LABORATORY DATA, PRESCRIBING DECISIONS, PATIENT OUTCOMES

DOES INTEGRATION OF LABORATORY DATA IMPROVE PRESCRIBING DECISIONS AND PATIENT OUTCOMES?

BY
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A THESIS SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE

MASTER OF SCIENCE

McMaster University Master of Science (Health Research Methodology) March 2012

Title: Does integration of laboratory data improve prescribing decisions and patient outcomes?

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Number of Pages: viii, 123

References: 111

Abstract

Integrating laboratory information into prescribing tasks may improve medication safety. This thesis addresses several methodological issues in the progress of two studies: a systematic review of randomized trials addressing the impact of drug-lab safety alerts on adverse drug events and changes in prescribing or lab monitoring and a randomized trial using an electronic survey to compare prescribing decisions in complex clinical scenarios including integrated lab data with those in which the lab data were available on request. The systematic review found 32 studies; 10 addressed multiple drug-lab combinations, and 22 addressed single drug-lab combinations, including 14 targeting anticoagulation. We report a benefit of anticoagulation-related alerts (OR of an adverse event (bleeding or thrombosis) 0.88 (95% CI 0.78-1.00) and improved prescribing in multi-drug studies (OR 2.22, 95% CI 1.19-4.17), but substantial study heterogeneity precluded combining studies of other drugs. Methodological issues addressed in the RCT include medication selection, scenario design, recruitment, and assessment of the representativeness of the sample. We selected medications for study scenarios that are commonly prescribed by Canadian primary care physicians, and are associated with clinically important harm that may be preventable through laboratory monitoring. Data sources included IMS Brogan data on prescribing patterns and the Discharge Abstracts Database (DAD) and the National Ambulatory Care Reporting System (NACRS) from 2006-2007 to 2008-2009. Our study had 148 completed surveys. The study sample differed from the population of Ontario family physicians by gender, and use of electronic medical records. We found no difference in prescribing decisions (OR 1.21, 95% CI 0.84-

1.75) between the study groups and no predictors of improved prescribing decisions. The lack of demonstrated impact of integrating lab data into clinical decision-making may be related to the study being underpowered, to a true lack of clinical benefit, or to a lack of discriminatory power in the scenarios.

Acknowledgements:

I would like to thank Dr. Anne Holbrook, Dr. Lisa Dolovich and Dr. Brian Hutchison for their support, thoughtful feedback, and patience throughout this process. Their guidance has made this an invaluable educational process.

I would like to thank Mosab El-Balas, Dr. Steven Handler for their roles as co-investigators in the systematic review. In addition, I would like to thank Dr. Brian Haynes, Dr. Steve Handler and Dr. Ann McKibbon for making citations from the Computerized Clinical Decision Support Systems and the Medications Management through Health Information Technology reviews respectively available to our group. I would also like to acknowledge the assistance of IMS Brogan and the Canadian Institute for Health Information for making data available to me.

In addition, I appreciate the assistance of the Ontario College of Family Physicians, Pat Payne at the Queens University Department of Continuing Health Education, and Diversified Business Communications for their assistance in distribution of my survey.

I would also like to thank Dr. Lehana Thabane and Chenglin Yi for advice on statistical matters and Gary Foster for assistance with database construction.

I would like to acknowledge the support of Stafford Murphy and the Kingston Community Health Centres for their great flexibility and support in accommodating my need for release time from clinical duties at crucial periods.

Finally, I would like to thank my family, particularly Maureen Buchanan for unwavering love, support and encouragement, and many sacrifices along the way.

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Chapter 1: Introduction

Primum non nocere.

First, do no harm.

A fundamental ethical responsibility in health care delivery is to avoid injuring individuals seeking care. Over the past decade, many OECD countries have identified improved patient safety as a health care priority and have summarized currently available knowledge in various sentinel reports including Making Health Care Safer (Eds. Shojania, Duncan, McDonald, Wachter, & Markowitz, 2001) and To Err is Human (Eds. Kohn, Corrigan, & Donaldson, 2000) in the U.S., and An Organization with a Memory (NHS, 2000) in the U.K. Australia established the Australian Charter of Healthcare Rights in 2008 (ACSQHC), which identified the right to receive safe and high quality care as one of seven rights each patient could expect in both public and private healthcare delivery. Such reports identified adverse drug events (ADEs), defined as injuries occurring as a result of medication use(Bates et al., 1995), as a major source of health care related harm and established the prevention of ADEs as a crucial priority for improved patient safety.

1.1 Definitions

Researchers have utilized various definitions of medication-related harm. Some have studied the incidence of adverse drug reactions (ADRs), defined by the World Health Organization as “any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy”. (WHO, 2008) This definition excludes therapeutic failures, intentional or accidental poisoning (i.e.

overdose), drug abuse and errors in drug administration or compliance (taking more or less of a drug than the prescribed amount). Other researchers have studied adverse drug events (ADEs), a more general term that includes adverse drug reactions and errors in medication use, arguing that the greater comprehensiveness of this concept makes it more clinically relevant and more amenable to prevention. (Bates, et al., 1995) ADEs have been further classified by the degree to which they are preventable (defined as events that occurred due to an error or were avoidable by any means available at the time) and by severity (Bates, et al., 1995). In one study, serious ADRs were defined as ADRs requiring hospitalization, prolonging hospitalization, causing permanent disability or resulting in death. (Lazarou, Pomeranz, & Corey, 1998) Other studies have not defined severity but have asked expert reviewers to categorize ADEs as fatal, life-threatening, serious or significant (Bates, et al., 1995).

Given that ADEs cannot be directly measured, research into ADEs requires many judgements, including assessments regarding whether the event is caused by medication use, and to determine preventability and severity. Minimum criteria for establishing an event as an ADE are that ingestion of the drug precedes the event and that the drug is known to have the described effect. Researchers have attempted to mitigate the potential bias introduced by these subjective decisions through dual expert review, reporting the degree of agreement, or the use of causality scales or algorithms (Naranjo et al., 1981) but this source of bias remains noteworthy. Another methodological problem stems from the limitations of chart review: clinical records may lack detail and clarity, potentially contributing to both underestimation and overestimation of the incidence of ADEs.

Patient interviews are infrequently utilized as a data source and while they may add further data, patients may have difficulty differentiating between disease-related and drug-related adverse effects, potentially contributing to overestimation of the incidence of ADEs.

1.2 Epidemiology of adverse drug events

The epidemiology of adverse drug events among adult patients has been investigated in various settings; most studies were conducted in hospitals, but some also reported on the incidence in nursing homes, in the emergency department and in ambulatory care settings. One systematic review (Winterstein, Sauer, Hepler, & Poole, 2002) reported on the prevalence of medication related admissions to hospital. They addressed a broad definition of drug-related morbidity that included both adverse drug reactions, errors in prescribing and administration and lack of therapeutic efficacy. They evaluated methods used to determine causality and preventability of adverse events and gave priority to studies in which explicit criteria were used to the identify ADEs. The researchers reported that the median prevalence rate was 7.1% (IQR 5.7-16.2%), of which the median preventable rate was 59% (IQR 50-73%). The authors found significant heterogeneity in the included studies and therefore did not report a meta-analytic summary statistic. Strengths of this review include a broad search, in which the authors found no evidence of publication bias. They did not however, assess study quality. They used meta-regression to identify study characteristics that influenced the prevalence, though the small number of studies limited this process. There was evidence of higher prevalence estimates among older patients (mean age>70) and in studies that used a more

comprehensive definition of drug related morbidity. Key studies assessing the epidemiology of ADEs in hospital patients, used either a prospective (Bates, et al., 1995; Bates, Leape, & Petrycki, 1993) or retrospective (Baker et al., 2004; Brennan et al., 2004) cohort design or a case-control design (Classen, Pestotnik, Evans, Lloyd, & Burke, 1997). Bates et al. (Bates, et al., 1995) estimated the incidence of ADEs to be 6.5/100 non-obstetrical admissions (based on 247 events) in a prospective cohort studies using a combination of logbooks, and chart review for case finding, of which 28% were classified as preventable. A case control study that used computer-generated signals and clinician self report for case-finding over a 4 year period, reported the incidence of ADRs to be 2.43/100 admissions and found a mortality rate of 3.5% among cases (compared to 1.65% among controls, $p<0.001$), and the mean attributable excess length of stay due to ADEs was 1.74 days ($p<0.001$) with an associated mean attributable excess cost of $2013 (1997 estimate)(Classen, et al., 1997). The only Canadian study assessing adverse events among inpatients reported an incidence rate of 7.5 adverse events/100 admissions (95% confidence interval 5.7-9.3), of which 23.6% were drug or fluid related (Baker, et al., 2004). With the exception of Baker et al. (Baker, et al., 2004), all the above studies over-represented tertiary care hospitals in their samples, limiting the generalizability of the results. All were also limited by the lack of blinding of assessors to patient outcomes, which may have skewed their findings, by the lack of a gold standard, the subjectivity of classification decisions, and limitations of chart review identified earlier.

The epidemiology of ADEs in emergency departments in the USA is described in the National Electronic Injury Surveillance System: Cooperative Adverse Drug Event

Surveillance (NEISS-CADES) project (Budnitz et al., 2006), an American national surveillance system which prospectively tracks adverse drug events treated in 63 emergency departments in a nationally representative size stratified sample. Participating hospitals had a 24-hour emergency department with at least 6 beds. Pediatric and psychiatric hospitals and penal institutions were excluded. Trained coders reviewed all emergency department records to report adverse drug events, defined as an incident ED visit for a condition that the treating physician explicitly attributed to a drug or drug specific effect. For diagnoses potentially related to drug effects, such as hypoglycemia, coders examined other parts of the record for evidence that the condition was drug related. In a 2 year period (2004-2005) 21,298 ADE were reported, representing 0.6% of ED visits for all causes (Budnitz, et al., 2006). Individuals older than 65 years were 2.4 times more likely to present with ADEs and almost 7 times more likely to be hospitalized for adverse drug events than younger individuals, though this is likely confounded by the number of medications used and the number of concurrent medical conditions. An updated NEISS-CADES report addressed ADEs among older people (older than 65 years) between 2007-2009 (Budnitz, Lovegrove, Shehab, & Richards, 2011), reporting on the basis of 12,666 cases. Drugs for which regular monitoring can prevent acute toxicity (including warfarin, insulin, oral hypoglycemic agents, digoxin, renin-angiotensin inhibitors, anticonvulsants and diuretics) accounted for 67.1% of ADE-related hospitalizations among individuals older than 65 While this study has the advantage of a large prospective sample, the identification of adverse drug events remains subjective and is a potential source of bias.

A Canadian study (Zed et al., 2008) described the epidemiology of medication-related problems in a tertiary care emergency department (ED) and reported that 12.0% of all ED visits (95% CI 10.1-14.2%) were medication-related (including adverse drug reactions, drug interactions, improper drug selection, untreated indication, subtherapeutic or supratherapeutic dosage and drug use without indication), of which 68.0% were determined to be preventable. Severity was classified as mild in 15.6%, moderate in 74.6% and severe in 9.8%. Strengths of this study include the fact that it was a prospective study in which patients were followed up for one month. The researchers used comprehensive and pre-defined classification system for determining causality, preventability, severity and type of drug related problem. They did not, however, report on the proportion of medication related problems that were potentially preventable through laboratory monitoring.

Estimates of the incidence of ADEs in nursing homes range from 1.19 to 9.8 ADE per 100 resident-months (Gurwitz et al., 2000; Gurwitz et al., 2005; Handler, Wright, Ruby, & Hanlon, 2006), as described by Handler et al. (Handler, et al., 2006) in a systematic review of the epidemiology of medication related adverse events among nursing home residents. The variation in estimates has been attributed to different case-finding methods. Researchers who utilized more comprehensive chart review together with computer-generated signals of an adverse drug event or predefined triggers found a higher incidence rate, which are more efficient and likely more valid (Handler, et al., 2006). None of the reported studies included any direct contact with nursing home residents or their family members in their case-finding methods. There was also

substantial variation in methods to assess causality of the adverse event, including implicit structured review, single or dual review and use of the Naranjo algorithm (Naranjo, et al., 1981). Several of the included studies identified the number of medications taken as a risk factor, independent of number of medical conditions. It was not possible to produce a meta-analytic summary statistic due to the heterogeneity of the included studies or to identify risk factors, because of insufficient detail in reporting nursing home characteristics.

In ambulatory care settings, where most medications are prescribed, the situation is more complex (Budnitz & Layde, 2007). The ambulatory environment is much less controlled than the inpatient setting. Patients with multiple comorbid conditions, taking multiple medications, may have multiple prescribers and may receive care in multiple settings. Furthermore, patients sometimes misunderstand directions, or decide not to take their medications as prescribed, because they attribute symptoms to medication side effects, particularly if their health literacy is poor. (Berkman, Sheridan, Donahue, Halpern, & Crotty, 2011) Patients also frequently self-medicate with over the counter medications, which may interact with their prescribed medications. Furthermore, there is ample evidence that primary care physicians' medication records contain many discrepancies with patient medication lists (Atkin et al., 1998; Frank et al., 2001; Kaboli, McClimon, Hoth, & Barnett, 2004; Stephens, Fox, Kukulka, & Bellamy, 2008).

Estimates of the incidence of ADEs in ambulatory care, reported in a systematic review by Taché et al. (Taché, Sönnichsen, & Ashcroft, 2011) vary widely between 2.8% and 34.7%, median 12.8% (IQR 5.5-24.5%), with a median estimate of the proportion

classified as preventable reported as 16.5% (IQR 12-23.8%). The higher estimates are seen among elderly persons and in retrospective designs. The researchers did not estimate the proportion of preventable ADEs attributable to inadequate laboratory monitoring. The authors did not report a pooled estimate due to the heterogeneity of the included studies. This review summarized observational studies, with the same methodological limitations previously identified, including subjectivity of ADE detection, limitations of chart review, and potentially presence of a Hawthorne effect for the prospective designs.

1.3 Impact of laboratory monitoring

Laboratory monitoring is important to ensure that a given medication is safe for a specific patient, to ensure appropriate dosing and to detect potential adverse drug events. Recommendations regarding lab monitoring are frequently based on pharmacokinetic and pharmacodynamics factors, such as in dose adjustment in the setting of chronic kidney disease (Verbeek & Musuamba, 2009), sometimes including population studies. Other sets of recommendations are based on consensus opinion (Handler et al., 2008; Tija et al., 2010) or serum levels of the medication may guide dosing; some drugs have a narrow therapeutic index, in which lower doses are ineffective and higher doses are toxic. Vitamin K antagonists, the most studied medication with a narrow therapeutic index, are associated with clinically important events when doses are either subtherapeutic (stroke or deep vein thrombosis) or supratherapeutic (bleeding events). The American Chest Physicians 2008 clinical practice guidelines (Ansell et al., 2008) on anticoagulation recommend that once the INR is stable, it be measured every 4 weeks, though they note that there is evidence to suggest that more frequent monitoring increases the time in

therapeutic range. There is clear evidence of harm which can be detected with laboratory monitoring related to many commonly prescribed drugs, including hyperkalemia with angiotensin converting enzyme inhibitors (ACEIs) (Palmer, 2004), chronic kidney disease with combination therapy with ACEIs and angiotensin receptor blockers (ARBs) (Mann et al., 2008), non-steroidal anti-inflammatory agents (NSAIDs) (Tannenbaum et al., 1996), or excessive diuresis (Mehta, Pascual, Soroko, & Chertow, 2002) and drug-induced hepatotoxicity.

Inadequate laboratory monitoring was identified in the ambulatory care and nursing home epidemiological surveys as a common source of medication error, though not specifically defined. Gurwitz et al. noted that inadequate laboratory monitoring of drugs was associated with 60.8% of the preventable adverse drug events they identified in their ambulatory care sample (Gurwitz et al., 2003) (approximately equally distributed between failure to order relevant lab tests and inadequate response to laboratory evidence of toxicity). The same author led two large studies of ADEs in nursing homes (described above) and reported inadequate laboratory monitoring as the leading cause of ADEs in nursing homes (Gurwitz, et al., 2000; Gurwitz, et al., 2005). In U.S. emergency departments, more than half the adverse drug events requiring hospitalization among older adults were due to toxicity of a limited number of medications for which regular lab monitoring is recommended to prevent toxicity and which are commonly prescribed in ambulatory settings (Budnitz, et al., 2006). In addition, large cohort studies from a large U.S. HMO have demonstrated that clinicians in ambulatory care settings initiating new medications failed to perform recommended laboratory monitoring in 39% of

prescriptions of study drugs (Raebel, Lyons, Andrade, et al., 2005). These observational studies suggest that there is a need for improved lab monitoring in relation to prescribing decisions in primary care, especially among older adults taking multiple medications. There is however, a gap in the literature regarding whether adherence to recommended laboratory monitoring routines improves clinical outcomes. Improved monitoring might potentially decrease the response time to ADEs and hence lessen their severity or possibly reduce the number of preventable ADEs altogether, if lab data are incorporated into the prescribing decision making process.

1.4 Impact of computerized drug-lab alerts

Policy makers have promoted electronic medical records (EMRs) with computerized alerts as a key initiative to improve patient safety and quality of care. However, computerization in health care lags behind other sectors of society mainly because of its expense, potential disruption of important work processes, and the lack of evidence from high quality studies that computerization of clinical processes improves patient outcomes (Holbrook et al., 2011). While several systematic reviews of randomized controlled trials addressing the impact of computerized physician order entry (CPOE) and computer decision support systems (CDSS) have reported changes in some clinician prescribing behaviours, these systems have not been shown to reduce ADEs (Chaudry et al., 2006; Eslami, Abu-Hanna, & De Keizer, 2007; Garg et al., 2005; Kaushal, Shojania, & Bates, 2003; Shojania et al., 2009). In addition, safety alerts are frequently overridden by clinicians (van der Sijs, Aarts, Vulto, & Berg, 2006) (49-96% of the time, reported in a systematic review), largely due to a high volume of alerts with

poor specificity and trivial importance (Lapane, Waring, Schneider, Dube, & Quillam, 2008). Furthermore, critics have raised concerns over new errors introduced through the use of information technology, such as through fragmentation of information (Ash, Berg, & Enrico, 2004; Koppel et al., 2005) poor quality decision support, and over-reliance on decision support (Ash, et al., 2004; Strom et al., 2010).

Drug lab alerts (defined as computer-based systems that remind prescribers to consider clinically relevant laboratory data during the prescribing process to enhance patient safety) have the potential to improve integration of clinically meaningful data that are needed to make appropriate prescribing decisions. The capacity to link relevant data within a patient record (such as medication lists and laboratory data) is a key feature that distinguishes electronic records from paper records. Published systematic reviews addressing the impact of drug-lab alerts (Fischer, Tjia, & Field, 2010; Hayward, Parnes, & Simon, 2009) have reported on improved laboratory monitoring as an outcome, but have not addressed prescribing decisions or ADEs as outcomes. Their findings are also limited by inclusion of both randomized and non-randomized trials, and exclusion of studies of alerts targeting anticoagulation, a clinically important domain investigated in many trials. More recently, a series of reviews on the impact of computer decision support systems on a variety of clinical processes was reported (Hemens et al., 2011; Nieuwlaat et al., 2011). However, the impact of drug lab alerts was not reported separately; rather these alerts spanned several domains in their review and it was, therefore not possible to evaluate the impact of drug lab alerts, in particular. In addition, a recent comprehensive AHRQ evidence report (McKibbon et al., April 2011) evaluated

the effectiveness of integrated health information technologies on all phases of the medication use process including prescribing and monitoring in all settings. However, this review also included randomized and non-randomized studies, reported on interventions that targeted patients or clinicians, and focused on a wide variety of process and clinical outcome measures. Therefore, the extent to which drug-lab alerts alone affect the quality of prescribing and clinically important outcomes in various clinical settings remains unclear, merits further study and will be examined in the next chapter. The findings of this systematic review informed the design of the LAMP-PC (Lab Monitoring in Prescribing Decisions in Primary Care) study, a randomized controlled trial, which tested the hypothesis that family physicians would make safer prescribing decisions if presented with relevant laboratory data during complex prescribing scenarios.

1.5 Thesis objectives

The objectives of this thesis are as follows:

- Report the methods and results of a systematic review and meta-analysis of the effectiveness of computerized drug lab alerts in all health care settings.
- Describe the study design and methodological issues related to medication selection, scenario design, and participant recruitment for LAMP-PC.
- Discuss the internal and external validity of the findings.

Chapter 2: Systematic Review and Meta-analysis

The extent to which drug-lab safety alerts (defined as computer-based systems reminding prescribers to consider clinically relevant laboratory data during the prescribing process to ensure patient safety) affect the quality of prescribing and clinically important outcomes remains unclear and merits further study. We sought to systematically evaluate evidence of the effectiveness of computerized drug lab safety alerts in any setting, and if possible to identify features of alerts that were predictive of greater effectiveness.

No external funding was used for this project.

2.1 Methods

We prepared a study protocol, which was not registered but is appended (Appendix A: Systematic review protocol).

Research Questions:

- Does the use of computerized drug-lab safety alerts for medications for which laboratory monitoring is recommended for patient safety, result in fewer ADEs and more appropriate prescribing as compared to usual care?
- Are there identifiable features of these electronic drug-lab safety alerts that make them more effective?

2.1.1 Study inclusion criteria

We included randomized controlled trials of computerized drug lab safety alerts addressing prescribing for adult patients. Both alerts that targeted prescribing of a single

drug (single drug systems) and of multiple drugs (multi-drug systems) were included. Multi-faceted intervention studies (studies in which drug lab safety alerts were one of a series of interventions) were included if it was possible to isolate the impact of the drug lab reminder system. Studies of systems with no clinician decision-making role (such as those using automated computer-modeled dose adjustment) or where drug lab alerts were not focused on improving prescribing safety (such as those addressing improved adherence to guideline based care, but not related to drug safety) were excluded. We included studies from all health care settings including hospitals, ambulatory care and nursing homes.

The primary outcome was reduction in adverse drug events (ADEs), defined as injuries occurring as a result of medication use (Bates, et al., 1995). Secondary outcomes included impact on hospitalization rates, mortality rates, proportion of lab tests ordered, proportion of prescriptions in which the medication was discontinued or the dose was changed, proportion of overridden alerts, quality of prescribing as measured with a validated tool, time in therapeutic range, and reduced costs or resource utilization.

2.1.2 Search strategy

Shortly after we began our study, we became aware of two large systematic reviews examining the impact of computerization on health care, namely the Computerized Clinical Decision Support Systems Systematic Review (CCDSSR) and the Medication Management through Health Information Technology (MMIT) projects. We based our search for citations on the databases from these two projects and updated the search Figure 1: PRISMA flow diagram. The study questions for these reviews differed

from ours, in that we included only randomized controlled trials, our study questions had a more limited scope and we included only studies in which the alert targeted a clinician, not a patient or family member. However, there was significant overlap in search parameters, and the two groups made their search results available for our review.

The Computerized Clinical Decision Support System Systematic Review (CCDSSR) project from McMaster University, updated their previous reviews of the effectiveness of computer decision support systems on a range of clinical activities, and reported their findings (Hemens, et al., 2011; Navdeep et al., 2011; Nieuwlaat, et al., 2011; Roshanov, Shikha, et al., 2011; Roshanov, You, et al., 2011; Souza et al., 2011). Their methods have been described elsewhere (Haynes & Wilczynski, 2010). Briefly, they searched Medline, EMBASE, EBM review databases, Inspec, and relevant reference lists from 1974 to Jan 6, 2010. Their inclusion criteria were: randomized controlled trials comparing CCDSS to no CCDSS, studies involving health care professionals in clinical practice or post-graduate medical trainees, computerized systems that provided patient specific advice to clinicians, reporting on process specific and/or patient specific outcomes. We obtained the citations for studies in two domains, namely drug prescribing and therapeutic drug monitoring, as the impact of drug lab safety alerts bridged both domains.

We also obtained citations for potential inclusion from the Medication Management through Health Information Technology (MMIT) project (McKibbon, et al., April 2011), an AHRQ (Agency for Healthcare Research and Quality) report on the impact of information technology on all phases of medication management. Articles from

their search that addressed medication monitoring were reviewed for inclusion. The detailed search strategy is attached. The search included peer reviewed electronic databases, grey literature sites, AHRQ resources and hand searches. Electronic databases searched included MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Reviews, IPA (International Pharmaceutical Abstracts), Compendex, INSPEC, LISTA, E-LIS, PsychINFO, Sociological Abstract and Business Source Complete. Supplemental searching included the New York Academy of Medicine, SIGLE, U.S. HHS Health Information Technology, Health Technology Assessment reports from the UK Centre for Reviews and Dissemination, ProQuest Dissertations, national Library for Health UK (which includes Bandolier), ProceedingsFirst, PapersFirst, National Technical Information Service and Google. The search strategy used combined search terms for medication management with computer and technology terms, limited to intervention studies with a comparison group (see example Appendix C: Search strategy MMIT group: MEDLINE).

We updated the search of the electronic databases MEDLINE, EMBASE and the EBM review databases to May 10, 2011 as delineated in Appendix D: Updated Search Strategy.

A single reviewer (IB or SMH) screened the abstracts of collected citations to determine whether they assessed computerized drug lab alerts. Two reviewers (IB and MB) independently examined these citations in full text, and determined whether the studies under consideration met the inclusion and exclusion criteria. We resolved disagreements through consensus, with adjudication by a third reviewer, if necessary.

2.1.3 Validity assessment

We assessed validity by systematically considering potential sources of error and bias, using the criteria described in the Cochrane Handbook (Higgins & Green, 2009). These include evaluations of randomization (sequence generation), concealment of allocation, blinded assessment, the proportion of patients and providers followed up to study end, selective outcome reporting (including intention-to-treat analysis), and other methodological issues such as protection against contamination and unit of analysis errors. The risk of bias in each domain was judged to be low, high or uncertain.

2.1.4 Data collection

One reviewer (IB) abstracted data from included studies (see Appendix C: Data extraction form). We piloted our data collection forms and modified them for clarity. We collected data on setting, baseline descriptions of prescribers, patients, descriptions of the intervention, process of selection of drug-lab alert, whether the systems were commercially available or locally developed, whether alerts were interruptive, and on selection and reporting of outcome measures. In the case of insufficient reporting in study results, we attempted to contact investigators for additional data.

2.1.5 Data analysis

Continuous measures were reported as mean differences and standard deviations or as standardized mean differences. Dichotomous outcomes were reported as odds ratios; point estimates and 95% confidence intervals are reported for all effect measures. A random effects model was used for analysis with $p<0.05$ (2-sided) considered statistically significant. Qualitative analyses of all outcomes were undertaken and in cases

where clinical and/or statistical heterogeneity was low, we considered combining studies to give a pooled estimate of effect. Study heterogeneity was evaluated qualitatively by assessing differences in study populations, interventions, outcome measures and study design, whereas statistical heterogeneity was assessed using the Cochran Q and I^2 statistics. Review results were summarized in a Summary of Findings table, in accordance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2008).

2.2 Results

We reviewed 107 citations for inclusion from the CCDSSR search (70 from the drug prescribing domain and 37 from the therapeutic drug monitoring domain) and 30 additional citations from the Medication Monitoring domain of the MMIT search. In total, 130 citations were considered from these 2 groups after duplicates were removed. We found 2 more citations with the updated search, yielding a total of 132 studies for inclusion (Figure 1: PRISMA flow diagram). Excluded studies did not asses drug-lab alerts, were not RCTs or failed to address an outcome of interest. Sixty-seven studies evaluated computerized drug lab safety alerts and were independently reviewed by two reviewers (IB, MB) in full text, of which 32 studies met all inclusion criteria (including 22 single-drug studies (Ageno & Turpie, 1998; Albisser, Wright, & Sakkal, 2007b; Carter, Taylor, & Becker, 1987; Cavalcanti et al., 2009; Claes et al., 2005; Fitzmaurice et al., 2000; Manotti et al., 2001; Marco, Sedano, Bermudez, Lopez-Duarte, & Zubizarreta, 2003; Mitra, Marciello, Brain, Ahangar, & Burke, 2005; Mungall et al., 1994; Paul et al., 2006; Peck, Sheiner, Martin, Combs, & Melmon, 1973; Poller et al., 2008; Poller et al.,

1998; Rood, Bosman, van der Spoel, Taylor, & Zandstra, 2005; Saager et al., 2008; Tierney et al., 2005; Vadher, Patterson, & Leaning, 1997a, 1997b; K. S. White, Lindsay, Pryor, Brown, & Walsh, 1984; R. H. White et al., 1987; R. H. White & Mungall, 1991) and 10 multi-drug studies (Demakis et al., 2000; Feldstein et al., 2006; Field et al., 2009; Judge et al., 2006; Lo, Matheny, Seger, Bates, & Gandhi, 2009; Matheny et al., 2008; McDonald, 1976; Palen, Raebel, Lyons, & Magid, 2006; Raebel, Lyons, Chester, et al., 2005; Terrell et al., 2010)), with an unweighted kappa statistic of 0.13. Disagreements were resolved by consensus. We excluded studies whose alerts did not address prescribing safety (n=21), addressed automated computer generated dose adjustment without clinician input (n=7), reported insufficient data (n=6) or were not an RCT (n=1).

The methodological rigour of the included studies varied and is summarized in Figure 2: Risk of Bias figure. Risk of bias is symbolized in this figure as high (red), low (green) or uncertain (yellow). The method of randomization was adequately described in only 16/32 studies (50%) (Albisser, Wright, & Sakkal, 2007a; Cavalcanti, et al., 2009; Claes, et al., 2005; Feldstein, et al., 2006; Fitzmaurice, et al., 2000; McDonald, 1976; Mitra, et al., 2005; Palen, et al., 2006; Paul, et al., 2006; Poller, et al., 1998; Raebel, Lyons, Chester, et al., 2005; Tierney, et al., 2005; Vadher, et al., 1997a, 1997b; K. S. White, et al., 1984; R. H. White, et al., 1987). Blinding of health care providers is not possible with such an intervention, but other recommended strategies to reduce bias such as blinding of outcomes assessors or data analysts were utilized in just 6/32 studies (18.75%) (Carter, et al., 1987; Feldstein, et al., 2006; Judge, et al., 2006; Paul, et al., 2006; Terrell, et al., 2010; K. S. White, et al., 1984). Eleven of 32 studies (34.4%)

randomized participants by clusters (clinics, wards or clinicians) (Claes, et al., 2005; Demakis, et al., 2000; Feldstein, et al., 2006; Field, et al., 2009; Judge, et al., 2006; Lo, et al., 2009; Matheny, et al., 2008; Paul, et al., 2006; Terrell, et al., 2010; Tierney, et al., 2005), but only 7 accounted for clustering in their analysis (Claes, et al., 2005; Demakis, et al., 2000; Feldstein, et al., 2006; Matheny, et al., 2008; Paul, et al., 2006; Terrell, et al., 2010; Tierney, et al., 2005). In 17/32 studies (53.1%), there was a strong likelihood of contamination since clinicians treated patients in both the intervention and control groups (Ageno & Turpie, 1998; Cavalcanti, et al., 2009; Field, et al., 2009; Judge, et al., 2006; Manotti, et al., 2001; Marco, et al., 2003; McDonald, 1976; Peck, et al., 1973; Poller, et al., 2008; Poller, et al., 1998; Rood, et al., 2005; Saager, et al., 2008; Vadher, et al., 1997b; K. S. White, et al., 1984; R. H. White, et al., 1987; R. H. White & Mungall, 1991) and may have been influenced by their exposure to the CDSS when caring for patients in the control group, which would tend to bias the findings in favour of the null hypothesis. Contamination was unlikely in 12/32 studies (34.4%), including 7 multi-drug studies (Demakis, et al., 2000; Feldstein, et al., 2006; Lo, et al., 2009; Matheny, et al., 2008; Palen, et al., 2006; Raebel, Lyons, Chester, et al., 2005; Terrell, et al., 2010) and 5 single drug studies (four addressing anticoagulation) (Claes, et al., 2005; Fitzmaurice, et al., 2000; Mungall, et al., 1994; Tierney, et al., 2005; Vadher, et al., 1997a) ; the issue of contamination was unclear in the remaining studies (Carter, et al., 1987; Mitra, et al., 2005; Paul, et al., 2006).

Twenty-two studies with 22,388 participants evaluated decision support systems targeting a single drug (Table 2: Characteristics of Included Studies). Of these, 14 studies

(18,569 participants) examined anticoagulation alerts. The remaining studies addressed antimicrobial, digoxin, insulin, or theophylline prescribing. Twelve of the single drug studies were conducted in ambulatory settings and 9 in inpatient settings (including 3 in ICU) and one in both (Vadher, et al., 1997b).

Ten studies enrolling 56,261 patients or patient prescriptions evaluated decision support systems with alerts targeting multiple medications (Table 2: Characteristics of Included Studies). Seven of the multi-drug studies were set in ambulatory care (Demakis, et al., 2000; Feldstein, et al., 2006; Lo, et al., 2009; Matheny, et al., 2008; McDonald, 1976; Palen, et al., 2006; Raebel, Lyons, Chester, et al., 2005), two in nursing homes (Field, et al., 2009; Judge, et al., 2006), one in the emergency department (Terrell, et al., 2010) and none in inpatient settings. The alerts targeted a large number of drugs that varied widely between studies.

Characteristics of the CDSS systems are summarized in Table 2: Characteristics of Included Studies. Nine of 32 studies (28.1%) tested commercially available systems (including multiple studies examining 2 commercial anticoagulation systems), 22/32 tested locally developed systems (68.8%) and 1/32 (3.1%) did not specify. Six of 32 studies (18.8%) examined non-interruptive systems (defined as computerized alerts which provide a warning on the screen but do not require user intervention to proceed), 7/32 (21.9%) examined interruptive systems and 19/32 (59.4%) did not specify. We used a $\chi 2$ test to determine whether these factors were more frequently associated with a positive study results and found that neither factor significantly increased the likelihood of a positive result ($p=0.36$ for developer and $p=0.83$ for interruptive systems). Most studies

targeted physicians (21/32 studies, 65.6%) or nurses (7/32 studies, 21.9%); a smaller number addressed the alerts to other providers, such as nurse practitioners (3/32 studies, 9.4%), pharmacists (2/32 studies, 6.3%), physician assistants (/322 studies, 6.3%) or the authors did not specify (5/32 studies, 15.6%). Further data on baseline characteristics of the participating clinicians were described in only 4/32 studies (12.5%) (Feldstein, et al., 2006; Lo, et al., 2009; Matheny, et al., 2008; Terrell, et al., 2010). With one exception (Terrell, et al., 2010), it was largely not possible to determine whether there were baseline differences between groups of clinicians participating in the studies.

Of fourteen studies evaluating anticoagulation decision support, 4 examined the effect on adverse events (2 combined bleeding and thrombosis (Fitzmaurice, et al., 2000; Poller, et al., 2008), one reported bleeding and thrombosis events separately (Vadher, et al., 1997a) and one reported on bleeding events alone(R. H. White, et al., 1987) (Table 3: Outcomes and Results in Studies of Drug-Lab Safety Alerts addressing Anticoagulation). These 4 studies were combined using a random effects model, yielding an odds ratio for experiencing an adverse event (either bleeding or thrombosis) of 0.88 (95% confidence interval 0.78-1.00, p=0.05) in favour of computerized alerts. There was little evidence of heterogeneity either qualitatively or statistically (I^2=0%, p=0.61 and confidence intervals for the individual studies overlapped as seen in Figure 3: Adverse events (Bleeding or thrombosis) in computerized anticoagulation alerts. When we examined only the subgroup of anticoagulation studies that addressed clinically important events as an outcome in which contamination was unlikely, we found the odds ratio for experiencing

an adverse event (bleeding or thrombosis) was 0.92 (95% confidence interval 0.37-2.28), with little evidence of heterogeneity (I^2=0%)

Eleven anticoagulation studies reported time in therapeutic range (TTR) as an outcome (Table 3: Outcomes and Results in Studies of Drug-Lab Safety Alerts addressing Anticoagulation); seven studies showed improvement and four found no change. Although most utilized the Rosendaal method (Rosendaal, Cannagieter, van der Meer, & Briet, 1993) to determine time in therapeutic range (which determines the total proportion of time in range, assuming that changes between measurements are linear), some authors reported this as a continuous outcome (reporting means and standard deviations), while others reported it as a categorical variable (and tested it using a χ^2 statistic). Furthermore, some studies reported TTR per person while others reported it per person-year. We tried to contact authors for additional data but received no responses. Because of these issues, we decided not to combine the results into a pooled estimate.

Other single drug systems addressed prescribing of antimicrobial agents (Paul, et al., 2006), digoxin (Peck, et al., 1973; K. S. White, et al., 1984), insulin (Albisser, et al., 2007a; Cavalcanti, et al., 2009; Rood, et al., 2005; Saager, et al., 2008), and theophylline (Tierney, et al., 2005). None of these studies addressed the impact of the intervention on adverse drug events. Outcomes reported included changes in prescribing patterns, time in target serum level, length of hospital stay, mortality, and hypoglycemic episodes (Table 4: Outcomes and Results in Studies of Drug-Lab Safety Alerts addressing a Single Drug class-Lab combination, excluding anticoagulation). There was evidence of benefit of the drug lab safety alert in prescribing of antimicrobials with greater likelihood of empirically

prescribing antimicrobials that were compatible with in vitro susceptibility. However, this was not seen after accounting for clustering in the analysis. (Paul, et al., 2006) There was also limited evidence of benefit in prescribing digoxin (combination of all physician actions including monitoring and prescribing actions) (Peck, et al., 1973; K. S. White, et al., 1984), as well as improved glycemic control and reduced frequency of hypoglycemic episodes in ICU patients receiving insulin (Albisser, et al., 2007b; Cavalcanti, et al., 2009; Saager, et al., 2008) compared to a strict protocol group but more hypoglycemic episodes than the group receiving conventional therapy. The single drug studies, other than those targeting anticoagulation, varied considerably in medications addressed, populations, rigour and outcomes and did not address adverse drug events. Consequently we did not attempt to combine the results into a pooled estimate of effect.

None of the multi-drug studies assessed ADEs as an outcome. The outcomes addressed (Table 5: Outcomes and Results in Studies of Drug-Lab Safety Alerts addressing Multiple Drug-Lab Combinations) were either judgements regarding appropriate laboratory monitoring (8 studies (Demakis, et al., 2000; Feldstein, et al., 2006; Field, et al., 2009; Lo, et al., 2009; Matheny, et al., 2008; McDonald, 1976; Palen, et al., 2006; Raebel, Lyons, Chester, et al., 2005), 52,785 events) or appropriate prescribing (3 studies (Field, et al., 2009; McDonald, 1976; Terrell, et al., 2010), 396 events). In one case (Judge, et al., 2006), the authors but did not differentiate between monitoring and prescribing actions.

Qualitatively, there was significant heterogeneity in the 8 multi-drug studies which measured change in lab monitoring, including in their populations, medications

addressed, and in alert-specific factors (such as whether they were locally developed and whether they were interruptive). This is also reflected in the very high statistical heterogeneity when these studies were combined (I^2 of 96%, $p<0.00001$, with confidence intervals that did not overlap). For this reason, we decided against combining these studies. When we examined the subgroup of multi-drug studies in which contamination was unlikely to be a factor, we still found substantial heterogeneity (I^2=96%), so we also decided against combining these studies.

The three studies examining appropriate prescribing were qualitatively diverse; one set in a diabetes clinic (McDonald, 1976), one in an university affiliated nursing home (Field, et al., 2009) and one in the emergency department (Terrell, et al., 2010). Two of the three targeted dose adjustment for renal disease (Field, et al., 2009; Terrell, et al., 2010). The three studies demonstrated significant statistical heterogeneity, I^2 of 64%, p=0.06 and when combined using a random effects model, yielded a pooled estimate of an odds ratio for more appropriate prescribing decisions with computerized alerts of 2.22 (95% confidence interval 1.19-4.17) (Figure 4: Impact on quality of prescribing decisions in studies of Drug-Lab Safety Alerts addressing Multiple Drug-Lab alerts).

Most of the studies used alerts triggered at the point of prescribing but two (Feldstein, et al., 2006; Raebel, Lyons, Chester, et al., 2005) tested different workflows. Raebel et al. (Raebel, Lyons, Chester, et al., 2005) studied an intervention in which pharmacists contacted patients who were missing recommended lab tests and ordered missing tests. Feldstein et al. (Feldstein, et al., 2006) tested email messaging to prescribers after the visit advising them of the need for laboratory follow up (in addition

to two other intervention groups which examined the impact of automated voice messaging to patients and a telephone call to patients from a pharmacy team member). When considering these two studies as a subgroup, there is statistical evidence of heterogeneity, with I^2 of 91% and p=0.001, so they were not combined into a pooled estimate, but both studies found statistically significant improvement in lab monitoring.

2.3 Discussion

Our systematic review of the impact of computerized drug-lab reminders found few studies addressing our primary outcome of adverse drug events. Only four of the anticoagulation studies reported on the impact on clinically important harms (including both thrombosis and bleeding); these were combined into a pooled estimate of borderline significance. Most studies addressed the subjective outcome of the author's judgement of improved lab monitoring and improved prescribing outcomes. We found most studies addressed the prescribing of a single drug, almost always a high risk, narrow therapeutic index drug This category was dominated by alerts to improve anticoagulation. Some of these medications are now rarely used in practice, such as theophylline. The lack of clear evidence of benefit among alerts targeting a single drug should trigger both further study and caution at a policy level in advocating widespread uptake of drug-lab safety alerts.

Studies investigating alerts for multiple drug-lab combinations more fully represent the complexity of prescribing in daily practice, in which clinicians consider many factors simultaneously when making prescribing decisions, usually with significant time constraints. None of the multi-drug studies addressed our primary outcome, adverse drug events. Surprisingly, only three RCTs addressed the impact of drug lab safety alerts

on prescribing decisions, of which none were conducted in community ambulatory care settings, where most medications are prescribed. This represents a significant gap in evidence regarding the impact of drug lab safety alerts used in common clinical settings, and should signal the need for better evidence before policy makers advocate widespread uptake of such alerts in a variety of clinical settings.

None of the multi-drug studies assessed our chosen primary outcome, the impact on adverse drug events. Improved lab monitoring is a relatively poor surrogate outcome that lacks relevance to patients, particularly as evidence suggests that clinicians fail to consider abnormal lab results in their prescribing decisions approximately as frequently as they fail to perform recommended lab monitoring. Only three multi-drug studies evaluated the impact on prescribing and demonstrated improved prescribing decisions, though with no clear direct benefit to patients. There is a gap in the literature regarding the question of whether prescribing changes to account for abnormal lab results are associated with improved clinical outcomes. The fact that none of the multi-drug studies assessed clinically important outcomes is another source of concern that should be addressed in future research.

Previous reviews of computerized decision support systems have identified poor methodological rigour as a problem, and though clearly improving since previous reports(Garg, et al., 2005), this remains an important concern based on our review. It is important for investigators to utilize strategies to limit contamination of the study groups. If clinicians are prescribing to patients in both the intervention and control groups, their prescribing patterns are likely to be influenced by their exposure to the reminder system.

Lack of control of contamination will tend to bias the results toward the null hypothesis and may reduce the likelihood of identifying a true difference between the systems. Future studies should address the concerns around contamination.

Strengths of this review include a thorough search, carried out by 2 teams of experienced researchers, and not restricted by language, setting, or drug class. There was dual full text review of studies for inclusion, thereby limiting bias.

Limitations include the possibility that relevant studies may have been missed, given that only one reviewer performed the initial screening of abstracts. There may be unpublished studies, which may be more likely to be smaller studies, to have negative findings and may have altered our findings. We did not undertake dual data abstraction, which may have introduced errors into our findings. Heterogeneity was marked in some study subsets in the domains of intervention design, populations, settings, systems used, outcomes measured and in methodological rigour, making it challenging to make overall conclusions about the efficacy of computerized drug lab alerts.

Currently, the evidence does not merit a recommendation to policy makers to include drug lab safety alerts as an essential component of decision support in electronic medical records. A systematic review on the effect of CDSS on prescribing reached similar conclusions (Hemens, et al., 2011). It remains unclear whether better studies or better decision support systems are needed to show benefit. Future studies should focus on multi drug systems, and be of sufficient duration and size to be able to demonstrate changes in patient important outcomes, such as reduced adverse drug events. Clinicians should be randomized rather than patients to avoid concerns about contamination and the

potential error of not demonstrating a true difference between the two groups, their demographic characteristics should be provided, and clustering of clinician responses should be addressed in the analysis plan. Alerts should be evidence based, clinically relevant, and tested in a variety of settings, including community based ambulatory care settings, where most medications are prescribed and in nursing homes, where residents are at greater risk of adverse drug events due to increased frailty, more comorbid conditions, and more prescribed medications. Key questions remain, such as how to strike the appropriate balance between clinically relevant alerts and disruptions to clinicians' workflow, and the potential for alert fatigue. It is also important to understand more about appropriate presentation of alerts, including whether they are interruptive or non-interruptive, the contextual information provided at the time of the alert, the appropriate communications medium or technology to present or deliver the alert (e.g., within the EMR, sent directly to mobile devices, pages, or through email), and whether they are best directed at prescribers, patients, or other members of the health care team such as pharmacists. Furthermore, it is not clear whether simply presenting laboratory information at the point of prescribing would be associated with improved prescribing decisions. This latter question is the focus of the remainder of this thesis.

2.4 Conclusion

There is evidence that 'improved' prescribing decisions, though not improved patient important outcomes are associated with computerized drug lab alerts in multi-drug systems. Evidence suggests that anti-coagulation related drug-lab alerts are associated with reduced adverse events, including both bleeding and thrombosis, but with borderline

statistical significance (p=0.05). Most studies measured surrogate outcomes and many had methodological flaws. Future research should focus on multi drug studies, be set in ambulatory care and nursing homes, be designed to address patient important outcomes and include an economic analysis. Policy makers should not implement these systems without evidence of cost-effectiveness.

Table 1 PRISMA checklist

Section/ topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	15
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Not included in thesis
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-15
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	15,16
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	36-40
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	15,16
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	16-18
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	42-44
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	18
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	19
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	19, 47-51

Section/ topic	#	Checklist item	Reported on page #
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	19
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	19,20
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	19,20
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	19
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	20,21,67
Study character-istics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	23-24, 52-57
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	21-23,68
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	24-28,60-65
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	24,25,27,69
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	68
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	28-32

Section/ topic	#	Checklist item	Reported on page #
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	30
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	32
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

Appendix A: Systematic review protocol

The impact of computerized drug lab alerts on process and clinical outcomes: A systematic review
Protocol

Background:

Adverse drug events are common and are thought to be frequently preventable(Thomsen, Winterstein, Sondergaard, Haugbolle, & Melander, 2007). In ambulatory care, where most medications are prescribed, estimates of the prevalence of adverse drug events vary between 4.0 and 91.3 per 1000 person-months, depending upon the population and case finding methods. The higher estimates are seen among elderly persons, especially those taking many medications and studies in which patient self-reports are considered as a potential data source. (1) Little data exists regarding the cost of adverse drug events. However, several American studies from the mid 1990s estimate the cost of increased length of stay to be between $US2262 to $US3244 per event. Inadequate drug monitoring has been associated with 60.8% of preventable adverse drug events in ambulatory care(Gurwitz, et al., 2003), including errors of failure to order relevant lab tests and failure to act on existing lab data. Improved drug monitoring and integration of lab data into prescribing is a central patient safety and public health issue.

Lab monitoring is important to ensure that a given medication is safe for a specific patient and to detect potential adverse drug events. Computerized drug lab alerts are computer-based systems reminding prescribers to consider clinically important drug lab interactions. The effectiveness of drug lab alerts is unclear. Several systematic reviews of computerized physician order entry (CPOE) and computer decision support systems (CDSS) have been done(Eslami, et al., 2007; Garg, et al., 2005; Kaushal, et al., 2003; Shojania, et al., 2009) and have demonstrated mixed results. While CPOE with CDSS has been shown in randomized controlled trials to change some clinician prescribing behaviours, no reliable evidence has demonstrated that these systems reduce adverse drug events. Some systematic reviews have included trials of drug lab alerts but have not addressed the impact of drug-lab alerts specifically. Clinical trials investigating drug-lab alerts have evaluated the number of lab tests ordered, but not the quality of prescribing.(Lo, et al., 2009; Palen, et al., 2006) Therefore, the extent to which drug-lab alerts affect the quality of prescribing and their impact on clinically important outcomes is unclear and merits further study.

Objectives:

In this review, we address the following questions:

- Do computerized drug-lab alerts for medications requiring lab monitoring, directed at prescribing clinicians at the time of prescribing, result in reduced adverse drug events and more appropriate prescribing as compared to usual care?
- Are there identifiable features of drug-lab alerts that make them more effective (such as whether alerts require clinician input or are part of a commercial system)?

Methods:

Criteria for considering studies for this review:

Types of studies: We include randomized controlled trials where the studies in question meet the quality criteria described below.

Types of participants: We include studies recruiting prescribing clinicians, including post-graduate medical trainees, primary care physicians, specialists, nurse practitioners and pharmacists and set in all health care settings including hospitals, ambulatory care and long-term care settings.

Types of interventions: We will include studies of computerized reminder systems alerting the prescriber to the need to consider clinically important drug lab interactions. Both multi drug systems and single drug systems will be included. Multi-faceted intervention studies will be included if it is possible to determine the impact of the drug lab reminder system alone.

Types of outcome measures:

- Primary outcomes:
    1. Rates of adverse drug events
- Secondary outcomes:
    1. Hospitalization rates
    2. Mortality rates
    3. Proportion of lab tests ordered
    4. Proportion of prescriptions with dosage change or discontinued medication
    5. Proportion of overridden alerts
    6. Improved prescribing as measured with a validated tool
    7. Costs or resource utilization

Study identification: The Computerized Clinical Decision Support System Systematic Review Team from McMaster University is in the process of updating their previous large-scale reviews of the effectiveness of computer decision support systems. Their methods have been described elsewhere.(Haynes & Wilczynski, 2010) Briefly, their team has searched Medline, EMBASE, EBM review databases, Inspec, and relevant reference lists from 1974 to Jan 6, 2010. Their inclusion criteria were: randomized controlled trials

comparing CCDSS to no CCDSS, studies involving health care professionals in clinical practice or post-graduate medical trainees, computerized systems that provided patient specific advice to clinicians, reporting on process specific and/or patient specific outcomes. They have made available to us citations of studies included in two domains, drug prescribing and therapeutic drug monitoring. Two reviewers will independently examine these citations in full text, and determine whether the studies under consideration meet our inclusion criteria. When disagreements occur, the two reviewers will discuss them and if unable to resolve by consensus, the conflict will be resolved by a third reviewer, Dr. Anne Holbrook. We will report agreement between coders using both the Kappa statistic and percentage agreement. A minimum a priori criterion will be that agreement as measured by Kappa should be greater than 0.65.

Validity assessment: We will assess validity by systematically considering potential sources of error and bias. We will use the criteria described in the Cochrane Handbook(Higgins & Green, 2009) to evaluate the validity of the studies included in the review. These include evaluations of randomization, concealment of allocation, blinded assessment, the proportion of patients and providers followed up, selective outcome reporting (including intention to treat analysis), protection against contamination and unit of analysis errors.

Data collection: Two reviewers will abstract results from eligible studies using the Study Data Collection Tool (Appendix 2). If data is insufficiently reported in the study results, we will write to the investigators where possible. It is otherwise not possible to distinguish between incomplete or incompletely reported results. To avoid introducing bias, unpublished information obtained from investigators should be clear, received in written form and abstracted in the same manner as other study results.

Analysis: Continuous measures will be reported as mean differences and standard deviations or as standardized mean differences, which will enable comparison of studies employing different measurements. Dichotomous outcomes will be reported as odds ratios. Point estimates and confidence intervals will be reported for all effect measures. Heterogeneity of identified studies will be analyzed both qualitatively and quantitatively, and will be reported using the I^2 and chi square statistics and through narrative description. The total number of participants and events in the control and intervention groups will be described for each outcome. The proportional weight of each study will be described. If appropriate, a test of overall effect utilizing a random effects model for meta-analysis will be reported.

Inferences and presentation of results: The results of the review will summarize the findings including tables summarizing the characteristics of included studies, data and analysis, relevant figures including forest plots, funnel plots, risk of bias plots, and a Summary of Findings table, using the GRADE framework(Guyatt, et al., 2008). The Summary of Findings table will summarize the evidence for all important outcomes of interest, including an assessment of the typical burden of the outcome, the magnitude of

effect of the intervention, the number of participants and studies addressing these outcomes, and an overall rating of the quality of the evidence base for each outcome. The level of the quality of evidence will be affected by factors such as study design limitations suggesting high likelihood of bias, indirectness of evidence, unexplained heterogeneity of results, lack of precision of results, and high chance of publication bias. Each of these factors involves subjective judgements. In order to evaluate the validity and reproducibility of these judgements, the review results will be reviewed by x (#?) reviewers, who will independently evaluate the evidence base for each outcome in each of the aforementioned domains. The agreement between reviewers will be reported in absolute percent agreement and the kappa statistic.

References

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Appendix B: Study eligibility form

Title:
Author:
Year of publication:

Study ID:
Reviewer:

Study design: Is the study described as randomized?	Yes	Unclear	No ⇨	Exclude
Participants: Are the participants health care professionals in clinical practice (not exclusively students)?	Yes	Unclear	No ⇨	Exclude
Intervention: Is the intervention a computerized drug lab reminder system?	Yes	Unclear	No ⇨	Exclude
Outcomes: Are at least one of the following outcomes assessed: ○ **Adverse drug events** ○ **Hospitalization rates** ○ **Mortality rates** ○ **Proportion of lab tests ordered** ○ **Proportion of prescriptions changed** ○ **Proportion of overridden alerts** ○ **Improved prescribing (using validated tool)**	Yes	Uncertain	No ⇨	Exclude
Included study	Yes ⇦	Uncertain		Excluded

Appendix C: Search strategy MMIT group: MEDLINE

MEDLINE® Ovid MEDLINE(R) <1950 to September Week 2 2009>
Date searched: Sept 21-09
Number of retrievals: 10767
1 electronic prescribing/ (61) 2 drug therapy, computer assisted/ (1151) 3 (electronic adj3 prescri*).mp. (351) 4 electronic medication*.mp. (116) 5 automated prescri*.mp. (25) 6 (automated adj3 medication*).mp. (72) 7 (online adj3 prescri*).mp. (39) 8 (online adj3 medication*).mp. (17) 9 e-prescri*.mp. (163) 10 eprescri*.mp. (12) 11 e-medication*.mp. (4) 12 emar*.mp. (169) 13 (bcma and (medication* or prescri* or drug)).mp. (24) 14 e-rx.mp. (11) 15 ((bar cod* or barcod*) and (prescri* or medication* or drug*)).mp. (280) 16 (computer* adj2 prescri*).mp. (310) 17 prescri* monitor*.mp. (89) 18 clinical pharmacy information systems/ (986) 19 prescri* order entry.mp. (56) 20 pharma* order entry.mp. (5) 21 computer* order entry.mp. (115) 22 automated dispens*.mp. (82) 23 or/1-22 (3403) 24 exp pharmaceutical services/ (38883) 25 exp medical errors/ (64473) 26 exp drug therapy/ (864020) 27 exp drug interactions/ (122756) 28 exp drug monitoring/ (9813) 29 exp medication systems/ (3386) 30 exp drug administration schedule/ (71159) 31 exp drug costs/ (9397) 32 exp dose-response relationship, drug/ (288539) 33 drug therapy, computer assisted/ (1151) 34 (prescri* or medication*).mp. (218668) 35 pharmacotherap*.mp. (14545) 36 pharmaceutical*.mp. (115354) 37 dispens*.mp. (18455)

38	exp therapeutic uses/ (3544181)
39	(safety or safe).mp. (310321)
40	error*.mp. (173803)
41	(adverse adj3 event*).mp. (46457)
42	(adverse adj3 effect*).mp. (79271)
43	mistake*.mp. (11308)
44	complication*.mp. (744423)
45	(risk adj5 manag*).mp. (21572)
46	(risk adj5 assess*).mp. (138608)
47	harm*.mp. (57502)
48	exp medical errors/ (64473)
49	safety management/ (11037)
50	patient safety/ (0)
51	medical error/ (8433)
52	medication error/ (7690)
53	risk management/ (11711)
54	risk assessment/ (109320)
55	adverse drug reaction reporting systems/ (4027)
56	or/24-55 (5187543)
57	cdss.tw. (355)
58	ccdss.tw. (2)
59	(comput* adj3 decision support*).mp. (603)
60	reminder system*.tw. (380)
61	decision support systems, clinical/ (3072)
62	reminder systems/ (1486)
63	therapy, computer assisted/ (3599)
64	decision making, computer assisted/ (2051)
65	(comput* adj3 order entry).tw. (714)
66	provider order entry.tw. (196)
67	cpoe.tw. (492)
68	clinician order entry.tw. (4)
69	physician order entry.tw. (443)
70	nurs* order entry.tw. (2)
71	pharma* order entry.tw. (5)
72	medical order entry systems/ (799)
73	patient portal*.mp. (67)
74	personal medical record*.mp. (42)
75	personal health record*.mp. (215)
76	(patient adj2 access* adj2 record*).mp. (728)
77	(patient adj2 carried adj2 record*).mp. (3)
78	(patient adj2 held adj2 record*).mp. (52)
79	(patient adj2 shared adj2 record*).mp. (14)
80	patient internet portal*.mp. (9)
81	phr.mp. (484)

82	ephr.mp. (11)
83	exp medical records/ and patient access to record*.mp. (478)
84	kiosk*.tw. (105)
85	point-of-care systems/ (4135)
86	computers, handheld/ (1396)
87	Medical Records Systems, Computerized/ (15799)
88	or/57-87 (31551)
89	56 and 88 (7973)
90	guideline adherence/ (12072)
91	exp patient compliance/ (38269)
92	(patient compliance or patient adherence).tw. (5892)
93	(comput* or online or internet or electron*).mp. (1263766)
94	or/90-92 (53419)
95	94 and 93 (3358)
96	56 and 95 (1775)
97	23 or 89 or 96 (11560)
98	97 not letter.pt. (11306)
99	98 not editorial.pt. (11144)
100	99 not news.pt. (11001)
101	animal/ not (human/ and animal/) (3351990)
102	100 not 101 (10767)

Appendix D: Updated Search Strategy

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 4 2011>
Search Strategy:

1 Artificial Intelligence/ (13441)
2 Decision Making, Computer-Assisted/ (1430)
3 Therapy, Computer-Assisted/ (3135)
4 Diagnosis, Computer-Assisted/ (8936)
5 Decision Support Systems, Clinical/ (3478)
6 Hospital Information Systems/ (5601)
7 Point-of-Care Systems/ (4762)
8 Computers, Handheld/ (1564)
9 decision support.mp. (12481)
10 Reminder Systems/ (1447)
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (48106)
12 clinical trial.mp. or Clinical Trial/ (309321)
13 random.mp. (119111)
14 search.mp. (91408)
15 meta analysis.mp. or Meta-Analysis/ (40168)
16 associated.mp. (1221142)
17 overview.mp. (48203)
18 12 or 13 or 14 or 15 or 16 or 17 or 18 (1699245)
19 11 and 19 (8641)
20 limit 20 to yr="2010 -Current" (824)
21 limit 21 to (humans and (comment or editorial or letter)) (8)
22 limit 21 to (humans and (clinical trial, all or comparative study or controlled clinical trial or meta analysis or "review")) (274)

Database: Embase <1996 to 2011 Week 18>
Search Strategy:
---

1 computer assisted therapy/ (2183)
2 computer assisted drug therapy/ (503)
3 artificial intelligence/ (9581)
4 decision support system/ (7387)
5 hospital information system/ (10666)
6 neural networks.mp. (9731)
7 expert system/ (2585)
8 medical information system/ (10435)
9 decision support.mp. (9980)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (51616)
11 random.mp. (106586)
12 clinical trial/ (666171)

13 15 or 16 (761219)
14 14 and 17 (2842)
15 limit 18 to human (2164)
16 limit 19 to (human and yr="2010 -Current") (250)
17 from 20 keep 47,84,98,134 (4)

Appendix E: Data extraction form

Computerized Drug Lab Alerts SR: Study Data Collection Tool

Study ID No.
Reviewer initials:
Citation:

A. Methods:
1. Study Duration:

2. Unit of randomization:
    1. Clinician _____
    2. Clinic/ hospital / unit _____
    3. Patient_____
    4. Prescription _____

3. Unit of analysis:
    1. Clinician_____
    2. Clinic / hospital/ unit _____
    3. Patient _____

4. Comments:

	Yes	**No**	**NR/ Unclear**	**Comments**
Sequence Generation: Was the allocation sequence adequately generated?				
Allocation sequence concealment: Was allocation adequately concealed?				
Blinding: Was knowledge of the allocated interventions adequately prevented during the study?				

	Yes	No	NR/ Unclear	Comments
Other concerns about bias: Was the study apparently free of other problems that could put it at a risk of bias?				

NR=not reported

B. Participants:

	Inter-vention	Control	NR	Comments
Clinicians				
Primary care physicians (n,%)				
Specialists (specify) (n,%)				
Postgraduate medical trainees (n,%)				
Nurse practitioners (n,%)				
Pharmacists (n,%)				
Others (specify)				
Age (y, SD)				
Gender (women, n,%)				
Years in practice (mean, SD)				
Patients				
Number at baseline (n,%)				
Number at study end (n,%)				
Age (y, SD)				
Gender (women, n,%)				
No. medications at baseline (mean, SD)				

	Inter-vention	Control	NR	Comments
No. chronic medical conditions at baseline (mean, SD)				
Missing lab test (n,%,specify interval)				
Adverse drug events (baseline)				

Are the groups equivalent at baseline?
Yes ____
No ____
Comments:

Was incomplete outcome data adequately addressed?
Yes ____
No ____
Unclear (describe)

C. Setting:

Inpatient hospital	
Ambulatory care	
Long term care	
Other (specify)	

D. Intervention:

	Yes	No
1**. System Developer**		
a. Commercial		
b. Homegrown		
2. **Clinician targeted alert**		
3**. Interruptive alert**		
4. Type of prescription:		

a. New prescription		
b. Repeat prescription		
5. Number of targeted drugs:		
a. Single drug (specify)		
b. Multiple drugs		
6. Medication Lab combinations		
7. Process of selecting drug/lab combinations		
8. Multifaceted intervention		
9. Describe intervention		

E. Outcomes:

Outcomes	Pre-specified (Y,N, NR)	Comments
Primary:		
Secondary:		

Are reports of the study free of suggestions of selective outcome reporting?
Yes _____
No _____
Unclear (describe)
_____
_____

F. Results:

	Int (n,%)	Control (n,%)	NR	p/ 95% CI	Comments

Adverse events, including adverse drug events					
Inpatient hospitalization					
Mortality rate					
ER visits					
Patient symptoms					
Change in lab monitoring (specify)					
Change in prescribing including medications discontinued, dose changes or improved prescribing using validated tool (specify change and/or tool)					
Time in therapeutic range					
Proportion of 'overridden alerts'					
Other relevant changes in prescriber behaviour (describe)					

G. Comments:

Table 2: Characteristics of Included Studies

Author, y	Setting	Providers	Sample size	Intervention	Rx type	Target Medications: Test Combinations
Anticoagulation studies						
Poller 2008 (Poller, et al., 2008)	Ambulatory care	MDs	13219 patients in 32 centres	Patient specific computer assisted dosing reviewed by MD at each visit.	New and repeat	Warfarin, Acenocoumarol, Phencoumon
Claes 2005 (Claes, et al., 2005)	Ambulatory care	MDs (GPs)	96 GPs 66 practices 834 patients	4 groups: 1. Computer assisted patient specific dosage advice. 2. Physician feedback 3. Point of care INR testing 4. Usual care	Repeat	Warfarin, Acenocoumarol, Phencoumon
Mitra 2005 (Mitra, et al., 2005)	Inpatient (Rehabilitation hospital)	MDs	30 patients	Patient specific real time computer assisted dosage advice	New and repeat	Warfarin
Marco 2005 (Marco, et al., 2003)	Ambulatory care	MDs (hematologists)	1880 patients	Patient specific real time computer assisted dosage advice	Repeat	Acenocoumarol
Manotti 2001 (Manotti, et al., 2001)	Ambulatory care	MDs	1251 patients in 5 clinics	Patient specific real time computer assisted dosage advice	New and repeat	Warfarin, Acenocoumarol
Fitzmaurice 2000 (Fitzmaurice, et al., 2000)	Ambulatory care (primary care)	Nurses	367 patients	Patient specific real time computer assisted dosage advice, together with nurse led point of care INR testing. Recommendations for dose change reviewed by MD.	Repeat	Warfarin
Ageno 1998 (Ageno & Turpie, 1998)	Ambulatory care	MDs Nurses	101 patients	Patient specific real time computer assisted dosage advice	New	Warfarin

Author, y	Setting	Providers	Sample size	Intervention	Rx type	Target Medications: Test Combinations
Poller 1998 (Poller, et al., 1998)	Ambulatory care	MDs	285 patients	Patient specific real time computer assisted dosage advice	New and repeat	Warfarin, Acenocoumarol
Vadher 1997 (Vadher, et al., 1997a)	Ambulatory care	NPs MDs (Medical residents)	177 patients	Patient specific real time computer assisted dosage advice to NPs compared with medical residents without computer assistance.	Repeat	Warfarin
Vadher(2) 1997 (Vadher, et al., 1997b)	Inpatients and outpatients	Medical trainees and NP	148 patients	Patient specific real time computer assisted dosage advice	New	Warfarin
Mungall 1994 (Mungall, et al., 1994)	Inpatients	Not described	51 patients	Computer assisted dosing compared with nomogram-based dosing	New	Heparin
White 1991 (R. H. White & Mungall, 1991)	Ambulatory care	Nurse	50 patients	Patient specific real time computer assisted dosage advice	Repeat	Warfarin
White 1987 (R. H. White, et al., 1987)	Inpatient	Not specified	75 patients	Patient specific real time computer assisted dosage advice	New	Warfarin
Carter 1987 (Carter, et al., 1987)	Inpatient	MDs	101 patients	Patient specific real time computer assisted dosage advice, compared to linear regression based dosing and to manual dosing	New	Warfarin
Antimicrobial agents						
Paul 2006 (Paul, et al., 2006)	Inpatient	MDs	2326 patients	Computer decision support based on causal probabilistic network. Probability of pathogen is predicted by place of acquisition and patient factors.	New	Antimicrobials

Author, y	Setting	Providers	Sample size	Intervention	Rx type	Target Medications: Test Combinations
Digoxin						
Peck 1973 (Peck, et al., 1973)	Ambulatory care	MDs	8 MDs (internists, cardiologists & residents) 42 patients	Patient specific real time computer assisted dosage advice	Repeat	Digoxin for heart failure
White 1984 (K. S. White, et al., 1984)	Inpatient	MDs	396 patients	Computer advice generated nightly, printed report put on front of patient chart.	Repeat	Digoxin
Insulin						
Cavalcanti 2009 (Cavalcanti, et al., 2009)	Inpatient (ICU)	Nurses	167 patients	Patient specific real time computer assisted dosage advice; compared with strict glycemic control protocol and with standard sliding scale	New and repeat	Insulin
Saager 2008 (Saager, et al., 2008)	Inpatient (ICU)	Not specified	40 patients	Patient specific real time computer assisted dosage advice	New and repeat	Insulin
Albisser 2007 (Albisser, et al., 2007b)	Ambulatory care	Not specified	22 patients	Computerized prediction of hypoglycemia based on patients' self monitored blood glucose readings, which were sent remotely to providers.	Repeat	Insulin
Rood 2005 (Rood, et al., 2005)	Inpatient (ICU)	Nurses	120 patients	Patient specific real time computer assisted dosage advice	New and repeat	Insulin
Theophylline						
Tierney 2005 (Tierney, et al., 2005)	Ambulatory care (primary care)	MD Pharmacist	274 MDs 20 pharmacists 706 patients	Patient specific real time computer assisted dosage advice	Repeat	Theophylline for asthma or COPD

Author, y	Setting	Providers	Sample size	Intervention	Rx type	Target Medications: Test Combinations
Multi-Drug studies						
Terrell 2010 (Terrell, et al., 2010)	Emergency department	MD	42 physicians 119 prescriptions	Interruptive alert triggered on medication order entry	New and repeat	10 drugs requiring dose adjustment with renal disease (based on Creatinine Clearance calculated with Cockcroft Gault equation)
Field 2009 (Field, et al., 2009)	Nursing home	MD	22 units 10 physicians 833 patients	Interruptive alert triggered on medication order entry	New	62 drugs requiring dose adjustment with renal disease (based on Creatinine Clearance calculated with Cockcroft Gault equation)
Lo 2009 (Lo, et al., 2009)	Ambulatory care (primary care)	MD NP PA	22 clinics 366 health care providers 2765 patients	Non-interruptive alert triggered on medication order entry	Repeat	160 alerts
Matheny 2008 (Matheny, et al., 2008)	Ambulatory care (primary care)	MD	20 clinics 303 physicians 1922 patients	Non-interruptive alert triggered on opening patient chart	Repeat	NSAID: Cr); ARB (Cr); Metformin (Cr); K+ (K+);Potassium sparing diuretic(K); Thiazide (K+); ACEI(K+); Statin(ALT Thyroxine: TSH Carbamazepine, cyclosporine, phenytoin, procNAPA, valproate,: therapeutic drug monitoring
Feldstein 2006 (Feldstein, et al., 2006)	Ambulatory care (primary care)	Not specified	15 clinics 100 primary care providers 433 patients	EMR intervention: Patient specific reminder email sent to PCP from chair patient safety committee. Other interventions- automated voice message sent to patient, and phone call to patient by pharmacy team member	New	ACEI/ARB (Cr, K+); Allopurinol (Cr); Carbamezepine (ALT or AST, Na+);Diuretic (Cr, K+);Metformin (Cr); Pioglitazone (ALT or AST); K+ (Cr, K+); Statins (ALT or AST); Terbinafine (Cr, AST or ALT)

Author, y	Setting	Providers	Sample size	Intervention	Rx type	Target Medications: Test Combinations
Judge 2006 (Judge, et al., 2006)	Nursing home	MDs NPs PAs	Long stay units of 1 home. 27 prescribers, (general internists, NPs and PAs)	Interruptive alert triggered at medication order entry.	New and repeat	42 categories of alerts; those related to drug lab alerts include: related to orders for warfarin; to potential renal insufficiency and electrolyte imbalance; to hypokalemia; to hypoglycemia; to orders for phenytoin; to low TSH level
Palen 2006 (Palen, et al., 2006)	Ambulatory care (primary care)	MDs	16 sites 207 primary care physicians	Non-interruptive alert triggered at medication order entry	New	ACEI/ARB (Cr, K+); Digoxin (Cr, K+); INH, rifampin (AST or AST); Allopurinol (Cr); Colchicine (CBC); Statins (AST or ALT); Gemfibrazol (AST or ALT); Niacin (AST or ALT); Diuretics (Cr, K+); Metformin (Cr); Pioglitazone (AST or ALT); K+ (Cr, K+); Carbamazepine (TSH, Cr, AST or ALT, CBC); Phenytoin (AST or ALT); Valproic acid (AST or ALT, CBC)
Raebel 2005 (Raebel, Lyons, Chester, et al., 2005)	Ambulatory care (primary care)	Pharmacists	10,169 patients	Pharmacists called patients with outstanding tests to remind them or order tests if needed.	New	Allopurinol (Cr); Amiodarone (ALT/AST, TSH); Azathioprine (ALT/AST, CBC); Carbamazepine (ALT/AST, CBC); Divalproex (ALT/AST, CBC); Felbamate (reticulocyte count, CBC, bilirubin, AST/ALT); Methotrexate (CBC, Cr, ALT/AST); Nefazadone (ALT/AST); Pioglitazone (ALT/ AST) Statin + gemfibrazol (in combination) (ALT/ AST); Isotretinoin (pregnancy test, ALT/ AST, lipids or TG); Lithium (Cr, CBC, TSH); Metformin (Cr); Ticlodipine (ALT/ AST, CBC

Author, y	Setting	Providers	Sample size	Intervention	Rx type	Target Medications: Test Combinations
Demakis 2000 (Demakis, et al., 2000)	Ambulatory care	MDs (residents)	275 residents	Patient specific alert triggered on opening chart.	New and repeat	Multiple standards of care, one drug lab related (warfarin monitoring q 45 days)
McDonald 1976 (McDonald, 1976)	Ambulatory care (diabetes clinic)	MDs including Residents, Interns, Medical students Nurse clinicians	63 clinicians	Printed form with computer generated reminders attached to front of each chart before clinical appointment.	NR	Renally cleared drugs (BUN, Cr); NSAIDS and steroids (Hb and Hct); Methyl dopa, Phenothiazines, Isoniazid (liver function tests); cardiac glycosides, K+ supplements and K sparing diuretics (K+).

MD=physician; NP= nurse practitioner; PA=physician assistant; CrCl= creatinine clearance; NSAID= non-steroidal anti-inflammatory drug; Cr= creatinine; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; Na+= sodium; K+=potassium; ALT=alanine transaminase; AST=aspartate transaminase; TSH=thyroid stimulating hormone; CBC=complete blood count; Hb= hemoglobin; Hct= hematocrit;proc=procainamide; NAPA=n-acetyl procainamide; COPD=chronic obstructive pulmonary disease.

Table 3: Comparison of Selected Characteristics of Drug-Lab Safety Alert Systems among Included Studies

Author, y	Commercial (C)/ Local (L),	Interruptive (I), Non-interruptive (nI)
Single drug systems		
Poller 2008 (Poller, et al., 2008)	C	NR
Claes 2005 (Claes, et al., 2005)	C	NR
Mitra 2005 (Mitra, et al., 2005)	C	NR

Author, y	**Commercial (C)/ Local (L),**	**Interruptive (I), Non-interruptive (nI)**
Marco 2005 (Marco, et al., 2003)	L	NR
Manotti 2001 (Manotti, et al., 2001)	C	NR
Fitzmaurice 2000 (Fitzmaurice, et al., 2000)	C	NR
Ageno 1998 (Ageno & Turpie, 1998)	C	NR
Poller 1998 (Poller, et al., 1998)	C	NR
Vadher 1997 (Vadher, et al., 1997a)	L	NR
Vadher(2) 1997 (Vadher, et al., 1997b)	L	NR
Mungall 1994 (Mungall, et al., 1994)	L	NR
White 1991 (R. H. White & Mungall, 1991)	L	NR
White 1987 (R. H. White, et al., 1987)	L	NR
Carter 1987 (Carter, et al., 1987)	L	NR
Paul 2006 (Paul, et al., 2006)	L	nI
Peck 1973 (Peck, et al., 1973)	L	NR
White 1984 (K. S. White, et al., 1984)	L	nI
Cavalcanti 2009 (Cavalcanti, et al., 2009)	L	NR
Saager 2008 (Saager, et al., 2008)	C	NR

Author, y	**Commercial (C)/ Local (L),**	**Interruptive (I), Non-interruptive (nI)**
Albisser 2007 (Albisser, et al., 2007b)	NR	I
Rood 2005 (Rood, et al., 2005)	C/L	I
Tierney 2005 (Tierney, et al., 2005)	L	I
Terrell 2010 (Terrell, et al., 2010)	L	I
Field 2009 (Field, et al., 2009)	C	I
Lo 2009 (Lo, et al., 2009)	L	nI
Matheny 2008 (Matheny, et al., 2008)	L	nI
Feldstein 2006 (Feldstein, et al., 2006)	L	I
Judge 2006 (Judge, et al., 2006)	L	I
Palen 2006 (Palen, et al., 2006)	L	nI
Raebel 2005 (Raebel, Lyons, Chester, et al., 2005)	L	nI
Demakis 2000 (Demakis, et al., 2000)	L	NR
McDonald 1976 (McDonald, 1976)	L	NR

NR=not reported

Table 4: Outcomes and Results in Studies of Drug-Lab Safety Alerts addressing Anticoagulation

Author,y	**Time in therapeutic range**			**Adverse events**		
	Intervention	**Control**	**p/95% CI**	**Intervention**	**Control**	**p/95% CI**
Poller 2008 (Poller, et al., 2008)	65.9% (16)	64.7% (17.0)	p<0.001	6.0/100 pt-yrs combined bleeding and thrombosis	5.5/100 pt-yrs	p=0.10
Mitra 2005 (Mitra, et al., 2005)	62%	44%	p<0.05			
Marco 2005 (Marco, et al., 2003)	67.3%	65.5%	p<0.002			
Claes 2005 (Claes, et al., 2005)	55%	63%	NS			
Manotti 2001 (Manotti, et al., 2001)	71.2%[1] 51.9%[2]	68.2%[1] 48.1%[2]	p<0.001[1] p<0.001[2]			
Fitzmaurice 2000 (Fitzmaurice, et al., 2000)	69%	62%	p<0.001	3/122 combined bleeding and thrombosis	10/245	NS
Ageno 1998 (Ageno & Turpie, 1998)	55.3%	55.2%	NS			
Poller 1998 (Poller, et al., 1998)	61.8% (27.1)[1] 66.4% (29.9)[2] 63.3% (28.0)[3]	54.0% (27.5)[1] 51.2% (28.4)[2] 53.2% (27.7)[3]	p=0.06[1] p=0.02[2] p=0.004[3]			
Vadher 1997 (Vadher, et al., 1997a)	60.7%[4] 67.6%[5]	51.6%[4] 70.1%[5]	NS NS	Bleeding 5 Thrombosis 2	Bleeding 6 Thrombosis 1	NS
Vadher(2) 1997 (Vadher, et al., 1997b)	59.4 days/100 pt-days[6] 63.7 days/100 pt-days[7]	52.2 days/ 100pt-days[6] 51.0 days/100 pt-days[7]	0.9 (0.7-1.0)[6] 0.8 (0.7-0.9)[7]			
Mungall 1994 (Mungall, et al., 1994)	78.0%	73.0%	P<0.002	4.0%[8] 24%[9]	7.7%[8] 0[9]	p=0.60[8] p=0.01[9]

Author,y	Time in therapeutic range			Adverse events		
	Intervention	Control	p/95% CI	Intervention	Control	p/95% CI
White 1991 (R. H. White & Mungall, 1991)			Report PT at study end, not TTR			
White 1987 (R. H. White, et al., 1987)				Bleeding 0	Bleeding 8.3%	NS

[1]Maintenance phase; [2]Induction phase; [3]Both phases; [4]INR=2-3; [5]INR=3-4.5; [6]inpatient; [7]outpatient; [8]Bleeding events; [9]Clinical events (chest pain, stroke, CHF); NS=not significant; pt yrs=patient years; pt=patient.

Table 5: Outcomes and Results in Studies of Drug-Lab Safety Alerts addressing a Single Drug class-Lab combination, excluding anticoagulation

Author,y Study outcome	Change in serum level/ Time in target range			Clinical outcome		
	Intervention	Control	p, RR, OR, HR (95% CI)	Intervention	Control	p, RR, OR, HR (95% CI)
Antimicrobial Prescribing						
Paul 2006 (Paul, et al., 2006) 1. Appropriate antibiotic prescribing 2. Length of stay 3. Mortality				1. 73% 2. 8.83 (11.29) 3. 14.3%	1. 64% 2. 9.45 (11.52) 3. 12.9%	1. OR 1.48 (0.95-2.29) adjusted for clustering 2. p=0.055 3. p=0.611
Digoxin						
Peck 1973 (Peck, et al., 1973) 1. Digoxin toxicity 2. Change in CHF index (no validation reported)	1. nil Results for achieving desired digoxin concentration reported separately for adherent and non-adherent to computer advice.	1. nil				2. No difference between intervention and control, no figures given

Author,y Study outcome	**Change in serum level/ Time in target range**			**Clinical outcome**		
	Intervention	**Control**	**p, RR, OR, HR (95% CI)**	**Intervention**	**Control**	**p, RR, OR, HR (95% CI)**
White 1984 (K. S. White, et al., 1984) Total number of physician actions (includes both lab ordering and prescribing changes)				175	136	p<0.03
Insulin						
Cavalcanti 2009 (Cavalcanti, et al., 2009) 1. Mean blood glucose (SD) 2. Patients with hypoglycemia (n,%) a) Strict protocol b) Conventional therapy	1. 125.0 mg/dl (17.7) (6.2 mmol/l)	1a) 127.1 mg/dl (32.2) 1b) 158.1 mg/dl (49.6)(=7.9mmol/l)	1a) p=0.34 1b) p<0.001	2. 12 (21.4)	2a) 24 (41.4%) 2b) 2 (3.8%)	2a) p=0.02 2b) p=0.006 (favours control)
Saager 2008 (Saager, et al., 2008) 1. Blood glucose in target range (%) a) In OR b) in ICU 2. Hypoglycemic episodes (n) a) In OR b) in ICU	1a) 49 1b) 84	1a) 27 1b) 60	1a) <0.001 1b) <0.001	2a) 1 2b) 4	2a) 0 2b) 1	2a) 1.00 2b) 0.60
Albisser 2007 (Albisser, et al., 2007b) 1. HbA1C 2. Hypoglycemic episodes (n/wk.)	1. Pre=8.0 (post=7.5)	1. Pre=7.8 Post 7.5	NS	2. 0.2	2. 2.0	Statistical testing compared to baseline, not between groups
Rood 2005 (Rood, et al., 2005) Time in target glucose range (%)	54.2%	52.9%	No p value reported			
Theophylline						

Author,y Study outcome	**Change in serum level/ Time in target range**			**Clinical outcome**		
	Intervention	**Control**	**p, RR, OR, HR (95% CI)**	**Intervention**	**Control**	**p, RR, OR, HR (95% CI)**
Tierney 2005 (Tierney, et al., 2005) Change in theophylline dose; Alert targeted: 1. Physician 2. Pharmacist 3. Both				1. 67% 2. 72% 3. 65%	67%	NS

Table 6: Outcomes and Results in Studies of Drug-Lab Safety Alerts addressing Multiple Drug-Lab Combinations

Author, y Outcome measure	Lab monitoring			Appropriate Prescribing		
	Intervention	**Control**	**p, RR, OR, HR (95% CI)**	**Intervention**	**Control**	**p, RR, HR, OR (95% CI)**
Terrell 2010 (Terrell, et al., 2010) Excessively dosed prescriptions for estimated creatinine clearance				57%	26%	0.001
Field 2009 (Field, et al., 2009) Proportion of appropriate prescriptions by recommended 1. Dose 2. Administration frequency 3. Avoidance				75.4%[1] 61.2%[2] 40.6%[3]	79.9%[1] 25.7%[2] 15.4% [3]	RR 0.95 (0.83-1.1)[1] RR 2.4 (1.4-4.4)[2] RR 2.6 (1.4-5.0)[3]
Lo 2009 (Lo, et al., 2009) Lab testing completed within 14 days of prescription	41%	39%	OR 1.048 (0.75-1.46)			
Matheny 2008 (Matheny, et al., 2008) Lab testing within 14 days of prescription	44.2%	46.0%	p=0.32			
Judge 2006 (Judge, et al., 2006) Appropriate response to alert (both monitoring and prescribing)				45.2%[4]	41.3%[4]	p=0.2104[4]
Feldstein 2006(Feldstein, et al., 2006) Lab testing within 25 days after prescription	48.5%	22.4%	HR 2.5 (1.8-3.5)			
Palen 2006 (Palen, et al., 2006) Lab testing within 15 days of prescription	56.6%	57.1%	p=0.31			

Author, y Outcome measure	Lab monitoring			Appropriate Prescribing		
	Intervention	**Control**	**p, RR, OR, HR (95% CI)**	**Intervention**	**Control**	**p, RR, HR, OR (95% CI)**
Raebel 2005 (Raebel, Lyons, Chester, et al., 2005) Lab monitoring within 14 days of prescription	79.1%	70.2%	p<0.001			
Demakis 2000 (Demakis, et al., 2000) Alerts addressed multiple standards of care; one for anticoagulation	67.3%	64.3%	p=0.63			
McDonald 1976 (McDonald, 1976) 1. Lab monitoring, as per protocol 2. Prescribing change, as per protocol	1. 36%	1. 11%	P<0.0001	28%	13%	p<0.026

[1]Appropriate dose; [2]Appropriate frequency; [3]Avoid drug, [4] Appropriate action- does not differentiate between prescribing actions and lab monitoring actions; RR=relative risk; OR=odds ratio; HR=hazard ratio

Table 7: Summary of Findings Table

Quality Assessment						**Summary of Findings**			
No. of studies (no. of events)	**Method-ological Limit-ations**	**Consist-ency**	**Direct-ness**	**Precision**	**Report-ing Bias**	**Relative Effect (95% CI)**	**Best estimate of group risk**	**Absolute effect**	**Quality (GRADE)**
Appropriate prescribing (multi-drug alerts)									
3 (396 events)	Serious limitations (-1)	No serious inconsist-ency	Serious in-directness (-1)	Serious im-precision (-1)	Unclear	OR 2.22 (1.19-4.17)	44.7%	6.6%	Moderate
Appropriate lab monitoring (multi drug alerts)									
9 (30 371 events)	Serious limitations (-1)	Serious inconsist-ency (-1)	Serious indirect-ness (-1)	No serious im-precision	Unclear	OR 1.47 (1.12-1.94)	56.4%	2.2%	Weak
Adverse events- anticoagulation									
5 studies 1115 events	Serious limitations (-1)	No serious inconsisten cy	No serious indirectness	No serious imprecisi on	Unclear	0.89 (0.79-1.00)	8.5% (vs. 7.6%)	0.9%	Moderate

Figure 1: PRISMA flow diagram

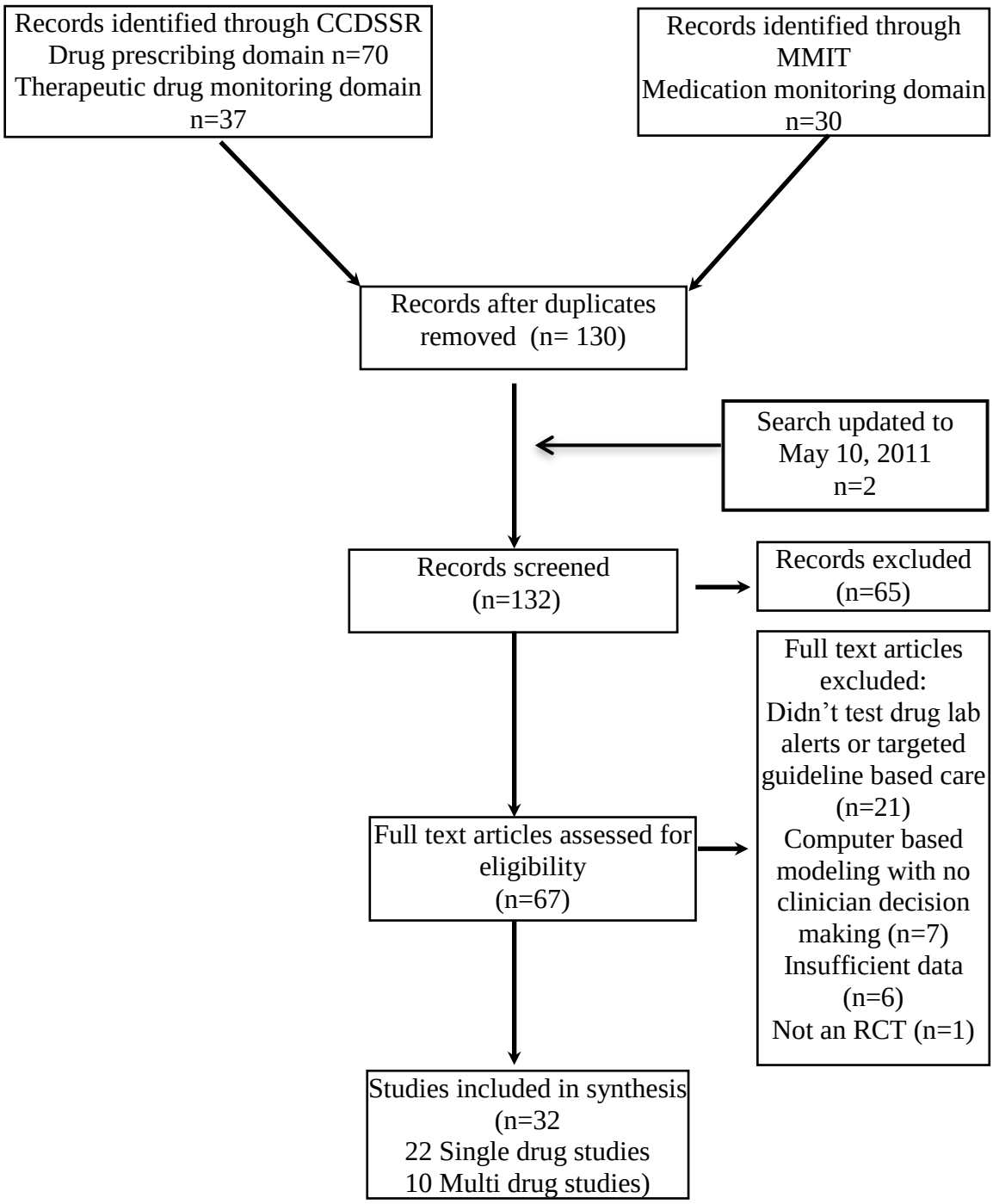


Figure 2: Risk of Bias figure

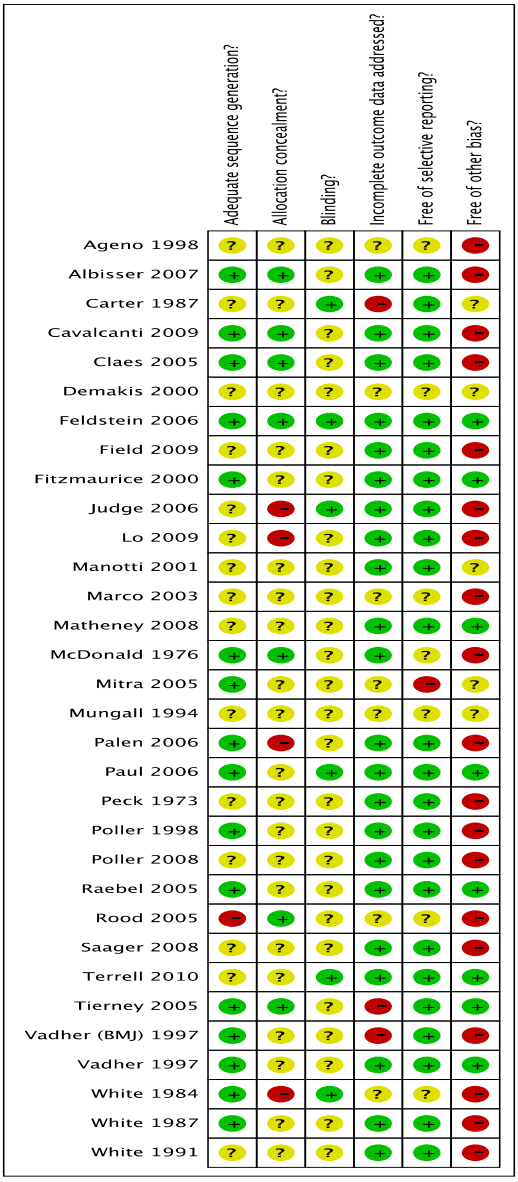


Figure 3: Adverse events (Bleeding or Thrombosis) in Studies of Drug-Lab Safety Alerts addressing Anticoagulation

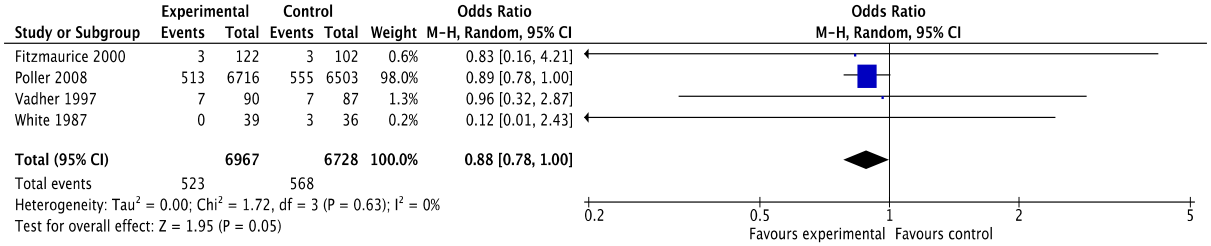
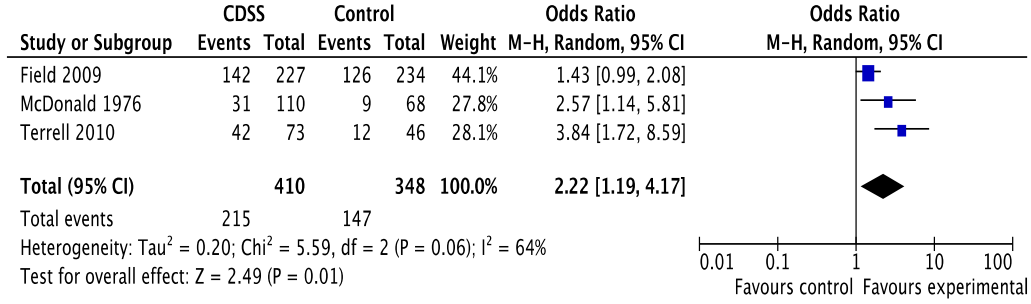


Figure 4: Impact on quality of prescribing decisions in studies of Drug-Lab Safety Alerts addressing Multiple Drug-Lab alerts



Chapter 3: Scenario design

The process of designing the scenarios represented one of the key methodological issues in this thesis and included the following steps:

1. Selecting medications for the scenarios.
2. Identifying key features for the scenarios.
3. Piloting scenarios.
4. Refining scenarios.

The objective of this chapter is to describe and critique the steps in the process of scenario and survey development.

3.1 Medication selection

Laboratory monitoring is recommended for many medications in order to detect potential adverse events (Handler, et al., 2008; Tija, et al., 2010). However, it is not clear which medications should be targeted in primary care for computerized reminders. This observation is reflected in the wide range of medications targeted in the studies identified in the systematic review. It was, therefore, important to identify a transparent and rational process for selecting medications for inclusion in the clinical scenarios. To this end, we developed the following pre-specified criteria for the selection of the medications for inclusion in the clinical scenarios:

1. Do Canadian primary care physicians commonly prescribe this medication?
2. Is there evidence that this medication is associated with clinically important drug related morbidity?

3. Is the drug related morbidity preventable through laboratory monitoring?

3.1.1 Commonly prescribed medications

In order to identify medications commonly prescribed in primary care, we received data from the Canadian CompuScript database from IMS Brogan, a multinational corporation that conducts pharmaceutical market research and audits prescriptions dispensed from approximately 5,700 pharmacies, representing approximately 70% of all Canadian retail pharmacies(IMS). IMS Brogan stratifies the data by province, pharmacy type and size and then projects them for each province and then adds provincial totals to generate national estimates.

The data received from IMS Brogan included the top 100 products dispensed from prescriptions written by family physicians or general practitioners, broken down by province and reported by product name and dose. Products were grouped in a step-wise fashion by generic name and drug class using ATC (Anatomical Therapeutic Chemical classification) codes. We generated provincial and national totals which are summarized in Table 6: IMS (Brogan) data on prescribing patterns among Canadian primary care physicians: Estimated number of dispensed prescriptions 2008.

3.1.2 CIHI data

To date, no reports of the epidemiology of adverse drug events in Canadian community settings have been reported. Canadian community based primary healthcare services are largely delivered by private practitioners, working in various models of care. Though there are efforts to capture data regarding clinical activities among primary care providers, these are still

underdeveloped and therefore, to date, there are no large databases on adverse events in primary care settings. In order to better understand the epidemiology of serious adverse drug events in community settings that required emergency department or inpatient hospitalization using existing data sources, we sought data from the Canadian Institute for Health Information (CIHI) regarding the epidemiology of adverse drug events in patients treated in hospitals or emergency departments in Canada. We received data from the Discharge Abstracts Database (DAD) (CIHI, 2008), which includes reports of acute inpatient hospitalizations and from the National Ambulatory Care Reporting System (NACRS) Database (CIHI, 2009), which includes data from emergency department visits in Ontario. We received data from both databases for the years 2006-07 to 2008-09 for adults older than 18 years with diagnostic codes for drugs, medicaments and biologic substances causing adverse effects in therapeutic use (ICD-10-CA codes Y40.0-Y57.9). Newborns, stillbirths or cadaveric donors were excluded, as were drugs taken accidentally in overdose or instances in which the wrong drug is given or taken in error.

The DAD database contains demographic, administrative and clinical data on all separations from acute care institutions including discharges, deaths, sign-outs and transfers from all Canadian provinces and territories except Quebec, including Day Surgery stays in some provinces (Ontario's Day Surgery reports are submitted to NACRS) (CIHI, 2008). The DAD coverage includes about 75% of all Canadian acute care separations, as Quebec accounts for about 25% of the total.

The NACRS database contains demographic, administrative and clinical data from Emergency Department visits, Day Surgery and some other ambulatory clinics, almost entirely

from Ontario (97.4-97.7% all NACRS visits from 2006-07 to 2008-09 are from Ontario emergency departments) (CIHI, 2009). We initially requested data broken down by gender, age (by 10 year increments) and province. However, this resulted in some small cells (n<5) and CIHI will not report small cell sizes, because it compromises the confidentiality of the data. As a consequence, we modified our data request to include reports broken down only by age (adults age 19-64 and over 65). We calculated overall prevalence of adverse drug events using the number of reports of adverse drug events and the overall total number of records reported in the respective databases.

3.1.3 Results from databases

In total, over 347 million prescriptions written by Canadian family physicians and general practitioners were dispensed in Canada in 2008 (Table 6: Dispensed prescriptions written by Canadian primary care physicians 2008: Total number, proportion in drug class). This represents over 19 billion dispensed units in total (data not shown). The 100 products most frequently dispensed represent 49.63% of all medications dispensed from prescriptions written by Canadian primary care physicians in 2008. Overall across the country and in individual provinces, cardiovascular drugs dominated, representing 22.5% of the total. The most commonly prescribed drug classes were lipid lowering agents, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), anticoagulants and antiplatelet agents. However, no single drug class represented more than 6% of the overall total.

The overall prevalence of adverse drug events identified in the DAD database from 2006-2008 was 2.127% and in the NACRS database was 0.408%. The drug classes most frequently

implicated among older adult inpatients were anticoagulants, antineoplastic agents, opioids, NSAIDs, and cardiac glycosides. Among younger adults, the corresponding drug classes are antineoplastic agents, opioids, anticoagulants, glucocorticoids and NSAIDs. In the emergency department, the drug classes most frequently reported to cause ADEs in both age groups were antineoplastic agents, opioids, systemic antibiotics; in addition, anticoagulants were the most common cause of ADEs in older adults in the NACRS data. Among older adults (over 65 years), cardiovascular drugs (including anticoagulants) accounted for 38.44% of the adverse drug events in DAD and 30.9% in NACRS, in contrast to the younger cohort (age 19-64 years) in which the corresponding figures are 14.82% and 9.84% respectively. Anticoagulants alone accounted for 15.4% and 14.18% of the events in DAD and NACRS respectively in the geriatric age group. Analgesic medications also represent a significant proportion of identified events. In the DAD, they were responsible for 17.01% and 13.86% of the adverse events among the older and younger cohorts respectively. The corresponding figures for the NACRS database are 11.94% and 14.6%, largely attributable in both databases and age groups to the impact of opioid medications. Anti-infective agents were responsible for 7.83% and 11.67% of adverse events in DAD in the older and younger cohorts respectively. However, anti-infective agents represented a much larger proportion of adverse events in the emergency room setting, namely 15.88% and 26.81% among older and younger adults respectively.

3.1.4 Discussion of database results

We used these data to address the pre-specified criteria for medication selection for the clinical scenarios outlined at the beginning of this chapter. To date, the epidemiology of adverse

drug events in Canada has only been described in one large hospital-based study (Baker, et al., 2004) and one emergency department study(Zed, et al., 2008) Though literature exists which describes the epidemiology of adverse drug events in community settings in other countries, to date no Canadian studies have been reported.

Methods for identifying adverse drug events have varied; most researchers have used a combination of chart review and computer generated signals, while some have utilized patients' self reports. Most reports have included a consensus based review process of potential ADEs. These methodologies are comprehensive but are also costly and labour intensive. There is limited literature regarding the reliability and validity of reports of adverse drug events from administrative databases generated from hospitals and emergency departments, which are already routinely captured. One study (Houghland, Xu, Pickard, Masheter, & Williams, 2006) reported the sensitivity and specificity of ICD-9 codes as compared to structured chart review of a random sample of 1961 inpatient charts was 10% and 97% respectively.

Our results contrast with published data from other reports, which assess the prevalence of ADEs among inpatients to be around 6.5% and that in the emergency department, around 2.5%, compared to our findings of 2.18% among inpatients and 0.408% in the emergency department. In part, this can be attributed to CIHI's coding standards (CIHI, 2008). Adverse effects in therapeutic use are classified as reactions, which "may occur when a substance (i.e. drug, medicament or biologic agent) is taken or administered correctly in therapeutic use. Correct administration of a substance in therapeutic use includes: correct substance given or taken, correct dosage of a drug given or taken (includes prescribed and self prescribed), 2 or more

prescribed drugs taken in combination, and 2 or more self-prescribed drugs taken as recommended." Substances taken incorrectly are classified as poisonings. However, an event occurring as a consequence of taking a combination of a prescribed drug and a self-prescribed drug is classified as a poisoning. Similarly, adverse events occurring as a result of an interaction between a prescribed drug and alcohol are classified as poisonings. Furthermore, adverse events are coded as such only if they are identified in this manner in the patient record. If the health professionals report the manifestations of an adverse drug event, but do not explicitly attribute causality to medications, the events will be coded exclusively by their manifestations. For example, a patient may be hospitalized due to an electrolyte imbalance caused by furosemide. If the admitting diagnosis is described as hypokalemia, but not attributed to an adverse effect of furosemide, the event would only be classified according to the electrolyte imbalance. These data, then, appear to reflect information bias in which abstractors and coders are systemically misclassifying events, and physicians are not appropriately describing adverse drug events in their clinical documentation. It is unclear whether this bias occurs differentially across different drug classes. This represents a major limitation in these data.

Notwithstanding these limitations, there is consistency between these data and published accounts regarding drug classes that represent the greatest risk of adverse events. In considering the first two criteria, overall frequency of prescribing and evidence of medication related harm, our findings indicate that anticoagulants, opiates, antibiotics, cardiovascular drugs and NSAIDs are associated with harm which is out of proportion with the frequency with which they are prescribed, particularly for older adults. The National Electronic Injury Surveillance System-

Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project (Budnitz, et al., 2006) reports indicate that among older adults, three drugs which require ongoing monitoring to prevent toxicity (warfarin, insulin and digoxin) were responsible for 33% of the adverse drug events treated in U.S. emergency departments. Other studies of adverse drug events in community settings among older adults have also identified cardiovascular drugs, diuretics, non-opioid analgesics, hypoglycemic drugs and anticoagulants as the drug classes most frequently associated with adverse events (Gandhi et al., 2003; Gurwitz, et al., 2003).

With advice from expert committee members, I reviewed the data regarding the first two criteria, namely drugs commonly prescribed among Canadian primary care physicians, and adverse drug events identified in the administrative databases and published literature. These medications were considered together with the criteria that medication related harm was potentially preventable through appropriate laboratory monitoring. The drug classes that satisfied the first two criteria (as noted above) were anticoagulants, opiates, antibiotics, cardiovascular drugs (such as ACE inhibitors, angiotensin receptor blockers, diuretics and digoxin) and NSAIDs. Next, we considered the criteria that medication related harm was preventable through appropriate routine laboratory monitoring and reached consensus that the medications meeting these criteria, which would be included in the clinical scenarios were warfarin, digoxin, an NSAID, and ACE inhibitors in combination with ARBs.

3.2 Scenario design

The scenarios were constructed to optimize validity, namely the capacity of the scenario to measure what it is intended to measure. In order to ensure good content validity, a number of

key data sources were utilized in scenario construction. The data sources included published descriptions of patients most at risk for adverse events, data from the large databases previously described, content experts consulted on potential key features of clinical scenarios and an iterative revision process utilizing pilot testing of the scenarios.

The health care literature describes the patients most at risk for adverse drug events, namely elderly patients taking multiple medications, with multiple medical problems, and multiple competing needs (Taché, et al., 2011; Winterstein, et al., 2002). Although such patients may receive care from various specialists, their primary care providers prescribe and review ongoing medications especially in consideration of the medications prescribed across a spectrum of specialists. Primary care appointments are utilized for prescription renewals, acute episodic illnesses, chronic disease management, to review functional status and address other assorted needs. The scenarios were intended to reflect the complexity of care, which is routine in Canadian community based primary care settings, in which complex patients present with multiple needs (Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005; Starfield & Kinder, 2011) and the health care provider is working under significant time constraints. Each scenario included multiple prescribing decisions, including some pertained to laboratory monitoring, but also included other prescribing issues such as drug-drug interactions, drug-disease interactions, inappropriate indications for medications and others. This decision was taken to attempt to reflect real world prescribing, in which clinicians must attend to multiple competing needs(Fortin, et al., 2005). Although there is minimal published literature regarding primary care

physicians' cognitive processes during prescribing decision making, particularly in the context of prescribing errors, we considered these factors to be important to emulate real world conditions.

Physician surveys are commonly utilized in health services research and are frequently characterized by low response rates (Braithwaite, Emery, de Lusignan, & Sutton, 2003; Field et al., 2002). Factors that have been reported to improve response rates include short survey length, financial incentives (even modest amounts) and sponsorship of a recognized professional body (Kellerman & Herold, 2001; VanGeest, Johnson, & Welch, 2007). We developed three clinical scenarios, in order to limit the length of the survey and offered participants entry into a lottery for a $100 gift card prize. We drafted three scenarios, initially targeting three prescribing decisions. The pilot scenarios were sent to 22 family physicians, of which 13 (59%) completed the survey. We collected feedback from the participant volunteers, and modified the survey for clarity, overall length and flow.

There is no standardized means of measuring content validity. However, the process of carefully ensuring that the clinical scenarios were constructed based on published research findings, independent data, expert opinion, an iterative process of feedback from experts and respondents and revision, it is reasonable to consider the content validity of the scenarios to be strong.

The final version of the survey contained three scenarios with 5 prescribing decisions and is attached in Appendix D: Scenarios.

3.3 Survey software:

We reviewed various types of survey software for use, ultimately selecting the Qualtrics software. This software was selected because it has the capacity to randomize participants to different streams within the survey. In addition, the software has the capacity for skip logic functions, which we used to create branches at key decision points in the survey. This was critical to the design, as laboratory data needed to be available to participants at their request.

3.4 Discussion

The process of scenario development was an iterative one, in which we obtained initial feedback from expert team members and subsequently from family physician volunteers. The most substantial changes to the scenarios were to increase the overall number of scored prescribing decisions, and to include multiple decisions within scenarios in order to avoid increasing the overall length or complexity of the survey. We determined that the development process was complete when we received no new or additional feedback from either source. Such a process involves subjective responses and as such, may be a source of bias. One of the major challenges in the scenario design process was to establish prescribing decisions that were neither obvious nor obscure, but rather decisions that could differentiate adequately between responses in order to assess the impact of the integration of lab data. This was especially difficult to establish given the limited number of respondents, and serves as a limitation in the scenario development process

Table 8: Dispensed prescriptions written by Canadian primary care physicians 2008: Total number, proportion in drug class

Drug class	Canada	BC	AB	SK	MB	ON	QC	NS	NB	PE	NL
Total Estimated no. Prescriptions Dispensed (million)	347.96	31.25	26.59	9.82	9.73	115.06	132.95	9.19	6.83	1.10	5.42
Cardiovascular											
Lipid lowering agents	19.76	1.40	1.13	0.65	0.47	6.57	8.31	0.49	0.33	0.07	0.33
ACEI/ ARB/ ARB +diuretic	18.16	1.53	1.17	0.71	0.50	5.89	7.82	0.41	0.31	0.04	0.28
Antiplatelet agents/ anticoagulant	14.48	0.49	0.19	0.23	0.26	2.80	9.89	0.14	0.09	0.02	0.10
Diuretics	10.40	1.30	0.68	0.34	0.35	3.74	3.22	0.33	0.24	0.03	0.17
CCB	8.98	0.63	0.47	0.30	0.26	2.80	4.04	0.21	0.13	0.02	0.10
Beta blockers	6.51	0.59	0.31	0.31	0.22	2.06	2.54	0.23	0.13	0.02	0.12
Respiratory											
Chronic respiratory	8.74	0.78	0.81	0.25	0.33	3.58	2.10	0.39	0.30	0.04	0.16
GI											
PPI	13.85	1.06	0.98	0.36	0.43	4.77	5.64	0.27	0.22	0.04	0.18
H2 Blockers	1.11	0.10		0.13	0.03			0.13	0.08	0.02	0.13
Endocrine											
Glucose lowering	7.86	0.58	0.45	0.21	0.18	2.59	3.20	0.23	0.14	0.03	0.14
Hormones	13.36	1.18	1.05	0.28	0.35	3.35	6.34	0.36	0.25	0.05	0.17

Drug class	**Canada**	**BC**	**AB**	**SK**	**MB**	**ON**	**QC**	**NS**	**NB**	**PE**	**NL**
(exc. Insulin)											
OC	4.31	0.40	0.52	0.11	0.13	0.35	2.40	0.12	0.13	0.03	0.12
Urologics	1.98	0.19	0.30	0.08	0.07	0.66	0.64	0.002	0.002	0.003	0.002
Bisphosphonates	4.31	0.19	0.16	0.08	0.03	1.89	1.86	0.06	0.02	0.003	0.01
Psychiatric											
Anti-depressants	12.32	1.38	1.03	0.47	0.38	5.05	3.16	0.38	0.25	0.04	0.16
Benzodiazepines and related	7.48	1.30	0.73	0.14	0.34	2.32	3.69	0.25	0.41	0.03	0.16
Anti-psychotic agents	2.75	0.42	0.25	0.03	0.07	1.06	0.82	0.03	.03		0.02
Analgesia											
Opiates	6.16	0.94	1.00	0.10	0.28	3.45		0.17	0.12	0.02	0.09
NSAIDs	2.78	0.24	0.31	0.16	0.11	1.38	0.40	0.07	0.08	0.007	0.06
Coxib inhibitors	2.05	0.13	0.12	0.06	0.06	0.72	0.81	0.06	0.05	0.01	0.03
Anti-infectives											
Anti-infective agents	5.32	0.75	0.67	0.30	0.22	2.70		0.25	0.14	0.02	0.20

Source: IMS (Brogan)
BC= British Columbia; AB=Alberta, SK=Saskatchewan; MB=Manitoba, ON=Ontario; QC=Quebec; NS=Nova Scotia; NB=New Brunswick; PE=Prince Edward Island; NL=Newfoundland and Labrador; ACEI= Angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; CCB= calcium channel blocker; GI=gastrointestinal; OC=oral contraceptive; NSAIDs=non-steroidal anti-inflammatory drug

Table 9: Adverse drug events in DAD (excludes Quebec), adults older than 65 y, most frequent codes: 2006-2008

ICD-10-CA code, description	2006 (n,%)	2007 (n,%)	2008 (n,%)
Y442 Anticoagulants	4449 (14.41)	4652 (15.50)	5122 (16.38)
Y433 Other antineoplastic drugs	3089 (10.01)	2927 (9.76)	3115 (9.96)
Y450 Opioids	2800 (9.07)	2730 (9.10)	2928 (9.36)
Y453 Other NSAIDs	1346 (4.36)	1356 (4.52)	1290 (4.13)
Y520 Cardiac stimulant glycosides	1347 (4.36)	1350 (4.50)	1285 (4.11)
Y420 Glucocorticoids	1220 (3.95)	1159 (3.86)	1245 (3.98)
Y517 Beta blockers not elsewhere classified	1216 (3.94)	1166 (3.89)	1144 (3.66)
Y408 Other systemic antibiotics	912 (2.95)	859 (2.86)	826 (2.64)
Y545 Other diuretics	910 (2.95)	791 (2.64)	816 (2.61)
Y543 Benzothiadiazine derivatives	649 (2.10)	652 (2.17)	710 (2.27)
Y524 ACEI	710 (2.30)	614 (2.05)	680 (2.17)
Y451 Salicylates	609 (1.97)	511 (1.70)	544 (1.74)
Y521 Calcium channel blockers	562 (1.82)	514 (1.71)	567 (1.81)
Y423 Insulin and oral hypoglycemic agents	508 (1.65)	525 (1.75)	518 (1.66)
Y579 Drug or medicament, unspecified	519 (1.68)	503 (1.68)	501 (1.60)
Y525 Other antihypertensive drugs not elsewhere classified	544 (1.76)	477 (1.59)	468 (1.50)
Y522 Other antidysrrhythmic drugs not otherwise classified	500 (1.62)	474 (1.58)	514 (1.64)
Y495 Other antipsychotics and neuroleptics	508 (1.65)	461 (1.54)	516 (1.65)
Y544 Loop [high-ceiling] diuretics	363 (1.18)	384 (1.28)	419 (1.34)
Y578 Other drugs and medicaments	394 (1.28)	362 (1.21)	383 (1.22)
Y471 benzodiazepines	336 (1.09)	356 (1.19)	361 (1.15)
Y575 X-ray contrast media	321 (1.04)	348 (1.16)	369 (1.18)
Y409 Systemic antibiotics unspecified	314 (1.02)	595 (1.98)	325 (1.04)
Y492 Other and unspecified antidepressants	305 (0.99)	298 (0.99)	312 (1.00)
Y401 Cephalosporins	268 (0.87)	275 (0.92)	285 (0.91)
Total	**30,869**	**30,004**	**31,268**

Table 10: Adverse drug events in DAD (excludes Quebec), adults age 19-64 y, 2006-2008

Diagnosis Code (ICD-10-CA code, description)	**2006 (n,%)**	**2007 (n,%)**	**2008 (n,%)**
Y433 Other antineoplastic drugs	4,625 (22.86)	4,613 (22.87)	4,552 (21.98)
Y450 Opioids	1,849 (9.14)	1,806 (8.95)	1,960 (9.47)
Y442 Anticoagulants	1,188 (5.87)	1,372 (6.80)	1,388 (6.70)
Y420 Glucocorticoids	1,110 (5.49)	1,075 (5.33)	1,125 (5.43)
Y453 Other NSAIDs	787 (3.89)	809 (4.01)	854 (4.12)
Y408 Other systemic antibiotics	684 (3.38)	725 (3.59)	750 (3.62)
Y495 Other antipsychotics and neuroleptics	598 (2.96)	628 (3.11)	660 (3.19)
Y483 Local anaesthetics	330 (1.63)	374 (1.85)	389 (1.88)
Y409 Systemic antibiotics unspecified	399 (1.97)	367 (1.82)	373 (1.80)
Y579 Drug or medicament, unspecified	419 (2.07)	371 (1.84)	354 (1.71)
Y400 Penicillins	314 (1.55)	322 (1.60)	325 (1.57)
Y578 Other drugs and medicaments	281 (1.39)	294 (1.46)	304 (1.47)
Y471 benzodiazepines	258 (1.28)	283 (1.40)	303 (1.46)
Y462 Hydantoin derivatives	296 (1.46)	296 (1.47)	302 (1.46)
Y401 Cephalosporins	288 (1.42)	264 (1.31)	276 (1.33)
Y434 Immunosuppressive drugs	269 (1.33)	269 (1.33)	272 (1.31)
Y427 Androgens	261 (1.29)	237 (1.17)	272 (1.31)
Y517 Beta blockers not elsewhere classified	279 (1.38)	274 (1.36)	271 (1.31)
Y431Antineoplastic antimetabolites	241 (1.19)	249 (1.23)	261 (1.26)
Y466 Other and unspecified antiepileptics	238 (1.18)	273 (1.35)	251 (1.21)
Y492 Other and unspecified antidepressants	238 (1.18)	269 (1.33)	249 (1.20)
Y524 ACEI	183 (0.90)	216 (1.07)	219 (1.06)
Y575 X-ray contrast media	227 (1.12)	200 (0.99)	218 (1.05)
Y545 Other diuretics	220 (1.09)	210 (1.04)	213 (1.03)
Y451 Salicylates	172 (0.85)	194 (0.96)	208 (1.00)
Total	**20,232**	**20,173**	**20,707**

Table 11: Adverse Drug events: most common codes: NACRS database, patients 65 years or older, 2006-2008

Diagnosis Code (ICD-10-CA, description)	**2006 (n,%)**	**2007 (n,%)**	**2008 (n,%)**
Y442 Anticoagulants	954 (13.55)	1,077 (15.08)	1,350 (13.97)
Y433 Other antineoplastic drugs	680 (9.66)	693 (9.70)	837 (8.66)
Y579 Drug or medicament, unspecified	500 (7.10)	479 (6.71)	821 (8.50)
Y450 Opioids	504 (7.16)	526 (7.36)	701 (7.26)
Y408 Other systemic antibiotics	340 (4.83)	315 (4.41)	456 (4.72)
Y578 Other drugs & medicaments	269 (3.82)	246 (3.44)	348 (3.60)
Y409 Systemic antibiotics unspecified	242 (3.44)	279 (3.91)	333 (3.45)
Y520 Cardiac stimulant glycosides	278 (3.95)	297 (4.16)	312 (3.23)
Y524 ACEI	145 (2.06)	147 (2.06)	255 (2.64)
Y453 Other NSAIDs	122 (1.73)	130 (1.82)	240 (2.48)
Y517 Beta blockers not elsewhere classified	154 (2.19)	158 (2.21)	211 (2.18)
Y400 Penicillins	132 (1.88)	149 (2.09)	194 (2.01)
Y418 Other specified systemic anti infectives	114 (1.62)	103 (1.44)	167 (1.73)
Y525 Other antihypertensive drugs not elsewhere classified	141 (2.00)	107 (1.50)	156 (1.61)
Y523 Coronary vasodilators, not elsewhere classified	111 (1.58)	109 (1.53)	153 (1.58)
Y521 Calcium channel blockers	97 (1.38)	97 (1.36)	150 (1.55)
Y420 Glucocorticoids	118 (1.68)	109 (1.53)	145 (1.50)
Y492 Other and unspecified antidepressants	112 (1.59)	94 (1.32)	143 (1.48)
Y423 Insulin and oral hypoglycemic agents	148 (2.10)	118 (1.65)	140 (1.45)
Y455 4-Aminophenol derivatives	78 (1.11)	80 (1.12)	120 (1.24)
Y575 X-ray contrast media	93 (1.32)	105 (1.47)	118 (1.22)
Y401 Cephalosporins	84 (1.19)	96 (1.34)	110 (1.14)
Y495 Other antipsychotics and neuroleptics	69 (0.98)	75 (1.05)	106 (1.10)
Y545 Other diuretics	52 (0.74)	64 (0.90)	103 (1.07)
Y410 Sulfonamides	99 (1.41)	95 (1.33)	97 (1.00)
Total	**7,040**	**7,143**	**9,662**

Table 12: Adverse drug events reported in NACRS, age 19-64, 2006-2008

Diagnosis Code (ICD-10-CA code, description)	**2006(n,%)**	**2007 (n,%)**	**2008 (n,%)**
Y579 Drug or medicament, unspecified	1,050 (8.20)	909 (7.25)	1,483 (9.01)
Y433 Other antineoplastic drugs	974 (7.61)	1,149 (9.17)	1,279 (7.77)
Y408 Other systemic antibiotics	924 (7.22)	850 (6.78)	1,128 (6.85)
Y450 Opioids	934 (7.30)	864 (6.89)	1,086 (6.60)
Y400 Penicillins	800 (6.25)	732 (5.84)	913 (5.55)
Y409 Systemic antibiotics unspecified	648 (5.06)	656 (5.23)	865 (5.26)
Y578 Other drugs & medicaments	638 (4.98)	539 (4.30)	746 (4.53)
Y492 Other and unspecified antidepressants	484 (3.78)	496 (3.96)	562 (3.41)
Y453 Other NSAIDs	308 (2.41)	350 (2.79)	559 (3.40)
Y442 Anticoagulants	342 (2.67)	495 (3.95)	558 (3.39)
Y495 Other antipsychotics and neuroleptics	286 (2.23)	238 (1.90)	354 (2.15)
Y418 Other specified systemic anti-infectives	207 (1.62)	197 (1.57)	321 (1.95)
Y401 Cephalosporins	251 (1.96)	239 (1.91)	317 (1.93)
Y403 Macrolides	212 (1.66)	249 (1.99)	292 (1.77)
Y452 Propionic acid derivatives	233 (1.82)	189 (1.51)	269 (1.63)
Y575 X-ray contrast media	173 (1.35)	220 (1.76)	266 (1.62)
Y455 4-Aminophenol derivatives	225 (1.76)	203 (1.62)	261 (1.59)
Y410 Sulfonamides	257 (2.01)	229 (1.83)	252 (1.53)
Y420 Glucocorticoids	221 (1.73)	165 (1.32)	242 (1.47)
Y524 ACEI	124 (0.97)	147 (1.17)	206 (1.25)
Y527 Peripheral vasodilators	146 (1.30)	130 (1.04)	188 (1.14)
Y466 Other and unspecified antiepileptics	121 (0.95)	142 (1.13)	180 (1.09)
Y471 Benzodiazepines	126 (0.98)	125 (1.00)	167 (1.01)
Y462 Hydantoin derivatives	143 (1.12)	118 (0.94)	158 (0.96)
Y430 Antiallergic and antiemetic drugs	140 (1.09)	156 (1.24)	156 (0.95)
Total	**12,799**	**12,532**	**16,459**

Appendix F: Scenarios

Scenario 1

Mrs. Irene Frank, age 72, comes for prescription renewals and her flu vaccination. She lives with her daughter and 2 adolescent granddaughters. Since you last saw her 5 months ago, she has developed intermittent urinary incontinence and now wears an undergarment. She is not feeling well today; she has felt nauseated for one week and has had diarrhea for 3 days. She still has refills of Fosavance but needs prescriptions for her other medications.

Active medical problems	**Medications**
Moderate cognitive impairment	Donepezil 10 mg OD
Congestive heart failure	Furosemide 80 mg OD
Hypertension	Ramipril 5 mg OD
Aortic mechanical valve replacement 2005	Amlodipine 5 mg OD
Osteoarthritis	Warfarin 5 mg OD
Osteoporosis	Digoxin 0.25 mg od
Overactive bladder	Fosavance 1 tab weekly
	Acetominophen 1000 mg TID
	Tolterodine LA 4 mg OD
	Zopiclone 7.5 mg HS
	ECASA 81 mg OD

She reports that she enjoys listening to music and watching her favorite TV programs. She receives some in home personal support services and enjoys the sociability of this time.

Her appetite is good but her sleep is frequently disturbed. She often naps in the afternoon.

Her daughter is tired but says they are doing fine for now. She takes care of her mother's medications and reports that she rarely forgets to take her medications.

Mrs. Frank reports that though she feels tired, she is managing her symptoms well at home. Her daughter adds that her mother is taking in plenty of fluids, doesn't have much appetite, but is not vomiting.

Physical exam:

BP 109/72, no postural drop

HR 58

RR 16

T 36.7

Chest good air entry bilaterally. No adventitial sounds heard.

Normal heart sounds, no murmurs or added sounds.

Abdomen soft non-tender. No hepatosplenomegaly.

	3 days ago	**2 wks. ago**	**6 wks ago**	**3 months ago**	**4 months ago**
Hb			125 g/l		
WBC			7.2 $x10^9$/l		
Plt			235 $x10^9$/l		
Cr	135 μmol/l				
eGFR	46				
INR	3.9	2.9	2.2	2.6	2.3
Warfarin dose		4mg od, alternating with 3mg od	4mg od, alternating with 3mg od	3 mg od	3 mg od
Na+	136 mmol/l		138 mmol/l		
K+	3.1 mmol/l		3.3 mmol/l		
Cl-	97 mmol/l		99 mmol/l		
Digoxin level (0.60-1.3 nmol/l)	2.2 nmol/l				

Scenario 2

Mrs. Evelyn Waugh, age 64, comes to see you for medication renewal. She lives alone and is managing well, though she doesn't get out much because of her arthritis.

Active Medical Problems	**Medications**
Osteoarthritis knees and right hip	Citalopram 10 mg od
Anxiety disorder	Naproxen 500 mg tid
Asthma	Fluticasone inhaler 500 mcg inhaled bid
Hyperlipidemia	Salbutamol prn
Leg edema	Atorvastatin 40 mg od
Hypertension	HCTZ 25 mg od
	Pantoprazole 40 mg bid
	Docusate sodium 100 mg bid

Vital signs:

BP 135/80

HR 78

Labs from 1 month ago:

Hb 123 g/L

WBC 7.2 $x10^9$/L

Platelets $149x10^9$/L

Cr 130 umol/L

eGFR 38

Na 133 mmol/L

K 4.1 mmol/L

Cl 101 mmol/L

Random blood sugar 7.5 mmol/L

Scenario 3

Mr. Brad Gordimer, age 77, comes to see you for his quarterly diabetic review and to renew his medications. He feels well and has no specific complaints. He lives alone, tries to be careful with his diet and walks 3 times weekly when the weather is good. He stopped smoking a few years ago after he had a TIA. His children live out of town. He plays bridge twice a week in a bridge club.

Active Medical Problems	**Medications**
Type II diabetes mellitus	Metformin 1000 mg bid
Hypertension	Candesartan 16 mg od
TIA 2009	Atorvastatin 60 mg od
Peripheral neuropathy	ECASA 325 mg od
Hyperlipidemia	Trazodone 50 mg hs
Gastroesophageal reflux disease	Rabeprazole 20 mg od
	Gliclazide MR 30 mg od
	Ramipril 5 mg od
	HCTZ 12.5 mg od

Labwork from 2 wks ago

Hb 138 g/L

WBC 5.6 x 10^9/L

Platelets 223 x 10^9/L

Fasting blood sugar 8.2 mmol/L

HbA1C 0.088

Creatinine 150 □mol/L

eGFR 39 ml/min

Na+ 137 mmol/L

K+ 5.9 mmol/L

Cl- 97 mmol/L

TC 3.6 mmol/L

LDL 2.2 mmol/L

HDL 0.9 mmol/L

TC/HDL 4.0 mmol/L

TG 3.8 mmol/L

Glucometer log:

Date	**Time**	**Blood Sugar**
Mar 1, 2011	8 am	8.9
Mar 4, 2011	3:30 pm	8.2
Mar 7, 2011	9:30 pm	10.1
Mar 8, 2011	7 am	8.5
Mar 11, 2011	11:30 am	7.6
Mar 20, 2011	6 pm	9.3
Mar 23, 2011	8:30 pm	11.2
Mar 28, 2011	2:30	13.0
Apr 1, 2011	6:30 pm	7.0

Vital signs:

BP 134/85; HR 78 regular; RR 16; Heart sounds normal; Chest clear; Feet-peripheral pulses palpable; not able to sense 10 g monofilament at 8/10 sites bilaterally

Glossary/ Abbreviations:

BP: blood pressure

HR: heart rate

od: once daily

bid: twice daily

hs: before bedtime

Hb: hemoglobin

WBC: white blood cell count

Cr: creatinine

eGFR: estimated glomerular filtration rate

Na+: sodium

K+: potassium

Cl-:chloride

TIA: transient ischemic attack

TC: total cholesterol

LDL: low density lipoprotein

HDL: high density lipoprotein

TG: triglycerides

ECASA: enteric coated aspirin

HCTZ: hydrochlorothiazide

mmol:millimol

L: litre

Appendix G: Scoring key

Scenario	Medication	Same dose	Increase dose	Reduce dose	Hold	Discontinue	No response
1	Digoxin	0	0	1	1	1	0
1	Warfarin	0	0	1	1	0	0
1	Furosemide	0	0	1	1	1	0
2	Naproxen	0	0	0	1	1	0
3	Candesartan	0	0	1	1	1	0

Total possible score=5

Chapter 4: Study methodology

In this chapter, we describe the methodology used in this randomized controlled trial to investigate the impact of integrating relevant laboratory information into clinical scenarios directed toward Ontario primary care physicians.

4.1 Objectives:

The objectives of the study were:

1. To examine whether the inclusion of relevant laboratory data into complex clinical scenarios improves prescribing decisions compared with the same scenarios in which laboratory data is available only if requested.
2. To identify physician related predictors of appropriate prescribing.
3. To identify medication related predictors of appropriate prescribing.

4.2 Research Methods:

4.2.1 Design:

We conducted a randomized controlled trial, using an internet-based survey of family physicians who were asked to make multiple prescribing decisions in hypothetical clinical scenarios.

4.2.2 Population: Family physicians in Ontario

Inclusion criteria: Family physicians in Ontario who are actively providing primary care clinical services.

Exclusion criteria: Non-physicians (including nurse practitioners and pharmacists), those engaged exclusively in administrative or other non-clinical work and undergraduate medical students.

4.2.3 Sample size

We aimed to enroll a minimum of 425 family physicians. This sample size reflects the sample required to demonstrate a difference in mean scores in the two groups of 0.30, standard deviation of 1.1, with α of 0.05 and β of 0.80. These estimates are derived from the pilot data of the survey and are consistent with the systematic review of the literature of randomized controlled trials evaluating the impact of drug lab alerts in all clinical settings. The review demonstrated substantial heterogeneity in studies but some studies showing benefit in prescribing decisions found a 25-30% improvement, which we felt was a clinically important improvement.

4.2.4 Outcomes:

The primary outcome was the number of correct prescribing decisions in each survey. Prescribing decisions were scored in a predetermined categorical manner as correct or incorrect. The answer key/ coding instructions are attached (Appendix B). Five prescribing decisions were scored in each survey.

4.2.5 Subject recruitment:

The Ontario College of Family Physicians (OCFP), a provincial voluntary organization representing more than 9,300 family physicians, agreed to send their members an invitation to participate in the project in their regular electronic

communications and not as a separate email invitation to participate in this survey. The invitation included an electronic link to the survey. Participants were offered an incentive to respond in the form of entry into a draw to win a $100 gift card from Chapters. A copy of the invitation to participate is appended here:

A survey of prescribing decision making in primary care

Drug safety is a major concern for physicians, policy makers, patients and their families. We are interested in clinical decision making during the prescribing process in primary care.

We invite Ontario family physicians to participate in a short survey regarding clinical decision making, which includes 3 brief clinical scenarios. This work constitutes the research component of Dr. Imaan Bayoumi's Masters thesis, under the supervision of Dr. Anne Holbrook at McMaster University. This study has been reviewed by the Hamilton Health Sciences/McMaster Faculty of Health Sciences Research Ethics Board (HHS/FHS REB). If you have any questions about your rights as a research participant, please call The Office of the Chair, HHS/FHS REB at 905 521-2100 x 42013.

The survey will take 10-15 minutes to complete.

As a token of appreciation, those who complete the survey are eligible to be entered into a draw for a $100 gift card from Chapters.

We hope you will take a few minutes to help us with this project!

Thanks for considering it.

To go to the survey, follow this link:

http://survey.qualtrics.com/SE/?SID=SV_6zXaTWZjqWlylak

In addition, Queens University Department of Continuing Health Education and Diversified Business Communications, a company which sponsors Primary Care Update, a privately sponsored educational event aimed at primary care providers distributed this electronic invitation to Ontario family physicians and general practitioners. Though the response rate in the pilot studies was good (59%) we anticipated a lower response rate with the electronic invitations. However, given the large population of recipients of the electronic invitation and the face-to-face requests, we anticipated that we would be able to recruit our target sample. We attempted to balance the need for a brief survey to support adequate response rates with the limitations of testing a limited number of scenarios. All respondents received all scenarios. We decided to restrict the number of scenarios to three but to embed multiple testable prescribing decisions within these scenarios, as would be the case with complex older patients with multiple medical conditions who are prescribed many medications. We excluded responses with identical IP addresses, indicating that the same computer had been used, to ensure that we assessed only one response for each participant, though we recognized that we may have lost data when more than one participant used the same computer.

4.3 Data analysis plan:

Demographic data were reported using descriptive statistics, including mean and standard deviation for continuous data and frequencies and proportions for discrete data. The demographic data from our sample was compared with

descriptive statistics from the 2007 National Physician Survey using a t-test to assess the degree to which the respondents were likely to be representative of the population of Ontario family physicians.

Each targeted prescribing decision was coded in a categorical fashion (correct/incorrect) Appendix E: Scoring key:. Data were analyzed using a generalized estimating equation to analyze binary responses, which may be correlated and to assess differences between the groups. We also used the GEE to identify predictors of appropriate prescribing. Potential physician factors that were considered included age, gender, years since completion of training, use of EMR, and working in primary care teams. We also examined differences in prescribing decisions between medications, to determine whether clinician responses differed according to which drug was being considered. We used a logistic regression model to test for significant predictors of appropriate prescribing of each individual drug. We tested the following variables for inclusion in the models: group allocation, gender, experience, patient records or payment model.

4.4 Ethics

The study was reviewed and approved by the Hamilton Health Sciences Research Ethics Board. Participation in the survey was entirely voluntary. There were no substantive risks to participants. We offered participants an incentive in the form of a draw in which the winner received a $100 gift card from Chapters. Participants were offered an answer key for their own feedback and a summary of results if they were interested. There were no other identifiable benefits to

participants. Data collected were anonymous, with the exception of the participant's email address, which they included if they wished to be included in the draw or to receive feedback or a summary of results. We requested data on demographic factors relevant to clinical practice but did not request personal information. At any time, participants could withdraw without penalty or risk to them. We kept all data confidential and analyzed them in de-identified format. We stored the data in an encrypted computer file, available only to the investigators.

Chapter 5: Results

The survey was open from June 15, 2011 to Oct 29, 2011. Ontario family physicians and general practitioners were invited to participate through several avenues. The Ontario College of Family Physicians sent an invitation to its members in their regular electronic communications on July 6, 2011 and Oct 11, 2011. In addition, the Queen's University Continuing Professional Development department distributed the invitation to family physicians and general practitioners on their mailing list on Aug 22, 2011. Finally, Diversified Business Communications, which coordinates Primary Care Update, a large continuing education event, delivered the invitation to Ontario general practitioners and family physicians on their mailing list on Sept 16, 2011.

In total, the survey was opened 350 times. We excluded responses in which the participant did not complete any of the scenarios (n=151), were identified as non-physicians (2 nurse practitioners, 1 community pharmacist), or whose postal codes were not from Ontario (n=31). For responses with duplicate IP addresses, we included only the most recently completed survey (n=17). There were 148 surveys remaining for analysis.

The response rate was calculated using estimates of all family physicians in Ontario, reported in the 2010 National Physician Survey (NPS). The NPS is a project sponsored by the Canadian Medical Association, the College of Family Physicians in Canada and the Royal College of Physicians and Surgeons of Canada, in which registered physicians, residents and second year medical students across Canada are surveyed every 3 years. In 2010 there were 11,768

registered family physicians in Ontario. Of the Ontario respondents to the NPS, 93.2% of family physicians are involved in clinical practice, corresponding to an overall estimate of 10,968 practicing family physicians in Ontario(NPS). Assuming that the invitations reached all practicing family physicians (which we cannot verify), the response rate was 1.35%. The participation rate was 42.3%.

The baseline characteristics of the two groups are summarized in Table 13: Baseline Characteristics of study groups. Though this was a randomized sample, there were proportionately more responses excluded from the intervention group than the control group. The two groups were similar in their baseline characteristics though there were proportionately fewer men (35.0% vs. 42.3%, χ^2=0.76, df=1, p=0.383), more physicians practicing primarily in office settings (85.7% vs. 74.9%, χ^2=3.023, df=5, p=0.696) and a greater proportion of respondents using primarily electronic medical records (72.3% vs. 67.1%, χ^2=1.10, df=2, p=0.551) in the integrated lab data group (intervention group) compared to the non-integrated lab data group (control group). We did not feel these differences were likely to be clinically relevant but included these domains as covariates in our analysis plan.

In order to evaluate the generalizability of the sample, the characteristics of the respondents were compared to data reported for Ontario family physicians in the 2010 National Physicians Survey and were statistically tested using χ^2 square or t-tests to determine whether the populations differed in baseline characteristics (Table 14: Characteristics of study population and Ontario Family Physicians in National Physician Survey, 2010). The study population differed

significantly from the NPS population by gender (χ^2= 22.13, df=1, p<0.0001), and system of patient records (paper vs. electronic) (χ2=160.35, df=2, p<0.0001).

Each participant made prescribing decisions for 5 scored medications in the three scenarios. Among participants in the integrated data group, 77.8% responded to all 5 decisions, compared with 84.2% in the non-integrated group. Overall, 70.3% of decisions were correct, and 29.7 were incorrect. There were fewer correct responses for the naproxen and candesartan prescribing decisions (Table 15: Correct responses overall and by group).

The logistic regression model testing for predictors of appropriate prescribing of each individual drug demonstrated that group allocation was not a significant predictor for any of the individual prescribing decisions. Women were more likely than men to make correct prescribing decisions for naproxen (OR 2.034, 95% CI 1.00-4.14) and warfarin (OR 2.59, 95% CI 1.06-6.36) and more experienced physicians were more likely to prescribe digoxin correctly with an OR for every 10 years experience of 1.68 (95% CI 1.03-1.72). There were no other significant predictors of correct prescribing decisions for individual medications.

We tested the overall likelihood of participants making correct prescribing decisions. In order to account for the lack of independence of prescribing decisions for individual respondents, we used a generalized estimating equation to model correlated binary data. Each individual participant was given a unique identifier. The within-subject effect was modeled by the medication in the scenario. We specified a binomial logit function, and exchangeable correlation

matrix, to account for the presumed correlation among prescribing decisions. Decisions were categorized as correct or incorrect and scored accordingly. The score was the dependent variable. Factors and covariates considered in the model were group allocation, gender, experience, remuneration, and type of patient records (electronic, paper or a mixture) Table 16: Generalized estimating equation model summary. None of the factors tested were identified as significant predictors of correct prescribing decisions. We calculated the interclass correlation coefficient (ICC), to account for the relatedness of prescribing decisions within each physician and found it to be 0.28

Conclusion

Despite a number of dissemination strategies, we failed to achieve our target sample size. The sample differed from the population of Ontario family physicians by gender and use of electronic medical records. Overall, 70.3% of the prescribing decisions were correct. Integration of laboratory data did not have a significant impact on the quality of the prescribing decisions.

Table 13: Baseline Characteristics of study groups

	Integrated lab data (n, % or mean, SD)	**Non-integrated lab data (n, % or mean, SD)**
n	65 (43.9)	83 (56.1)
Gender		
Male	21 (35.0)	33 (42.3)
Remuneration		
Fee for service	20 (30.8)	28 (34.1)
Salary	17 (26.2)	19 (23.2)
Capitation	24 (36.9)	28 (34.1)
Other	4 (6.2)	7 (8.5)
Practice setting		
Office	54 (85.7)	69 (74.9)
Hospital	7 (11.1)	5 (6.3)
Emergency department	2 (3.2)	3 (3.8)
Long term care home	0 (0)	2 (2.5)
Patient records		
Paper	9 (13.4)	10 (12.2)
Electronic	47 (72.3)	55 (67.1)
Mix	9 (13.8)	17 (20.7)
Location		
Large city	27 (42.2)	35 (42.7)
Small city	25 (39.1)	29 (35.4)
Small town	9 (14.1)	8 (9.8)
Rural	3 (4.7)	10 (12.2)
Experience (y)	17.3 (11.9)	17.5 (11.8)
Practice Model[1]		
Solo	5 (7.7)	13 (14.5)
Group	22 (33.8)	30 (36.1)
FHT	19 (29.2)	23 (27.7)
FHO	15 (23.1)	24 (28.9)
Interdisciplinary team	12 (18.5)	11 (13.3)
CHC	4 (6.2)	4 (4.8)
FHG	10 (15.4)	10 (12.0)

[1]These models are not mutually exclusive; totals exceed 100%; FHT= Family Health Team, FHO= Family Health Organization, CHC= Community Health Centre, FHG= Family Health Group

Table 14: Characteristics of study population and Ontario Family Physicians in National Physician Survey, 2010

	Study population (%)	**NPS Ontario Family Physicians (%)**
n	148	2283
Gender		
• Male	36.5	56.68
Remuneration		
• Fee for service	32.4	33.5
• Salary	24.3	6.7
• Capitation & other	42.5	47.4
Practice setting		
• Office	83.1	68.8
• Hospital	8.1	14.1
• Emergency department	3.4	6.8
• Long term care home	1.4	0.9
Patient records		
• Paper	12.8	31.6
• Electronic	68.9	19.8
• Mixture	17.6	36.8
Location		
• Large city	41.9	69.0 (inner city, urban, suburban)
• Small city	36.5	
• Small town	11.5	15.6
• Rural	8.8	9.9 rural and remote
Practice Model		
• Solo	12.2	24.9
• Group	35.1	51.5
• FHT	28.3	
• FHO	26.4	
Interdisciplinary team	22.3	16.0
CHC	5.4	
FHG	13.5	

Table 15: Correct responses overall and by group

Drug	Overall Correct (n,%)	Correct Integrated (n,%)	Correct Non-integrated (n,%)
Furosemide	122 (82.5)	52 (80.0)	70 (84.3)
Digoxin	129 (87.2)	60 (92.3)	69 (83.1)
Warfarin	120 (81.1)	51 (78.5)	69 (83.1)
Naproxen	93 (62.8)	44 (67.7)	49 (59.0)
Candesartan	56 (37.8)	26 (40.0)	30 (36.1)

Table 16: Generalized estimating equation model summary

Parameter	B	SE	Wald χ^2	df	p	OR (95% CI)
Intercept	0.595	0.38	2.49	1	0.12	1.81 (0.87-3.79)
Group (integrated)	0.192	0.19	1.05	1	0.31	1.21 (0.84-1.75)
Gender (female)	0.112	0.22	0.27	1	0.61	1.12 (0.73-1.71)
Other payment model	-0.348	0.43	0.66	1	0.42	0.71 (0.30-1.64)
Salary	0.374	0.26	2.07	1	0.15	1.45 (0.87-2.42)
Capitation	0.24	0.6	0.88	1	0.35	1.27 (0.77-2.10)
Mix paper and electronic	.011	0.40	0.001	1	0.98	1.01 (0.46-2.23)
Electronic	0.14	0.5	0.15	1	0.70	1.14 (0.57-2.28)
Years in practice (scale=1 y)	-0.006	-0.008	0.58	1	0.45	0.99 (0.98-1.01)

Chapter 6: Discussion

This randomized controlled trial compared prescribing decisions made by family physicians in clinical scenarios in which laboratory data was integrated compared to those available on demand. We did not find a difference in the quality of prescribing decisions made between the two groups and did not identify any significant predictors of correct prescribing decisions.

6.1 Methodological considerations:

6.1.2 Internal validity:

The clinical scenarios were developed in a rigorous and transparent manner, using pre-specified criteria and Canadian data, where available. The data regarding frequency of prescribing by primary care physicians from the IMS database represents prescriptions dispensed from about 70% of Canadian pharmacies, and likely has good external validity for representing prescribing patterns of Canadian family physicians and general practitioners. The CIHI data regarding adverse drug events associated with hospitalizations and ED use appear to have poor internal and external validity. Some methodological concerns stem from the criteria for coding adverse drug events, likely resulting in under-identification of adverse drug events, thereby limiting the generalizability of the data for describing patterns of adverse drug events in Canada. Nevertheless, the medications identified in these data are consistent with those identified elsewhere in the medical literature. And while there are necessarily judgements involved in medication selection, the process of predefined criteria, based on established data helps to mitigate bias in the selection process.

The scenarios were constructed to mimic complex situations encountered on a daily basis in primary care settings. They were pilot tested and revised accordingly. The process of testing and revising helps to support the face validity and therefore, the internal validity, of the scenario development process. However, the extent to which decisions made in the context of internet-based clinical scenarios mimic real practice decision-making is unclear. Time constraints are a factor in both situations, but in real life primary care is complex and includes many other distractions from medication prescribing decisions that may influence decision-making.

We found that overall, across all scenarios, 70.3% of the prescribing decisions were correct, ranging from 37.8% to 87.2% correct for individual medications. The lack of difference between the two groups may reflect either that there was no true difference, that the sample size was too small to demonstrate a difference, or the presence of a ceiling effect, in which there is little room to demonstrate improvement from the integration of lab data. We did not meet our sample size targets, representing a significant limitation in the data.

For two of the medications (warfarin and furosemide), correct decisions occurred in both groups with very high frequency, suggesting that the scenario with these decisions demonstrated poor discriminatory power, and likely contributed to a ceiling effect.

6.1.3 External validity

The external validity of the study is limited by the poor overall response rate. The invitation to participate was sent by independent organizations. We did

not have direct access to family physicians' email addresses, so could not send the invitation directly. This could represent an advantage, in that members may be more likely to read an email from a recognized organization in which they are involved, rather than from an unknown individual. However, family physicians receive many requests to participate in surveys, likely contributing to a low response rate. We were dependent on the OCFP to send the reminder. They were willing to do so, but did not want to overburden their members with email messages. Therefore, they preferred to bundle both the initial invitation and the reminder in a newsletter with other information, resulting in a significant delay of two months between the initial invitation and the reminder, and only a single reminder. No reminders were sent by the other two organizations. More reminders have been shown to significantly improve response rates (Asch, Jedrziewski, & Christakis, 1997; Braithwaite, et al., 2003; Field, et al., 2002). It was not possible to send additional reminders given the lack of direct access to physicians, and the lack of infrastructure in an unfunded study to support other recruitment strategies. Furthermore, the project was launched during the summer months, which may have contributed to the low response rate, though the reminder and the invitation from other parties were sent in the fall. The low response rate contributes to the lack of representativeness of the sample and limits its generalizability. Although the two groups are approximately equivalent, the overall sample differs from the general population of Ontario family physicians in terms of gender, model of remuneration, and use of electronic medical records. These results suggest a response bias in which some characteristics of the study sample differed systematically from the target population. Furthermore, 43.1% of

those who entered the survey failed to complete any of the scenarios. This group may have differed systematically from the group that did complete the survey (which we could not establish because of the high proportion of missing data), further contributing to response bias. These factors all limit the external validity of the findings.

6.2 Implications:

Given the aforementioned limitations on internal and external validity, it is difficult to draw reliable conclusions regarding the implications of this research. It may be more appropriately viewed as an exploratory or pilot study, whose main purpose is to better understand key methodological issues. Physicians have the mean lowest response rates in a sample of health related surveys published in medical literature (Field, et al., 2002). Systematic reviews of strategies to improve response rates to postal surveys have identified evidence for some key strategies to improve response rates, including use of prepaid financial incentives, personalized contact, and recorded delivery system or registered mail (Field, et al., 2002). Evidence regarding size of the financial incentive is inconsistent, with some reports that even a nominal prepaid incentive effectively increases response rates (Robertson, Walkom, & McGettigan, 2005). Internet based surveys typically have lower response rates (Braithwaite, et al., 2003; Im & Chee, 2004). Some authors report increased response rates with the use of up to 5 reminders (Braithwaite, et al., 2003), but we are not aware of any research evaluating the optimal number of reminders. Some ethics review committees have expressed concern that participants may feel harassed with the use of multiple reminders. In

fact responses to the National Physician Survey have also significantly declined from 31.2% in 2004, 31.64% in 2007 to 18.05% in 2010 (NPS), despite use of such strategies as reducing survey length, offering some financial incentives to residents and students and greater use of online responses (Grava-Gubins & Scott, 2008). One group reported response rates which improved from 48% to 74-76% in a series of surveys of physicians participating in a practice based research network (Thorpe et al., 2009). They used unconditional financial incentives ($25 gift certificates for bookstore) and recorded delivery/registered mail. They theorized that the use of registered mail signaled the importance of the material to office staff, who forwarded it directly to the physician, thereby bypassing the gatekeeper function of secretarial staff.

There are some clear advantages of Internet based surveys over print surveys. They are significant cost savings, with no costs of paper, mailing and lower administrative costs. Our survey tool had the capacity to download data directly into a database, making for a more efficient and likely more accurate result. Furthermore, an internet-based survey allowed for a more interactive survey, which was important for our purposes.

A future study should utilize different recruitment techniques. It may be more fruitful to focus on a narrower sampling frame and to attempt to contact a random sample of physicians directly. The challenge with direct contact is that while mailing information, telephone and fax numbers are generally accessible through physician directories at self-regulating physician colleges, there is no established database of physician electronic mail addresses. A more successful recruitment strategy may be to send printed recruitment materials, ideally with

recorded delivery, with a prepaid incentive, which include the web based survey link.

We calculated the intraclass correlation coefficient at 0.28, confirming the importance of utilizing analytical methods that account for correlated data. The ICC could be utilized for future sample size calculations.

We found no difference in the quality of prescribing decisions made whether lab data was integrated or available only by request. While this finding may be related to a poor response rate and the failure to achieve the target sample size, it is also conceivable that the intervention is itself ineffective. This conclusion would be compatible with the literature which has largely failed to demonstrate a significant impact from the use of computerized decision support for integration of appropriate lab data in prescribing decision making, particularly with non-interruptive alerts. It is likely that other strategies would be necessary for decision support to significantly improve care, such as alerts that are integrated into a quality improvement program through optimal utilization of all team members, including pharmacists, rather than those targeting clinicians at the point of prescribing. It is possible that the clinical encounter is already too burdened by many competing needs, and as such the intensity of the intervention is ineffective.

6.3 Conclusion

Integration of laboratory information into complex clinical scenarios did not result in improved prescribing decisions by Ontario primary care physicians. This may be because our study was underpowered, that the intervention was

ineffective or due to the presence of a ceiling effect. Future studies should address recruitment challenges and should utilize scenarios with a greater demonstrated range of responses. Future research should also test interventions occurring outside the point of prescribing and including multiple team members.

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