Enabling Drug-Drug Interaction Alerts in an Electronic Medication Management System: Impact on Prescriber Alert Burden

ANMOL PREET KAUR SANDHU – B.PHARM (HONS)

A thesis submitted as partial fulfilment of the requirements of the degree of Master of Research

1 May 2019

Australian Institute of Health Innovation
Faculty of Medicine and Health Sciences

MACQUARIE University
SYDNEY·AUSTRALIA

ST VINCENT'S HOSPITAL
SYDNEY

Supervisors:
Associate Professor Melissa Baysari
Professor Johanna Westbrook

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ABSTRACT

Background and objectives

The volume of clinical decision support (CDS) alerts encountered by prescribers (i.e. alert burden) within electronic medication management (EMM) systems is likely to influence whether CDS alerts are read and acted upon. This study aimed to determine the impact of introducing drug-drug interaction (DDI) alerts on the total alert burden experienced by prescribers.

Method

This was a simulated cohort study. Clinical data for a given study date were extracted from a 'live' EMM system in use at a tertiary teaching hospital. No DDI alerts were enabled in the hospital at the time (Alert Condition 1). The same medication orders were then replicated via manual entry into a simulated version of the EMM system where DDI alerts were enabled (Alert Condition 2). CDS alert data from Alert Condition 1 and 2 were extracted and compared.

Results

With DDI alerts in place, prescriber alert burden increased from 38% to 72% of a prescriber's medication orders triggering at least one alert. Alerts were encountered by almost all doctors (91%), and each doctor received approximately four times more alerts (15 alerts vs 3.8 alerts per doctor) than in the absence of DDI alerts.

Conclusion

DDI alerts, if enabled, would significantly increase the alert burden on prescribers and are likely to lead to alert fatigue. To reduce their impact on prescriber alert burden and improve alert effectiveness, DDI alerts should be refined prior to their implementation.

DECLARATION

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

This work has received approval from the St Vincent's Hospital Human Research Ethics Committee (HREC Reference Number: LNR/15/SVH/415)

Signed: 

Date: 09/03/2019

ACKNOWLEDGEMENTS

Firstly, I would like to extend profound gratitude to my supervisors, **Associate Professor Melissa Baysari** and **Professor Johanna Westbrook**. I feel tremendously fortunate to have had the opportunity to learn from and be guided by two highly regarded researchers at the forefront of their fields.

I wish to thank **Professor Westbrook** for her ever present support, expertise and wisdom, particularly during the most challenging aspects of this research endeavour. I am grateful to **Associate Professor Baysari** for being so generous with her time, for her approachable nature and for giving me the freedom to learn and explore new ideas, yet also providing structure and support when it was needed. I am sincerely thankful to both for imparting their knowledge, providing constructive feedback and for their overwhelmingly genuine support in seeing this thesis to its fruition.

My deepest gratitude goes to **Dr Dennis Armstrong** for providing the subject matter expertise required to undertake this work and to **DXC Technology** for supporting this endeavour. Dr Armstrong went above and beyond with regards to provision of his time and expertise (even once he had retired), and for that I am deeply grateful.

I wish to thank **Dr Wu Yi Zheng** who played a critical role in assisting me with data entry and to **Dr Scott Walter** for his assistance with statistical analyses and both for their pragmatic advice. I am indebted to **Jagjot Singh** for imparting his technical know-how, and for empowering me to swiftly and confidently analyse what would otherwise have been an overwhelming amount of data.

I would like to acknowledge **Terry Melocco** and **Despina Limiatis** (St Vincent's Hospital Pharmacy) for their support and understanding during this time, and for appreciating the value of my research to the department. I am very grateful to my **EMM colleagues** past and present, the **IT team** and to the **St Vincent's Hospital Drug and Therapeutics Committee** for commissioning this work and for affording me the opportunity to undertake it.

Thanks also goes to staff at the **Australian Institute of Health Innovation**, the **Faculty** and the **Higher Degree Research Office** at Macquarie University.

Last, but by no means least, my heartfelt thanks goes to **my husband and family**. It would perhaps not be recommended to have your firstborn child halfway through a Master's degree, but their unfettered support allowed me to see this to completion. I am so grateful to my family for selflessly sharing the load of parenthood, so that I could accomplish this feat.

LIST OF ABBREVIATIONS

A&I	Allergy & Intolerance
AC1	Alert Condition 1
AC2	Alert Condition 2
ADE	Adverse drug event
AIDS	Acquired immune deficiency syndrome
CDS	Clinical decision support
CPOE	Computerised physician order entry
DDI	Drug-drug interaction
DR	Dose range
EMM	Electronic medication management
EMR	Electronic medical record
HIV	Human immunodeficiency virus
LR	Local restriction
NSW	New South Wales
RR	Rate ratio
SQL	Structured Query Language
SVHS	St Vincent's Hospital, Sydney
TD	Therapeutic duplication

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1. INTRODUCTION

1.1 Electronic medication management systems and clinical decision support

Adverse drug events (ADEs) resulting from medication errors constitute a significant, but preventable cause of patient harm.[1-4] Medication errors are the second most frequently reported incident type in hospitals,[5-7] with up to half reported to occur during the prescribing (order entry) process.[8] Electronic medication management (EMM) systems; also known as computerised physician order entry (CPOE) systems, have been identified as promising tools to prevent and minimise these medication errors, particularly those occurring during prescribing.[9] A seminal Australian study undertaken at two Sydney hospitals demonstrated a reduction in the rate of prescribing errors by more than 55% after the implementation of an EMM system.[10] Further studies have also shown EMM systems can reduce prescribing errors by improving completeness of prescriptions, improving legibility and by providing users with guidance via clinical decision support (CDS) at the point of prescribing.[4, 9, 11, 12] CDS is an intelligent feature commonly integrated within EMM systems. It provides relevant clinical content and patient data to clinicians in order to facilitate clinical decision making.[13, 14] It is important to note that whilst there are many well-documented benefits of EMM systems, particularly with respect to reducing medication errors, there is less evidence demonstrating how these systems ultimately result in favourable patient outcomes i.e. reduction of ADEs or patient mortality.[15-18]

Specifically in Australia, the National Digital Health Strategy identifies digital medicines management as a strategic priority, recognising the role it plays in improving medication safety.[19] Propelled by these national eHealth initiatives, the use of EMM systems with integrated CDS is no longer limited to early adopter sites. In New South Wales (NSW) for example, eHealth NSW plans to complete implementation of EMM systems across NSW public hospitals by the end of 2019.[20, 21]

1.2 Challenges associated with CDS alerts

Computerised alerts that trigger at the point of prescribing are a common form of CDS used to notify users of a potential adverse outcome.[14] These medication safety alerts can be used to warn clinicians of a dose range breach, therapeutic duplication, allergy-drug interaction or a drug-drug interaction. More advanced alerts notify of drug-pathology interactions, drug-diagnosis interactions, and genomic considerations.[22, 23] Computerised alerts are viewed to

be ‘accepted’ if the clinician selects the recommended action on the alert screen and modifies or cancels an order, and ‘overridden’ if the clinician moves past the alert screen and continues with their original prescription or action (see **Figure 1**).[24]

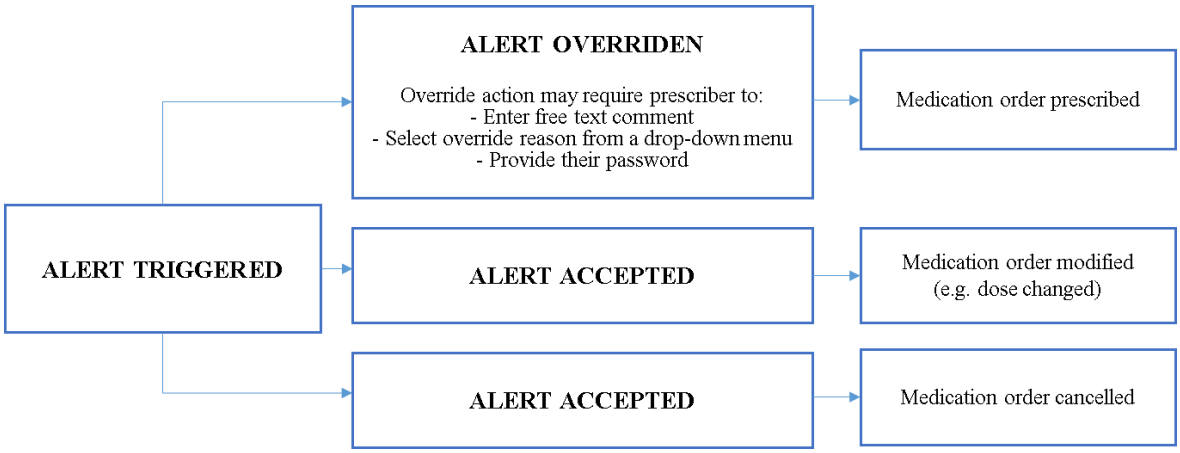

Figure 1: Actions possible following alert presentation. An alert, once triggered, can be overridden or accepted by the prescriber.

Despite the increasing prevalence of EMM systems, both in Australia and internationally, there remains a scarcity of formal standards or guidelines to direct effective implementation of CDS.[23, 25] The complexities of CDS mean that without such direction or guidance, institutions do not always realise the full benefits of their CDS implementations.[23, 26] Many organisations, in lieu of evidence-based guidelines, rely on local investigations, observations, and anecdotal feedback from their users or other organisations to inform decisions on the type of medication safety alerts to enable.[27-29] In 2005, the United States based Joint Clinical Decision Support Workgroup identified four broad barriers that hamper effective utilisation of CDS interventions. These are: functionality (limited features, poor user acceptability), data (inability to integrate with relevant data repositories), knowledge (lack of standards, expertise to manage) and cost (implementation and maintenance).[13] Almost 15 years on, these barriers are still present and continue to prove challenging to overcome.[22]

In the absence of implementation guidance or standards, several institutions have enabled a large number of medication safety alerts, across all severity levels, resulting in an EMM system that generates large volumes of alerts with high sensitivity and low specificity.[30] This high alert exposure or alert burden (see **Box 1**) in turn desensitises clinicians, such that they bypass or override both clinically significant and insignificant alerts, a phenomenon known

as 'alert fatigue'.[31-33] Alert fatigue can undermine the desired safety gains of CDS and remains a persistent problem, despite its identification several years ago.[33] A frequent complaint from users is that large numbers of irrelevant alerts are triggered, resulting in alerts being ignored.[34] Enabling only a small number of alerts, so as to minimise alert fatigue is critical (although an 'optimal' level of alerting has not yet been defined in the literature), as EMM systems resulting in too many alerts being triggered have been rejected by users and can in some cases be decommissioned for this reason alone.[35, 36] The CDS Five Rights model suggests that for CDS to be effective, the right information should be presented to the right clinician(s), in the right format, via the right platform and at the right time in workflow.[37] For medication safety alerts, this equates to well-designed alerts, containing relevant and pertinent information, presented to clinicians at the point of decision-making.[38]

Box 1: Definition of prescriber alert burden and how it is measured

- In this thesis, prescriber alert burden is defined as the volume of alerts encountered by a prescriber
- Prescriber alert burden is measured by determining the rate of alerts encountered per prescriber, or the proportion of a prescriber's medication orders that generated alerts
- High prescriber alert burden is likely to result in alert fatigue

Another challenge associated EMM systems with CDS software is ensuring that this technology is designed and used in a safe manner, and does not contribute to patient harm.[39] There are increasing requirements for software to be registered as a medical device and therefore meet stringent regulatory requirements, particularly in Europe and the United States. A consultation and review process is currently underway to inform the regulation of software as a medical device (SaMD) in Australia.[40]

1.3 Challenges associated with drug-drug interaction alerts

Drug-Drug Interactions (DDIs) are a predictable and therefore preventable cause of harm, occurring when one drug increases or decreases the concentration of another drug, resulting in increased toxicity, or reduced therapeutic effect.[41, 42] It has been reported that between 33 to 67% of hospital inpatients experience one or more potential DDIs during their admission.[43] The predictability and high prevalence of potential DDIs make them ideal candidates for inclusion in CDS. As such, DDI alerts are one of the most frequently

implemented CDS alert type, with their most common deployment in the form of interruptive, 'pop-up' alerts.[27, 28] Despite their widespread use, strong evidence to demonstrate positive clinical outcomes (e.g. reduction in ADEs following DDI alert implementation) is still lacking.[15, 17, 44-47]

DDI alert implementation is not without its challenges. A number of issues relating to DDI alerts have been identified, including a lack of standardisation in defining clinical significance, inconsistent DDI severity ratings between drug knowledgebases (i.e. the databases containing clinical content used to inform the DDI alerts), limited software customisation, and poor alert design.[38, 48-50] Excessive DDI alert generation has been identified as a major impediment to the utility of DDI alerts.[27] Commercial DDI knowledgebases are highly sensitive and particularly prone to excess alerting due to the sheer number of known drug interactions[51] and overzealousness in including any or all interactions for fear of litigation.[52-54] There is also an inherent lack of specificity in the underlying alert algorithm (i.e. the clinical rules that determine under which context an alert is generated), which means prescribers are exposed to large volumes of non-specific and inappropriate alerts.[22, 38] High override rates (up to 95%) and alert fatigue subsequent to the heightened alert burden associated with DDI alerts are well documented in literature.[54-57] Attempts have previously been made to reduce DDI alert burden and therefore alert fatigue, however even with fine tuning and customisation, alert volume and override rates remain high.[56, 58] A summary of the current research on optimisation strategies for DDI clinical decision support is shown in **Table 1**.

Table 1: Summary of strategies used to optimise DDI alerts.

Strategy or mechanism used to optimise CDS related to DDI
▪ Deployment of a core set or high-priority DDI alerts only[59-62]
▪ Use of human factors principles to inform alert interface design (e.g. prioritisation, content, visibility, colour)[8, 22, 63-75]
▪ Advanced alert logic to increase alert specificity and relevance – 'context-aware' alerts. o Inclusion of contextual or modulating factors relating to the patient, drug, prescriber, organisation or alert[22, 76-82] o Machine based learning; dynamic alert filtration (suppression), dynamic severity re-categorisation[58, 83]
▪ Modification of drug knowledgebase (e.g. re-classification of severity levels based on clinical significance or the exclusion of clinically irrelevant alerts). Expert panel or compendia review may inform this work[37, 50, 52, 84-93]
▪ Changing presentation or level of interruption of alerts based on their severity or clinical significance ('tiering')[24, 86, 90]
▪ Modification of prescriber response based on alert severity e.g. mandatory submission of password or reason to override alert, selection from drop-down menu and complete hard stops to disallow prescription of contraindicated drug pairs[94-97]
▪ Redirection of alerts to non-medical clinicians (pharmacists, nurses) e.g. DDI alerts recommending separated administration of two medicines to be re-directed to nurses, or alerts recommending warfarin monitoring to be re-directed to anticoagulation monitoring service.[98, 99]
▪ Alternatives to alerts e.g. on-demand DDI checkers, on-demand CDS alert log to allow for review at prescriber's discretion, use of an visual alert dashboard to inform decisions regarding the removal of non-critical DDI alerts[100-103]

Whilst many of the strategies outlined in **Table 1** have shown to be effective in improving the utility of DDI alerts, their broader deployment within healthcare organisations has been limited due to a number of challenges. For example, modification of a commercial drug knowledgebase requires the organisation to have robust in-house technical expertise as these changes require both an intimate understanding of the knowledgebase structure, and the architecture of the EMM system.[52] The organisation must then maintain the knowledgebase as new interactions are identified, and ensure content or version updates from the software vendors do not overwrite in-house customisations.[52, 54]

Given the complexities associated with deploying these strategies, many healthcare organisations have chosen to implement the vendor-based DDI decision support unchanged, in spite of known issues with excessive alert generation and low specificity.[27, 49, 54] The development of a centrally managed, national repository of DDI decision support data has been flagged by researchers in the United States as a possible solution to some of the aforementioned challenges.[27, 49, 104]

1.4 Study context, rationale and aim

Since implementing their EMM system in 2005, the study site, St Vincent's Hospital, Sydney (SVHS) has maintained a judicious approach to CDS implementation, opting for a 'less is more' approach. Finding the right balance between burdening prescribers with high numbers of alerts, thereby risking alert fatigue, and ensuring alerts warn of potential ADEs associated with DDIs is a challenge. Quantitative and qualitative evaluation of CDS in use at SVHS has seen several changes and refinements made over the years.[105] In recognising the potential alert burden associated with DDI alerts, the study site chose initially not to implement this alert type. Functionality at the time also precluded the implementation of DDI alerts at a specific severity classification (i.e. it was 'all or nothing'). In recent years, functionality has improved such that customisation of CDS is now possible, including the ability to implement DDI alerts at a particular severity level. This prompted the hospital's Drug & Therapeutics Committee to consider the enabling of DDI alerts in their EMM system.

This study represents a first step in understanding what impact a decision to enable DDI alerts at SVHS would have on prescribers. Previous studies which have quantified alerts have focused primarily on outcomes related to medication orders or patients (e.g. proportion of all medication orders that generated an alert)[106]. This current study took a unique approach in focusing on the alert burden to prescribers (see **Box 1**). In adopting a prescriber-centric view of alerts, it is important to examine cumulative alert burden, the burden experienced by prescribers as a result of all medication safety alerts triggered, not just DDI alerts. Thus, this study aimed to determine the alert burden experienced by prescribers with existing CDS functionality, and then how this would change if DDI alerts were added to the EMM system.

Findings from this study will directly inform the organisation's decision to enable DDI alerts and if so, at what level of severity. No Australian guidelines currently exist to inform DDI alert implementation in hospitals and as such, this research will also provide useful data to inform their development.

2. METHOD

2.1 Study site and setting

The study was conducted at SVHS, a 379-bed hospital in Sydney, Australia. SVHS functions as a principal referral and tertiary, public teaching hospital with specialties including heart and lung transplantation, bone marrow transplantation, cardiology, cancer care, AIDS/HIV, respiratory medicine, mental health and drug and alcohol services.

SVHS practices a team-based model of care, whereby the patient's admitting team is responsible for the patient's care, and as such do the majority of prescribing for that patient. Exceptions to this occur if the patient is in the Intensive Care Unit, where prescribing is shared or during after-hours. A patient is always admitted under a single team however, a doctor may belong to and work for multiple, usually closely related teams e.g. Neurology and Acute Stroke Unit. Doctors use the same EMM system login, irrespective of the team they are working for at the time. Teams are generally made up of a staff specialist (admitting medical officer), a registrar and an intern/resident.

The EMM system used at the study site is DXC Technology's MedChart® solution (http://www.dxc.technology). The system was implemented in 2005, and is used throughout the inpatient hospital wards with the exception of the emergency department. The EMM system is used for prescribing, administration and clinical pharmacy review and includes both passive and active clinical decision support features for a range of clinician types including doctors, nurses, pharmacists and dietitians. All medicines are managed on the system with the exception of complex infusions, insulin and patient controlled analgesia. These items are managed on specialised paper charts, however a corresponding electronic flag is entered by users into the EMM system to serve as a reminder that a paper chart is in use.

The EMM system includes a mirrored Test (simulation) environment which is used by SVHS to test versions of incoming software or to develop and validate new functionality. The Test environment was used for the current study. At the time of this study, the Live (Production) environment was using version 5.3 B1 of the MedChart® software, whilst the Test environment used version 8.2.1 R5. Any differences in functionality or database structure between the two versions did not impact the research outcomes.

2.2 Clinical decision support at the study site

At the time of the study, CDS enabled for doctors included allergy and intolerance, dose range and therapeutic duplication (substance and class) alerts. In addition to this, a suite of locally developed medicine restriction rules and pregnancy alerts were also enabled by the hospital (see **Table 2**). DDI alerts were not enabled in the live EMM system, however an on-demand DDI checker was available to all clinicians via an integrated medication reference viewer.

Table 2: The context in which CDS alerts are triggered and the prescriber response required to process alerts. The prescriber response varies for dose range and local restriction CDS alerts and is assigned to each alert individually by the EMM Pharmacist. Note: DDI alerts were not enabled in the live EMM system at the time of the study.

CDS alert type	CDS alert trigger & example	Alert response
Allergy & intolerance	Triggers if the prescribed medicine (i.e. generic substance) is the same or belongs in the same medicine class as the one a patient has a recorded allergy or intolerance to in the EMM system. *E.g. amoxicillin is prescribed for a patient with a class allergy to penicillin recorded in the EMM system.*	R3
Dose range	Triggers if the dose of a prescribed medicine does not comply with pre-defined dosing criteria. The criteria can specify upper and/or lower dose limits, a maximum single dose or a cumulative dose within a specified time frame. Additional criteria can be applied with regard to patient age or weight, or the medicine's form or route of administration. *E.g. the prescribed dose of alendronate tablet exceeds 70mg in 7days.*	R1 R2 R3 R4 R5
Therapeutic duplication (substance & class)	Triggers if the prescribed medicine is the same, or belongs in the same medicine class as a medicine that is currently on the patient's medication chart (or has been ceased in the last 24 hours). *E.g. atorvastatin is prescribed and pravastatin is already on the patient's medication chart.*	R2
Local restriction rule	Triggers if the prescribed medicine meets the conditions set out in the pre-defined restriction rule. These rules are used to restrict or discourage inappropriate prescribing or to relay information to prescribers on a certain topic e.g. local hospital guidelines or use of a medicine in pregnancy. *E.g. meropenem is prescribed and the user is informed it is a restricted antimicrobial at SVHS and requires approval for prescribing.*	R1 R2 R3 R4 R5
Drug-drug interaction (not enabled in Live system)	Triggers if the prescribed medicine interacts with a medicine that is currently on the patient's medication chart (or was ceased in the last 24 hours). Alert generation is determined by drug –drug interaction pairs listed in the EMM system's knowledge base. *E.g. itraconazole is prescribed and dabigatran is currently on the patient's medication chart*	R2

CDS =clinical decision support; EMM = electronic medication management
R1 = Alert is for information only, and does not require an override
R2 = Alert can be overridden (without providing a reason)
R3 = Alert can be overridden if a reason is provided
R4 = Alert cannot be overridden, but medication details can be changed
R5 = Alert cannot be overridden

In the EMM system, when a doctor receives an alert, they can override the alert and continue finalising the medication order, however depending on the type of CDS alert, they may be required to enter a reason into a comment box or alter the medication order details before they are permitted to override the alert. The comment box is a free text field and does not present any coded options. The prescriber response for a given alert type is listed in **Table 2**. Alternatively, the doctor can choose to cancel the medication order, as shown in **Figure 1**.

All CDS alerts in the system are synchronous (real-time) and interrupt the user's prescribing workflow by invoking a specific alert window. Prescribers can be presented with one or more alerts at the same time, within the same alert window. The CDS alerts are grouped onscreen firstly by the triggering medication order (i.e. medication order being prescribed), then by alert type and then in descending order of severity. All CDS alerts, regardless of type, have similar design features (including colours, font and text size). An example of an alert window with multiple alert types is shown in **Figure 2**. The knowledge bases used to inform the CDS alerts are provided by DXC Technology and MIMS (www.mims.com.au). Knowledge bases are kept current via monthly drug data updates.

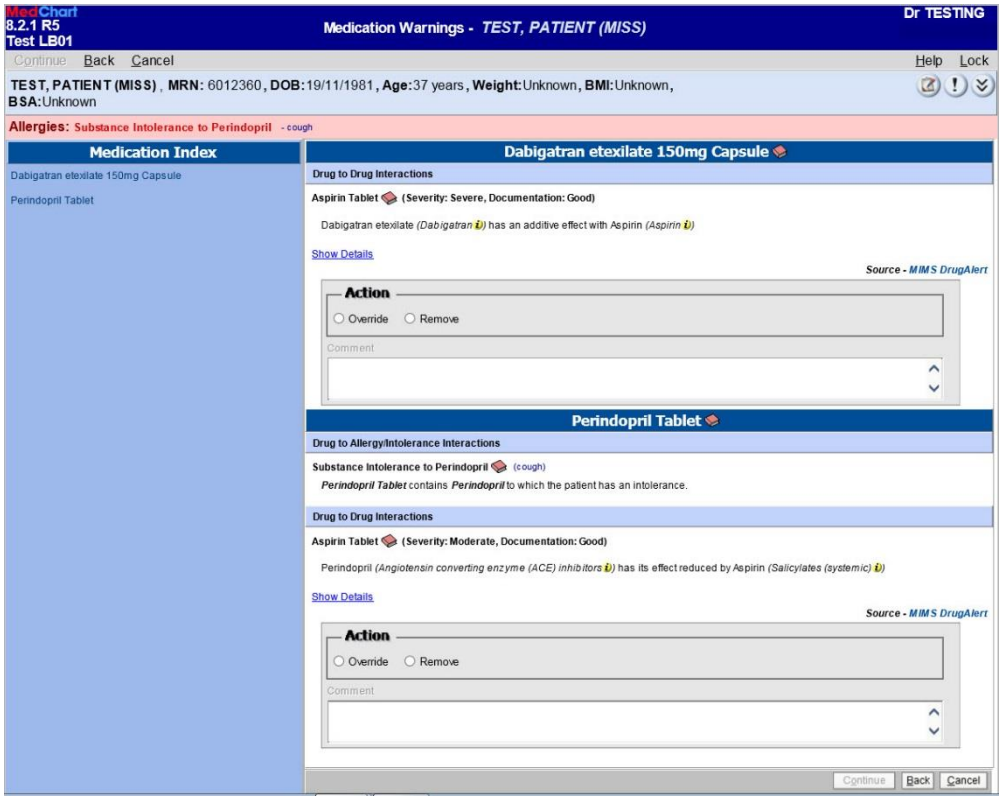

Figure 2: Example of an alert window interface. The doctor has ordered two medicines: dabigatran and perindopril. The dabigatran medication order has triggered a DDI alert, whilst the prescription of perindopril has triggered both an allergy/intolerance alert and a DDI alert.

2.2.1 Drug-drug interaction alerts

DDI alerts, when enabled, use the MIMS Drug Alerts knowledge base which classifies DDI pairs according to their clinical severity (**Table 3**). The DDI pairs constitute drug-drug interactions, drug-class interactions and class-class interactions. Both moderate and severe DDI alerts were enabled in the Test EMM system for the current study.

Table 3: Number of DDI pairs by severity classification in the MIMS Drug Alerts knowledge base (as at February 2018).

Severity classification	No. of DDI pairs (% of total)
Caution	830 (6%)
Minor	1302 (10%)
Moderate	7702 (58%)
Severe	3498 (26%)
Total	**13332**

DDI = drug-drug interaction

DDI alerts are also triggered if there is no interaction information available in the knowledge base about the prescribed drug pair. These types of DDI alerts will be referred to in this thesis as 'unknown DDI alerts'. It is of relevance to note that the 'unknown DDI alerts' are not logged in the EMM system's database in the same way as the other CDS alerts. Therefore details about the drug pair that triggered the alert, or whether the alert was presented alone or in conjunction with other alerts in the same alert window were not available. DDI alerts are not generated for edited or ceased medication orders.

2.3 Study design and procedure

Two different alert conditions were compared in this study, as per **Table 4**.

Table 4: Clinical decision support alerts configured in Alert Condition 1 and 2.

	Allergy & Intolerance	Dose Range	Local restriction rules	Therapeutic Duplication	DDI (Moderate, Severe & Unknown)
ALERT CONDITION 1 (Live EMM system)	✓	✓	✓	✓	✘
ALERT CONDITION 2 (Test EMM system)	✓	✓	✓	✓	✓

DDI = drug-drug interaction

Alert Condition 1 (AC1), reflected the alert configuration in the Live EMM system at the time of the study and therefore served as the 'reference' alert condition. All CDS alerts were enabled in this condition with the exception of DDI alerts. Alert Condition 2 (AC2) differed in that, in addition to the CDS alert types functional in AC1, DDI alerts were also enabled.

As depicted in **Figure 3**, data relating to patients and their medication orders were extracted from the Live EMM system (i.e. Alert Condition 1) and then replicated via manual entry into the Test EMM system in order to elicit results for Alert Condition 2.

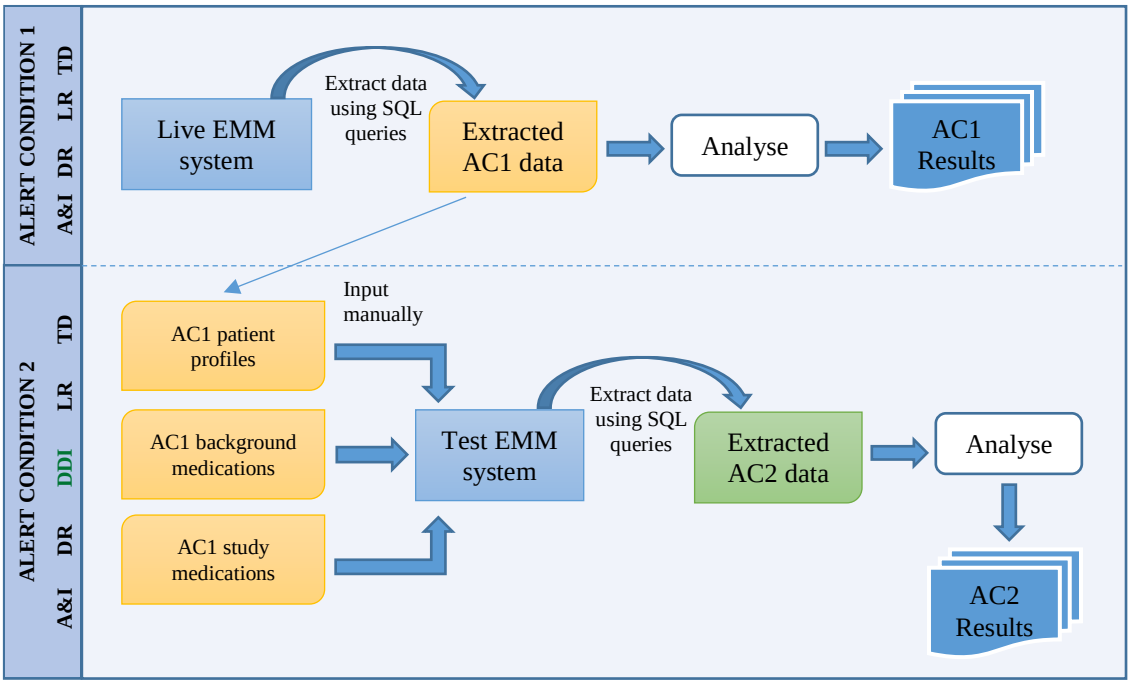

Figure 3: Process undertaken to extract clinical data in the context of the two different alert conditions.

EMM = electronic medication management; SQL = standard query language; AC1 = Alert Condition 1; AC2 = Alert Condition 2; A&I = allergy & intolerance alerts; DR = dose range alerts; DDI = drug-drug interaction alerts; LR = local restriction alerts; TD = therapeutic duplication

The following steps outline the study procedure in further detail:

Step 1: Development and validation of SQL queries and extraction software

To facilitate the extraction of clinical data from the EMM systems (Live and Test), a series of SQL (Structured Query Language) queries were initially developed. The queries were designed and constructed by a subject matter expert from the EMM system vendor, DXC Technology, and a specialist EMM Pharmacist (MRes student, AS). Two suites of SQL queries were designed to accommodate the two different versions of software in use (v5.3 B1 and v8.2.1 R5). Furthermore, due to the structure of the underlying databases, a stand-alone extraction application was also developed to facilitate extraction of CDS related

data specifically. The queries and extraction application underwent a number of refinement and validation cycles to ensure required data elements were captured as accurately and comprehensively as possible. Validation entailed the manual prescription of medication orders (>150) into the Test system, encompassing all possible permutations of medication orders to ensure robustness of the queries, followed by a detailed review of the extracted data. The validation process identified some minor data anomalies – please see study limitations section. The data elements captured by the queries are summarised in **Table 5.**

Table 5: Summary of data elements by type extracted by the Standard Query Language (SQL) queries & clinical decision support application

Type	Data elements
Patient data	Patient identifiers, admission date, allergy & intolerances, admitting doctor (staff specialist) and team
Prescriber data	Prescriber name and role
Medication order data	Medication order identifier, Medication order name, substance composition, medication order details (dose, form, route, frequency, duration, qualifier comment), prescribed on and commence on date/time, ceased/completed on date/time, order type (e.g. linked 'and', 'then' or variable dose), order category (e.g. inpatient or discharge), edited medication order identifier
Clinical Decision Support Data	CDS alert: alert identifier, alert window identifier, created on date/time, alert type Prescriber: permissible prescriber action, prescriber action taken (e.g. override, continue), prescriber comment DDI alerts: severity, documentation, prescribed class/ingredient, interacting class/ingredient, alert text, recommended action Allergy/intolerance alerts: class, substance or brand to which allergy/intolerance recorded against, prescribed substance Class duplication alerts: duplicated class, prescribed substance, interacting substance Substance duplication alerts: medication name and substance Dose range alerts: substance, dose range parameter Local restriction rules: rule name, message, trigger (index)

Step 2: Data extraction from Live EMM system

On the chosen study date (19 June 2018), all electronic medication orders prescribed by doctors for patients at SVHS were extracted from the Live EMM system using the customised SQL queries and CDS extraction application. Only patients that had a status of 'admitted inpatient' on the study date were included. The relevant patient, prescriber, medication order and CDS alert related data for each patient's entire admission, up until the study date were extracted. Prior to analysis of the data, all records pertaining to non-medical prescribers, as well as CDS alerts targeting nurses, pharmacists and dietitians were excluded. The study date was chosen as it was midweek, thereby avoiding the surge of activity that occurs after a weekend, and it fell midway through both junior and senior doctors' rotation cycles, minimising unfamiliarity with the EMM system e.g. if a doctor had just rotated to SVHS and was not familiar with the EMM system.

Step 3: Data entry into Test EMM system

The patient and medication order data extracted from the Live EMM system were manually entered into the Test environment through the following process. Electronic patient profiles with the same identifiers, demographics and allergies/intolerances were manually re-created in the Test environment. Similarly, medication orders were replicated by manually prescribing them to the respective test patients using the Test EMM system's user interface. This prescribing process was completed in two steps. Firstly, medication orders that were active on the patient's chart, but had been prescribed *before* the study date (herein known as 'background medications') were first entered for each patient. Medication orders that had ceased the day before the study date were also included in this group as they were still capable of triggering a CDS alert.

Following this, medication orders that were prescribed on the study date (herein known as 'study date medications') were then manually entered. Importantly, these were re-prescribed in the same chronological order as the original prescribing sequence to ensure alerts triggered accurately. The discrete entry of background medications and study medications allowed for isolation of the CDS alert data generated specifically by the prescription of the 'study date medications'.

Step 4: Data extraction from Test EMM system

Relevant clinical data were extracted from the Test EMM system using the SQL queries and CDS application (i.e. extracted AC2 data). Due to the large volume of data that required manual entry, a validation process was applied to ensure the study date medications from the Live system had been accurately replicated in the Test system. This validation entailed a detailed comparison of the corresponding medication orders in the AC1 and AC2 data extracts using an Excel® VLOOKUP function. Any differences in medication orders between the two data extracts related only to on-screen formatting changes between the two versions of software e.g. the presence of brackets around the medication strength in one version and not the other. These differences were cosmetic in nature and did not impact the integrity of the results.

Step 5: Test environment maintenance

Medication orders prescribed into the Test EMM system over the course of the study automatically produced a pharmacy review flag as well as an administration event for doses that were due to be given. Where possible, administration events were disabled to minimise the accumulation of overdue medication doses however, to keep the Test environment functional, it was necessary to manually clear pharmacy reviews and administer overdue medication doses on a regular basis.

2.4 Statistical analysis

Descriptive analyses were performed using Microsoft Excel® (Microsoft Corporation, 2013). Comparative statistics were calculated using the SAS system for Windows (version 9.4). Rates were assumed to follow a Poisson distribution. Comparison of rates between alert conditions was then performed with Poisson regression where a categorical variable indicating the different alert conditions was the only covariate. Differences were estimated as a rate ratio where Alert Condition 1 was treated as the reference. Proportions were compared with a similar model structure but using logistic regression to generate odds ratios.

2.5 Approval and funding

This study has received approval from the SVHS Human Research Ethics Committee (HREC Reference Number: LNR/15/SVH/415) and was supported by a St Vincent's Clinic Research Grant. With the exception of developing the SQL queries and CDS application, DXC Technology did not have input in study design, study conduct, data analysis or reporting of results.

3. RESULTS

3.1 Patient and medication orders

Data extracted from the Live EMM system revealed there were 254 admitted inpatients present on the study date with a total of 3304 active medication orders. Of these, 2728 constituted background medications (i.e. current orders prescribed before the study date) and 576 study date medications. The study date medications were prescribed to a subset of 133 patients, resulting in a mean value of 4.3 (range: 1-21) study date medication orders per patient.

3.2 CDS alert profile

3.2.1 Overall alert volume

The addition of DDI alerts under Alert Condition 2 saw a five-fold increase in the number of alerts generated by the study medications (n=1063), when compared to Alert Condition 1 (n=209) as shown in **Table 6**. Under Alert Condition 2, an additional 203 medication orders triggered at least one alert. This constituted a significant increase in the proportion of total medication orders that triggered at least one alert, from 25.2% to 60.4% of all orders (p<0.0001). The mean alert rate (alerts per alerted medication order) also more than doubled from 144 alerts/100 medication orders in Alert Condition 1 to 310 alerts/100 medication orders in Alert Condition 2 (p<0.0001).

Table 6: Change in numbers and rates of CDS alerts from AC1to AC2. (n=133 patients who received 576 medication orders on the study date in AC1 and AC2)

	AC1	**AC2**	**Change**
Total no. study date medication orders	**576**	**576**	N/A
Total alerts triggered	**209**	**1063**[1]	**+508.6%** 95% CI: 438.5, 589.9%
No. of medication orders which triggered at least one alert (% of all orders)	**145 (25.2%)** 95% CI: 21.8, 28.9%	**348 (60.4%)** 95% CI: 56.4, 64.3%	**+240%*** 95% CI: 197.7, 291.3%
Mean no. of alerts per alerted medication order (range)	**1.4 (0-4)** 95% CI: 1.3, 1.7	**3.1 (0-11)** 95% CI: 2.9, 3.2	**+211.8%*** 95% CI: 182.7-246%

* p<0.0001; Change = the additional alert burden as a result of adding DDI alerts

AC1 = Alert Condition 1; AC2 = Alert Condition 2; 95% CI = 95% Confidence Interval

[1] Three alerts present in AC1 were not able to be extracted in AC2 due to technical reasons. Expected total alerts for AC2 were n=1066, however extracted total was n=1063. Results are reported on extracted data.

3.2.2 Alert volume by CDS alert type

In Alert Condition 1, therapeutic duplication alerts were the most frequently occurring CDS alert type, followed by local restriction alerts, allergy/intolerance alerts, and then dose range alerts (see **Figure 4**). The alert composition changed markedly in Alert Condition 2 where DDI alerts accounted for the vast majority of alerts.

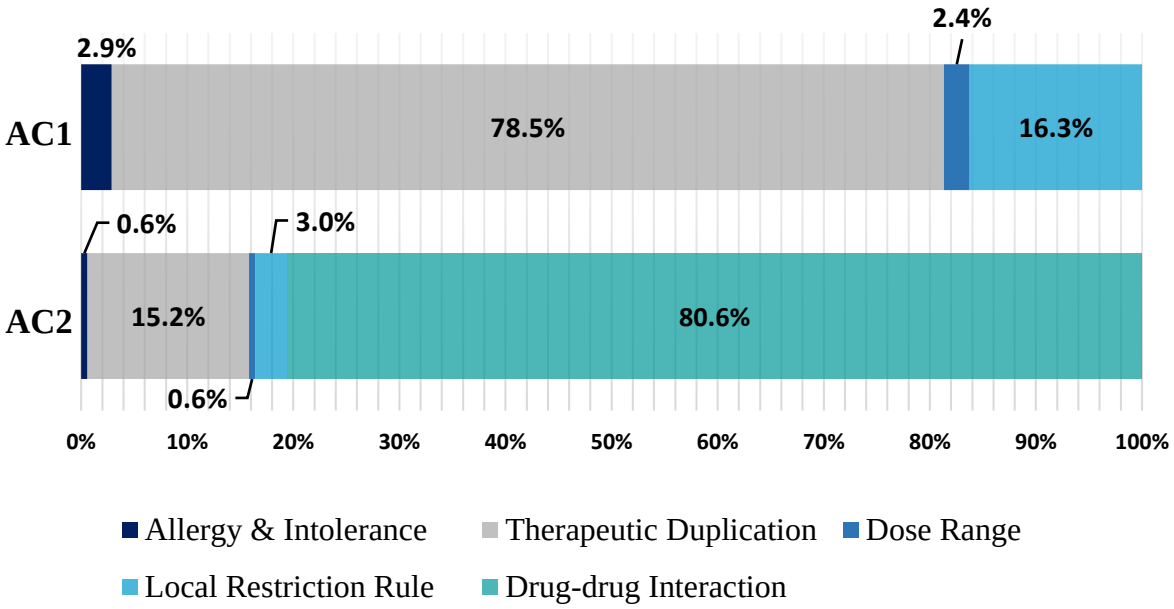

Figure 4: Change in distribution of clinical decision support alerts by type from Alert Condition 1 to Alert Condition 2.
AC1 = Alert Condition 1; AC2 = Alert Condition 2

3.3 Prescriber alert burden

A total of 576 medication orders were prescribed on the study day by 78 unique doctors, resulting in a mean of 7.4 medication orders (range: 1-28) prescribed per doctor.

3.3.1 Alerts by prescriber

Not all doctors received an alert. In Alert Condition 1, 55 doctors (70.5%) encountered at least one alert. However, under Alert Condition 2, almost all doctors (n=71; 91.0%) received one or more alerts whilst prescribing (p=0.002).

Each doctor encountered on average 3.8 alerts (range: 1-13) under Alert Condition 1. This rate increased to 15 alerts per alerted doctor (range: 1-85) with the addition of DDI alerts in Alert Condition 2 (Rate Ratio 3.9, 95% CI 3.4, 4.6, p<0.0001).

In examining the proportion of medication orders that triggered an alert for each individual prescriber (i.e. alerted medication orders / total medication orders), it was observed that in Alert Condition 1, 38.3% of a prescriber's medication orders triggered an alert, whilst in Alert Condition 2 this alert burden almost doubled to 72%.

3.3.2 CDS alert window content

The mean number of alerts encountered by prescribers in an alert window (see example in Methods **Figure 2**) was 1.4 (range: 1-8) and 2.2 (range: 1-9) alerts per window in Alert Condition 1 and Alert Condition 2 respectively. A difference was observed in the proportion of alert windows that contained more than one alert across alert conditions (**Figure 5**). In Alert Condition 1, there were equal numbers of alerts that triggered alone and alerts that triggered in combination with other alerts. In Alert Condition 2 however, there were considerably more alerts that were presented to prescribers together with at least one other alert (78.0%).

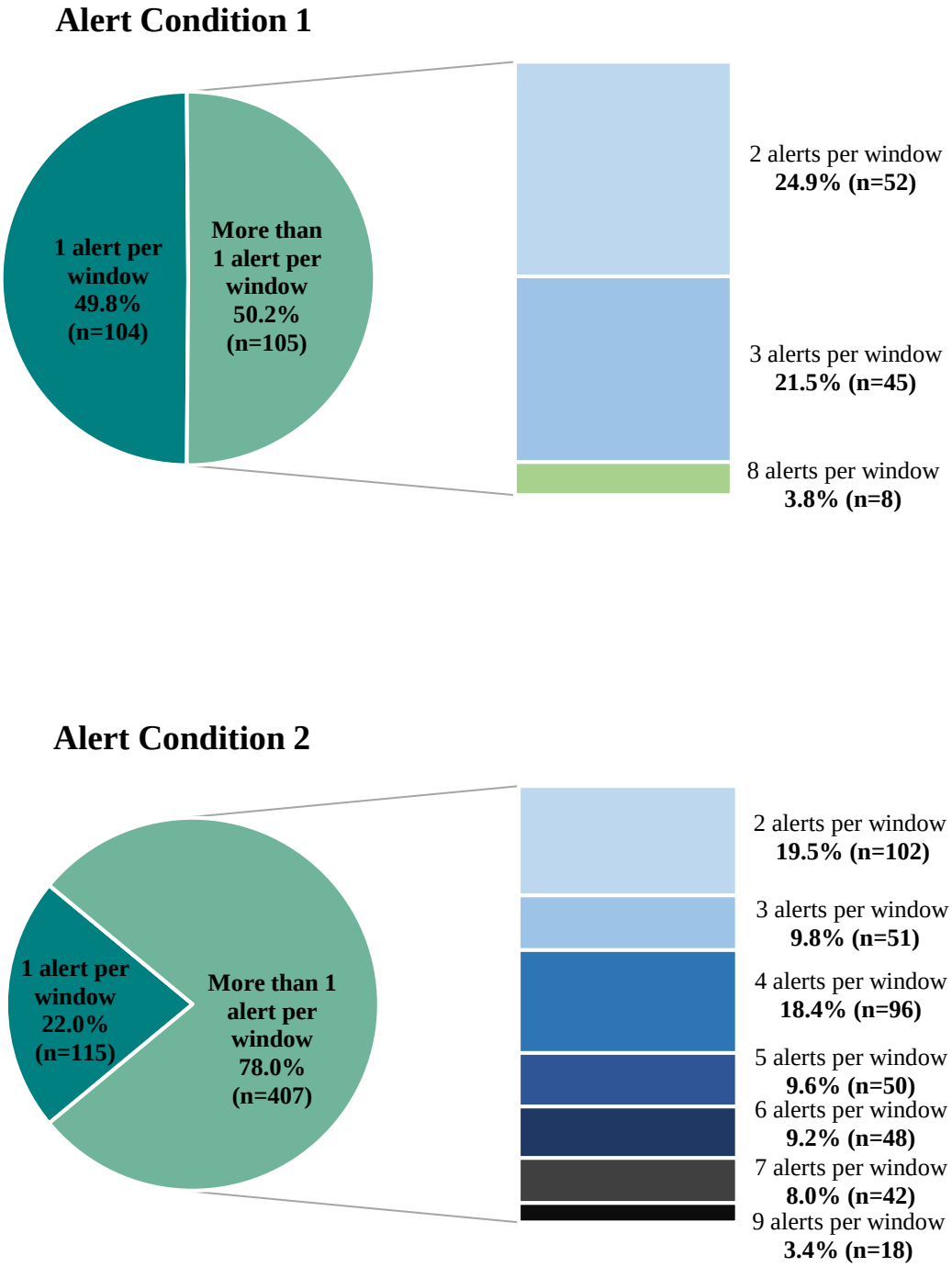

Figure 5: Proportion of alerts in Alert Condition 1 and 2 that were presented to prescribers alone or in combination with at least one other alert.

Note – 'Unknown DDI alerts' (n=541) were excluded from this analysis due to database constraints.

3.3.3 Response to alerts by prescribers

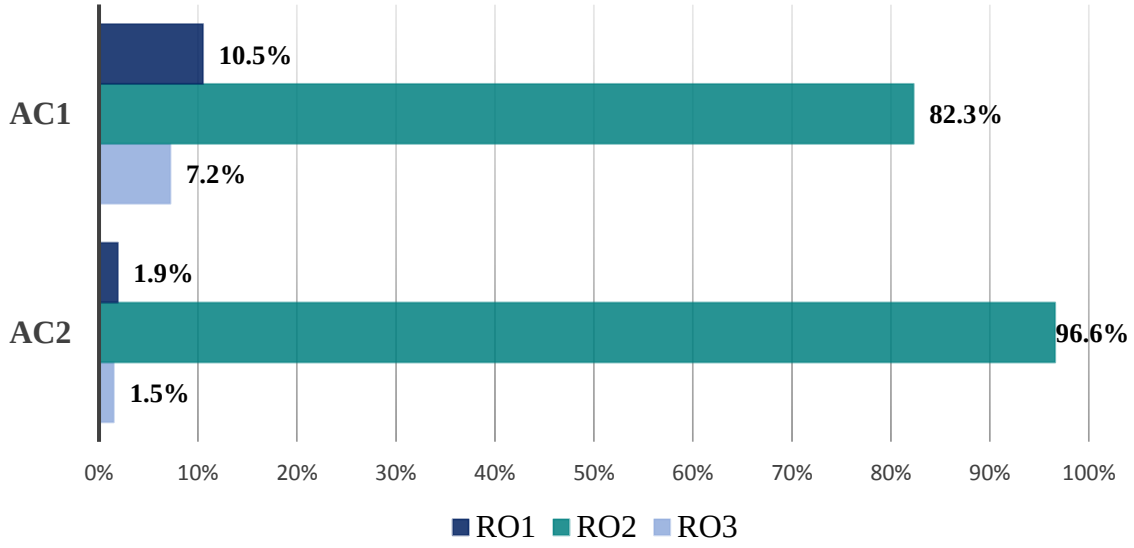

Figure 6: Distribution of alerts in Alert Condition 1 and 2 according to prescriber response option.

AC1 = Alert Condition 1; AC2 = Alert Condition 2;
RO1 = Alert is for information only, and does not require an override;
RO2 = Alert can be overridden (without providing a reason);
RO3 = Alert can be overridden if a reason is provided;

Whilst all CDS alerts were interruptive in that they disrupted the user's workflow to invoke the CDS alert screen, the prescriber's response required to process the alert varied depending on the type of CDS alert (See Methods **Table 2**).

In Alert Condition 1, most alerts (82.3%) allowed the prescriber to override the alert without the need for an override reason (RO2) – see **Figure 6**. The addition of DDI alerts did not change this as DDI alerts can be overriden without a reason required. The addition of DDI alerts in Alert Condition 2 did however result in prescribers having five times more alerts (n=1063) to process and respond to in comparison to Alert Conditon 1 (n=209).

3.4. DDI alert profile

3.4.1. DDI alerts by severity rating

Table 7: Distribution of DDI alerts with regard to severity classification.

Drug-drug interaction severity rating	No. of Alerts	% of Total
Known DDI alerts	**316**	**36.9%**
Moderate	245	28.6%
Severe	71	8.3%
Unknown DDI alerts No interaction information available on drug pair	**541**	**63.1%**
Total	**857**	**100%**

DDI = drug-drug interaction

Approximately one third of DDI alerts were of moderate severity and 8% were severe. Approximately two thirds (63.1%; n= 541) of the DDI alerts fired to warn the prescriber that no information was available regarding the drug pair in the knowledge base (**Table 7**).

Thus 'unknown DDI alerts' represented half (51.0%; n=541) of all CDS alerts triggered in Alert Condition 2. An example of an 'unknown DDI alert' is shown in **Figure 7**. The 'unknown DDI alerts' were not logged in the database in the same way as the other CDS alerts and therefore information such as the drug pair that triggered the alert was missing.

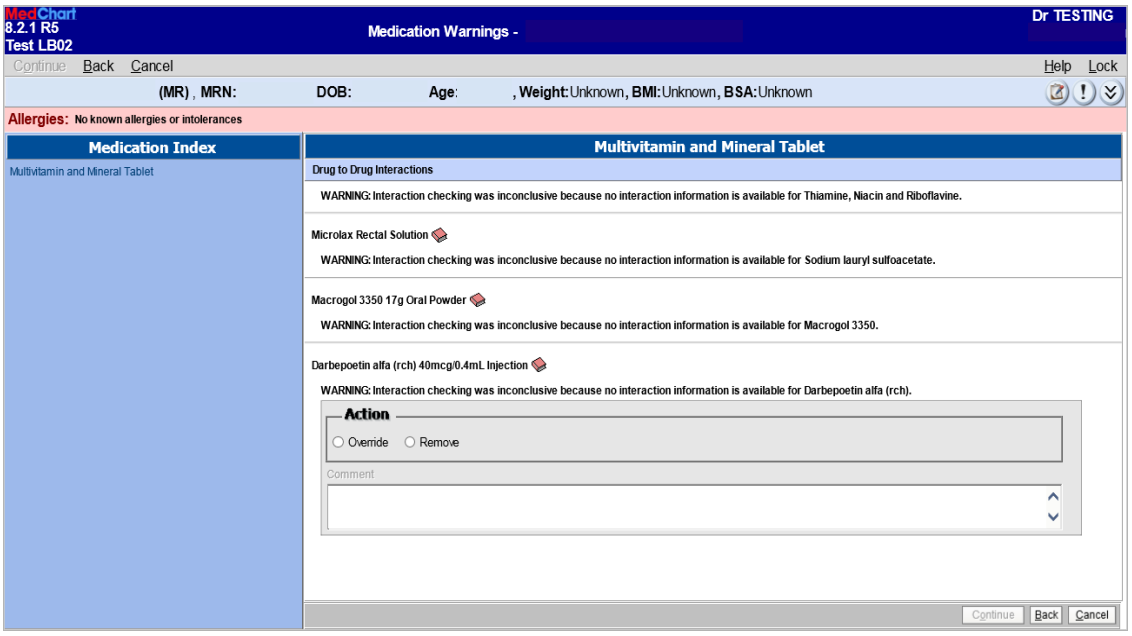

Figure 7: An example of a CDS alert window where four 'unknown DDI alerts' have triggered as a result of a medication order for multivitamin and mineral tablets.

3.4.2 Composition of DDI alert pairs

Of the total known DDI alerts that were triggered (n=316; see **Table 7**) in Alert Condition 2, 142 unique DDI drug pairs were observed. Most DDI alert pairs triggered only once (n=83) or twice (n=33) on the study date. The DDI alerts that triggered most often are shown in **Table 8**. These top five DDI alert pairs represented just over a quarter (26.9%) of all the DDI alerts triggered. All but one of the five pairs included the 'opioid agonist' class as a precipitant. A complete list of the DDI alert pairs and the frequency at which they occurred is available in **Appendix A**.

Table 8: The top five most frequently alerted DDI pairs with details of alert count and severity rating.

DDI alert pair	No. of times DDI alert pair triggered	Severity
Opioid agonists + Benzodiazepines	40	Moderate
Opioid agonists + Opioid antagonists	17	Severe
Opioid agonists + Various general anaesthetics	10	Moderate
Opioid agonists + Pregabalin	9	Moderate
Benzodiazepines + Antipsychotics	9	Severe

DDI = drug-drug interaction

Note – 'unknown DDI alerts' were excluded from analysis as the drug pairs were not identifiable.

4. DISCUSSION

This study aimed to determine the impact of the addition of DDI alerts on prescriber alert burden within an EMM system. With DDI alerts in place, prescriber alert burden increased from 38% to 72% of a prescriber's medication orders triggering at least one alert. Over 60% of the additional alert volume was due to 'unknown DDI alerts'. Overall, the addition of DDI alerts led to a five-fold increase in total alert volume, resulting in more prescribers receiving alerts and at significantly higher rates. With DDI alerts in place, alerts were encountered by almost all doctors (91%), and each doctor received approximately four times more alerts (15 alerts vs 3.8 alerts per doctor). More medication orders generated alerts (25% vs 60%) and each medication order triggered twice as many alerts. With DDI alerts enabled, a higher proportion of alerts were also presented together within the same alert window.

DDI alerts significantly increased prescriber alert burden

For an individual prescriber, the introduction of DDI alerts had a substantial impact on the number of alerts encountered while prescribing. As an example, one of the prescribers in the sample prescribed 28 medication orders on the study day, of which 20 would have produced at least one alert if DDI alerts were enabled. Each of these medication orders would generate on average three alerts, resulting in the prescriber encountering approximately 60 alerts over the course of the day. Prior to the addition of DDI alerts, the same prescriber would have encountered only 15 alerts. Whilst it is not known what volume of alerts need to be experienced for alert fatigue to set in,[36] encountering alert rates of this magnitude is likely to cause alert fatigue and likely to result in prescribers disengaging from all CDS alerts.

Comparison of the current study's results with those reported in the literature was challenging as few studies reported outcome measures directly related to prescriber alert burden (see Introduction **Box 1**). Override rates are often used as a surrogate marker of alert fatigue or alert effectiveness,[28, 36, 106] but no studies were identified that reported rate of alerts encountered per prescriber or the proportion of a prescriber's medication orders that generated alerts. Future work should focus on prescriber-related outcome measures of alert burden, including a focus on cumulative alert burden, as has been done here in the current study. This is particularly important as alert burden is likely to increase with the development and inclusion of more advanced CDS functionality such as drug-lab, drug-condition and drug-gene interactions.[13, 23] It is also important to consider the growing number of non-

medication-related alerts generated from Electronic Medical Records (EMRs), for example alerts that notify prescribers of an abnormal pathology result. EMM systems are rarely implemented in isolation of EMRs, and thus it is critical to consider the cumulated alert exposure for prescribers from both these systems. No studies that have investigated this aggregated alert burden could be identified.

A more common approach used to quantify alerts is to report the proportion of total medication orders (not specific to a prescriber) which triggered at least one alert. In this study, prior to DDI alert addition, approximately a quarter of orders triggered at least one CDS alert. This is consistent with a previous study undertaken at the study site (manual chart review), which reported a proportion of 27.2% of medication orders with an alert.[105] However, with the addition of DDI alerts, the proportion of alerted medication orders rose significantly to approximately 60%. This rate is considerably higher than rates reported in other studies (13.1% - 37.1%, studies of inpatients);[106-110] (6.6% - 15.5%, studies of outpatients).[111, 112]

There are several potential reasons for the comparatively higher proportion of alerted medication orders seen at the study site. Firstly, enabling the 'unknown DDI alerts' within the alert configuration settings substantially inflated the alert volume and in turn the alert burden to prescribers. To our knowledge, it does not seem to be common practice for EMM systems to alert prescribers about the absence of information or evidence of a DDI. Although not available in the database logs for formal review, it was noted during data entry that many of the 'unknown DDI alerts' were triggered by relatively low risk substances such as thiamine supplements, macrogol laxatives and multivitamin tablets.[113] It has been suggested that alerts with low levels of clinical significance be either suppressed, or made non-interruptive to reduce the probability of alert fatigue.[24, 28, 114] In keeping with these recommendations and common practice at other healthcare organisations, it is suggested that 'unknown DDI alerts' not be enabled as part of the DDI alert set. For the current study, if 'unknown DDI alerts' were to be excluded from the alert set, the proportion of alerted medication orders would reduce to ~40%, which is more in line with, however still higher, than previous reports.

Secondly, the alerts generated in the EMM system are currently informed only by the medication order and the content of the knowledgebase. The alert burden could be reduced

if alerts were made context-aware.[91] Contextual factors may include those relating to the patient (e.g. age, gender, renal function, genotype), drug (dose, route of administration), prescriber (speciality, professional experience) and organisation (patient acuity and epidemiological characteristics).[115, 116] For example, the severity of the interaction between simvastatin and verapamil is reduced if the prescribed dose of simvastatin in less than 20mg. The dose of the prescribed drug can therefore be used as a context or modulating factor to determine if this DDI alert is triggered, and if so, at what severity rating. Seidling et al. (2009) reported a 55% reduction in the number of statin-drug interactions if the dose of the HMG-CoA reductase inhibitor (statin) is considered in the alert algorithm.[78] A reduction in alert burden using context-aware alerting models, particularly for DDI alerts, has been reported by a growing number of research groups,[77, 79, 82, 83, 116, 117] although there have been few implementations in practice. The adoption of this approach is constrained by limited interoperability between EMM systems and clinical repositories, and by the lack of advanced CDS algorithms within drug knowledgebases.[38, 50, 52, 118] This nonetheless represents a promising strategy to improve alert specificity and therefore reduce alert burden. Further development by EMM system and knowledgebase vendors at the study site could facilitate implementation of this strategy.

Another factor contributing to the increased alert volume is that the databases informing CDS alert generation at the study site, like many other commercial databases, are overly inclusive and therefore predisposed to excess alert generation.[52] Strategies to reduce associated alert burden have been put forth in the literature (see Introduction **Table 1**) and could be applicable to the study site. One such approach is 'tiering' or changing the presentation format of alerts in accordance with their clinical severity. For example, making high severity alerts interruptive, whilst those deemed less critical non-interruptive,[24, 90, 114, 119] an approach supported by a US-based expert working group who recently published one of the first comprehensive set of recommendations to improve DDI decision support.[63] Again, further development of the CDS functionality and underlying knowledgebases by respective vendors is needed to facilitate this strategy locally. In making recommendations to the vendors, reference should be made to the recent guidelines released by the American Society of Hospital Pharmacists which suggest a set of core capabilities that should be made available by vendors to reduce alert burden.[37]

Another possible explanation for the high alert burden encountered at the study site is the relative complexity and acuity of patients presenting to the hospital, as it is a tertiary referral centre. It is also one of very few organisations in Australia which conducts heart, lung and bone marrow transplantation. Transplant patients are prescribed many medications, often including those that are highly prone to drug interactions (e.g. antifungals and immunosuppressants).[120] This patient complexity may also explain why in this sample, senior doctors encountered a higher proportion of medication orders that triggered alerts than their junior counterparts. It is hypothesised that senior doctors prescribe for and manage the more complex patients and hence encounter relatively more alerts.

An alternative way to conceptualise the alert burden imposed on prescribers, is to consider the actions required or work generated as a consequence of alert presentation. That is, the level of response required by the user in order to manage the alert (e.g. to override the alert, or cancel the order). In this study, the number of alerts that required a response by the prescriber increased five-fold with the addition of DDI alerts. Previous work has focused on level of interruptiveness of alerts (i.e. do they require users to stop work)[24] but the notion of extra work resulting from alert generation is important to consider and is likely to be a major contributor to prescriber burden.

Although not the focus of this study, alert burden could be reduced by undertaking a comprehensive content review of the knowledgebases that currently inform the various types of CDS alerts. This is because prescribers could receive the same information presented across different alert types. For example, both a DDI alert and a therapeutic duplication alert would be triggered for the concomitant prescription of clopidogrel and aspirin. Ideally, content overlap between the knowledgebases should be minimised in order to reduce presentation of duplicated alerts however it is acknowledged that this is complex and requires software vendor collaboration.

Distribution of CDS alert types changed markedly with DDI alerts

The addition of DDI alerts markedly changed the distribution of CDS alerts. There were approximately five times as many DDI alerts (~80% of total alert volume) as there were therapeutic duplication alerts (~15% of total alert volume), whereas prior to the addition of DDI alerts, therapeutic duplications constituted the majority of alert types (~80% of total alert volume). The innovative approach taken in this study in considering the alert burden

arising from all CDS alert types led to the finding that DDI alerts were the major contributor to the overall alert burden and thus strategies to reduce DDI alert volume would have the most impact on overall alert volume. When comparing results of this study to published literature, it was noted that there was high heterogeneity in alert distribution across studies, with the proportion of alerts comprising DDI alerts ranging from 0.6% to 98.3%.[86, 108, 110, 112, 121] This reflects the variable implementation of CDS across organisations and emphasises the importance of conducting site-specific investigations. This notion is re-iterated by a number of recent studies that report that even when the same EMM system is used at a different site, the resulting CDS generated can be vastly different.[122-124]

Types of DDI alerts triggered

The five most frequently triggered DDI alerts constituted approximately a quarter of all DDI alerts triggered. Of these, one DDI alert pair which triggered 17 times, involved an interaction between the opioid agonist and opioid antagonist classes, more specifically, oxycodone, morphine or fentanyl (opioid agonists) and the oral combination product Targin®, which contains oxycodone and the opioid antagonist naloxone. When naloxone is administered orally, it does not produce clinically relevant systemic effects,[125] therefore this alert unnecessarily contributed to the alert burden and is a prime example of one which could be modulated by contextual factors, in this case the route of administration of the drug.[116] It is interesting to note that none of the top five alerting DDI pairs in this study featured on the set of high priority drug interactions developed as an initiative of the United States Office of the National Coordinator for Health Information Technology.[60] This suggests that further work is needed to ensure DDI alerts being triggered are those which are relevant and potentially the most serious.

The bulk of work on DDI alerts has been undertaken overseas.[13, 28, 60, 89] The results from this study offer one of the first insights into the incidence of the types of DDI alerts in an Australian hospital and can be used as a starting point to identify a standardised list of critical drug interactions within an Australian context.

Alerts per window increased with DDI alerts

Although not the main focus of the study, an interesting finding that emerged was that as a by-product of DDI alert implementation, more alerts were presented to prescribers within the same alert window. The majority of alerts (78%) appeared in combination with at least

one other alert. Some prescribers encountered up to nine alerts within the same alert window. The presence of multiple alerts within one alert window was identified to be a key barrier to prescriber workflow in an observational/interview study of American doctors.[126] Interview respondents commented on the challenging screen display associated with multiple alerts, with one prescriber stating he/she simply did not read through all alerts if there was more than one presented in the window. Potential safety implications of displaying multiple alerts in one alert window were noted by two further studies. A disguised observation study assessing the type of errors made during handling of alerts found that when a second alert was presented in the same alert screen, prescribers overlooked it and inadvertently overrode the alert.[127] Russ et al (2015) noted that if the user was required to use a scrolling mechanism to view alerts beyond the visual field, this could also lead to prescribers inadvertently missing relevant CDS alerts.[128] Further usability studies are required to assess unintended consequences of displaying multiple alerts within the same window, however, based on these findings, the number of alerts per window should be minimised and the use of scrolling mechanisms within the alert window avoided, in order to ensure all alerts are seen and read.

Strengths, limitations and challenges

This study was unique in that it considered the cumulative impact of enabling a specific type of CDS alert, in this case DDI alerts, on total alert burden. This approach can facilitate the judicious planning and implementation of future CDS alerts, specifically more advanced CDS alert functions. It also examined prescriber-focused outcome measures, which allowed us to quantify the burden to individual users. Another strength is the simulation methodology. The magnitude of impact of the 'unknown DDI alerts' would not have been revealed unless a study of this nature was conducted.

This investigation had several limitations. It focused only on alerts generated secondary to medication orders prescribed for hospitalised patients over the course of a single day, using a single commercial EMM system at only one hospital site. Therefore, with other patient types, acuities or care settings the results may vary. Moreover, the use of a different EMM system or knowledge base may also have altered the results. Alert generation is a function of prescribing activity and thus results may vary day to day. The single day cross sectional study design was limited in that the patient's day of admission was not controlled for. It is expected most DDI alerts would be generated on the patient's first day of admission i.e. when existing medications are first prescribed, and thus results may vary depending on the

patient's stage of admission at time of sampling. Other factors that can influence alert burden such as alert design and utility were not comprehensively investigated in this study. Finally, the study did not examine changes in prescribing decisions or potential patient safety benefits (i.e. reduction in ADEs) that may have transpired with inclusion of the DDI alerts. It is however relevant to note that the large majority of the DDI alerts (i.e. 'unknown DDI alerts') afforded no additional information to prescribers, and thus are unlikely to alter prescribing decisions.

The highly manual and laborious nature of the patient profile setup and medication order entry hampered scalability, limiting the sample to medication orders prescribed over the course of one day. Furthermore, manually clearing the overdue medication administration events to ensure the Test environment remained functional also required considerable time and effort. This work brings to the forefront many issues and challenges faced by organisations looking to effectively analyse CDS data. Development of an automated simulation environment, predictive alert models, advanced reporting and live dashboards by the vendor can alleviate these issues and facilitate further research.[103, 129]

Additional challenges that were encountered related to the EMM system's database structure. It was not possible to quantify alerts that resulted in a medication order being cancelled as these are logged elsewhere in the database and are not linked to a medication order. This also precluded the accurate reporting of override rates and thus these were excluded from the outcome measures. Pertinent data regarding the 'unknown DDI alerts' were not logged in the database and hence could not be included in the analyses. A small number of data anomalies were also encountered during the SQL query validation phase however these could not be replicated.

Recommendations

Further steps are recommended to refine the DDI alerts prior to their implementation at the study site in order to minimise alert burden and associated alert fatigue. Exclusion of the 'unknown DDI alerts' from the alert set is recommended as a first step, and then review of the moderate and severe DDI alerts to assess their clinical significance and appropriateness.[91] Clinical content review of the drug knowledgebases could help to identify opportunities to refine the alert algorithms and incorporate contextual factors to increase alert specificity and reduce alert burden. From an EMM system vendor perspective, CDS alert design should be

improved to meet the recommendations put forward in the literature,[28] enhancements should be made to reporting and analytical tools, and steps be taken to improve interoperability and facilitation of data exchange.

5. CONCLUSION

DDI alerts, if enabled, would significantly increase the alert burden on prescribers and is likely to lead to alert fatigue. To reduce their impact on prescriber alert burden and improve alert effectiveness, DDI alerts should be refined prior to their implementation, in particular the 'unknown DDI alerts' should be removed from the alert set and clinical relevance of the remaining alerts should be assessed further. Looking ahead, the formation of a centralised body to develop and curate evidence-based clinical decision support content and drug knowledgebases for an Australian context would ensure that there is standardisation across healthcare organisations. Importantly, future work should specifically consider prescriber related outcomes for alert burden and the cumulative alert burden experienced by clinicians as they navigate through the increasing number of e-health applications currently in use, and those that will be deployed in the future.

6. APPENDIX

Appendix A: Description of DDI drug pairs and number of times each pair triggered an alert on the study date.

DDI drug pair	No. of times DDI drug pair triggered an alert
Opioid agonists and Benzodiazepines	40
Opioid agonists and Opioid antagonists	17
Opioid agonists and Various general anaesthetics	10
Opioid agonists and Pregabalin	9
Antipsychotics and Benzodiazepines	9
Potassium (all salts) and Low molecular weight heparins	7
Loop diuretics and Beta2-receptor sympathomimetics	6
Potassium (all salts) and Heparin	6
Oxycodone and Selective serotonin reuptake inhibitors	5
Heparin and Cephalosporins with N-methylthiotetrazole or a similar side chain	5
Oral Hypoglycaemic Agents and Glucocorticoids (topical)	5
Benzodiazepines and Imidazole and triazole derived antifungals	4
Loop diuretics and Proton pump inhibitors	4
Antipsychotics and Anticholinergics	3
Imidazole and triazole derived antifungals and Glucocorticoids (systemic)	3
Opioid agonists and Levomepromazine	3
Opioid agonists and Phenothiazine agents	3
Proton pump inhibitors and Posaconazole	3
Amiodarone and Thyroid hormone	3
Ciclosporin and HMG-CoA reductase inhibitors	3
Fentanyl and Imidazole and triazole derived antifungals	3
Glucocorticoids (systemic) and Tacrolimus (systemic)	3
Mycophenolic acid (all salts) and Tacrolimus (systemic)	3
Ondansetron (all salts) and Methadone	3
Ondansetron (all salts) and Mirtazapine	3
Tricyclic antidepressants and related agents and Opioid agonists	3
Antipsychotics (QT prolonging) and Ondansetron (all salts)	2
Antipsychotics and Phenothiazine agents	2
Benzodiazepines and Phenytoin and related compounds	2
Ciclosporin and Glucocorticoids (systemic)	2
Ciclosporin and Imidazole and triazole derived antifungals	2
Clonidine and Beta-blockers	2

DDI drug pair	No. of times DDI drug pair triggered an alert
Fentanyl and Phenytoin and related compounds	2
Furosemide and Salicylates (systemic)	2
Loop diuretics and Amiodarone	2
Loop diuretics and Haloperidol	2
Metoclopramide and Ondansetron (all salts)	2
Nephrotoxic Glycopeptide Antibiotics and Aminoglycosides	2
Nondepolarising Neuromuscular Blocking Agents and Glucocorticoids (systemic)	2
Opioid agonists and Buprenorphine	2
Oral anticoagulants (vitamin K antagonists) and Amiodarone	2
Oral anticoagulants (vitamin K antagonists) and Salicylates (systemic)	2
Oral anticoagulants (vitamin K antagonists) and Thyroid hormone	2
Pregabalin and Benzodiazepines	2
Sulfonylureas and Phenothiazine agents	2
Tricyclic antidepressants and related agents and Sulfamethoxazole	2
Tricyclic antidepressants and related agents and Trimethoprim	2
Urinary alkalinisers and Salicylates (systemic)	2
Aciclovir and related antiviral agents and Mycophenolic acid (all salts)	2
Aciclovir and related antiviral agents and Tacrolimus (systemic)	2
Angiotensin converting enzyme (ACE) inhibitors and Ciclosporin	2
Angiotensin converting enzyme (ACE) inhibitors and Salicylates (systemic)	2
Angiotensin converting enzyme (ACE) inhibitors and Trimethoprim	2
Benzodiazepines and Omeprazole	2
Benzodiazepines and Tricyclic antidepressants and related agents	2
Calcium-channel blockers - dihydropyridine type and Imidazole and triazole derived antifungals	2
Imidazole and triazole derived antifungals and Tacrolimus (systemic)	2
Magnesium (antacid) and Mycophenolic acid (all salts)	2
Mycophenolic acid (all salts) and Proton pump inhibitors	2
5HT3-receptor antagonists and Selective serotonin reuptake inhibitors	1
Alpha-blockers and Calcium-channel blockers	1
Aminoglycosides (systemic) and Piperacillin	1
Aminoglycosides and Aciclovir and related antiviral agents	1
Aminoglycosides and Loop diuretics	1
Amiodarone and Beta-blockers	1

DDI drug pair	No. of times DDI drug pair triggered an alert
Anaesthetics (inhalation) and Opioid agonists	1
Antifungal antibiotic and Glucocorticoids systemic	1
Aripiprazole and Haloperidol	1
Beta-blockers (systemic) and Sulfonylureas	1
Calcium (all salts) and Levothyroxine	1
Calcium-channel blockers and Erythromycin (all salts)	1
Ciclosporin and Aciclovir and related antiviral agents	1
Ciclosporin and Amlodipine	1
Ciclosporin and Sulfonamides	1
Ciclosporin and Trimethoprim	1
Ciclosporin and Ursodeoxycholic acid	1
Clopidogrel and Salicylates (systemic)	1
Colony stimulating factors and Cyclophosphamide and related products	1
Cyclophosphamide and related products and Allopurinol	1
Deferasirox and Aspirin	1
Deferasirox and Ciclosporin	1
Deferasirox and Glucocorticoids (systemic)	1
Digoxin and derivatives and Beta-blockers	1
Digoxin and derivatives and Tetracyclines	1
Donepezil and Beta-blockers	1
Doxorubicin and derivatives and Cyclophosphamide	1
Esomeprazole and Clopidogrel	1
Fentanyl and Diltiazem	1
Fentanyl and Selective serotonin reuptake inhibitors	1
Fluconazole and Phenytoin and related compounds	1
Fluticasone (systemic) and Cobicistat	1
Furosemide and Risperidone	1
Heparin and Nonsteroidal anti-inflammatory drugs	1
HMG-CoA reductase inhibitors metabolised by CYP3A4 and Amiodarone	1
Imidazole and triazole derived antifungals and Everolimus	1
Influenza vaccines (inactivated) and Oral anticoagulants (vitamin K antagonists)	1
Lithium (all salts) and Olanzapine	1
Lithium (all salts) and Serotonin and noradrenaline reuptake inhibitors	1
Loop diuretics and Cardiac glycosides	1

DDI drug pair	No. of times DDI drug pair triggered an alert
Loop diuretics and Glucocorticoids (systemic)	1
Loop diuretics and Methadone	1
Low molecular weight heparins and Angiotensin II antagonists	1
Low molecular weight heparins and Salicylates (systemic)	1
Magnesium (all salts) and Tetracyclines	1
Magnesium Sulfate and Calcium-channel blockers	1
Methadone and Fluoroquinolones (QT prolonging)	1
Methadone and Quetiapine	1
Metoprolol (all salts) and Venlafaxine	1
Nondepolarising Neuromuscular Blocking Agents and Magnesium Sulfate	1
Nonsteroidal anti-inflammatory drugs and Angiotensin II antagonists	1
Nonsteroidal anti-inflammatory drugs and Low molecular weight heparins	1
Nonsteroidal anti-inflammatory drugs and Tenofovir	1
Nonsteroidal anti-inflammatory drugs and Thiazide and related diuretics	1
Olanzapine and Donepezil	1
Olanzapine and Valproic acid and derivatives	1
Ondansetron (all salts) and Azithromycin	1
Oral Hypoglycaemic Agents and Glucocorticoids (systemic)	1
Paracetamol and related compounds and Flucloxacillin	1
Paracetamol and related compounds and Oral anticoagulants (vitamin K antagonists)	1
Potassium (all salts) and Angiotensin II antagonists	1
Potassium (all salts) and Cardiac glycosides	1
Potent inducers of CYP3A4 and Buprenorphine	1
Quetiapine and Amiodarone	1
Quetiapine and Citalopram and Enantiomers	1
Quinolones and Glucocorticoids (systemic)	1
Risperidone and Haloperidol	1
Rituximab and HMG-CoA reductase inhibitors	1
Rivaroxaban and Low molecular weight heparins	1
Rosuvastatin and Cobicistat	1
Salicylates (systemic) and Calcium-channel blockers	1
Salicylates (systemic) and Glucocorticoids (systemic)	1
Salicylates (systemic) and Heparin	1
Sotalol and Loop diuretics	1

DDI drug pair	No. of times DDI drug pair triggered an alert
Sotalol and Ondansetron (all salts)	1
Tacrolimus (systemic) and Diltiazem	1
Tetracyclines and Penicillins	1
Thiazide and related diuretics and Amiodarone	1
Thiazide and related diuretics and Sotalol	1
Tramadol and Ondansetron (all salts)	1
urinary alkalinisers - sodium salts and Lithium (all salts)	1
Vancomycin and Furosemide	1
Vancomycin and Piperacillin	1
VincristineColony and stimulating factors	1

DDI = drug-drug interaction

Appendix B: Ethical and scientific approval letter

St Vincent's Hospital

A facility of St Vincent's & Mater Health Sydney

St Vincent's Hospital Sydney Ltd
ABN 77 054 038 872
390 Victoria Street
Darlinghurst NSW 2010
Australia

T + 61 2 8382 1111
F + 61 2 9332 4142
www.stvincents.com.au

17 November 2015

Ms Anmol Sandhu
Pharmacy Department
St Vincent's Hospital
Darlinghurst NSW 2010

Dear Anmol,

SVH File Number: 15/273
Project Title: Enabling Drug-Drug interactions in an electronic medication management systems: Impact on prescriber alert burden
Short Title: Alert burden associated with enabling drug-drug interaction alerts
HREC Reference Number: LNR/15/SVH/415

Thank you for submitting the above project for ethical and scientific review.

Based on the information you have provided and in accordance with the NHMRC National Statement 2007 and NSW Health Policy Directive PD2010_055 'Ethical and Scientific Review of Human Research in NSW Public Health Organisations', this project has been assessed as low/negligible risk and is therefore exempt from full HREC review.

This HREC has been accredited by NSW Ministry of Health as a Lead HREC under the model for single ethical and scientific review and Certified by the NHMRC under the National model for Harmonisation of Multicentre Ethical Review (HoMER). This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. No HREC members with a conflict of interest were present for review of this project.

I am pleased to advise that the HREC Executive at a meeting on 17 November 2015 has granted ethical and scientific approval of the above **single** project.

You are reminded that this letter constitutes *ETHICAL* and *SCIENTIFIC* approval only. You must not commence this research project at a site until a completed Site Specific Assessment Form and associated documentation have been submitted to the site Research Governance Officer and Authorised. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The project is approved to be conducted at **St Vincent's Hospital (Sydney)**.

If a new site(s) is to be added please inform the HREC in writing and submit a Site Specific Assessment Form (SSA) to the Research Governance Officer at the new site.

The following documents have been approved:

- Protocol Version 1.0, dated 23 October 2015

The Low and Negligible Risk Research Form (LNRF) reviewed by the HREC was LNRF **AU/6/C012214.**

Please note the following conditions of approval:

- HREC approval is valid for **5 years** from the date of the HREC Executive Committee meeting and expires on **11 November 2020**. The Co-ordinating Investigator is required to notify the HREC 6 months prior to this date if the project is expected to extend beyond the original approval date at which time the HREC will advise of the requirements for ongoing approval of the study.
- The Co-ordinating Investigator will provide an Annual Progress Report beginning in **November 2016**, to the HREC as well as a Final Study Report at the completion of the project in the specified format.
- The Co-ordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project and any complaints made by participants regarding the conduct of the project.
- Proposed changes to the research protocol, conduct of the research, or length of approval will be provided to the HREC Executive for review, in the specified format.
- The HREC Executive will be notified, giving reasons, if the project is discontinued before the expected date of completion.
- Investigators holding an academic appointment (including conjoint appointments) and students undertaking a project as part of a University course may also be required to notify the relevant University HREC of the project. Investigators and students are advised to contact the relevant HREC to seek advice regarding their requirements.

Please note that only an electronic copy of this letter will be provided, if you require the original signed letter please contact the Research Office and we will be happy to provide this.

Should you have any queries about your project please contact the Research Office, Ph: (02) 8382-2075 or by E-mail: SVHS.Research@svha.org.au. The HREC Terms of Reference, Standard Operating Procedures, *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and standard forms are available on the Research Office web-site to be found at: https://svhs.org.au/home/research-education/research-office

Please quote **SVH File Number: 15/273** in all correspondence.

The HREC wishes you every success in your research.

Yours sincerely,

Sarah Charlton
HREC Executive Officer
St Vincent's Hospital Research Office
Level 6, de Lacy Building

TRIM REF: D/2015/63953

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