$800.00 (4 nights, based on an estimate of $200.00 per night, as the hotel is unknown)	$320 (breakfast, lunch and dinner x4)	$2020.00
FMF 2014 (Quebec City)	$500.00 (Westjet)	$75.00	$1,030.00 (4 nights, at $250.00 per night)	$320 (breakfast, lunch and dinner x4)	$1,925.00
NAPCRG 2014 (New York)	$700.00 (Westjet)	$50.00 (estimate, do not yet know location)	$1,000.00 (4 nights, based on an estimate of $250.00 per night, as the hotel is unknown)	$320 (breakfast, lunch and dinner x4)	$2,070.00
CAHSPR 2015 (Location TBD)	$850.00	$50.00 (estimate, do not yet know location)	$1,000.00 (4 nights, based on an estimate of $250.00 per night, as the hotel is unknown)	$320 (breakfast, lunch and dinner x4)	$2,220.00

RELEVANCE FORM | FORMULAIRE DE PERTINENCE

Title of Research Proposal l Titre de la proposition de recherche :

Assessing Potentially Inappropriate Prescribing (PIP) and predicting patient outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)

Relevant Research Area |Thème de recherche pertinent *:*

Aging (Bridge Funding)

Title of Priority Announcement | Titre de la proposition de recherche :

Aging (Bridge Funding)

Description | Description :

Adverse drug events (ADE) are common in the elderly, who are particularly vulnerable to them due to changes in their physiology that occur with aging and disease. Many of these adverse drug events are avoidable if due attention is directed toward identifying and preventing inappropriate drugs and undesirable drug combinations. The PIP/STOPP study will use the modified Screening Tool of Older Persons' for potentially inappropriate Prescriptions (STOPP) criteria and Ontario health administrative databases to assess the impact of inappropriate prescribing on individual patients as well as on the health care system.

The study will describe the occurrence of potentially inappropriate prescribing (PIP) in Ontario's elderly (>65 years) population, assess the health and economic burden associated with it, and evaluate a measure aimed at mitigating its effects. Identifying significant associations could provide evidence to support important policy interventions aimed at effectively reducing PIP and its consequences.

By pursuing research designed to reduce inappropriate prescribing in elderly populations, this study is particularly relevant to promoting healthy and successful aging, health services and policy relating to older people, as well as aging and maintenance of functional autonomy. With better prescribing and fewer adverse drug events, elderly people are more likely to spend more time in good health.

ASSOCIATION MÉDICALE CANADIENNE
CANADIAN MEDICAL ASSOCIATION

August 22, 2012

Dear Dr. Lise Bjerre:

It is my pleasure to write a letter of support for the *PIP-STOPP* project. As Canadian demographics change and the population matures, an ever-increasing number of people are dependent on medication prescribed by their primary health practitioner. Research suggests that Potentially Inappropriate Prescribing (PIP) in patients over the age of 65 results in costly emergency room visits and unplanned hospitalizations, to say nothing of the impact suboptimal prescribing can have on the individual. The overprescribing of some medication and the underuse of others is well documented in the hospital setting but we know less about what happens at the population level and the associated costs to the health care system. This proposed study, using existing data from Ontario's health administrative database, will fill in some of those gaps and help to create a more complete picture of suboptimal prescribing while aiding in the development of tools to improve prescribing practices in primary care.

The *PIP-STOPP* project promises to examine many of the questions that the Optimal Prescribing Working Group I represent has identified as important to our understanding of suboptimal prescribing. This working group, supported by an initial grant from the Canadian Institute for Health Research and comprised of medical organizations, partners from the non-profit sector and pharmacists, is united in its commitment to optimal prescribing practices and working with various stakeholders to achieve that goal. Further details of our initiative may be found in the *Canadian Family Physician* 2012; 58: 820-22.

In recent years there has been significant interest in the assessment of optimal prescribing practice and in using that knowledge to affect change in areas where suboptimal prescribing is taking place. The *PIP-STOPP* project will advance our understanding of prescribing activities and offers great potential for direct knowledge translation to influence the clinical behaviour of individual prescribers.
I am delighted to support this timely and relevant project and look forward to the results.

Kind regards,

Samuel Shortt, MD PhD, FCFP
Director of Knowledge Transfer and Practice Policy

ICES Institute for Clinical Evaluative Sciences

Twenty Years • 1992-2012

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CANADA

September 4, 2012

Dr. Doug Manuel
Scientist
Institute for Clinical Evaluative Sciences
- Ottawa Site
c/o G1 06, 2075 Bayview Avenue
Toronto, ON M4N 3M5

Dear Dr. Manuel: Doug

Re: **Grant Title:** "Assessing Potentially Inappropriate Prescribing (PIP) and predicting patient outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)"

The Institute for Clinical Evaluative Sciences (ICES) is pleased to provide support for the detailed grant application by you and your colleagues, entitled "*Assessing Potentially Inappropriate Prescribing (PIP) and predicting patient outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)*".

While the project falls within the general mandate of ICES, it is not on our schedule of projects, and therefore we cannot cover the costs from our own budget. However, we will provide 'in-kind' support. Thank you for taking the initiative regarding obtaining funds from the Canadian Institutes of Health Research (CIHR).

We have estimated the costs of data analysis and other support services at ICES related to the project. These figures are included in your budget.

ICES has considerable experience with data linkages, and these will be done under the strictest conditions of security and confidentiality.

We wish you every success with the application.

Yours sincerely.

David Henry, MBChB MRCP FRCP (Edin) & Carl van Walraven, MD FRCP(C) MSc
President and CEO Site Director, ICES@uOttawa Facility

BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2010.03628.x

Potentially inappropriate prescribing and cost outcomes for older people: a national population study

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Keywords
elderly, inappropriate prescribing, medication cost, population based, Screening Tool of Older Peoples Prescriptions (STOPP)

Received
24 September 2009

Accepted
13 January 2010

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Potentially inappropriate prescribing (PIP) refers to medications that should generally be avoided in older populations and doses or frequencies of administrations that should not be exceeded. Studies of PIP have been primarily based on US indicators of appropriateness such as the Beers criteria due to the lack of European specific indicators.
- PIP has not been assessed in full national samples.
- The total cost of PIP drugs and the cost in relation to overall national pharmaceutical expenditure have not been described.

WHAT THIS STUDY ADDS

- One third of the Irish population aged ≥70 years were prescribed at least one potentially inappropriate medication in 2007 based on European criteria.
- There was a signficant association between polypharmacy and the risk of PIP. Polypharmacy was evaluated as the number of different repeat drug classes (≥ three prescription claims) per claimant.
- The most prevalent PIP drugs were: proton pump inhibitors at maximum therapeutic dosage for >8 weeks (40 mg daily omeprazole, pantoprazole and esomeprazole, 30 mg daily lansoprazole and 20 mg daily rabeprazole); non-steroidal anti-inflammatories for >3 months; long-acting benzodiazepines for >1 month and drug duplication within the same therapeutic class.
- The total expenditure on potentially inappropriate drugs was €45 631 319 in 2007 which is 9% of the overall expenditure on pharmaceuticals in those aged ≥70 years in Ireland.

AIMS

Optimization of drug prescribing in older populations is a priority due to the significant clinical and economic costs of drug-related illness. This study aimed to: (i) estimate the prevalence of potentially inappropriate prescribing (PIP) in a national Irish older population using European specific explicit prescribing criteria; (ii) investigate the association between PIP, number of drug classes, gender and age and; (iii) establish the total cost of PIP.

METHODS

This was a retrospective national population study (n = 338 801) using the Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database. The HSE-PCRS uses the WHO Anatomical Therapeutic Chemical (ATC) classification system and details of every drug dispensed and claimants' demographic data are available. Thirty PIP indicators (STOPP) were applied to prescription claims for those ≥70 years in Ireland in 2007. STOPP is a physiological system based screening tool of older persons' potentially inappropriate prescriptions assessing drug–drug and drug–disease interactions, dose and duration.

RESULTS

In our study population PIP prevalence was 36% (121 454 claimants). The main contributors to this were: 56 560 (17%) prescribed proton pump inhibitors at maximum therapeutic dose for >8 weeks, 29 691 (9%) prescribed non-steroidal anti-inflammatories for >3 months, 17 676 (5%) prescribed long-acting benzodiazepines for >1 month and 16 201 (5%) prescribed duplicate drugs. The main determinant of PIP was polypharmacy. The likelihood of PIP increased with a significant linear and quadratic trend ($P < 0.0001$) with the number of drug classes. The maximum net ingredient cost of PIP was estimated to be €38 664 640. Total PIP expenditure was estimated to be €45 631 319, 9% of the overall expenditure on pharmaceuticals in those ≥70 years in 2007.

CONCLUSIONS

The findings identify a high prevalence of PIP in Ireland with significant cost consequences.

Introduction

Optimization of drug prescribing in older populations is a priority due to the significant clinical and economic costs of drug related illness. Inappropriate prescribing in older people is associated with increases in morbidity, adverse drug events, hospitalization and mortality [1, 2]. However the selection of appropriate medication in older people is a challenging and complex process. Older people are particularly vulnerable to inappropriate prescribing because of their multiple drug regimens, co-morbid conditions and age associated physiological changes which can alter their pharmacokinetics and enhance their pharmacodynamic sensitivity to specific drugs [3]. In general, medicines in older people are considered appropriate when they have a clear evidence-based indication, are well tolerated in the majority and are cost-effective. In contrast, medicines that are potentially inappropriate have no clear evidence-based indication, carry a substantially higher risk of adverse side-effects compared with use in younger people or are not cost effective [4].

Appropriateness of prescribing in older people can be assessed by process (i.e. what providers do) or outcome measures (i.e. patient outcomes) which are implicit or explicit [3]. Implicit process measures are based on a clinician's judgment of appropriateness for the individual patient [5]. Explicit process measures are criterion based and are developed from published reviews, expert opinion and/or consensus techniques and should be generalizable across countries [6]. These measures consist of drugs to be avoided in older people, independent of diagnoses or in the context of certain diagnoses [7–9].

The US Beers criteria are the most frequently used and validated explicit process measure [10, 11]. However in the context of European prescribing Beers criteria have several limitations. Some of the limitations include the fact that almost half of the drugs that make up the criteria are unavailable for prescribers [12, 13], several of the drugs are not contra-indicated in older people as per the British National Formulary (BNF), e.g. doxazosin [4], whereas other contra-indicated drugs are omitted [13]. The Beers criteria do not consider drug–drug interactions, duration of treatment, varying indications for certain drugs, e.g. low-dose amitriptyline and neuropathic pain (BNF) and underuse of indicated drugs [3, 4]. Given the limitations of the Beers criteria, a more comprehensive explicit process measure of potentially inappropriate prescribing (PIP) has recently been developed and validated for use in European countries, the Screening Tool of Older Peoples Prescriptions (STOPP) [14].

There have been few studies of PIP in the general population of older people [12, 15, 16]. Previous research is limited by having focused on specific groups in particular settings such as geriatric units, nursing homes and hospitals as well as having measured PIP using Beers criteria. There is also a limited understanding of the risk factors associated with PIP and results from previous studies have been inconclusive [11, 15, 17]. The overall aim of this study was to estimate the prevalence of PIP in the national Irish population aged ≥70 years, in 2007 using thirty STOPP criteria. Additional objectives included: (i) estimation of the prevalence of PIP per individual STOPP criteria by physiological system; (ii) investigation of the association between PIP, number of drug classes, gender and age and; (iii) establishing the total cost of PIP drugs and the cost in relation to overall national pharmaceutical expenditure.

Methods

Study population

The National Shared Services Primary Care Reimbursement Service of the Health Service Executive in Ireland (HSE-PCRS) pharmacy claims database of dispensed medications was used to identify the study population. The HSE-PCRS general medical card scheme provides free health services including medications to eligible persons in Ireland. The HSE-PCRS scheme is means tested for those less than 70 years of age, and free to all those ≥70 years between July 2001 and December 2008. It is estimated that over 97% of this age group nationally avail of the scheme [18].

The HSE-PCRS pharmacy claims database provides details on monthly dispensed medications for each individual within the scheme. Prescriptions are coded using the World Health Organisation Anatomical Therapeutic Chemical (ATC) classification system [19] and prescriber information, defined daily doses (DDD), strength, quantity, method and unit of administration of each drug dispensed, ingredient costs and pharmacist dispensing fees per item dispensed are available. Gender, age group and health board region of each claimant is also recorded, but no diagnosis or outcomes are reported.

Explicit measurement of potentially inappropriate prescribing

STOPP is a physiological system based screening tool and comprises sixty-five clinically significant criteria which take drug–drug and drug–disease interactions, drug doses and duration into consideration [14]. STOPP considers cost-effectiveness as well as clinical effectiveness and includes the removal of any potentially unnecessary drugs. STOPP was validated using the Delphi consensus technique by an eighteen member expert panel in geriatric pharmacotherapy from the UK and Ireland. Inter-rater reliability is high [14, 20].

Thirty STOPP criteria were applied to prescription claims data for all those aged 70 years and older in Ireland in 2007 (supplemental Table S1). The thirty criteria were considered applicable to pharmacy claims data without diagnosis information on a consensus basis by an

expert panel of five members in geriatric pharmacotherapy, clinical pharmacology, pharmacoepidemiology and academic general practice. Prescription drugs for the treatment of certain disease conditions were identified and used as proxies for diagnosis where possible, e.g. dementia (ATC, N06D), Parkinson's disease (ATC, N04), epilepsy (ATC, N03, excluding gabapentin and pregabalin as also prescribed for neuropathic pain, BNF 4.7.3), chronic obstructive pulmonary disease (COPD) (ATC, R03BA, R03BB, R03CC02, R03CC03, R03DA04), glaucoma (ATC, S01ED), type 2 diabetes (ATC, A10B), gout (ATC, M04AA01) [18, 21]. Duplicate classes of medicine (on the same prescription claim) were assessed for five medications – opiates, non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin re-uptake inhibitors (SSRIs), loop diuretics and angiotensin converting enzyme inhibitors (ACE inhibitors).

Criteria which specified a particular duration were assessed by consecutive months of prescription refills for the period commencing January 2007 to December 2007 (lead-in period October to December 2006 included) e.g. long-acting benzodiazepines >1 month, NSAIDs >3 months. Criteria which specified a particular dosage that should not be exceeded e.g. proton pump inhibitors (PPIs) at maximum therapeutic dosage for >8 weeks (40 mg daily omeprazole, pantoprazole and esomeprazole, 30 mg daily lansoprazole and 20 mg daily rabeprazole) were evaluated by calculating the prescribed daily dose for each claimant according to details on the DDD, strength, quantity, administration, unit of measurement and packsize of the dispensed medication for the specified time period. The duration and dosage of PPI prescribing was assessed for a 1 year continuous period for each claimant e.g. January 2007 to January 2008 (baseline period 8 weeks at maximum therapeutic dosage). PPI dosage was classified as maximum or maintenance dosage at the end of each month according to the calculated prescribed monthly dose.

Claimants were categorized by gender and age group (70–74 years) and (≥75 years). The total number of prescriptions for each different drug class (the first three characters of the ATC code) was calculated for each claimant over the year; each claimant was required to receive at least three prescriptions per different drug class to be included as a measure of a repeat drug class. Polypharmacy was evaluated as the number of different repeat drug classes per claimant ranging from zero (reference group) to ten or more drug classes [15, 22, 23]. Costs were calculated as the net ingredient cost (NIC) of the dispensed drug and the total expenditure which included NIC, value added tax and pharmacist dispensing fee. Costs were adjusted for claimants receiving the same medication for more than one criteria. Costs also excluded the duration of prescribing that was deemed appropriate, e.g. 1 month for long-acting benzodiazepines, 3 months for NSAIDs.

Data analysis

The overall prevalence of PIP and the prevalence per individual STOPP criteria in 2007 were calculated as a proportion of all eligible persons ≥70 years. The association between any (*vs.* no) PIP and polypharmacy (categorized as 0 *vs.* 1, 2, ... 10+ repeat drug classes), age and gender was assessed using logistic regression presenting adjusted odds ratios (OR) and 95% confidence intervals. Finally, the maximum NIC and total expenditure for all potentially inappropriate medications in 2007 were calculated. Data analysis was performed using SAS statistical software package version 9.1 (SAS Institute Inc. Cary, NC, USA). Statistical significance at $P < 0.05$ was assumed.

Results

Population descriptive statistics

In 2007, a total of 338 801 people ≥70 years in Ireland were identified from the HSE-PCRS pharmacy database of which 194 460 (57%) were female and 210 515 (62%) were aged ≥75 years.

Overall prevalence of PIP in 2007

The overall prevalence of PIP in 2007 considering all thirty STOPP criteria was 36% (121 454). A quarter of the population, 83 959 individuals, were prescribed one potentially inappropriate medication, 27 392 (8%) were prescribed two and 10 103 (3%) were prescribed three or more.

Prevalence of PIP according to individual STOPP criteria in 2007

Table 1 presents the prevalence of each of the individual STOPP criteria by physiological system. PPIs at maximum therapeutic dosage for >8 weeks was the most frequently prescribed potentially inappropriate drug (56 560, 17%). In this group, 42 151 (75%) continued on PPI therapy for 6 consecutive months with 23 263 (41%) on PPI therapy for a 1 year continuous period. Of those on PPI therapy for a 1 year continuous period, the majority 22 067 (95%) of individuals were prescribed maximum therapeutic dosage (Figure 1).

The second most frequently prescribed potentially inappropriate drugs were NSAIDs for >3 consecutive months, followed by long-acting benzodiazepines and duplicate drugs on the same prescription claim. NSAIDs and opiates were the most frequently prescribed duplication drugs (Table 1). Other STOPP criteria had lower prevalence rates but some were noteworthy as a proportion of the population taking a particular drug for a particular condition, e.g. one-fifth of those with COPD were prescribed β-adrenoceptor blockers.

Factors associated with overall PIP

There was a strong association between PIP and polypharmacy. The likelihood of PIP increased with a significant

Table 1

Prevalence of potentially inappropriate prescribing by individual STOPP criteria in 2007

Criteria description	*n*	%	Proportionate prescribing per indication (%)*
Cardiovascular system			
Digoxin >125 μg day^{-1} (increased risk of toxicity)	1 211	0.36	4.97
Thiazide diuretic with gout (exacerbate gout)	1 216	0.36	10.34
β-adrenoceptor blocker with COPD† (risk of increased bronchospasm)	7 924	2.34	21.20
β-adrenoceptor blocker with verapamil (risk of symptomatic heart block)	800	0.24	–
Aspirin and warfarin without histamine H_2-receptor antagonist (except cimetidine) or PPI† (high risk of gastrointestinal bleeding)	3 693	1.09	2.69
Dipyridamole as monotherapy for cardiovascular secondary prevention (no evidence of efficacy)	219	0.06	–
Aspirin >150 mg day^{-1} (increased bleeding risk)	5 712	1.69	3.58
Central nervous system and psychotropic drugs			
TCA† with dementia (worsening cognitive impairment)	609	0.18	4.34
TCA and glaucoma (exacerbate glaucoma)	465	0.14	4.44
TCA and opiate or calcium channel blockers (risk of severe constipation)	6 944	2.05	–
Long-term (i.e. >1 month), long-acting benzodiazepines (risk of prolonged sedation, confusion, impaired balance, falls)	17 676	5.22	40.37
Long-term (i.e. >1 month) neuroleptics (risk of confusion, hypotension, extrapyramidal side-effects, falls)	5 688	1.67	13.96
Long-term (i.e. >1 month) neuroleptics with parkinsonism (worsen extrapyramidal symptoms)	1 298	0.38	13.87
Anticholinergics to treat extrapyramidal side effects of neuroleptic medications (risk of anticholinergic toxicity)	1 527	0.45	71.43
Phenothiazines with epilepsy (may lower seizure threshold)	813	0.24	7.69
Prolonged use (i.e. >1 week) of first-generation antihistamines (risk of sedation and anti-cholinergic side-effects)	3 248	0.96	85.71
Gastrointestinal system			
Prochlorperazine or metoclopramide with parkinsonism (risk of exacerbating parkinsonism)	726	0.21	7.66
PPI for peptic ulcer disease at maximum therapeutic dosage for >8 weeks‡ (dose reduction or earlier discontinuation indicated)	56 560	16.69	38.89
Respiratory system			
Theophylline with COPD (risk of adverse effects due to narrow therapeutic index)	4 008	1.18	10.69
Nebulized ipratropium with glaucoma (exacerbate glaucoma)	50	0.01	0.32
Musculoskeletal system			
Long-term use of NSAID† (i.e. >3 months) for pain relief (simple analgesics preferable)	29 691	8.76	23.19
Warfarin and NSAID (risk of gastrointestinal bleeding)	2 535	0.75	–
Urogenital system			
Antimuscarinic drugs with dementia (risk of increased confusion, agitation)	1 568	0.46	7.21
Antimuscarinic drugs with chronic glaucoma (>3 months) (risk of acute exacerbation of glaucoma)	0	<0.01	–
Endocrine system			
Glibenclamide or chlorpropamide with type 2 diabetes mellitus (risk of prolonged hypoglycemia)	976	0.29	3.27
Duplicate drug class prescription (optimization of monotherapy within a single drug class)			
Two concurrent opiates	4 185	1.24	6.18
Two concurrent NSAIDs	7 532	2.22	5.88
Two concurrent SSRIs†	79	0.02	0.19
Two concurrent antidepressants	834	0.25	4.56
Two concurrent loop diuretics	332	0.10	0.58
Two concurrent ACE inhibitors†	3 643	1.08	4.10
All duplicates	16 201§	4.78	–

*Proportionate prescribing per indication, e.g. prevalence of STOPP criteria as a proportion of the overall disease or drug prevalence, e.g. digoxin >125 μg as a proportion of overall digoxin prevalence, β-adrenoceptor-blocker with COPD as a proportion of COPD prevalence. †COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; TCA, tricyclic antidepressant; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin re-uptake inhibitor; ACE inhibitors, angiotensin converting enzyme inhibitors. ‡Proton pump inhibitor (PPI) at maximum therapeutic dose = 40 mg daily omeprazole, pantoprazole and esomeprazole. 30 mg daily lansoprazole and 20 mg daily rabeprazole. §Adjusted for those receiving more than one duplicate prescription.

linear and quadratic trend ($P < 0.0001$) with the number of different drug classes (Figure 2). PIP was more likely in females *vs.* males after adjusting for age [odds ratio 1.10, 95% confidence intervals (CI) 1.08, 1.12] and those aged ≥75 years compared with 70–74 years after adjusting for gender (OR 1.28, 95% CI 1.26, 1.30). The strength of the association between PIP and gender and age was reduced after additionally adjusting for polypharmacy (gender (F *vs.* M), OR 0.91, 95% CI 0.90, 0.93); (age (≥75 years *vs.* 70–74 years) OR 0.95, 95% CI 0.93, 0.96). No significant collinearity was found between age, gender and polypharmacy.

Factors associated with individual STOPP criteria

There was an association between gender and age and the individual STOPP criteria after adjusting for polypharmacy

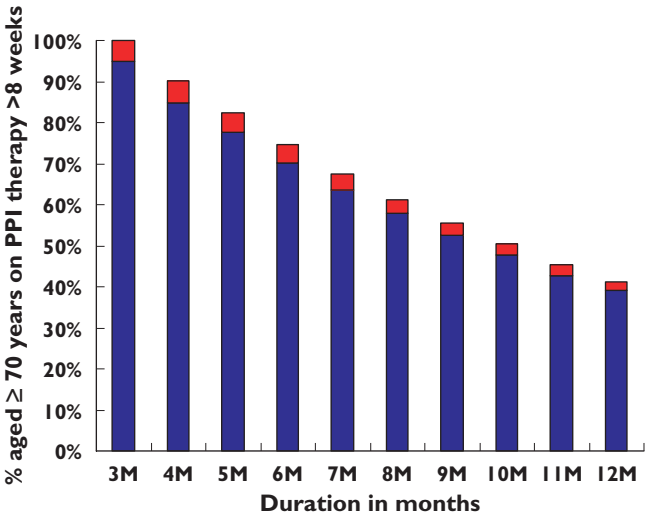

Figure 1

Duration and dosage of PPI therapy for a 1 year continuous period in patients aged ≥70 years on PPI therapy for >8 weeks at maximum therapeutic dosage. 1 year period- January 2007 to January 2008, February 2007 to February 2008. Dosage is the dose at the end of each month. Maximum therapeutic dose = 40 mg daily omeprazole, pantoprazole and esomeprazole, 30 mg daily lansoprazole and 20 mg daily rabeprazole. Maintenance therapeutic dose = 10–20 mg daily omeprazole, 20 mg daily pantoprazole and esomeprazole, 15 mg daily lansoprazole and 10 mg daily rabeprazole. Maintenance dosage (■); Maximum dosage (■)

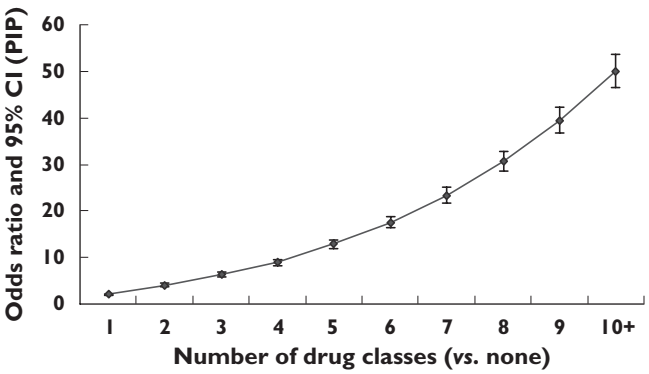

Figure 2

The association between polypharmacy and PIP in 2007. Repeat prescriptions (minimum of three per year). Odds ratio = odds ratio of any potentially inappropriate drug adjusted for gender and age (reference = 0)

(Table 2). Psychotropic drugs such as tricyclic antidepressants (TCAs) and long-acting benzodiazepines, NSAIDs for >3 months duration and duplicate drug classes on the same prescription claim were more likely to be prescribed in females compared with males. Potentially inappropriate cardiovascular drugs, e.g. aspirin >150 mg day^{-1} and respiratory drugs were more likely to be prescribed in males compared with females. The prescribing of digoxin >125 µg, TCAs and antimuscarinic drugs with dementia and duplicate loop diuretics was twice as likely in the older age group (≥75 years) compared with the younger age group (70–74 years).

Cost of potentially inappropriate prescribing in 2007

The total NIC of PIP in 2007 was estimated to be €38 664 640, on average €318 per claimant per year. The total expenditure was estimated to be €45 631 319 which was 9% of the overall expenditure on pharmaceuticals in those aged ≥70 years in Ireland in 2007 [24]. Table 3 presents a breakdown of the NIC and total expenditure on potentially inappropriate medication in 2007 for the highest cost items.

Discussion

Principal findings

This national population based study found that 36% of those ≥70 years received at least one potentially inappropriate medication in 2007 according to the STOPP criteria. The most prevalent PIP drugs were PPIs at maximum therapeutic dosage for >8 weeks, followed by NSAIDs for >3 months and long-acting benzodiazepines for >1 month. The majority of older people prescribed PPIs in 2007 were on PPI therapy for 6 or more consecutive months at maximum therapeutic dosage. Drug duplication on the same prescription claim was also highly prevalent with NSAIDs and opiates as the most frequently prescribed duplication drugs.

Polypharmacy was shown to be strongly associated with PIP. The strength of the overall association between PIP and gender and age was not significant after adjusting for polypharmacy. PIP had a significant impact on the national prescribing budget in 2007 (9% of overall expenditure for those ≥70 years).

Context of PIP in Europe

This study is the first population study to apply the explicit STOPP screening tool for appropriate review of medications in older populations. There have been few studies of PIP in Europe due to the lack of European specific criteria and differences in national drug formularies [13]. Previous population studies in the UK and the Netherlands applied the US Beers criteria and reported lower PIP prevalence rates of 28% and 20%, respectively, with long-acting benzodiazepines and amitriptyline as the most frequently prescribed potentially inappropriate drugs [12, 16].

PPI prescribing for a greater duration and dosage than recommended in the National Institute for Health and Clinical Excellence (NICE) guidelines is not unique to Ireland [25]; 25% to 70% of patients on PPIs have been reported as having no appropriate indication worldwide [26]. PPIs have a high level of efficacy and short-term use is recommended for treating a large range of acid-peptic conditions [25, 26]. Long-term use (≥1 year) in older

Table 2

The association between gender and age and PIP by individual STOPP criteria in 2007

Criteria Description	OR gender* F *vs.* M	95% CI Gender	OR age* ≥75 *vs.* 70–74 years	95% CI Age
Cardiovascular system				
Digoxin >125 μg day^{-1}	0.79	0.70, 0.88	2.20	1.90, 2.55
Thiazide diuretic with gout	0.32	0.28, 0.36	0.83	0.74, 0.93
β-adrenoceptor blocker with COPD†	0.53	0.51, 0.56	0.84	0.80, 0.89
β-adrenoceptor blocker with verapamil	1.07	0.93, 1.24	0.74	0.64, 0.85
Aspirin and warfarin without histamine H_2-receptor antagonist (except cimetidine) or PPI†	0.40	0.37, 0.43	1.02	0.95, 1.09
Dipyridamole as monotherapy for cardiovascular secondary prevention	0.73	0.56, 0.95	2.44	1.73, 3.42
Aspirin >150 mg day^{-1}	0.59	0.56, 0.62	1.05	0.99, 1.11
Central nervous system and psychotropic drugs				
TCA† with dementia	1.68	1.40, 2.01	1.98	1.62, 2.42
TCA and glaucoma	1.18	0.97, 1.43	1.39	1.12, 1.71
TCA and opiate or calcium channel blockers	1.59	1.50, 1.67	0.74	0.70, 0.78
Long-term (i.e. >1 month), long-acting benzodiazepines	1.72	1.65, 1.78	0.89	0.87, 0.92
Long-term (i.e. >1 month) neuroleptics	1.04	0.99, 1.10	0.86	0.81, 0.91
Long-term (i.e. >1 month) neuroleptics with parkinsonism	0.80	0.72, 0.90	0.62	0.55, 0.69
Anticholinergics to treat extrapyramidal side effects of neuroleptic medications	0.96	0.87, 1.06	0.60	0.54, 0.66
Phenothiazines with epilepsy	1.10	0.95, 1.27	0.92	0.79, 1.06
Prolonged use (i.e. >1 week) of first-generation antihistamines	0.98	0.91, 1.05	0.84	0.78, 0.90
Gastrointestinal system				
Prochlorperazine or metoclopramide with parkinsonism	1.16	0.99, 1.35	1.58	1.32, 1.89
PPIs for peptic ulcer disease at maximum therapeutic dosage for >8 weeks‡	0.80	0.78, 0.81	1.05	1.02, 1.07
Respiratory system				
Theophylline with COPD	0.63	0.59, 0.67	1.10	1.03, 1.18
Nebulized ipratropium with glaucoma	0.41	0.23, 0.71	7.30	2.27, 23.51
Musculoskeletal system				
Long-term use of NSAIDs† (i.e. >3 months)	1.25	1.22, 1.28	0.78	0.76, 0.81
Warfarin and NSAIDs	0.57	0.53, 0.62	1.02	0.94, 1.11
Urogenital system				
Antimuscarinic drugs with dementia	1.24	1.11, 1.38	3.19	2.74, 3.70
Endocrine system				
Glibenclamide or chlorpropamide with type 2 diabetes mellitus	0.68	0.54, 0.69	0.96	0.84, 1.10
Duplicate drug class prescription (optimization of monotherapy within a single drug class)				
Two concurrent opiates	1.15	1.07, 1.22	0.96	0.90, 1.03
Two concurrent NSAIDs	1.51	1.44, 1.59	0.62	0.59, 0.65
Two concurrent SSRIs†	2.24	1.31, 3.84	1.78	1.02, 3.10
Two concurrent antidepressants	1.32	1.14, 1.52	0.86	0.75, 1.00
Two concurrent loop diuretics	0.65	0.52, 0.81	2.27	1.70, 3.04
Two concurrent ACE inhibitors†	0.79	0.74, 0.85	0.73	0.68, 0.78
All duplicates	1.19	1.15, 1.23	0.74	0.71, 0.76

*OR Gender = odds ratio adjusted for age and polypharmacy. OR Age = odds ratio adjusted for gender and polypharmacy. Multicollinearity was tested between age, gender and polypharmacy using the collinearity diagnostics statistics (tolerance and variance inflation factor). †COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitor; TCA, tricyclic antidepressant; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin re-uptake inhibitor; ACE inhibitors, angiotensin converting enzyme inhibitors. ‡Proton pump inhibitor (PPI) at maximum therapeutic dose = 40 mg daily omeprazole, pantoprazole and esomeprazole. 30 mg daily lansoprazole and 20 mg daily rabeprazole.

patients has been associated with accelerated osteoporosis and an increased risk of hip fracture and *Clostridium difficile* hospital infections [27, 28]. The extent to which older people remain on long-term PPI treatment has significant cost consequences (Table 3).

Long term NSAID use is associated with gastrointestinal adverse effects and hospitalization [29, 30]. Gastroprotective agents are co-prescribed to reduce the risk of adverse effects, if NSAID therapy cannot be stopped [31]. In this study 41% of older patients on PPI therapy of >8 weeks duration were co-prescribed NSAIDs in 2007. NSAID prescribing also had significant cost consequences (Table 3). Long-acting benzodiazepine prevalence rates were higher in Ireland (13%, 5% >1 month) than in population studies from the UK (4%) and the Netherlands (5%) despite the fact that long-acting benzodiazepines have been associated with an increased risk of falls, hip fractures, impaired cognition and dependence problems [12, 16, 32].

PPI therapy withdrawal in older patients requires careful monitoring for disease recurrence but dosage reduction or cessation of treatment is recommended [25, 31]. Long-term users have been shown to cease therapy with no adverse effects to dyspepsia symptom severity and quality of life [33]. Physical therapy and exercise for

Table 3

The highest NIC and total expenditure (>€500 000) for the individual STOPP criteria as a proportion of the overall NIC and total expenditure of PIP in 2007

Criteria description	NIC €	NIC %	Total expenditure €	Total expenditure %
PPI maximum therapeutic dosage for >8 weeks	22 352 240*	58	24 715 010*	54
Neuroleptics >1 month **Neuroleptics >1 month with parkinsonism** **Anticholingerics for neuroleptic side-effects**	5 612 192*†	15	6 079 905*†	13
Duplicates drugs	4 531 160	12	5 499 118	12
NSAIDS >3 months **Warfarin and NSAIDS**	3 969 629*†	11	5 050 640*†	11
TCA and opiate or calcium channel blocker	1 329 275†	3	1 864 433†	4.09
Antimuscarinic drugs with dementia	578 800	1	660 478	1
Long-term (i.e. >1 month) long-acting benzodiazepines	572 009*	1	1 352 209*	3

Supplemental Table S2 outlines costs for the each of the individual STOPP criteria. *Exclude the duration of prescribing that is deemed appropriate, e.g. 8 weeks PPIs. †Adjusted for claimants receiving the same medication per more than one criteria.

musculoskeletal complaints may be more appropriate and effective for some older patients than long-term NSAIDs use or simple or compound analgesics [34, 35]. Gastroprotective agents such as PPIs only reduce the risk of adverse effects but do not eliminate the risk. Withdrawal of long-term benzodiazepine use is limited by dependence problems but gradual discontinuation programmes and intervention strategies have been shown to be successful though labour intensive [31, 36, 37]. Indicators for appropriate initiation of benzodiazepine prescribing may provide a more realistic method to reduce potentially inappropriate use [38].

The strong association between polypharmacy and PIP was in accord with previous studies [15, 39]. The prescription of multiple medications in older adults is associated with an increased risk of unnecessary and non-clinically indicated drugs, drug interactions, adherence problems, increased drug costs and adverse drug events; increasing to 58% for five medications [39]. Contrary to this study, previous studies found that women have an increased risk of being prescribed a potentially inappropriate medication compared with men but similarly found no age effect after adjusting for the number of different medications [11, 15, 17]. Polypharmacy and PIP are also associated with the under-prescribing of indicated medicines but this study did not assess this aspect of medication management in older populations [23, 40, 41].

Costs of PIP

There has also been little research on the costs of PIP in relation to overall government pharmaceutical expenditure. STOPP and the newer explicit screening tools for appropriate medication review, consider cost control alongside improving the quality of prescribing [31]. The discontinuation of potentially inappropriate or marginally effective medications can result in significant savings for prescribing budgets; even for potentially inappropriate medications with relatively low prevalence rates, e.g. neuroleptics >1 month (Table 3). Unnecessary duplication of drugs in the same therapeutic class may have adverse effects and increases costs unnecessarily (Table 3); concurrent use of more than one NSAID has been shown to increase the risk of gastrointestinal toxicity [31]. Studies have shown diuretics, warfarin, NSAIDs, SSRIs, β-adrenoceptor blockers and ACE inhibitors to be the drugs most commonly associated with adverse drug events in older populations [29, 30]. Equally the addition of medications to treat an unrecognized adverse reaction – the 'prescribing cascade' e.g. anticholingerics for neuroleptic side-effects can also result in additional adverse effects and increases costs.

Strengths and limitations

Our study has a number of possible limitations and it is likely that estimates of PIP are conservative. The lack of detailed diagnosis information in the database limited the applicability of all of the STOPP criteria and the investigation of individual patient factors and differences in drug indication. The STOPP criteria were based on dispensed medications and there may be older people who have not yet been diagnosed with a condition, misdiagnosed or who are not receiving prescribed medication for their diagnosis. The pharmacy claims database is related to prescriptions dispensed and is used to reimburse pharmaceutical costs in Ireland; in general claimants' recorded drug use should reflect actual drug use but it is not known whether patients adhered to their medications. In addition, the database does not include over-the-counter (OTC) items, although this is not likely to be a significant factor as the scheme provides free medical treatment and patients must pay for OTC items.

Notwithstanding the limitations this study has provided Irish population based data on PIP in an older population where limited data have been available [42]. Few national population studies have been undertaken to date and they are important in identifying common PIP issues

that may require further investigation, followed by guidelines or incentives to encourage reduction [12, 15, 16]. The application of the STOPP criteria to national population dispensing data rather than prescribing data also provides an opportunity to provide feedback and comparative information on certain key criteria at practice or physician level.

Future research

This study measured an economic outcome, e.g. cost of potentially inappropriate drugs but it did not investigate the association between the STOPP criteria and health outcomes in older populations (e.g. morbidity, mortality). In order to have acceptance in everyday clinical practice explicit process measures of PIP need to be linked to health outcomes. To date there is limited and conflicting evidence [43, 44]. Further research is planned to investigate the association between STOPP and other explicit process measures of PIP and health outcomes, health service utilisation and the overall economic impact of PIP on the health system. Further comparative European population studies are also planned.

Policy implications

Polypharmacy does not imply inappropriate prescribing but it is consistently associated with the risk of PIP (Figure 2) and reducing the number of drugs used by older people through medication review may reduce the risk of PIP, adverse medication outcomes and improve adherence and reduce costs [15, 39]. PIP has been shown to add unnecessary costs to prescribing budgets without providing any additional therapeutic benefits. However while cost control is an important element of a medication review it should not surpass patient safety or access to appropriate medication. Generic prescribing and therapeutic substitution are methods of cost control that do not affect the quality of patient care and offer alternatives when potentially inappropriate medication withdrawal is complex or patients do not concur.

Reduction in PIP requires changes in prescribing behaviour but prescribing guidelines by themselves do not necessarily change behaviour. Computerized screening and clinical decision support tools to implement guidelines by assessing the appropriateness of the medication, the dosage, duration of treatment, drug–disease and drug–drug interactions while balancing the risks of underuse of potentially beneficial drugs are required [3]. While screening tools will never be substitutes for clinical assessment and judgment they can be used to improve prescribing practices and monitor medication use in older populations. Given that life expectancy is increasing worldwide and there will be an associated increase in multimorbidity, polypharmacy, health service utilisation and drug costs, the development and use of comprehensive, practical and computerized prescribing screening tools for appropriate, safe and effective monitoring of drug prescribing is crucial.

Competing interests

None declared.

Ethical approval: Not required.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 STOPP criteria applied to HSE-PCRS prescription claims data for all those aged ≥70 years in Ireland in 2007
Table S2 NIC and total expenditure for the individual STOPP criteria as a proportion of the overall NIC and total expenditure of PIP in 2007

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Operating Grant 2012-09-17

Application Number 287245 **ResearchNet ID** 173076

Suggested Peer Review Committees

1st: Health Policy & Systems Management Research 2nd:

Nominated Principal Applicant

Surname	Given Names	PIN
BJERRE	Lise	46830

Project Title

Assessing Potentially Inappropriate Prescribing (PIP) and predicting patient outcomes in Ontario's elderly population using the modified STOPP criteria in large administrative health databases (the PIP-STOPP study)

Relevant Research Area:	**Title of Priority Announcement/Funding Pools:**

Linked Programs:

Applicant Signatures

The applicants are in the following order: Principal Applicant(s) and Co-Applicants. It is agreed that the general conditions governing grants, as well as the statement "Meaning of Signatures on Application Forms" as outlined in the CIHR Grants and Awards Guide, apply to any grant made pursuant to this application and hereby accepted by the applicant(s).

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Institution	**Faculty**	**Department**	**Date**
Royal College of Surgeons in Ireland (UK)			6th September 2012

Surname	Given Names	Role	Signature
HALIL	Roland	Co-Applicant	x
Institution	**Faculty**	**Department**	**Date**
Elisabeth Bruyère Health Centre (Ottawa)/Centre de santé Élisabeth-Bruyère			

Surname	Given Names	Role	Signature
MANUEL	Douglas	Co-Applicant	x
Institution	**Faculty**	**Department**	**Date**
Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa			

Surname	Given Names	Role	Signature
RAMSAY	Timothy	Co-Applicant	x
Institution	**Faculty**	**Department**	**Date**
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Institution	**Faculty**	**Department**	**Date**
Elisabeth Bruyère Health Centre (Ottawa)/Centre de santé Élisabeth-Bruyère	Medicine	Family medicine	Sept 4, 2012

Surname	Given Names	Role	Signature
MANUEL	Douglas	Co-Applicant	X
Institution	**Faculty**	**Department**	**Date**
Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa			

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MANUEL	Douglas	Co-Applicant	x
Institution	**Faculty**	**Department**	**Date**
Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa			SEPT 4, 2012

Surname	Given Names	Role	Signature
RAMSAY	Timothy	Co-Applicant	x
Institution	**Faculty**	**Department**	**Date**
Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa			

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Institution	**Faculty**	**Department**	**Date**
Ottawa Hospital Research Institute/Institut de recherche de l'Hôpital d'Ottawa			Sept. 4, 2012

Surname	Given Names	Role	Signature
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Institution	**Faculty**	**Department**	**Date**

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