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Potential Drug-Drug Interactions in a Canadian Tertiary-Care Hospital

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Potential Drug-Drug Interactions in a Canadian Tertiary-Care Hospital

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Drug-Drug interactions (DDIs) are an important focus of patient safety because they account for a substantial number of adverse drug events and are preventable.

Objective: To study DDIs in a Canadian hospital, a retrospective observational study was completed using the Ottawa Hospital Data Warehouse.

Study Cohort: Admissions to the Ottawa hospital between January 1, 1999 and September 30, 2005

Methods: Potential drug-drug interactions were identified by examining all co-administered medications for combinations of drugs previously reported to have potential interactions. Poisson regression was used to examine potential patient and hospital factors associated with drug-drug interactions.

Results: Between 1999 and 2005, we found at least one DDI in 19.3% of all hospitalizations and 18.8 % of hospitalization time. Category 1 (drug combinations to be avoided) and Category 2 (drug combinations usually avoided) interactions were rare, accounting for only 0.022% and 1.4% of hospitalization time, respectively. Category 3 interactions (drug combinations requiring alteration) occurred with 5.7% of all drug orders and were present for 17.4 % of hospitalization time. Poisson regression analysis found that DDIs were significantly more likely to occur in patients who were: older; admitted to a surgical service; had a greater number of comorbidities; and were prescribed a greater number of drugs.

Conclusion: Drug-Drug interactions occurred frequently during hospitalization. Future study is required to determine if the interactions identified are associated with important clinical outcomes.

This work is dedicated to my family; Erika, Christian, Adam and Robert Pettigrew

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POTENTIAL DRUG-DRUG INTERACTIONS IN A CANADIAN TERTIARY-CARE HOSPITAL

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1 INTRODUCTION

Patient safety has become a major public concern since 1999 when the Institute of Medicine published its report "To Err is Human: Building a Safer Health System" (1). This report exposed the extent to which medical errors occurred along with their impact. Since then, the Canadian Adverse Events Study (2) was completed in 2004 and found for hospitalized Canadians an adverse event incidence rate of 7.5% per admission or 185,000 events per year. Seventy thousand of these events were thought to be preventable, highlighting the need for action in this area. In response to these findings, the Canadian government budgeted $50 million over 5 years for the creation of the Canadian Patient Safety Institute. One of the goals of this organization is to raise awareness with stakeholders, patients and the general public about patient safety. Many other healthcare organizations have initiated efforts in patient safety as well.

1.1 PATIENT SAFETY TERMINOLOGY

This thesis will address one specific component of patient safety – the safety of medication use in hospitals. We will use standard terminology throughout this document to define outcomes or processes relevant for measuring patient safety. **Adverse outcomes** are poor health results. **Adverse events** are adverse outcomes that are directly due to medical care rather than the natural history of disease (2) or 'bad luck'. Adverse events caused by medication are termed **adverse drug events (ADEs)**. An **error** is a failure to achieve an intended goal, due to a failure to implement the correct plan or because of failure to execute the plan correctly. An adverse drug event

due to an error is a **preventable adverse drug event.** An error related to medication use which does not cause harm but has the potential to do so is a **potential adverse drug event**. Clinical examples illustrating these terms are shown in and the relationship of the terms are summarized in **Figure 1** (3).

Textbox 1: Clinical Examples of Patient Safety Terminology

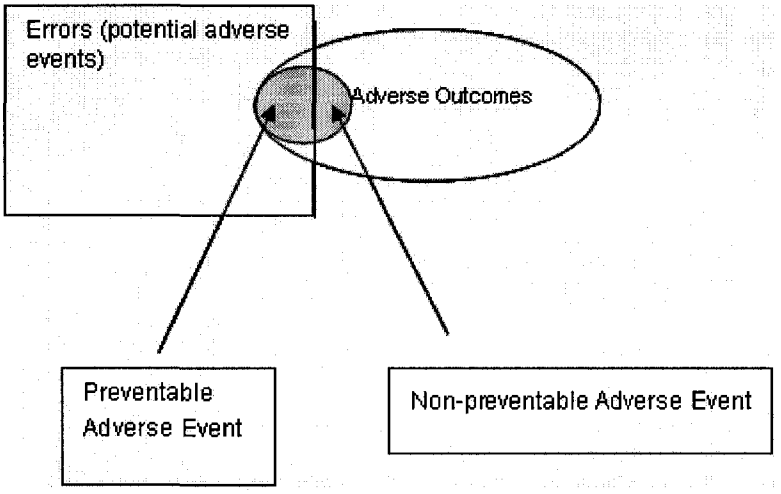
Adverse Outcome (AO): Gastrointestinal bleed in pneumonia patient due to a duodenal ulcer. In this case the bleed is caused by an underlying disease process.

Adverse Drug Event (ADE): Gastrointestinal bleed in pneumonia patient who happens to be taking warfarin for atrial fibrillation. At the time of the bleed the patient's International Normalized Ratio (INR), which measures the appropriateness of the warfarin dose is within the therapeutic range. In this case the bleed is caused by the warfarin but is not due to an error

Preventable ADE: Gastrointestinal bleed in pneumonia patient who is taking warfarin for atrial fibrillation. The physician prescribse clarithromycin for the pneumonia, which is known to potentiate warfarin effect. The INR at the time of bleeding was supra therapeutic. In this case the bleed is caused by the supra-therapeutic warfarin dose, which should have been adjusted.

Potential ADE: Warfarin and clarithromycin ordered concomitantly in a patient. There is no additional INR monitoring and it rises well above the therapeutic range. Fortuneately, the patient experiences no bleeding or other untoward event. This has the potential to cause harm but fortuneately does not. This particular event is also an example of a drug drug interaction or **DDI.**

Figure 1: The Relationship between Medical Errors, Adverse Outcomes, and Adverse Events



Adverse outcomes are poor health results. **Adverse events** are adverse outcomes that are directly due to medical care rather than the natural history of disease or bad luck. A **medical error** is care that is inappropriate for a particular patient at a particular time. An adverse event due to an error is a **preventable adverse event.** Conversely, a non-preventable adverse event is one that is not due to an error.

The shaded area in yellow represents all adverse events. This thesis will address drug-drug interactions. All adverse outcomes due to drug-drug interactions are medical errors since they are due to medical administrations that are inappropriate for the patient (i.e. are adverse events) and are preventable. Modified from Bates (1).

The term 'adverse drug reaction' requires special consideration. This is because it is a focus of pharmacovigilance programs established for post marketing surveillance and has been used in some studies evaluating medication safety. The World Health Organization defines an **adverse drug reaction (ADR)** as any response to a drug "which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis or therapy or for the modification of physiological function" (4;5). By definition, ADRs are always considered an adverse drug event.

On the other hand there are lots of preventable ADEs that would not be considered ADRs. This is because ADRs are defined as 'responses to drugs' occurring at appropriate doses. This implies, for example, that a patient receiving an excessive dose of a medication who suffers harm as a result would not be considered to have experienced an ADR. However, the event is clearly important from the individual patient's and from a quality improvements perspective.

In addition, there are many errors in medication administration (or potential ADEs), which do not cause any noxious or unintended response but are still important. For example, there are many medications that are safe if ordered alone but may lead to increased risk if ordered together (termed a potential drug-drug interaction). If the risk of adverse events is very high then it could be considered an error to order them together. A patient prescribed these medications together may not experience an adverse drug event but the risk may be high enough to warrant identifying the situation.

This thesis will use the terms ADEs, preventable ADEs and potential ADEs rather than ADRs. This is because they can represent all of the potential harmful effects of medication use. It should be noted that the terminology proposed by Bates et al, which is endorsed by the Institute of Medicine, incorporated into the WHO patient safety taxonomy conventions, and is used throughout the patient safety literature. This thesis will refer to ADRs in certain instances as they have been the principal outcome in some of the pre-existing studies on medication safety.

1.2 THE IMPORTANCE OF MEDICATION SAFETY

Errors made during the process of delivering health care are important. They have recently been recognised as a significant cause of death in both Canadian and American

hospitals. It is estimated that 24 000 Canadians die from hospital-based medical errors annually (2) and up to 98 000 Americans die from similar causes (6). In the studies used to estimate the number of deaths due to errors in medical care, the proportion of events caused by medication use was 20%-30%.

As ADEs and preventable ADEs are an important cause of all adverse events they represent an important focus of quality improvement efforts. Studies of ADEs demonstrate they are common and account for a significant number of hospitalizations and deaths each year in the United States. In 1994, an estimated 2.2 million hospitalized patients had at least one serious ADE prior to or during hospitalization. During the same year, 106,000 patients had a fatal ADE. As a result, one study estimated that ADEs are between the fourth and sixth leading cause of death in the USA (7).

Other studies confirm these data. In a landmark study Bates et al(8) studied 4031 adult, non-obstetrical admissions over 6 months and reported event rates of 6.5 ADE and 5.5 potential ADE per 100 admissions. Of all ADE, 1% were fatal, 12% life-threatening, 30% serious, and 57% significant. Twenty-eight percent were considered to be preventable. In a follow-up study in which he examined the costs of ADEs, he showed the estimated post-event costs attributable to an ADE were $2595 for all ADEs and $4685 for preventable ADEs. Based on these costs and data about the incidence of ADEs, we estimate that the annual costs attributable to all ADEs and preventable ADEs for a 1000-bed teaching hospital such as the Ottawa Hospital are $5.6 million and $2.8 million, respectively. The substantial costs of ADEs to hospitals justify investment in efforts to prevent these events(9).

1.3 DDIS: ONE CAUSE OF ADVERSE DRUG EVENTS

Drug-drug interactions (DDIs) are defined as drug combinations resulting in a pharmacological or clinical response which differs from responses to the agents when either is given alone (2;7;10-12). DDIs can cause ADEs (in which case many would be considered preventable). For example some 'famous' DDIs have led to medications being pulled from the Canadian market. Cisapride can cause arrhythmias which are significantly more common if administered with other commonly prescribed drugs, such as macrolide antibiotics. Another example is the interaction of spironolactone and ACE inhibitors that may result in life-threatening hyperkalemia. DDIs can also be considered potential ADEs in the case where no harm is experienced.

DDIs are important because they represent a common cause of ADEs and because they might be preventable. McDonnell and Jacobs (13) conducted a retrospective chart review of 437 consecutive ADRs that prompted hospitalization to a university hospital during an 11-month period. Over one quarter (26%) of ADRs were due to DDIs. It was estimated that 25% of ADRs due to DDIs led to serious or life-threatening events. Mannesse *et al.* (14) found that the risk of severe or fatal drug reaction increased as the number of drugs that a person was prescribed increased. They conducted a cross-sectional study of 106 elderly patients admitted to a single hospital to determine which factors were associated with severe ADRs requiring hospitalization. Using multiple logistic regression, they found that the use of three or more drugs increased the odds of a severe ADR by 9.8 times ($P = 0.04$). This result was confirmed in a retrospective Norwegian study (15) in which 38.3% of patients who died in hospital of a fatal ADR took more than 6 drugs compared to 28.6% of matched controls. In summary, DDIs are an important target for

improving patient safety because by definition they can be considered a medical error and are therefore preventable. If they occur frequently, they commonly contribute to poor patient outcomes.

1.4 LITERATURE REVIEW

Given the importance of DDIs for patient safety, they have been studied relatively infrequently. A total of 837 studies have been filed on MEDLINE with the MESH HEADING keywords "hospital drug interactions" between 1969 and 2004 (Limits=English/Human). Of these 837 publications, 27 measured DDIs as an outcome in a defined population. These studies are described in Appendix A.

An ideal study of the incidence and prevalence of DDIs should have the five following characteristics:

1. **Comprehensiveness**: the study should include all potential DDIs and not limit itself to a few selected DDIs. Studies that do not include all potential DDIs will underestimate the true incidence and prevalence of DDIs. Studies that include all potential DDIs will provide the most complete assessment of the burden that DDIs play in health care.

   The comprehensiveness of the DDI studies varied widely among the 27 studies listed in appendix A. In six studies of the twenty-seven, the DDIs that were examined in the study were not specifically disclosed (13;16-20). The sole Canadian study limited its examination to only 3 DDIs (21). Five studies (22-26) used computer software to screen charts (23;25) and databases (22;24;26) for DDIs but the sensitivity of the software for determining a true DDI was only reported in one study and was extremely low at 58% (22). Eight (27-34) studies used Hansten's and Horn's

Interactions (35) to define the DDIs of interest while five other studies used other similar publications (26;36-39). Hansten and Horn's publication, "Drug Interactions, Analysis and Management", is a standard reference source of drug-drug interactions and is commonly used in everyday pharmacy practice to analyze potential DDIs. Despite using such well-known reference sources to define the DDIs, none of these studies stated whether all potential DDIs were studied. In summary, no previously published study has definitively measured the prevalence of all DDIs in a defined patient population.

2. **Generalizability**: the study should include a large and diverse patient population to ensure study generalizability and that heterogeneity between patient populations in DDIs can be identified. The results of studies involving a focused patient population will have questionable relevance to other patient populations.

   Of the 27 studies reviewed, 22 studies focused on inpatients. Four of these studies were conducted on geriatric wards alone (18;22;30;38), 10 studies (15;16;23;24;27;28;34;39-41) were done on medical wards alone, five were isolated to the ER department (17;20;29;32;37), and one to the Psychiatric-Liaison Consulting service (42). One study combined Medicine and Surgery patients (33) while one study only included inpatient heart failure patients (26). No study examined an entire inpatient population (i.e. all wards of the hospital) or examined a random sample drawn from the entire hospital population.

3. **Epidemiologic Completeness:** the study should provide the incidence and prevalence of DDIs in the selected population. Incidence is defined as the number of DDIs that occur in a defined patient population during a specific time period. Because DDIs are

considered a preventable adverse event, DDI incidence is important because it represents the frequency of potentially preventable adverse events.

Of the 27 studies, 18 estimated DDI incidence in the study population (17;20;23-30;32-34;38;39;41;43;44). These interventions included providing medication profiles to the prescribers (31;37), notifying MDs of DDIs (36), and using computerized screening to identify DDIs (22). Two studies estimated the incidence of DDIs responsible for ADRs with an ADR surveillance program (13;16). Two studies examined the relationship between DDIs and hospitalization (19;21). One study examined only specific interactions but did not report an incidence measure (42).

4. **Relevance:** the study should measure the potential clinical significance of the DDI to determine its relevance to patient health. Studies that do not measure the potential severity of DDIs will have questionable clinical relevance. Only eight studies (13;17;23;24;27;30;32;38) commented on the severity of the drug interactions. However, no standard definitions were used to define the severity of the DDIs.
5. **Predictors:** to start identifying methods to decrease the risk of DDIs, the study should determine which factors are associated with DDIs. Studies that fail to do this will not inform future research regarding methods to decrease DDIs. Only six studies examined factors associated with DDIs (15;26;29;32;44;45). One study (32) examined the association of the number of drugs with the risk of having a DDI.

The published literature regarding DDIs has many notable limitations (Appendix A). Overall, they were not comprehensive, had limited generalizability, were not epidemiologically complete, had limited clinical relevance, and did not identify predictors of DDIs. None of the studies satisfied all 5 criteria specified.

These points are summarized in **Table 1,** which includes the most relevant studies from Appendix A.

In summary, drug-drug interactions represent an important component of patient safety. To date, there has been no thoroughly comprehensive study of drug-drug interactions. Because of the limitations identified in the previous literature review, there is an incomplete basic epidemiologic knowledge in this important area. The following study was conducted to address these deficiencies.

Table 1: A Summary of the Most Important Studies Regarding Drug-Drug Interactions

Red =Criterion not met Orange=Uncertain if criterion met Green=Criterion met

AUTHORS	COMPREHENSIVENESS Inclusion of all potential DDIs?	GENERALIZABLE Random sample drawn from population?	EPIDEMIOLOGIC COMPLETENESS: Incidence/prevalence measures?	RELEVANCE Severity of DDI defined?	PREDICTORS Predictor Variables?
Egger(23)	No Computer-screened DDIs	No Discharged Geriatric patients	747 potential DDIs in 500 patients	Yes. DDIs Rated minor, Moderate, severe	Therapeutic class
Raschetti (17)	Method of screening for DIs not specified	No, only Emergency Room Patients Included	3.8% of visits due to DDIs	Most patients with a DDIs were admitted to hospital	None Examined
Wiltink (27)	Yes Reference Source: Hansten	No, only Cardio/ Pulmonary inpatients	39-65% in patients with DDIs	0.12% DDIs clinically significant	None Examined
Gronoos (24)	Computer-screened DDIs	No, only Medicine inpatients	6.8% patients with DDIs	Only Potentially Serious DDIs studied	None Examined
Doucet (18)	Method of screening not specified	No, only Geriatric Inpatients	1087 DDIs/538 patients	Yes ADRs resulting from DDIs described	None Examined
Huic (28)	Yes Reference Source: Hansten	No, only internal medicine and Cardiology patients	DDIs caused 23.8% ADRs	Yes All DDIs associated with ADR	None Examined
Herr (29)	Yes Reference Source: Hansten	No, only Emergency Room Patients	Sig. more DDIs with patients currently using medications	"clinically relevant" DDIs were not defined	Age >60 yrs sole predictor of relevant DDI's
Prince (20)	Method of screening not specified	No, only Emergency Room Patients	1% ADRs due to DDI	24% patients admitted	Examined most common drug classes
Gosney (38)	Yes BNF used to define DDIs	No, only geriatric Inpatient	23.7% patients with DDI	7 patients developed an ADR	None Examined
Karas (32)	Yes Reference Source: Hansten	No, only Emergency Room Patients	Interactions in 16% patients	20% clinically significant	90% interactions involved one of 10 drugs

2 METHODS:

2.1 OBJECTIVES

1. Determine the cumulative incidence and incidence density of potential drug-drug interactions (DDIs) in patients hospitalized at the General Campus of the Ottawa Hospital between 1999 and 2005.
2. Determine if the cumulative incidence or incidence density of potential DDIs has changed at the General Campus of the Ottawa Hospital during the study period.
3. Measure the severity of potential DDIs at the General Campus of the Ottawa Hospital during the study period using the classification system of DDIs by Hansten and Horne(46)
4. Identify patient and hospital factors associated with the development of potential DDIs during the hospitalization.

2.2 STUDY DESIGN

This is a seven year retrospective study using administrative data from the Ottawa Hospital Data Warehouse (OHDW).

2.3 HOSPITAL DESCRIPTION

The Ottawa Hospital (TOH) is one of the largest tertiary care hospital hospitals in Canada and has services located on three campuses, named the Civic, General, and the Riverside. TOH has approximately 125,000 emergency visits and 47,000 hospitalizations

.annually. Inpatients are divided between the Civic and General campuses. In total, TOH has 987 inpatient beds with an average length of stay of 8.6 days.

2.4 PATIENT POPULATION

Patients enrolled in this study were all admitted patients to the Ottawa Hospital, General Campus between 1 January 1999 and 30 September 2005. The OHDW contains data back to 1996, but the data between 1996 and 1999 were not included because a non-negligible number of pharmacy entries were absent between 1997 and 1999. This was due to problems stemming from switching pharmacy computer systems.

This study included all hospitalizations to all services, including critical care and obstetrical hospitalizations. Pediatric patients are usually not admitted to the Ottawa Hospital and all patients under18 years of age were excluded from the study. We excluded all outpatient visits, emergency room visits, and day surgery encounters along with other same-day visits. Same-day encounters were excluded because their respective medication profiles are incompletely captured by the OHDW and the duration of these encounters are very brief. Finally, hospitalizations to the Civic campus of the Ottawa Hospital were excluded because the OHDW only captures Civic drug orders after 2004.

2.5 STUDY DATABASE

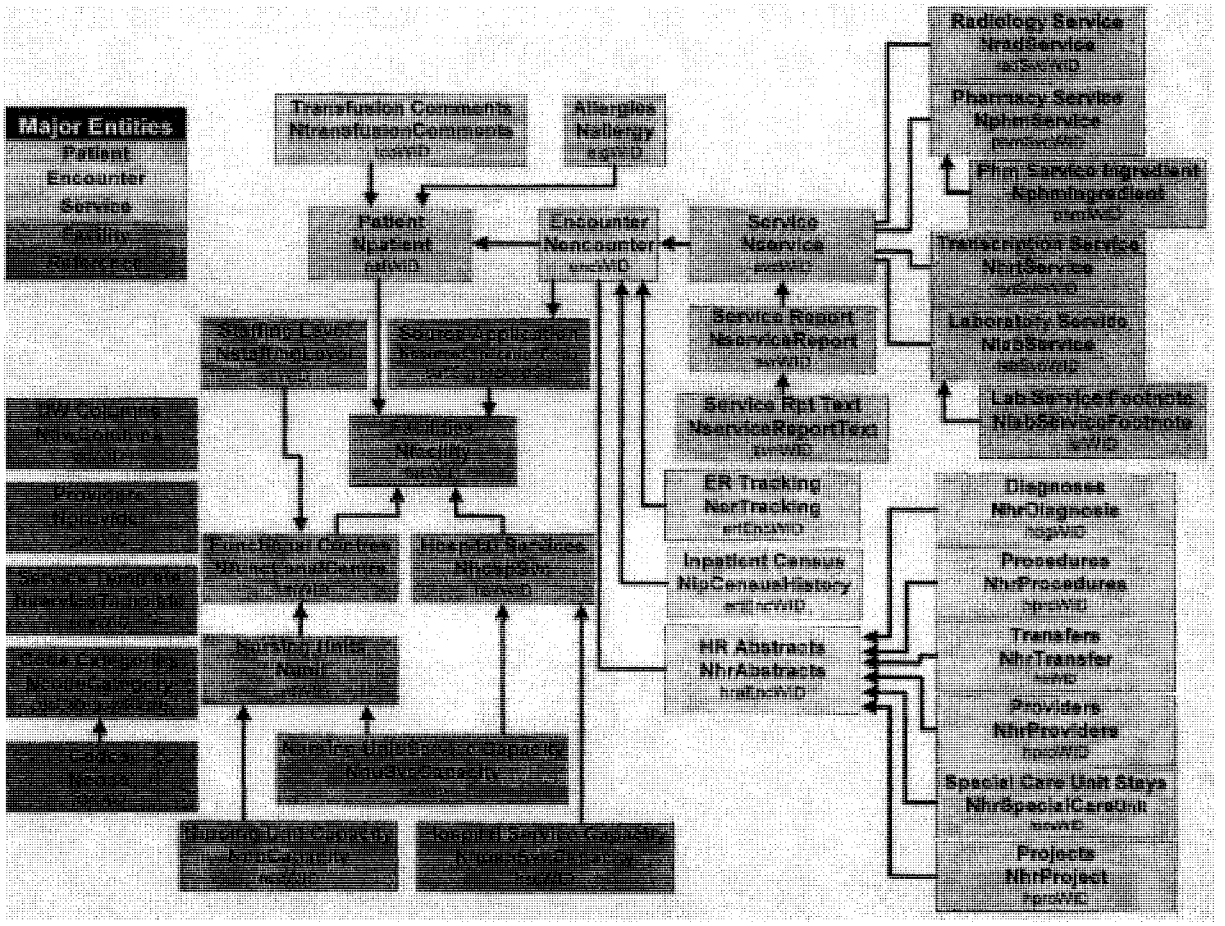
2.5.1 The Ottawa Hospital Data Warehouse (OHDW)

The OHDW is a data repository containing clinical and administrative data for the Ottawa Hospital from 1996 to the present. The OHDW data is extracted weekly from several transactional data systems which are used by hospital personnel to care for

patients. The OHDW is a relational database with entities representing 'Patients', 'Encounters', 'Services' , 'Providers' and 'Facilities'. There are also a number of 'sub'-entities which describe attributes of entities. For example, 'Encounters' represent visits to the hospital. During each encounter, a patient may be diagnosed with a number of diagnoses. Diagnosis information is stored in the 'Abstracts' sub-entity. Entities and sub-entities are represented in the OHDW by different tables and the records contained within these have unique identifiers, which are used for linking purposes.

The relationship of these tables along with the entities and subentities are shown in **Figure 2** below:

Figure 2: Database Map of the Ottawa Hospital Data Warehouse



For this project, I used the following entities:

2.5.1.1 Patients

The patient table (npatient) describes patient-level data. Each row represents a different patient and is represented by the variable patWID. This variable is a sequential, unidentifiable number assigned to each patient. The only variable from this table used in the thesis was the patWID.

2.5.1.2 Encounters

The encounter table (nencounter) describes encounter-level data. Each row represents a separate encounter identified by the variable enc. The variables used from this table were the encounter number (encWID), patient number (enc PatWID), campus identifier (EncCampusCd). The source data system the data warehouse uses for these data is the Oacis clinical repository which currently contains demographic information, allergy information, transfusion medicine orders, encounter (inpatient, outpatient, emergency room) data, laboratory results, diagnostic imaging results, pharmacy orders, discharge summaries, and clinic transcriptions.

The following 'Encounter' sub-entities o were also required for the study:

a) hraAbstracts (nhrabstracts)

This table contains information about each hospital admission. The variables used in this table were the encounter identifier (hraEncWID) which links the variable to the nencounter table, patient age (HraAge), patient gender (hraGender), length of stay (hraLOS), admitting service (hracmgtypecd), resource intensity weight (HraRIW). Resource Intensity Weight (RIW) is a relative resource allocation methodology for estimating hospitalization costs for both acute and day procedure care. The source data

system is the Eclipsys and Decision Support System. These systems currently are used by the hospital's Decision Support Department to track hospital Discharge Abstracts.

b) hraDiagnosis (nhrDiagnosis)

This table contains the health records abstract diagnostic information. The variables used in this table were the encounter identifier (hdghraEncWID) that links to the hraAbstracts table), ICD9 and 10 diagnostic codes (hdgCd), and the diagnosis type (hdgType). The source data system is the Eclipsys data system.

2.5.1.3 Service

Each row in the service (nservice) table represents a specific service for a patient during an encounter. The variables used in this table were the service unique identifier (svcWID), encounter identifier (svcEncWID), and priority code (svcPriority Cd). The source data system is the Oacis clinical repository.

The following sub-entities were also required for the study:

a) pharmacy service (nphmservice) table

Each row in the nphmservice table represents a new dug order, written by the prescriber and entered into the pharmacy computer system by the pharmacist. The variables used for the study were the drug name (phmorderdesc), route of administration (phmroute), administration start date (phmstartdtm), and administration end date (phmenddtm).

b) pharmacy ingredient (nphmingredient) table

Each row in the nphmservice table represents a dispensed drug order. The variables used for the study included unique pharmacy identifier,(phmiWid), drug identification number (phmiDIN), therapeutic category.

c) Lab service (nlabservice) table

Each row in the nlabservice table represents laboratory-specific information. The variables used in this table are unique laboratory identifier (labSvcWid), laboratory test results (labsingleresult), and units associated with the results (labunits).

2.6 MEDICATION PRESCRIBING PROCESS

At the Ottawa Hospital, several steps occur between a physician ordering a medication for a hospitalized patient and the patient receiving that medication. This process begins with the physician prescribing the medication in the orders section of the patient's chart. A physical copy of this order is transferred to and examined by a pharmacist or pharmacy technician. In the absence of major errors, the order is entered into the pharmacy computer system (either Cerner or SMS). All drug orders are entered by using the name of the drug but this process has not been standardized yet. The majority of times, the pharmacist will pick the name of the drug to be dispensed from a list of potential names. If the drug they seek does not appear in the standard list, the pharmacist can enter the name of the drug directly and this name will permanently be added to the list of drug names in the corresponding dataset.

Electronic methods are used to screen for drug-drug interactions at the time of order entry. The software that the pharmacy computer system used to screen for DDIs was developed by First Databank™. This software uses drug identification numbers

(DIN) numbers to screen for potential DDIs. The DIN numbers in this software are obtained from Health Canada's drug product database. If a DDI is detected at the time of order entry, the pharmacist will contact the physician to clarify the order and make any necessary changes prior to dispensing the medication. DDIs corrected in this manner would not be detected in this study because only those orders entered in the computer were included.

Once the drug is entered into the pharmacy system, the dispensary fills the order and sends the drug to the hospital ward. The drug is then given to the patient according to the prescribing directions.

Every patient admitted to the Ottawa Hospital is represented by a unique identification number in the OHDW. Similarly, every medication prescribed is represented by a Drug Identification Number (DIN). With few exceptions, every medication entered in the pharmacy computer will subsequently be administered to the patient.

Once the drug is entered into the pharmacy system, the resulting record is sent to the clinical repository (OACIS) system. These data are subsequently uploaded to the OHDW. Consequently, the OHDW contains a comprehensive record of all pharmaceutical administrations for all patients admitted to the Ottawa Hospital. Within the OHDW, every drug that is prescribed is listed in a table along with other variables that identify the drug, dose, dosage form, route of administration (i.e. intravenous; oral), directions for use provided by the prescribing physician, start date and time, and stop date and time.

2.7 DRUG IDENTIFICATION AND NOMENCLATURE

In order to understand how I identified DDIs it is important to understand how drugs are named. The INN (International Non-Proprietary Names) establishes non-proprietary names of pharmaceutical substances or ingredients. These names represent generic drug names and are recognized at a global level (47). Proprietary or brand names are chosen by the manufacturer and approved by Health Canada at the time of review.

2.7.1 Drug Identification Numbers

Drug identification numbers (DINs) are a standard coding system used to identify all medications. Once a drug is approved for use in Canada, it is assigned a unique 8 digit DIN that permits the manufacturer to market the drug. A DIN is required for any prescription drug product to be marketed in Canada. The DIN lets the user know that the product has undergone and passed a review of its formulation, labelling, and instructions for use. The DIN also helps in the monitoring of drugs on the market, recall of products, inspections, and quality monitoring. Each unique combination of drug, dose, formulation, and manufacturer in Canada has a unique DIN. For example, digoxin has six different DINs and verapamil has 41 different DINs

2.7.2 Anatomic and Therapeutic Classification System (ATC)

The purpose of the ATC system is to serve as a tool for drug utilization research. One of the barriers to doing such research is because drugs can be used for various purposes and at varying doses, which may not be standardized across international borders. The ATC classification system is a way of standardizing these differences so that researchers can compare drug utilization information within countries and internationally. The ATC classification is described in more detail in Appendix B.

2.8 STUDY OUTCOME: CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS

For this study, the drug interactions of interest are those identified by Hansten and Horn (46) in "Drug Interactions, Analysis and Management". This is a standard reference of drug-drug interactions and is commonly used in everyday pharmacy practice to analyze potential DDIs. In addition to its completeness, this comprehensive reference also classifies DDIs by their possible clinical outcome and severity. Hansten identifies the potential risk of DDIs using a five tier ordinal scale as follows:

1. Category 1 - Drug combinations to be avoided.
2. Category 2 - Drug combinations that are usually avoided.
3. Category 3 - Drug combinations that should be altered to minimize risk.
4. Category 4 - No action needed.
5. Category 5 - No Interaction.

Examples of these five types of DDIs and the possible consequences of them are described in the following table.

Table 2: Examples of DDIs by Class of Interaction and Possible Consequences

Drug A	Drug B	Class Interaction	Possible Consequences
Clarithromycin	Rifabutin	1	increased plasma concentrations of rifabutin causing increased toxicity (gi upset, myalgia, neutropenia). Loss of efficacy of clarithromycin.
ASA	Warfarin	2	Increased risk of bleeding due to decreased platelet function and ulcer disease. Benefit may outweigh risk if low-dose ASA used. Monitor hemoglobin and INR.
Digoxin	Furosemide	3	Diuretic-induced hypokalemia may induce digoxin toxicity. Monitor K+ and Mg+ levels.
Carbamazepine	Nifedipine	4	Carbamazepine may reduce serum concentration levels of Nifedipine by increasing metabolism. Monitor BP response
Sertraline	Olanzapine	5	No Interaction

For the present study, only drug-drug interactions in categories 1, 2 and 3 were considered because they are the most clinically relevant and are the only interactions with the only potential to cause adverse drug reactions.

To determine if any of these DDIs occurred during a hospitalization, a **Drug-Drug Interaction Look-up Table** that listed all possible DDIs from Hansten was required. We also created a table of all co-administered medications during each hospitalization, which we called the **Co-Administered Drug Table**. This was created from each patient's medication profile in the OHDW. Therefore, any drug-drug coadministration in the Co-Administered Drug Table that was also present in the Drug-Drug Interaction Look-up Table was classified as a potential drug-drug interaction.

The following steps were taken to identify potential DDIs:

1. Creation of the Drug-Drug Interaction Look-up Table
    a. Creation of the Drug-Drug Interaction Table
    b. Creation of the Reference Drug Table

c. Creation of the Drug-Drug Interaction Look-up Table

2. Creation of the Co-Administered Drug Table

    a. Standardization of DINs in the OHDW

    b. Creation of the Cumulative Drug Profile

    c. Creation of the Co-Administered Drug Table

3. Identification of Potential Drug-Drug Interactions

Each of these steps is described in the following sections.

2.8.1 Step 1- Creation of the Drug-Drug Interaction Look-up Table

2.8.1.1 Creation of the Drug-Drug Interaction Table

The Drug-Drug Interaction Table contains all possible combinations of drugs that constitute a drug-drug interaction of category 3 or lower according to Hansten and Horn (46). This table recorded the two drugs involved in the DDI (Drug A, Drug B) as well as the interaction category (i.e. category 1, 2, or 3). The Drug-Drug Interaction Table was created by manually typing the drug-drug interactions of interest, from Hansten and Horne, into a using Microsoft Excel® spreadsheet having the following headings:

Table 3: Drug-Drug Interaction Table

Drug A	Drug B	Interaction Category

Drug names were standardized according to the ATC category name developed by the WHO Collaborating Centre for Drug Statistics Methodology (48). There were a total of 1017 DDI pairs in interaction categories 1, 2 and 3. Once the Drug-Drug Interaction Table was created, it was imported into SAS® and converted to a SAS® dataset.

2.8.1.2 Creation of the Reference Drug Table

The Reference Drug Table contains the ATC drug name and DIN numbers of all marketed drug products approved for use in Canada for the duration of the study. This comprehensive reference source was required to convert the text, containing the ATC drug/category name, in the drug-drug interaction table created in step 1 (**Table 3**) to DIN

numbers. This step also ensured that each ATC drug name listed in the drug-drug interaction table was linked to all possible DIN numbers representing that drug. This is required because many drugs are represented by more than one DIN.

Unfortunately, no readily accessible reference file containing ATC drug names and DINs exists. As a result, the Reference Drug Table containing this information for all marketed products in Canada during the study dates was created for this study. This was accomplished by downloading text files from Health Canada that list active products, inactive products, ingredient tables, and therapeutic classifications. Health Canada is the gold standard source for this information since it alone is responsible for assigning and recording all DINs for drug products in Canada. Therefore, these files record all drugs that have ever been approved for use in Canada. With the exception of a few rare and very special situations, no medication can be prescribed in Canada without existing in these files.

The Health Canada Drug Product Database was located at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index_e.html. Component tables from the Drug Product Database were extracted and downloaded. These files contained the information required to build the Reference Drug Table and consisted of active products ("active.txt"), inactive products ("inactive.txt"), ingredient tables ("drug.txt"), and therapeutic classification tables ("ther.txt").

To create the Reference Drug Table, the extract tables were downloaded and opened using Microsoft Excel® and imported into SAS®. These files were then appended to each other using the common variable (drug_code). The inactive drug extract file was only partially complete because ingredient information (i.e. generic drug names) and

therapeutic class information (i.e. ATC drug names) were unavailable for inactive drug products. There was no other reliable reference source for the inactive products other than this limited file through Health Canada. Given that this study was retrospective in nature, it was imperative that the inactive DINs and therapeutic classification information (ATC drug names) be included in the reference drug table. In order to complete the reference drug table, ATC drug names were added manually for all inactive products containing drugs in the drug-drug interaction table.

The final Reference Drug Table included products ("active.txt"), inactive products ("inactive.txt"), ingredient tables, along with a list of all DINs for active products and inactive products. The variables in this table included Brand Name, Generic Name, DIN (drug identification number), ATC (Anatomic Therapeutic Classification) class name, and AHFS class (American Hospital Formulary System) (**Table 4**).

Table 4: Reference Drug Table

Brand Name	*Generic Name*	*DIN*	*ATC Drug Name*	*AHFS Class*

2.8.1.3 Creation of the Drug-Drug Interaction Look-up Table

The Drug-Drug Interaction Look-up Table contains all DINs for each drug in the DDI interaction table along with the severity of the interaction. It was created by identifying all DINs for each drug in the Reference Drug Table that make up a single drug-drug interaction and creating a cross product table. This ensured that all possible DIN combinations for each of the DDI are recorded in the Drug-Drug Interaction Look-up

Table. An example of the first 6 rows of the drug interaction look-up table is shown below. Drug A (Ritonavir) has 2 DINS (02243643, 02243644) while Drug B (Disulfiram) has 3 DINs (00002534, 02041375, 02041391). The cross product of these DINs is shown in the look-up table below:

Table 5: Example of Drug-Drug Interaction Look-up Table

DIN 1 (Drug A)	*DIN 2 (Drug B)*	*Interaction Category*
02243643	00002534	1
02243644	00002534	1
02243643	02041375	1
02243644	02041375	1
02243643	02041391	1
02243644	02041391	1

Rows in the Drug-Drug Interaction Look-up Table for a single DDI between a drug with two DINs (DIN1) and a drug with three DINs (DIN2)

To allow for all possible combinations of DDIs, the mirror image of this table was created (i.e. DIN1 and DIN2 in each row were exchanged) and appended to the table to create the final Drug-Drug Interaction Look-up Table. This ensured that the drug order was immaterial for identifying the DDI (ie: Drug A: Drug B as well as Drug B: Drug A interactions detected).

2.8.2 Step 2-Creation of the Co-Administered Drug Table

2.8.2.1 Standardization of DINs in the OHDW

The DINs contained in the OHDW are not completely reliable for identifying drugs. This data problem results from the fact that drugs are entered in the pharmacy

computer system by product name (generic) and not by DIN. As a result, it is not routine pharmacy practice to ensure that the product names are associated with a correct DIN number.

To identify DINs that may not be unique to a drug name, a table was created in SAS® that displayed the frequency of each drug name for every DIN number in the dataset. This table identified 48,265 non-unique DIN-drug name combinations for 1016 DINs between 1996 and 2005. To determine how many rows of the npharmservice and nphmingredient tables were represented by a non-unique DIN-Drug product combination, a table was created that linked these 1016 DINs with the nphmingredient and nphmservice tables. Overall, 31% (1016/3320) of the DINs found in the pharmacy tables were associated with more than one drug product name. These DINs also accounted for a high percentage of all drug orders (2 223 116 of a total of 3 507 369, 63%).

To correct this problem, the drug names associated with a non-unique DIN had to be re-assigned to a valid DIN obtained from the Reference Drug Table. A table was created that linked the non-standardized drug orders in the OHDW to a proper ATC drug name. This text matching procedure was accomplished using the RXmatch function in SAS.® Drug names that were not linked using the RXmatch function were manually assigned to ATC drug names. Once the correct ATC drug name was assigned to all drug names in the OHDW, a valid DIN could be assigned to the drug name from the Reference Drug Table. In this way, all OHDW drug names with non-unique DINs were reassigned a valid DIN.

Once the DINs had been correctly assigned to the OHDW drug names, a table was created to check that the drug names in the OHDW matched correctly to the ATC drug

name. This table contained the OHDW drug name, the newly assigned DIN from the Reference Drug Table, and the ATC drug name. This table was then manually checked to ensure that there were no discrepancies between the OHDW drug name and the ATC drug name.

For those drugs in the OHDW that were assigned to a unique but incorrect DIN (ie: the OHDW drug name did not match the ATC drug name), a new DIN was assigned using the same method as described above for the non-unique DIN problem. Once the DINs were corrected, a similar table was created to check that the OHDW drug names had been matched to a correct ATC drug name.

2.8.2.2 Creation of a Cumulative Drug Profile for each Hospitalization

The Cumulative Drug Profile contains the DIN, the start date and time, and the end date and time for every drug prescribed during the hospitalization. This information was summarized in a dataset with the following layout (**Table 6**):

Table 6: Layout of the File Summarizing Drug Utilization for Each Hospitalization

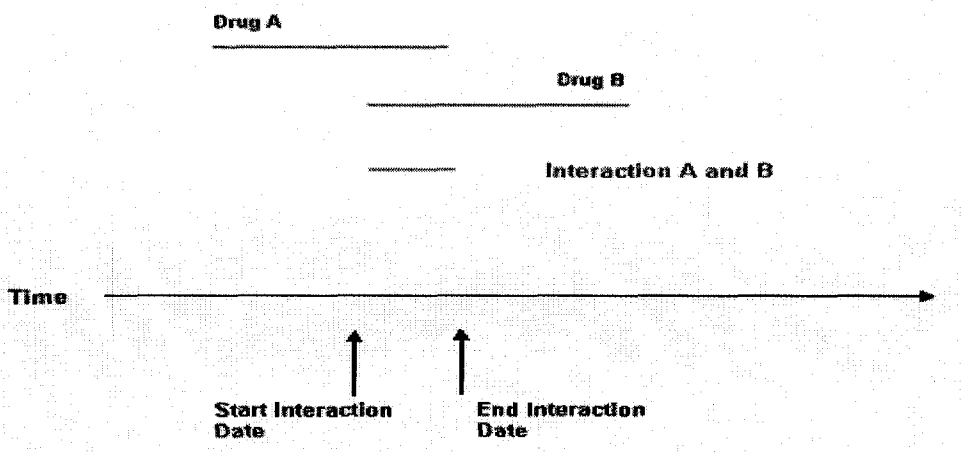
Encounter Unique ID	*Patient Unique ID*	*Drug 1*	*Start Date Drug 1*	*End Date Drug 1*	*Drug 2*	*Start Date Drug 2*	*End Date Drug 2*	*Drug 3*	*Start Date Drug 2*	*End Date Drug 2*	...	*Drug X*

It should be noted that this file did not include information about drugs that were ordered and administered on an 'as needed' (or 'PRN') basis. PRN drugs were not considered because the OHDW does not record their actual administration to patients. With the exception of nitroglycerin and sildenafil, very few prn-dosed drugs have category 1 or 2 interactions.

2.8.2.3 Creation of the Co-Administered Drug Table

For each hospitalization, **Table 6** was used to identify all possible pairs of co-administered drugs. This was done by taking each single drug exposure and comparing it to all other drug exposures during the hospitalization. Drug exposure time was determined to be the duration of drug administration. If the exposure time of these 2 drugs overlapped, this drug-drug exposure was added to the Co-Administration Drug Table. The start of the co-administration was the start of the overlapped time interval. The end of the co-administration was the end of the overlapped time interval. The duration of the co-administration was the difference of these two dates. The determination of the interaction start and end dates as well as the duration of the interaction is illustrated in **Figure 3**.

Figure 3: Relationship between Co-Administered Drugs and Interaction Dates



This figure illustrates two interacting drugs (Drug A and Drug B) and the relationship of the start and end times of the 2 drugs to the interaction start and end times. The overlapping time period is equivalent to the duration of the interaction with the interaction start date equal to the start date of Drug B and the interaction end date equal to the end date of Drug A.

Table 7 lists all variables of the Co-Administered Drug Table with the start and end dates of each drug along with the duration of the co-administration.

Table 7: Co-Administered Drug Table

DrugA	DrugB	DinA	DinB	Interaction Start Date	Interaction End Date	Interaction Duration (Days)

The Co-Administered Drug Table dataset allowed us to determine if and when a potential DDI occurs during a particular hospitalization.

2.8.3 Step 3-Identifying Drug-Drug Interactions

The final step to identifying all DDIs was to link **Table 7** (Co-Administered Drug Table) with **Table 5** (Drug-Drug Interaction Look-up Table). A drug-drug interaction was identified if DIN1 in the Drug-Drug Interaction Look Up Table was identical to DINA in Co-Administered Drug Table and DIN 2 in Drug-Drug Interaction Look Up Table was identical to DINB in Co-Administered Drug Table. The interaction category was denoted in the Drug-Drug Interaction Look-up Table (**Table 5**) and the duration is denoted in the Co-Administered Drug Table (**Table 7**). Using this linkage method, the Drug Interaction Table (**Table 8**) was produced containing the following headings:

Table 8: Drug Interaction Table

DrugA	DrugB	DinA	DinB	Interaction Start Date	Interaction End Date	Interaction Duration (Days)	Interaction Category

The Drug interaction Table was then manually checked against the Hansten and Horne's reference source (35) to ensure that this method identified correct DDIs. This was done by creating a frequency table of all identified unique DDIs. The names were then cross-checked against the names contained Hansten and Horne's reference source.

2.9 CALCULATION OF DRUG-DRUG INTERACTION TIME

The Drug Interaction Table (**Table 8**) identified all drug-drug interactions along with their duration for a hospitalization. Unfortunately, the duration of the interactions cannot simply be summed up to determine the total interaction time for each hospitalization. This is because many of these interactions occur concurrently. As a

result, simply summing up all DDI time could exceed the total hospitalization time. Therefore, for every hospitalization with at least one interaction, the interaction time was calculated as the time where **at least one** interaction was present. Therefore, when a patient had 2 distinct DDIs occurring at the same time, only one was calculated in the DDI incidence. This was accomplished by writing a program that examined every minute of each admission and added that minute to the interaction time if at least one interaction was present during that minute. This method calculated the interaction time accurately for the entire hospitalization and allowed the calculation of the DDI incidence density. The DDI incidence density was therefore defined as the number of days of at least one DDI divided by the number of hospitalization days. Times for category 1, category 2, and category 3 interactions were also calculated using this method.

2.10 CREATION OF THE FINAL STUDY DATASET

In addition to identifying all drug-drug interactions, the Charlson Comorbidity Index was calculated. The Charlson Comorbidity Index (49) is a scale developed to predict mortality based on specific comorbidities. It is an ordinal scale with four levels and is calculated using weights assigned to the comorbidities. The assigned weights are shown in Appendix D. For this study, the Charlson Comorbidity Index was calculated using a coding algorithm with International Classification of Diseases (ICD 9 and ICD-10) codes. The Nhrabstract table and Nhrdiagnosis tables of the OHDW contained the relevant information required for this classification. The ICD codes used calculate the Charlson Index were identified by Quan et. al. (50). The weights used to calculate the cormorbidity score were taken from Schneeweiss et. al. (51).

2.11 ANALYSIS

The univariate and multivariate analysis plan is presented below with reference to the primary thesis objectives:

Objective 1: To determine the incidence of potential DDIs in hospitalized patients at the Ottawa Hospital between 1999 and 2005.

Drug-drug interactions were measured using a **cumulative incidence rate** for which the numerator was the total number of patients having at least 1 DDI during their hospitalization and the denominator was the total number of hospitalizations during the study period.

To account for the duration of DDIs and hospitalizations, the DDI **incidence density** was also calculated. For each hospitalization, the numerator was defined as the total number of days during which at least 1 DDI occurred. The denominator was the total duration of hospital stay (days). The DDI incidence density is a more appropriate measure of the burden of DDIs in hospital inpatients since it will account for the duration of hospitalization, which is usually strongly associated with the duration and number of medications administered. These will, in turn, influence the risk of DDIs.

Objective 2: To determine whether the cumulative incident rate of potential DDIs at the Ottawa Hospital changed during the study period.

Cumulative incidence rates were analyzed to see if there were any significant trends or changes over time. The Mantel-Haenszel Chi-Square test for linear trend was used to determinine if there was any significant change in the proportion of patients having at least 1 DDI over the study period. It was postulated that as the number of

medications prescribed over time increases, the proportion of patients having at least 1 DDI will increase as well.

Objective 3: To determine the severity of potential DDIs at the Ottawa Hospital during the study period.

Drug-drug interactions were expressed as an incidence density, calculated as the number of interaction days per hospital patient days. This incidence density rate was stratified by DDI severity Category 1, 2, or 3.

Objective 4: Identify patient and hospital factors associated with the development of potential DDIs during the hospitalization.

The frequency distribution of the number of DDIs was best characterized by a Poisson distribution. Using Poisson regression allowed us to model not only the number of DDIs in a given admission but also the incidence density. The latter outcome considers the exposure time (i.e. hospital length of stay), which is important because longer patient hospitalizations will increase drug exposure, thereby increasing the risk of DDI.(26)

Poisson regression was used to determine the association of the predictor variables of interest with potential DDI incidence density. The predictor variables included in the model were: total number of medications prescribed during the hospitalization; patient age; patient gender; total length of stay; hospital service; resource intensity weight; and the Charlson Comorbidity Index.

Resource Intensity Weight (RIW) is a relative resource allocation methodology for estimating hospitalization costs for both acute and day procedure care. Resource Intensity Weights provided data concerning the medical and financial burdens of a

hospitalization. RIWs were developed in the early 1990s by the Hospital Medical Records Institute to account for the fact that different hospitalization diagnoses were associated with different costs (52). RIWs are essentially ratios that measure the expected use of resources. For example, the diagnosis of pneumonia in a community hospital may be associated with a lower cost of care than the same diagnosis in a tertiary care hospital due to patient comorbidities, length of stay, and interventions required during the hospitalization (ie bronchoscopy or CT scans that may be done in tertiary care hospital and not available in the community). To account for these differences in the cost of care, the RIW was developed to assist in funding allocation to different types of Canadian hospitals.

The Charlson Comorbidity Index is a weighted index that considers the number and seriousness of comorbidities (49). It uses adjusted relative risks of mortality as weights. Our model results did not change when the total Charlson Comorbidity Score was used instead of the ordinal Charlson Comorbidity Index. Therefore, only the Charlson Comorbidity Index was used in the analysis. Proc GENMOD, with the Dist=Poisson and link=log options in the model statement, was used to create the Poisson regression models in SAS®.

For all continuous predictor variables, an exploratory Log-means plot was produced to visualize the relationship between the variable and the logarithm of the DDI interaction time. Such a 'log-means plot' facilitates the identification of non-linear relationships between continuous variables and count outcomes(53). This is important to establish whether there the relationship between the outcome variable and a predictor

variable is linear. If a non-linear relationship exists, variable transformation was used to achieve such a linear relationship.

To create a log-means plot, the continuous predictor variable was 'binned' into 10 equally sized groups with the proc rank procedure in SAS®. The mean value of the continuous variable for each of these 10 groups was then plotted against the log of the mean DDI time for that binned group. The resulting plot was then visually examined for evidence of non-linearity. Any deviation from a straight line drawn between the outcome and predictor variables indicates a departure from linearity. Any visual evidence of non-linearity was confirmed using the likelihood ratio test (LRT) between a model with the continuous variable and a model in which the predictor variable was categorized into quintiles. If the LRT between the models was statistically significant, then further evidence for departure from linearity was present.

For continuous predictor variables having a non-linear relationship in the log (mean DDI interaction time) plot, several techniques were employed in order to correct the non-linearity. These techniques involved converting the continuous variable to a categorical variable or by transforming the variable. If the log-means plot showed an exponential relationship between any of the predictor variables (number of drugs ordered, length of stay and RIW) and the outcome variable, a log transformation was used to achieve a linear relationship with the outcome variable. The log-means plot was then repeated with the log-transformed variable to ensure that a linear relationship was achieved.

3 RESULTS

A total of 140,349 hospitalizations occurred between January 1, 1999 and September 30, 2005 during which 2, 859,591 drug orders were processed. 45.5% of hospitalizations were for people who were admitted only once during the study. The rest (54.5%) of hospitalizations involved patients who had multiple encounters during the study period. All hospitalizations were at the General campus of the Ottawa Hospital.

3.1 DATA COMPLETENESS

In the OHDW dataset, there were 2632 drug orders (0.09%) with missing DINs. These were excluded since the drug-drug interactions could not be identified without the DIN number.

In the final dataset, the variables with missing data included patient age, RIW, gender, service, and disposition. There was 1 admission missing a hospital service code. The Charlson Comorbidity index could not be calculated for 12 hospitalizations. These 13 admissions were excluded from the multivariate analysis due to this missing data. Overall, of the 140,349 evaluable hospitalizations identified, 13 (0.009%) were omitted from the analysis due to missing data.

3.2 UNIT OF ANALYSIS

The unit of analysis was the hospitalization which is identified by a unique encounter number in the dataset. Each row in the final dataset represented one hospitalization.

3.3 OUTCOME (DEPENDENT) VARIABLE

The primary outcome of interest was the cumulative incidence of drug-drug interactions (DDIs), measured as the number of hospitalizations having at least one DDI during the study period. 113,292 hospitalizations (80.7%) had no DDIs. The descriptive statistics for the total number of potential DDIs per hospitalization is shown in **Exhibit 1**. There was a mean of 1.3 interactions per hospitalization, ranging from 0 to 443. **Exhibit 1** also provides the descriptive statistics of the continuous predictor variables.

Exhibit 2 presents the cumulative incidence of DDIs by year. The mean number of drug-drug interactions per hospitalization per year ranged from 1.0 to 1.4 per hospitalization and fluctuated mildly from year to year with no specific pattern. The mean number of interactions was lowest in the final study year at 1.0 per hospitalization. The distributions are highly skewed for all years because the majority of patients had no DDIs during their hospitalization. A Spearman correlation coefficient identified a significant negative linear trend between the mean number of drug-drug interactions per hospitalization and year of admission ($p<0.0001$), although the correlation coefficient was very small at -0.018.

The frequency distribution for the DDI cumulative incidence is shown in **Exhibit 3.** This visually confirms the highly skewed distribution suggested in **Exhibit 2. Exhibit**

3 shows the DDI cumulative incidence to be highly skewed to the right and does not follow a normal distribution pattern.

3.4 CUMULATIVE INCIDENCE AND INCIDENCE DENSITY

The cumulative incidence of DDIs is defined as the percentage of hospitalizations developing at least one DDI during the study period. The cumulative incidence is shown in **Exhibit 4** by year of hospitalization. Overall, 19.9% of patients developed at least 1 DDI during their hospitalization between 1999 and 2005. The annual cumulative incidence appeared to decrease over time from 19.7% in 1999 to 17.7% in 2005. This downward trend was confirmed with a significant Mantel-Haenszel Chi Squared Test for Linear Trend ($p<0.0001$).

To better describe the burden of DDIs, the DDI incidence density was calculated. The DDI incidence density controls for the exposure time by having as the numerator the number of days with at least 1 potential DDI (hereafter termed "interaction time") and as the denominator the number of days of hospitalization. In essence, this statistic presents the proportion of time in hospital during which the patient was exposed to at least one potential DDI. No time was double counted for more than one DDI coexisting and the numerator represents the time that at least 1 DDI was present. **Exhibit 5** lists the DDI incidence densities by year. The Spearman correlation coefficient between DDI incidence density and year of admission was -0.25 and was not statistically significant ($p=0.59$).

The annual observed DDI incidence density from **Exhibit 5** is shown graphically in **Exhibit 6**. By inspection, there appears to be no association between DDI incidence density and year. **Exhibit 7** displays the observed DDI incidence density for each year

from 1999 to 2005 stratified by month. No seasonal trends are apparent for any study year.

In addition to the total number of DDIs (**Exhibit 2** and **Exhibit 3**), the total DDI duration (or total interaction time) is also important since it is the numerator of the DDI incidence density. Descriptive statistics for the total DDI duration are shown in **Exhibit 8** by year. There was no significant linear trend by using the Spearman correlation (0.18).

The DDI interaction time frequency distribution is also important in determining the most appropriate regression method when DDI incidence density is the outcome (dependent) variable. The frequency distribution of interaction time is shown in **Exhibit 9**. This figure demonstrates that the frequency distribution of interaction time is highly skewed to the right and does not follow a normal distribution pattern. The mean drug interaction time is 1.46 days with a SD of 7.27 days and a skewness of 30.16. Given this skewed distribution of interaction time, a Poisson regression analysis was the most appropriate method for regressing these data.

Exhibit 15 demonstrates the percent of hospitalizations with at least 1 DDI plotted against the hospital length of stay. As the length of stay increases, the percent of hospitalizations with at least 1 DDI increases and eventually approaches 100%.

3.5 DRUG-DRUG INTERACTIONS BY CATEGORY

The number and category of drug interactions are shown in **Exhibit 10**. Relatively few Category 1 and Category 2 interactions occurred during the study period. **Exhibit 11**, **Exhibit 12**, and **Exhibit 13** show the annual incidence density of Categories 1, 2, and 3 interactions, respectively. The incidence density of Category 1 interactions appeared to decrease over the study period but the Spearman correlation was not significant.

Category 2 and Category 3 interactions did not change significantly during the study period.

Exhibit 14 lists the frequency of the most common DDIs by severity category. The most common Category 1 DDI was clarithromycin and rifabutin. It occurred in 59 hospitalizations, 0.002% of orders, and 0.018% of hospital time. The most common Category 2 DDI was warfarin and ASA . It occurred in 2258 hospitalizations, 0.43% of orders, and 0.63% of hospital time. The most common Category 3 DDI was digoxin and furosemide. It occurred in 3120 hospitalizations, 0.28% of orders, and 3.0% of hospital time.

3.6 PREDICTOR (INDEPENDENT) VARIABLE DESCRIPTION

The predictor variables of interest included number of drugs ordered per hospitalization, hospital service, patient age, length of stay, resource intensity weight, patient gender, discharge disposition and Charlson comorbidity index.

3.6.1 Continuous Variables

3.6.2 Number of Drugs Ordered per Hospitalization:

Descriptive statistics for the number of drug orders are presented in **Exhibit 1.** There was a mean of 20.9 drug orders (SD 22.7) per hospitalization. **Exhibit 16** displays this by admission year. The mean number of drugs ordered appears to have increased throughout the study period with the exception of 2005. To test for a linear correlation, the Spearman correlation coefficient was found to be 0.075, between the number of drugs ordered and year of admission, which was significant at the $p<0.0001$ level.

To examine the relationship between the number of drugs ordered per hospitalization and the logarithm of total interaction time per hospitalization, a log-means

plot was created (**Exhibit 17).** This showed a curvilinear relationship between these two variables with a possible plateau effect after a mean of 40 orders. Conducting a logarithmic transformation of the mean number of drugs ordered straightened the log-means plot (**Exhibit 18**).

3.6.3 Patient Age

Descriptive statistics for patient age can be found in **Exhibit 1**. The mean age was 51.9 years (SD 20.3). **Exhibit 19** displays the summary statistics for age by year. A small increase in mean patient age during the study period was apparent but there was no evidence of linear trend (Spearman correlation coefficient of 0.008, p=0.19).

The log-means plot of mean patient age and logarithm of mean interaction time appeared to show a linear relationship between the two variables (**Exhibit 20**). However, closer examination shows that a linear relationship may not be present in ages less than 40. The likelihood ratio tests between Poisson models in which age was a continuous variable compared to age categorized into 5 groups (18-30, 31-45, 46-60 and 61-75 and >75) was significant ($p<0.001$), suggesting a notable departure from linearity. These 5 age groups were chosen based on quintiles which were rounded to the nearest multiple of 5. Due to evidence of departure from linearity by the likelihood ratio test, age was categorized into the 5 groups listed above.

3.6.4 Hospital Length of Stay

Descriptive statistics for hospital length of stay are presented in **Exhibit 1**. The mean length of stay was 7.8 (SD 14.8 days). Summary statistics for length of stay by year are displayed in **Exhibit 21**. There was a trend towards a smaller length of stay during the study period with the mean length of stay decreasing from 8.1 in 2000 to 7.0 in

2005. However the Spearman correlation coefficient of 0.003 did not reach statistical significance (p=0.31) between these two variables.

The log-means plot of length of stay and logarithm of mean interaction time showed a curvilinear relationship with a plateau effect after 14 days (**Exhibit 22**). This relationship was improved by logarithmically transforming the length of stay (**Exhibit 23**).

3.6.5 Resource Intensity Weight (RIW):

Descriptive statistics for RIW can be found in **Exhibit 1** and **Exhibit 24**. The mean resource intensity weights appeared to be highest in 2000 and were lowest in 2005. The maximum RIW decreased throughout the study from 282.9 in 1999 to 50.5 in 2005 with a step-like drop in 2002. This likely corresponds to changes in both the RIW calculation method and disease coding systems from ICD-9-CM to ICD-10-CA. There was evidence of a linear association between RIW and year (Spearman correlation coefficient = -0.85, $p<0.0001$).

The log-means of mean RIW and logarithm of mean interaction time showed showed a curvilinear relationship between the two variables with a plateau effect after a mean RIW of 3 (**Exhibit 25**). This relationship was improved by performing a logarithmic transformation of RIW (**Exhibit 26**).

3.6.6 Categorical Variables

There were four categorical variables in the dataset of interest.

3.6.7 Patient Gender

Descriptive statistics for gender can be found in **Exhibit 27 .** The number of drug interactions was higher in men than women (1.80 vs 1.01).

3.6.8 Hospital Service

Descriptive statistics for service are found in **Exhibit 28**. The number of DDIs was higher in surgical services vs medicine services (1.37 vs. 1.27).

3.6.9 Hospital Discharge Disposition

Descriptive statistics for hospital disposition are found in **Exhibit 29**. The number of DDIs varied among the various dispositions. There greatest difference appeared between those who signed out against medical advice and those who expired (0.91 vs 4.00).

3.6.10 Charlson Comorbidity Index

Descriptive statistics for comorbidity index are found in **Exhibit 30.** The mean number of DDIs varied amongst the categories. There was an increase in the number of DDIs between indices 0, 1-2, 3-4 but this does not continue for an index >5.

3.7 UNIVARIATE ANALYSIS

3.7.1 Crude DDI Rate

The observed DDI incidence density for the study period is presented in **Exhibit 5, Exhibit 6, and Exhibit 7**. Poisson regression analysis was also used to estimate the unadjusted DDI rate for the study period with no predictor variables in the model. There was evidence of overdispersion with the value of the Goodness of Fit (GF) statistic divided by the DF greatly exceeding 1. To correct this overdispersion, a Pearson scale

was used. With a Pearson scaling, the estimate for the crude DDI incidence density was 0.1876 (0.1859-0.1893) with GF statistic/DF of 0.86 (scaled deviance) and 1.00 (Pearson X2). This meant that based on the poisson model, patients spent 18.76% of their hospital time with at least one DDI. The model-based estimate of 0.1876 (0.1859-0.1893) includes the observed crude DDI incidence density presented in **Exhibit 5**.

3.8 OVERDISPERSION

In a Poisson distribution, the variance and the mean are equal. Overdispersion occurs when observed variance exceeds the mean for a particular distribution. Overdispersion occurs from outliers in the data, subject heterogeneity from factors not specified in the regression model, or correlation between the observations. Overdispersion results in an underestimation of the standard error and overestimation of the Chi-square statistics which will increase the risk of a type 1 error. Underdispersion also occurs – albeit much less frequently – and results in an overestimation of the standard errors and an underestimation of the chi-square statistics thereby increasing the risk of a type II error (53).

Overdispersion in the Poisson regression model is identified by dividing the Pearson Chi-Square value for model goodness of fit to the degrees of freedom for that model. When this ratio is close to 1, little evidence for over- or under-dispersion exists. However, when the ratio exceeds 1, overdispersion is present. There was evidence of overdispersion in each of the Poisson regression models. To correct for this, the Poisson models were refit using a scaling factor (in these examples the Pearson Q statistic divided by its degrees of freedom).

3.8.1 Predictor Variables

Exhibit 31 gives the univariate Poisson regression parameter estimates for all predictor variables. The parameter estimates of all predictor variables were statistically significant with a p-value <0.0001. All incidence density ratios are greater than one indicating that each predictor variable was associated with an increase in DDI incidence density.

Exhibit 32 shows the LR statistics for the type III analysis from the univariate Poisson regression analysis for the eight predictor variables. Although all were significant at the p<0.0001 level, the F-values and Chi-square values are shown for comparison. Log (number of drugs) had the highest F-value followed by Log(length of stay) and Log (resource intensity weight). Hospital service had the lowest F-value.

Exhibit 33 displays the model-based estimated DDI rate for all of the continuous and categorical variables. DDI incidence density ranged from 7 percent in 18-30 year olds to 25 percent in those >75 years, indicating that drug-drug interactions occurred during 25 percent of the admission time in patients greater than 75 years of age. Male patients had a higher DDI incidence density at 21% of admission time versus female patients at 17% admission time. Medicine patients also had a higher DDI incidence density (19%) as compared to surgical patients (18%). Patients discharged from hospital had a lower DDI incidence density at 16% versus expired patients (27%). Calculations for DDI incidence density for log (number of drugs ordered), log (length of stay) and log (resource intensity weight) are shown below **Exhibit 33.**

3.9 MULTIVARIATE ANALYSIS:

Univariate analysis revealed that all of the variables were significant at the $p<0.0001$ level. Therefore, all eight predictor variables of interest were included in the multivariate model. These were added in order of the F-value obtained from the univariate analysis (**Exhibit 32**). The changes in both intercept and parameter estimates between the univariate and multivariate models are shown in **Exhibit 34**. There was at least a ten percent change in the intercept and parameter estimates between the models suggesting that each predictor had an important influence in the multivariate model. This could be due to confounding but the fact that the intercepts changed from the univariate to multivariate models suggests multicollinearity as well. All predictor variables were considered to be clinically relevant to the outcome variable and provided further justification to including all eight predictors in the final model.

Exhibit 35 shows the LR statistics for the multivariate model. All variables were significantly associated with DDI incidence density, with all of the variables having a p-value less than 0.0001. Although all predictor variables were statistically significant, the log (number of drugs ordered), hospital service and patient age were the most important predictors based on the adjusted F-value of each parameter estimate.

Exhibit 36 presents the DDI incidence density ratios for all variables in the multivariate model. Most predictor variables were associated with a DDI incidence density ratio greater than 1. Hospital disposition, log (length of stay) and log (resource intensity weight) were exceptions to this observation although their relative importance is less than the other predictor variables mentioned above.

3.10 REGRESSION DIAGNOSTICS

Regression diagnostics are techniques used for exploring problems with a regression analysis and for determining whether certain assumptions have been fulfilled(54). Regression assumptions were assessed by using several of regression plots which were generated to test the assumptions of constant variance and linearity. The outcome variable had already been determined to follow a non-normal distribution **(Exhibit 9)**, which was the reason for selecting Poisson regression.

Residuals are the difference between the observed values and values predicted by the regression equation. Partial residual plots enable the assumptions of linearity and heterscedasticity to be examined. The deviance residual is the measure of deviance contributed from each observation. In general the deviance residual is preferred to the Pearson residual for model diagnostics because its distributional properties are closer to the residuals arising in linear regression models (55).

The partial residual plots were generated by plotting the standardized deviance residuals against the predicted values (**Exhibit 37**) and the absolute value of the standardized deviance residuals against the adjusted predicted values **(Exhibit 38)**. **Exhibit 37** demonstrates a small reduction in the standardized residual variance as the predicted values of the independent variable increased. If the line was horizontal to the x-axis and the residuals were evenly spaced around the line, this would indicate that the model fits the data perfectly. There should not be any funnel effect whereby the residuals spread out as the predicted values increased. The regression diagnostics for the final poisson model shows that not only does the line appear to slightly dip but there may be a

slight funnel effect visible. This indicates that the fit of the model is not perfect (model misspecification) or there is overdispersion present.

Exhibit 38 is a plot of the standardized deviance residuals by the adjusted predicted values. If there is constant variance and assumption of linearity, the line should be horizontal and the scatter around the line should be equal. However, the smoothed line shows a positive linear trend and demonstrates that the assumption of constant variance of the model is violated. Exhibit 36 and 37 demonstrate that there is changing variance. This can result from a misfit model or overdispersion.

To examine if an adequate link function was used in the regression, a plot of the adjusted linear predictor by the estimated linear predictor was generated. **Exhibit 39** shows a straight line with a positive slope, indicating that the link=log function was acceptable. If the line curved up, then a higher order link function should have been used. I the line curved down, then a lower order link function should have been used. In this analysis, the link=log function appears to have been appropriate.

Exhibit 40 shows the influential data point identified by Cook's D. One influential observation is visible. This encounter was for very long hospitalization (806 days), had numerous drug orders (58) and drug interactions (25). It does not represent the typical hospital hospitalization. When this observation was removed from the dataset, the results of the multivariate analysis did not change significantly therefore, they were left in the final analysis.

4 DISCUSSION

This retrospective observational study has determined that between 1999 and 2005, DDIs occurred in 19.2% of hospitalizations at the Ottawa Hospital. At least 1 DDI was present, on average, during 18.8 % of all hospitalization time. Category 1 and Category 2 interactions were rare, accounting for only 0.003% and 0.78% of all drug orders and 0.022% and 1.4% of hospitalization time respectively. Category 3 interactions accounted for the majority of the interactions (88%). They occurred with 5.7% of all drug orders and were present for 17.4 % of the hospitalization time. DDIs were more likely to occur with an increase in the number of drugs prescribed, patient age, length of stay, RIW, and comorbidity index. An increased number of DDIs were observed more frequently in men and in surgery patients.

4.1 CUMULATIVE INCIDENCE

This study examined the cumulative incidence of DDIs over a 7 year period in a large tertiary-care Canadian hospital. From1999 to 2005, 19.2 percent of patients hospitalized had at least 1 potential DDI during the hospitalization. Due to the comprehensiveness of the Ottawa Hospital Data Warehouse, the cumulative incidence of DDIs could be determined for all inpatients during the study period.

The small decrease in cumulative incidence (from 19.7 to 17.7) is statistically significant by the Mantel-Haenszel Chi-Square at $p<0.0001$. However, the sample size is large and may account for the statistical significance. To our knowledge, no study has previously studied changes in the prevalence of DDIs over time. However, because of the large sample size of the study, even small differences are statistically significant and the

clinical significance of these differences is essential. The absolute decrease of 2 % in the cumulative incidence of DDIs means that assuming an average of 20, 539 admissions per year, the number of people exposed to at least 1 DDI decreased by 410 to 20, 128 over the study period. This decrease is important if the potential DDIs are risky.

The decrease in the cumulative incidence of potential DDIs was surprising for several reasons. The number of drugs per hospitalization increased throughout the study. This would be expected to increase the number of DDIs. However the number of DDIs per hospitalization decreased over the study period, resulting in a decrease in the number of hospitalizations experiencing at least one DDI during the study period. One possible explanation for this decrease in DDIs may include increased screening for DDIs by pharmacists or DDI software or increased awareness of DDIs by prescribers. This study did not analyze drugs started in the hospital or continued from the community separately. It may be that the drugs used in the community had fewer DDIs due to enhanced community pharmacy screening.

Another explanation for the reduction in DDIs may relate to the DDI definitions that may have changed throughout the study period. The DDI definitions used for this study were current as of October 2005 and some of the DDIs identified at this date would not have been identified earlier in the study. For example, cisapride had a number of interactions that were not identified until the drug had been used extensively. It was withdrawn from the Canadian market in late 2000 and there would be no DDIs with this medication after this date. Another example would be the use of spironolactone following the publication of the RALES trial, which increased in Ontario from 34 per 1000 prescriptions in 1994 to 149 per 1000 patients in 2001(56). With the publication of

increased mortality related to hyperkalemia in 2004, the use of spironolactone in CHF patients is now reserved for refractory CHF not responsive to other therapy and the use has decreased. While these two drugs have decreasing utilization during the study due to unacceptable toxicity profiles, other drugs viewed as safer medications may have been prescribed in their place, resulting in a net increase in the number of drugs prescribed over the study period and a decrease in the number of DDIs.

This study included all inpatients 18 years of age or older, admitted to the Ottawa Hospital. No previous study has described the DDI incidence in a similar hospital population. Bacic (39) reported a DDI incidence of 7.7% in 4951 inpatient internal medicine prescriptions over a 25 week period. Witlink et al(27) reported DDIs on three internal medicine wards (682 patients). They found potential DDIs to be present in 39.2-64.6% patients. Groonos (24) studied 2547 inpatient internal medicine medication profiles over 13 months and found 6.8% of all patients had several drug combinations that may have led to serious consequences. Gosney (38) examined 573 geriatric inpatient charts and found DDIs in 3.2% of prescriptions that affected 23.7% of patients. Egger (23) et al examined 500 patients discharged from the internal medicine wards and found 747 potential DDIs. Beers et al(37) reported a 10% incidence of DDIs when a new medication was prescribed during emergency department visits (non-admitted patients). Raschetti (17) examined 5497 emergency charts and reported DDIs in 3.9% of visits but these were more serious as many of them led to a hospitalization. Prince (20) examined 10,000 emergency visit records and found drug-related illnesses in 2.9% of visits resulting in admission in 24% cases. Karas (32) identified DDIs in 16% of emergency patients, 20%

appeared to be significant. These reported incidence measures differ due to the inclusion of different inpatient subspecialties and the methodology used to identify the DDIs.

4.2 INCIDENCE DENSITY

To our knowledge, no study has previously measured or reported potential DDIs as an incidence density. Drug-Drug Interactions were present for 18.8% of all hospitalisation time. This implies that patients who had a DDI experienced the interaction for a substantial proportion of their hospitalisation as only 19% of patients experienced at least one DDI at some point during the hospitalisation. In addition, the substantial DDI incidence density can be partially explained by the influence of length of stay on DDI risk, as we demonstrated, the probability of having at least 1 DDI increases to 100% as the length of stay increases.

Two factors explain why we observed an incidence density of 18.8% despite a cumulative incidence of 19%. First longer admissions were more likely to have a DDI and they also have more influence on the incidence density. Second, the DDI incidence density for patients with DDIs is 0.57 (0.05-0.98). This indicates that for patients exposed to at least one DDI, the exposure to the DDI occurred, on average, during 57% of the hospitalization time. Perhaps many of these DDIs are due to continuing the patients' prescriptions from the community. If this is the case, one would imagine that their seriousness may be reduced because the ADR would have occurred prior to admission. Also, the longer a DDI exists, the lower the probability of having a clinically significant ADR that is undetected.

4.3 CLINICAL SIGNIFICANCE OF DRUG-DRUG INTERACTIONS

In an attempt to determine DDI severity, DDIs identified in this study were stratified by interaction category. Category 1 interactions are recommended to be avoided and Category 2 interactions are recommended to usually avoid due to the high probability of an adverse drug reaction. In this study, category 1 and 2 interactions were rare, accounting for only a small percentage of hospitalization time (maximum 1.4%).

Category 3 interactions accounted for the majority of the interactions (88%) and accounted for 17% of hospitalization time. It is recommended that the doses of these drugs in this category are altered to minimize risk. However, this study was not designed to evaluate whether a dose adjustment occurred when these DDIs occurred. In contrast to the category 1 and 2 interactions, category 3 interactions may not always be associated with an adverse reaction. In category 3 interactions, the outcome depends on the dose of medication prescribed, the duration of the interaction, and other patient comorbidities that would determine the patient's susceptibility to the interaction. For example, a number of DDIs, such as digoxin and verapamil, are worse in patients with renal dysfunction due to reduced elimination of increased drug levels that are a function of the DDI.

The significance of any interaction depends on two things: the risk-benefit ratio of the co-administration and the degree of monitoring for any potential adverse effects. Patients often have two or more co-morbidities requiring two interacting drugs. For example, patients with coronary artery disease often have atrial fibrillation so may require ASA to prevent myocardial infarction and warfarin for stroke prevention. The co-administration in this case may be appropriate given the potential benefit of the drugs. However, it needs to be acknowledged that the risk of adverse events increases when the

drugs are being prescribed concomitantly and enhanced monitoring of side-effects should ensue. As all patients in our study were inpatients who could be closely monitored with vital signs and frequent laboratory work, it is possible that physicians performed this risk benefit analysis and decided to order the medications regardless of a known interaction. Future studies should evaluate whether this, in fact, happened.

4.4 FACTORS ASSOCIATED WITH DDIS

4.4.1 Number of Drugs Ordered

The number of drugs ordered increased significantly throughout the study period. This finding is consistent with Canadian drug utilization trends that have been documented in the late 1990s and early 2000's (57) that show a continuous increase in expenditure on patented medications. This increased drug utilization may be secondary to a number of factors including: an aging population; increased co-morbidity in the population; the introduction of clinical practice guidelines aimed at not only treatment but prevention; the development of medications for diseases that were previously untreated pharmacologically. It also is expected that as the number of drugs ordered increased, the number of DDIs would also increase. This was observed consistently over this study period. A number of other studies also found an association between increased DDIs and the number of drugs prescribed (29;33;37;58). In one study of DDIs in the emergency department, an increased risk of DDIs was associated with the prescription of three or more medications (29). This was also reported in patients recently discharged from hospital in which DDIs were more likely to be in patients prescribed 3 or more drugs and the proportion of patients with DDIs increased with the number of drugs prescribed. Another study also found that over 12 drugs had a 100% chance of experiencing a class 1-

4 DDI (33). The different inclusion criteria make it difficult to compare the results to our study due to the different DDI categories included.

4.4.2 Patient Age

As patients age, their co-morbidities increase resulting in increased drug utilization and an increased risk of DDIs. This observation has also been found in one study of emergency patients in which patient age exceeding 60 years was the only predictor variable found to be significantly associated with DDIs in this department(29). Age was not found to be a significant predictor in one study of recently discharged patients but very few young patients were included and the mean age exceeded 70 years(33).

4.4.3 Length of Stay

Hospital length of stay decreased during the study period. This same trend has been reported by CIHI (59) which showed a 15% reduction in hospital length of stay from 1995/1996 to 2004/2005. Given that hospital length of stay is decreasing, this may reduce the number of DDIs observed during the study period.

4.4.4 Resource Intensity Weight

During the study period, resource intensity weight decreased from a maximum of 1.9 in 2000 down to 1.5 in 2005. The Spearman correlation coefficient (-0.85) was significant at the $p<0.0001$ and suggest a trend towards a reduction of RIW throughout the study. Such a change could be due to a change in coding system from ICD-9 to ICD 10. Since the RIW calculation uses these codes, we can assume that the acute change in RIW values, seen at the time of the change in coding systems, was due to this change.

In the univariate model, the incidence density ratio for logRIW was 1.36 meaning that the IDR was 1.36 for every log increase in RIW. In the multivariate model, the logRIW was associated with a reduced DDI incidence density. Although this was close to 1, with an IDR of 0.94 (0.92-0.96), the RIW was no longer associated with an increased DDI incidence density once all other predictor variables were included in the multivariate model. This variable was still found to be statistically significant and therefore was included in the model as RIW adjusts for the cost of care in the Ottawa Hospital. We could find no other studies identified in the medical literature that examined the relationship between RIW and DDIs.

4.4.5 Gender

This study found that DDIs were more common in men. The number of DDIs was higher in men than in women (mean number of DDIs=1.8 vs 1.0). In the univariate analysis, gender had a DDI incidence density ratio of 1.21 (1.19-1.23) indicating a 20% higher incidence of DDIs in males vs females. When adjusted for other predictor variables in the multivariate model, this ratio was lower at 1.06 (1.04-1.07) $p<0.0001$. This indicates that when adjusted for other predictor variables, gender differences were still significantly associated with DDI incidence density although the DDI incident density ratio is relatively small.

Domecq (60) studied the differences in ADRs between women and men and found ADRs to be significantly more frequent in women ($p<0.0001$). There was no discussion concerning how many of these ADRs were secondary to DDIs.

4.4.6 Service

DDIs occurred more often in surgery patients. However, the DDI incidence density was higher in medicine patients [0.191 (0.190-0.194) vs 0.182 (0.180-0.185)] as shown in **Exhibit 33**. This indicated that although there were more interactions occurring in surgery patients, DDIs occupied a greater proportion of admission time in medicine patients. The longer the length of interaction, the increased risk of an adverse drug reaction such that the DDI incidence density is a more important clinical outcome. To our knowledge, no previous studies have compared DDI incidence density between different hospital services.

4.4.7 Hospital Discharge Disposition

Hospital discharge disposition was significantly associated with DDI incidence density both in the univariate and multivariate models. In the univariate model, discharged patients were the reference category and all DDI incidence density ratios were greater than one, indicating an increased incidence density in the other discharge categories. In the multivariate model however, after adjusting for the other predictor variables, the DDI incidence density ratios for other discharge categories were all less than 1. A stratified multivariate analysis by discharge disposition showed that only expired patients and discharged patients had other predictor variables that were all significant. The other 2 strata (discharged with services and transferred), had a variety of other predictor variables that were not significant. This may account for the DDI incidence density ratio changes between the univariate and multivariate models. If discharge disposition is changed into a categorical variable (discharged=1 if discharged, 0 if not),

then the DDI incidence density ratio in the multivariate model becomes 1.13 (1.10 – 1.15) $p<0.0001$ with all predictor parameters still significant at the $p<0.0001$.

There were no studies reported in the literature that included discharge disposition as a predictor variable.

4.4.8 Comorbidity Index

Comorbidity index is significantly associated with DDI incidence density ($p<0.0001$). There is also an increase in the DDI incidence density ratio for indices <4. Previous studies have found that an increased comorbidity index is associated with an increased one year mortality (49;61). This study has found that an increased comorbidity index was associated with an increased DDI incidence density. The DDI incidence density drops slightly for index 5 but still significantly exceeds 1, indicating that there is a increased DDI incidence density associated with category 5 as well.

No previous studies have examined the association of the Charlson comorbidity index with DDI incidence density.

4.5 DRUG-DRUG INTERACTION SCREENING

This study has exposed the significant incidence and prevalence of DDIs for all inpatients over the seven year period. The fact that DDIs have occurred, despite screening by the physician, pharmacist and computer, may be due to several reasons. First, drug combinations in the Drug Interaction table are current as of 2005. However this was a retrospective study and some of the category 1 and category 2 DDIs would not have been identified when the two drugs were initially prescribed. This may occur when the drugs are newly marketed. For example clarithromycin and rifabutin were once used for the

treatment of Mycobacterium Avium Complex. Only after the drugs were used clinically did the knowledge of the DDI become available and published in the medical literature. This resulted in a newly defined DDI (62). Given that the DDI was identified after the clinical use began, the combination can still be detected in the OHDW.

Second, drug-drug interactions may have been missed due to an incomplete screening process. The fact that a high proportion of DINs in the dataset were incorrect suggests that the interaction software, used by the pharmacy, would not be able to screen all potential interactions. This is because the interaction software used by The Ottawa Hospital used DINs to identify DDIs. If the dataset is not meticulously maintained, then the effectiveness of DDI interaction software will of course be reduced. If the DDI identification software uses only DIN numbers, then a significant number of DDIs will be missed or incorrectly identified during the years of this study. Given that the interaction software alerts pharmacists to possible interactions, it is then up to the pharmacist to determine the clinical significance of the interaction. The potential for numerous irrelevant alerts, due to incorrect DINs in the database, may have been present during the study and it is possible that many of these alerts may have been discarded. Unfortunately, as this is a retrospective study, this aspect of DDI screening could not be examined. What has be come apparent however is the great need for clinically accurate DDI-screening software and utilization databases. This is exceeding difficult to maintain over the years and requires frequent up-grades, additions, and numerous support staff but it is mandatory if the computer is to play an important role in screening for DDIs.

Finally, the physician may have determined that the interaction was not significant and prescribed the combination anyway. For example, Asprin and warfarin are

listed as a category 3 interaction. If the combination is to be used for antithrombotic purposes, then Hansten mentions that the benefit may outweigh the risk of the combination (46). However, if the asprin was to be used for antipyretic or analgesic properties, then the risk of the combination with coumadin likely outweighs the benefit. This analysis is difficult to incorporate into DDI screening software since the indication for the two drugs is not always known. The prescribing physician decides, in such a circumstance, what is the risk/benefit in the individual patient and will then be able to make a decision regarding the appropriateness of the drug combination.

Despite the difficulty in determining the significance of the identified interactions, it is important to document their incidence in a general hospital population. We found that DDIs account for a significant proportion of the drugs ordered. While not all of these interactions may cause serious adverse events, there are many that have the potential to do so. Predicting which DDIs will cause adverse events is exceedingly difficult. One study on an internal medicine ward, found that physicians considered only 12% of all identified DDIs to be clinically significant (27). This has very important implications in the development of order-entry computer systems which would automatically screen every drug order that the physician enters in the computer. Often the DDI alerts are so numerous that the physician will be unable to determine the relevance of such interaction alerts. If 5% of the ordering generates a DDI interaction alert of questionable significance, then this will have a huge impact on work load and a tendency to disregard potentially important DDIs

4.6 LIMITATIONS

This study has several limitations. As demonstrated in the review of the medical literature, no gold standard exists to define DDIs. In this study, Hansten and Horn's publication was used since it is comprehensive and updated quarterly. It also lists DDIs by individual drug names, not by therapeutic classes, which was required for computer identification of the DDIs. Theoretically, there may be potential DDIs that result from co-administration of drugs from interacting classes. If this is the case, this study underestimates the actual number of DDIs that occur not only between interacting drugs but between interacting drug classes. For example, enalapril is the only ACE inhibitor interacting with spironolactone listed in the interaction table but it is likely that all ACE inhibitors have the potential for this interaction. If all ACE inhibitors were considered as possibly interacting with spironolactone, this would greatly increase the number of DDIs identified. Therefore, while Hansten and Horne is likely to be the most complete DDI reference presently available, it might have missed some DDIs resulting in our study underestimating their prevalence.

The use of the OHDW has resulted in a very comprehensive study database but there were considerable inconsistencies in some variables such as DIN numbers and therapeutic classification. The DIN numbers were cleaned via computer and manual matching. The therapeutic classification variable could not be used due to >30% missing values. All DDI interaction pairs were inspected to ensure the right interactions were identified. However, the need to manually verify this work impeded the efficiency of the DDI computer identification.

Although the majority of drug orders are entered through the process described in this study, there may have been a few drug orders missed if given without a processed order. This may happen in the case of an admitted patient remains in the emergency department for an extended period of time due to lack of beds on the floor. When patients remain in the emergency room prior to admission, the input of their drug orders into the computer system is delayed. These situations generally happen infrequently and are unlikely to have a major influence on the results of the study however the number of DDIs may be slightly underestimated due to these reasons. Drug orders given on an "as needed" or prn basis were also excluded. While most of the category 1 and 2 interaction drugs are not usually given on a prn basis, some category 3 interactions include "prn" medications and excluding them will result in an underestimation of category 3 DDIs.

DDI exposure time was defined as co-administration time of the two interacting drugs. However, the duration of the interaction is also dependent on the time that the drugs are present together in vivo, which extends beyond the last dose administered. The true duration of interaction would depend on the mechanism of the interaction and the pharmacology of the two interacting drugs. Several important components of drug disposition (absorption, distribution, metabolism and excretion) of each drug would affect the time that the interaction was important. Given that these mechanisms vary widely in patients, it is impossible to accurately account for this extended interaction time and therefore this study underestimates the true biological drug-drug interaction time.

As this is a retrospective study, all DDIs identified represent only potential drug-drug interactions. In contrast to electronic DDI-screening software that has been shown to produce a high number of signals but overestimate potential DDIs (22), the program

developed for this study identified only category 1,2 and 3 potential DDIs and therefore did not over-estimate the incidence of these events. However, due to the immense scope of the study, it was impossible to assess the clinical outcome of the interactions. It has been shown however that only a small proportion of DDIs result in clinically important outcomes (21;22;25;26). By limiting the study to the interactions that were category 1,2 or 3, the potential for adverse events can be identified. The DDIs most likely to cause adverse events (category 1 and 2) were found to be rare and are consistent with other research findings (33).

Overall, our study likely underestimated the true number of DDIs since we limited our analyses to DDIs consisting of prescription drugs, ASA, iron and antacids. We did not consider interactions with calcium and other vitamin preparations because these often exist in combination products and are difficult to identify in the database. In addition, we also did not consider DDIs involving vaccines, natural products, or other non-prescription products because these are difficult to identify in the database. Finally, IV solutions with potassium and other nutritional replacement solutions/products were excluded as it is difficult to differentiate physiologic supplementation from therapeutic use of these products. Exclusion of these products would result in a small decrease in our measured DDI incidence.

4.7 NEXT STEPS

4.7.1 Should patients/providers/administrators be concerned?

This study was not designed to examine the adverse outcomes as the result of the DDIs identified. However, these potential DDIs are significant because they increase the risk of an adverse event and are might be avoidable. Potential DDIs are like driving a car

15km/h over the speed limit. This is generally thought to be low-risk behaviour but under certain circumstances this may be more or less acceptable. For example, if this were to occur in a school zone, on a snowy day, the risks are greater than if this were to occur on a highway under optimal driving conditions.

In the case of potential DDIs, potential DDIs may become more important when other defences are impeded. In the case of potential DDIs, these may become more significant when patients have hepatic or renal disease that may reduce drug elimination and increase drug levels. Defences may also be reduced during a time of physician cross-coverage on the weekend. For example, if a new drug is started before the period of cross-coverage, the cross-covering physician may not know to monitor closely for DDIs as they were not the original prescriber.

This research highlights the challenge physicians, nurses and pharmacists face in trying to be aware of all potential DDIs. While the category 3 DDIs often only require increased monitoring or a dose adjustment, this will not occur if the health care providers are unaware of the interaction. Computerized order entry may assist making these DDIs known to the prescriber but given the frequent occurrence of DDIs, the computer alerts generated can be overwhelming. Reducing the number of alerts may help to solve this problem but may give the prescriber a false sense of security that all DDIs have been screened for. Pharmacists working in close proximity to the medical team and directly interacting with the prescribers and nurses also help to increase communication and awareness of potential DDIs. Perhaps their involvement in screening higher risk patients (those with impaired hepatic/renal function and elderly patients) may help reduce DDIs.

Finally, it has been shown in the medical literature that prevention of DDIs happen most often at the prescribing phase but very few are prevented at the administration stage(8). Safeguards have been put in place at most institutions to double check potentially toxic medications such as chemotherapy, before administration, but this primarily deals with drug dosing and not necessarily DDIs. Further safety mechanisms could be put in place to increase monitoring (ie. Daily INRs automatically ordered) when two interacting drugs are prescribed that need increased surveillance of CBCs and INRs and other laboratory tests.

This research has also highlights the challenge in maintaining DDI software to screen for DDIs. There are a significant number of technical issues that need to be addressed on a continual basis given the number of product changes, formulary changes and DIN number changes. This requires a dedicated team who are able to maintain the database and modify it when these changes occur. The value of the DDI screening program will depend on how the database and screening software interact and are maintained.

4.7.2 Next research steps

It is clear that the next research steps will be to determine the clinical significance of these potential DDIs. Given the large number of DDIs, the focus will need to be on selected DDIs, looking for specific syndromes related to the DDI (ie. hyperkalemia with ACE and spironolactone). This may be achieved by studying different categories of DDIs to determine their clinical significance. The exposure time for different DDIs might also provide a signal of risk if it can be found that DDIs

prescribed for short durations have toxic adverse outcomes. The ratio of incidence density to the cumulative incidence may provide a signal for high risk DDIs.

4.8 SUMMARY

Drug-Drug interactions occurred frequently in this very large hospital population. Despite only occurring in 19 percent of the admitted patients, DDIs occur during almost 19 percent of admission time and account for up to 5% of drug orders. The clinical significance of such interactions may be limited, however and this has yet to be determined. Factors associated with DDIs include the number of drugs ordered, surgical service, increased patient age, increased comorbidity index, particular discharge disposition, decreased length of stay, decreased resource intensity weight and male gender.

5 LIST OF ABBREVIATIONS

ATC	Anatomic and Therapeutic Classification
AHFS	American Hospital Formulary System
BNF	British National Formulary
CCI	Charlson Comorbidity Index
DDI	Drug-Drug Interactions
DF	Degree(s) of Freedom
GF	Goodness of Fit
IDR	Incidence Density Ratio
LRT	Likelihood Ratio Test
MAX	Maximum
MIN	Minimum
NB	Negative Binomial
OHDW	Ottawa Hospital Data Warehouse
P5	5^{th} Percentile
P25	25^{th} Percentile
P50	50^{th} Percentile
P75	75^{th} Percentile
P95	95^{th} Percentile
RIW	Resource Intensity Weight
SD	Standard Deviation

APPENDIX A : PUBLISHED STUDIES

Published Studies of Drug-Drug Interactions in a Defined Patient Population

Author/ Country	Methodology	Number	Study Population	Duration	Method of detection of DDI	Conclusions
Egger(22) Germany	Prospective Survey	163 Geriatric patients	Inpatient	4mo	Computer-identified DDI program in comparison to a pharmaco-epidemiologic team	Database had a Sensitivity of 58% for identifying the DI's. In 14 out of 24 DDI-positive patients, at least one computer signal indicated a real DDI.
Juurlink(21) Canada	Nested Case-Control Database	All Ontario residents>65	Outpatient	6yr	3 pre-specified drug interactions	Patients on glyburide, admitted for hypoglycemia, were more than 6 times as likely to have been treated with co-trimoxazole in the previous week (adjusted odds ratio, 6.6; 95% confidence interval, 4.5-9.7). Patients admitted with digoxin toxicity (n=1051) were about 12 times more likely to have been treated with clarithromycin (adjusted odds ratio, 11.7; 95% confidence interval, 7.5-18.2) in the previous week,. Patients treated with ACE inhibitors admitted with a diagnosis of hyperkalemia (n = 523) were about 20 times more likely to have been treated with a potassium-sparing diuretic (adjusted odds ratio, 20.3; 95% confidence interval, 13.4-30.7) in the previous week. Many hospitalizations of elderly patients for drug toxicity occur after administration of a drug known to cause drug-drug interactions. Many of these interactions could have been avoided

Author/ Country	Methodology	Number	Study Population	Duration	Method of detection of DDI	Conclusions
Egger(23) Switzerland	Retrospective Chart Review	500 discharged pts	General Medical Inpatient	4mo	Computer-identified	747 potential DDIs at discharge were identified. These were rated as potentially minor 72 (17.9%), moderate 281 (69.9%), and major 49 (12.2%) severity. Anticoagulants, CNS depression and hypoglycemics most important therapeutic classes.
McDonnell(13) USA	Retrospective Database	ADR reports	Inpatient	11 months	Not specified	Over 11 months, 158 ADRs were directly related to hospital hospitalization. 96 (62.3%) of these events were considered potentially preventable, with 23 (24%) considered severe to life-threatening. Drug-drug interaction accounted for 26% ADR's identified.
Hunzikier(16) Switzerland	CHDM database	48,005IM Hospitalizations 12,785 ADR's	Internal Medicine Inpatients	19 yrs	Not specified.	7% of ADR's were due to DI's
Raschetti(17) Italy	1-year prospective collection of data on visits performed at an emergency department.	5497 ER visits	Emergency Patients	1yr	Investigator review	3.8% of ED visits were due to a drug-drug interactions. These visits were typically more severe and most patients were subsequently hospitalized.
Wiltlink(27) Netherlands	Cohort Study	682 patients	Three internal medicine Inpatient Wards	Not specified	Investigator review	39.2-64.6% patients had potential interactions. Only 0.12% were clinically significant (minor). Physicians only consider a small number of interactions clinically significant
Adson(42) Germany	Retrospective Chart review	100 charts	Psychiatric Consultations on Inpatients	4mo	Investigator review	Patients took a mean of 8.8 medications; 12.9 for those undergoing organ transplantation. Of 100 patient profiles reviewed, 14 potential DDIs involving P450

Author/ Country	Methodology	Number	Study Population	Duration	Method of detection of DDI	Conclusions
						isoenzymes were identified.
Gringos(24) Finland	Retrospective database	2547 patients	Internal Medicine Inpatients	13 months	Computer DDI program	6.8% of all patients had one or several drug combinations that could lead to serious clinical consequences
Doucet(18) USA	Cohort	1000 patients >70 years of age	Geriatric Inpatients		Investigator review	Five hundred thirty-eight patients were exposed to 1087 DDI. The most frequently involved drugs were cardiovascular and psychotropic medications. There were 189 side effects observed in 130 patients. The most frequent side effects were neuropsychological impairment, hypotension, and acute renal failure
Huic(28) Croatia	Cohort study	5,227 hospitalizations	2 inpatient departments	1year	Investigator review	Drug interactions caused 23.8% of ADRs. Only 11 (8.5%) of patients suspected that the drug might have caused the ADR
Jankel(19) Greece	Literature review of 9 ADR studies	9 Studies	Inpatients	1year	Investigator review	The incidence of hospital hospitalizations due to D-DIs ranged from 0 to 2.8%
Herr(29) USA	Prospective review of medication profiles	341 Patients	Emergency Room Patients	1year	Computer	The incidence of clinically relevant interactions was significantly higher among current medication (9.7%) than medication added in the ED (3.1%). Clinically relevant interaction from both current and ED-initiated medication was associated with taking three or more medications on ED arrival (P = .016 and .045, respectively). Multiple regression showed age of 60 years or older to be the sole predictor of clinically relevant interaction among current medication (P = .05).

Author/ Country	Methodology	Number	Study Population	Duration	Method of detection of DDI	Conclusions
Prince(20) USA	Retrospective chart review	10,184 patients	Emergency room patients	4months	Investigator review	Of 10,184 patients who visited the emergency department, 293 (2.9%) had drug-related illness; 71 (24%) of these patients were admitted. The drug classes most commonly involved were drugs of abuse (23.2%), anticonvulsants (17.1%), antibiotics (12.6%), respiratory drugs (8.9%), and pain medications (8.9%). The most common category of drug-related illness was overdose or abuse (35%) followed by non-compliance (28%), ADR (28%), toxicity (8%), and drug interaction (1%). The average length of stay for patients who were admitted was 5.8 days, and the average cost of hospitalization was $8888.
Schneider(36) USA	Retrospective chart review	463	Outpatients	12 months	Investigator review	Physician action was taken on 84% identified DDI's The four most frequent DDI's were Digoxin/Quinidine, Theophylline/Cipro, Digoxin/Verapamil Theophylline/Cimetidine.
Beers MH(37) USA	Retrospective survey	476	ER department	2 months	Computer and investigator review	47% of visits led to an added medication. In 10% of the visits in which at least one medication was added, the newly added medication resulted in a DDI. In the emergency departments studied, a medication history was recorded on every patient and was available to physicians, but physicians did not routinely screen for potential DDIs.
Tamai,I.Y(30) USA	Prospective chart review	138	Geriatric Inpatients	15 days	Investigator review	Of the 24 suspected interactions that were identified, 11 had potential clinical importance, and all 11 involved drug combinations that could alter the metabolism or action of one of the

Author/ Country	Methodology	Number	Study Population	Duration	Method of detection of DDI	Conclusions
						drugs. However, only two patients were exposed to any substantial degree of risk, and dosages of the drugs involved were adjusted.
Gosney,M(38) UK	Prospective survey	573	Geriatric Inpatients	30days	Investigator review	Patients received an average of 2.14 drugs at admission, 5.48 during inpatient stay, and 3.47 on discharge. Contraindicated or adversely interacting drugs were identified in 200 (3.2%) of 6160 prescriptions. 136 (23.7%) patients were affected. 7 patients received drugs to which they had had adverse reactions. There were a further 60 contraindicated and 133 adversely interacting drugs. 117 prescriptions were potentially hazardous and another 27 interactions may have led to sub-optimal treatment. 131 (65.6%) undesirable prescriptions were deemed avoidable and a further 36 (18%) were probably so. The frequency of errors was higher in hospitalization medication (5.3%) than in hospital prescriptions (2.9%).
Koepsell,T.(31) USA	Prospective intervention trial	3097 patients (med profiles available) and 3089 controls	Outpatient clinic	21 months	Computer	The incidence of preventable drug-drug interactions and redundancies was very low and was unaffected by the availablility of medication profiles. In this setting, it appears that the prescribing of interacting or redundant drugs is more often due to inadequate provider knowledge than to inaccessible patient-specific drug data.
Karas S(32) USA	Prospective random chart Review	355 patients	Emergency Room Patients	6months	Computer	Interactions were present in 57 patients (16%), with an incidence ranging from 5.6% for those taking two drugs to 100% for those taking seven

Author/ Country	Methodology	Number	Study Population	Duration	Method of detection of DDI	Conclusions
						drugs. From the total of 76 potential drug interactions identified, 69 involved one of only 10 drugs, and 15 interactions (20%) appeared to be potentially clinically significant.
Bacic(39) Croatia	Prospective prescription review	1303 Patients	Internal Medicine Hospital Wards	25 weeks	Investigator Review	4951 records for 1303 Patients were reviewed. Incidence of medical errors was 14.7% (incorrect dose, interval, duplications and drug-drug interactions). The incidence of DDI was 7.2% but only 0.2% were clinically significant as classified by the AHFS system. Patients had an average of 3.8 drugs prescribed.
Cannon(44) USA	Retrospective OACIS chart review	786 Patients with 452 different	Home HealthCare Patients (Outpatient Geriatrics >65 yrs)	1 year	Investigator Review	DDIs identified in 10% of patients. In those patients with polypharmacy (>9drugs). DDIs were identified in 20% patients.
Chen(25) UK	Retrospective Chart Review	1135 patients	General Practice Outpatients	1 year	Computer identified	1.9 (1.2-2.3) DDI/Drug-Disease Interactions per 1000 patient years were identified. 4.3 per 1000 people (3.2-5.4) prescribed 2 or more drugs.
Glingborg(33) Denmark	Cross-sectional survey	200 patients	Medicine/Surgery		Investigator	No Class 1 interactions. 51% of patients had Class 2 or 3 interactions. No clinically significant interactions occurred.
Lane(34) Finland	Retrospective	169 patients	Medicine Inpatients	2 yrs	Investigator	The number of patients without a potential interaction was 44.4% at pre-hospitalization, 39.6% at discharge, and 39.1% at post-discharge. Patients with potential interactions had a mean of 2.8, 2.7, and 2.4 interactions at each of the time points. Classes of

Author/ Country	Methodology	Number	Study Population	Duration	Method of detection of DDI	Conclusions
						interacting drugs were identified.
Mirco(41) Portugal	Prospective	162 patients	Medicine Inpatients	1 yr	Investigator	DDIs accounted for 1.7% of errors.
Straubhaar(26) Switzerland	Retrospective	400 patients	Heart Failure Inpatients	15 months	Computer (Micromedex)	68% Patients had a potential DDI. The median number of DDIs per patient was 1.5 (0-3). Potential DDIs were associated with more drugs prescribed (median number of 8 vs 5)

APPENDIX B: DRUG NOMENCLATURE

DRUG NOMENCLATURE

Several different names can be used to identify a drug and can complicate research if not standardized. Common names that are used to identify drugs include chemical name, generic name, and brand or trade name. The chemical name describes the chemical and molecular structure of the drug. The generic name describes the common name of the drug used in clinical practice. The trade name is the name specified by the manufacturer. There are a number of expert committees and international groups that standardize drug nomenclature and establish rules governing the classification of new substances. They include the United States Adopted Names (USAN), World Health Organization (WHO), British Approved Name (BAN) and International Proprietary Name (INN).

ATC CLASSIFICATION SYSTEM IN DRUG UTILIZATION RESEARCH

The field of drug utilization research has attracted increasing interest since its infancy in the 1960s. At a symposium in Oslo, it was agreed that an internationally accepted classification system for drug consumption studies was needed. At the same symposium, the Drug Utilization Research Group (DURG) was established and was tasked with the development of internationally applicable methods for drug utilization research.

By modifying and extending the European Pharmaceutical Market Research Association (EPhMRA) classification system, Norwegian researchers developed a system

known as the Anatomical Therapeutic Chemical (ATC) classification. The ATC classification system involves a classification of drug and also determines the Defined Daily Dose (DDD) to be used in drug utilization studies.

In 1996, WHO recognized the need to use the ATC/DDD system as an international standard for drug utilization studies (48). The purpose of the ATC/DDD system is to serve as a tool for drug utilization research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels. A major aim of the Centre and Working Group is to maintain stable ATC codes and DDDs over time to allow trends in drug consumption to be studied without the complication of frequent changes to the system.

In the classification system, drugs are classified in groups at five different levels. The drugs are divided into fourteen main groups (1st level), within one pharmacological/therapeutic subgroup (2nd level). The 3rd and 4th levels are chemical/pharmacological/therapeutic subgroups and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups.

For example the complete classification of the drug metformin illustrates the structure of the code:

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Oral blood glucose lowering drugs (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	Metformin (5th level, chemical substance)

1. Nomenclature used by the ATC/DDD classification system prefers International non-proprietary names (INN). If INN names are not assigned, USAN (United States Adopted Name) or BAN (British Approved Name) names are usually chosen.

6 APPENDIX C: EXHIBITS

Exhibit 1: Descriptive Statistics for Outcome and Continuous Predictor Variables

	Mean	Median	Std	Min	Max
OUTCOME VARIABLES					
Number of Potential Drug-Drug Interactions per Hospitalization	1.3	0.0	6.1	0	443.0
Interaction Time (Days)	1.5	0.0	7.3	0	837.1
PREDICTOR VARIABLES					
Number of Drug Orders per Hospitalization	20.2	14.0	22.7	0	862.0
Patient Age (Years)	52.3	52.0	20.1	18.0	107.0
Charlson Comorbidity Index	0.9	0.0	1.3	0	4.0
Hospital Length of Stay (Days)	7.8	3.8	14.8	0	1113.6
Resource Intensity Weight	1.7	1.0	2.9	0.1	282.9

January 1, 1999 to September 30, 2005

Summary statistics for these outcome and continuous predictor variables are provided. The statistics are based on the hospitalization as the unit of analysis.

Interaction time was the time during which at least 1 interaction occurred.

The Charlson Comorbidity Index has four levels based on the Charlson score: 0, 1-2, 3-4 and >5. The CCI was calculated by using assigned weights for the comorbidities (49). The assigned weights are also shown in Appendix D.

RIW (Resource Intensity Weight) is a relative resource allocation methodology for estimating the costs of a hospitalization for both acute and day procedure care.

(Std=Standard Deviation; Min=Minimum; Max=Maximum)

Exhibit 2: Number of Drug-Drug Interactions per Hospitalization

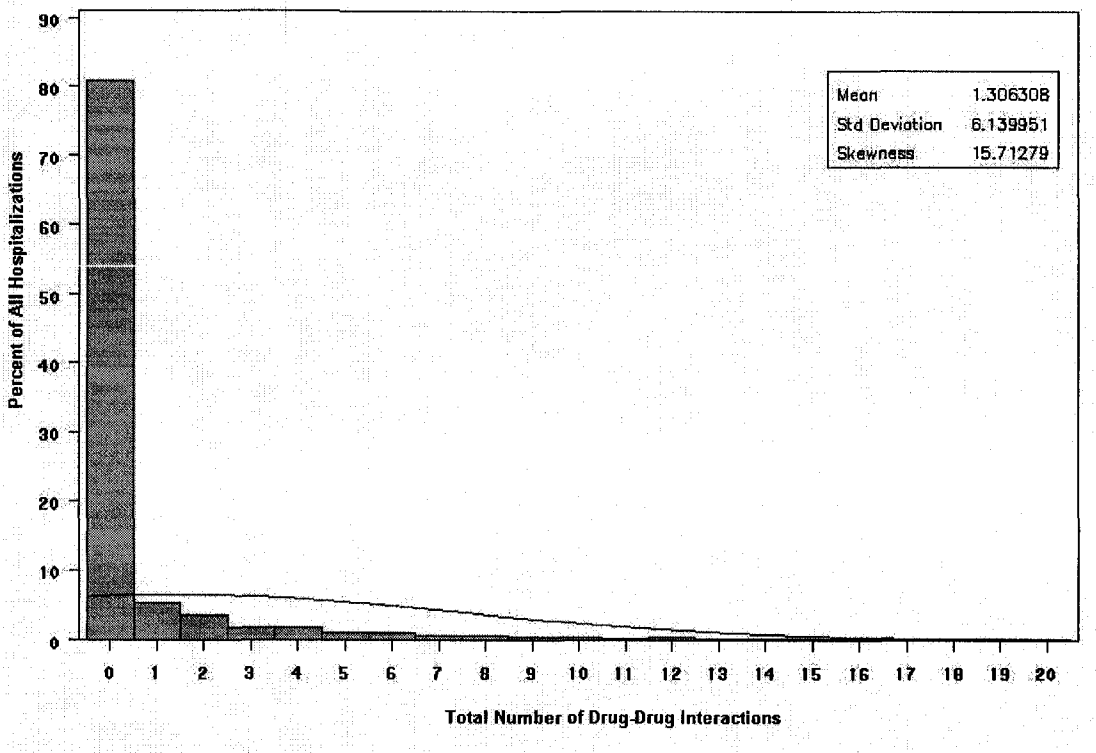
	DDI Cumulative Incidence (Number of Drug-Drug Interactions per Hospitalization)								
	Mean	Std	Min	Max	P5	P25	P50	P75	P95
Year									
1999	1.39	6.39	0.00	276.00	0.00	0.00	0.00	0.00	7.00
2000	1.46	6.79	0.00	252.00	0.00	0.00	0.00	0.00	7.00
2001	1.26	6.03	0.00	294.00	0.00	0.00	0.00	0.00	6.00
2002	1.41	7.04	0.00	443.00	0.00	0.00	0.00	0.00	7.00
2003	1.34	6.02	0.00	200.00	0.00	0.00	0.00	0.00	7.00
2004	1.18	5.50	0.00	176.00	0.00	0.00	0.00	0.00	6.00
2005	1.03	4.40	0.00	171.00	0.00	0.00	0.00	0.00	6.00

* January 1-September 30, 2005

Summary statistics for the number of drug-drug interactions per hospitalization are shown by year. The last two years show a reduction in the number of drug-drug interactions. A Spearman correlation, used to identify a negative linear trend between the number of drug-drug interactions and year of admission, was significant at $p<0.0001$ but was only -0.018.

(Std=Standard Deviation; Min=Minimum; Max=Maximum; P5=5th Percentile; P25=25th Percentile; P50=50th Percentile; P75=75th Percentile P95=95th Percentile)

Exhibit 3: Frequency Distribution of the Total Number of Drug-Drug Interactions per Hospitalization



The frequency of the total number of drug-drug interactions per hospitalization is shown by the vertical bars. The solid line represents the line of normal distribution. This shows an obvious discrepancy between the frequency of the number of drug interactions per admission and the line of normality due to the skewed frequency of drug interactions. The skewness is a measure of the tendency of the deviations from the mean to be larger in one direction than in the other (63). This 'skewness distribution' is represented in the summary statistics showing a low mean, large standard deviation and increased skewness. .

Exhibit 4: Cumulative Incidence (Percentage of Hospitalizations with at Least One DDI)

	Year of Admission							
	1999	2000	2001	2002	2003	2004	2005	Overall
Number of Hospitalizations without any DDIs	17070	16864	16986	16397	16482	17134	12359	113292
Percentage of Hospitalizations without a DDI	**80.32**	**80.02**	**80.19**	**80.23**	**80.78**	**81.62**	**82.35**	**80.72**
Number of Hospitalizations with at Least 1 DDI Present	4182	4210	4196	4041	3921	3858	2649	27057
Percentage of Hospitalizations with at Least 1 DDI Present	**19.68**	**19.98**	**19.81**	**19.77**	**19.22**	**18.38**	**17.65**	**19.28**
Overall	21252	21074	21182	20438	20403	20992	15008	140349
Mantel-Haenszel Chi-Square					1df	Value=38.3		p<0.0001

Cumulative Incidence is defined as the percentage of hospitalizations developing at least one DDI during 1999-2005. The cumulative incidence is stratified by admission year with the incidence for the entire study period shown in the column labeled "Overall". From 1999 to 2005, the cumulative incidence is 19.28 meaning that 19.28 percent of hospitalizations had at least one DDI.

There appears to be a progressive reduction in the cumulative incidence over the study period. A formal test of trend (Mantel-Haenszel Chi-Square) was used to test this observation. This was significant at the $p<0.0001$ level and statistically confirms the observed reduction in the cumulative incidence in DDIs over the study period.

Exhibit 5: Drug-Drug Interaction Incidence Density by Year

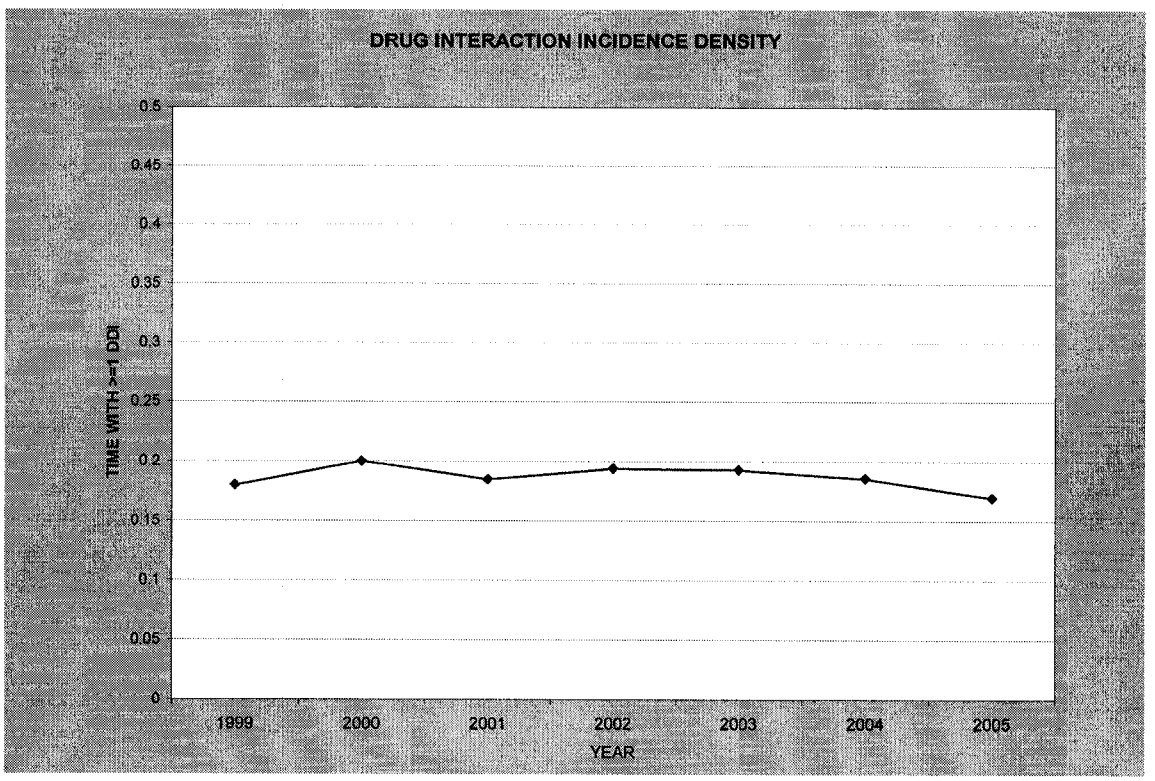
	Number Days Exposed to at Least 1 DDI A	Total Number of Hospitalization Days B	DDI Incidence Density C= A/B
Year			
1999	27562.9	153454.9	0.180
2000	34586.9	173303.0	0.200
2001	31274.3	168966.0	0.185
2002	31772.3	163548.0	0.194
2003	30528.3	158461.9	0.193
2004	29729.6	160079.8	0.186
2005	19116.5	112731.9	0.170
Overall	204570.8	1090545.4	0.188

* January 1-September 30, 2005

The number of hospital days in which patients were exposed to at least 1 DDI is presented in column A. When this is divided by the total number of hospitalization days (column B), the drug interaction incidence density is obtained (column C). The DDI incidence density represents the proportion of hospitalization days during which at least one potential drug-drug interaction occurred. For example, the DDI incidence density in 1999 of 0.180 indicates that at least one potential drug-drug interaction occurred during 18.0% of the hospitalization time.

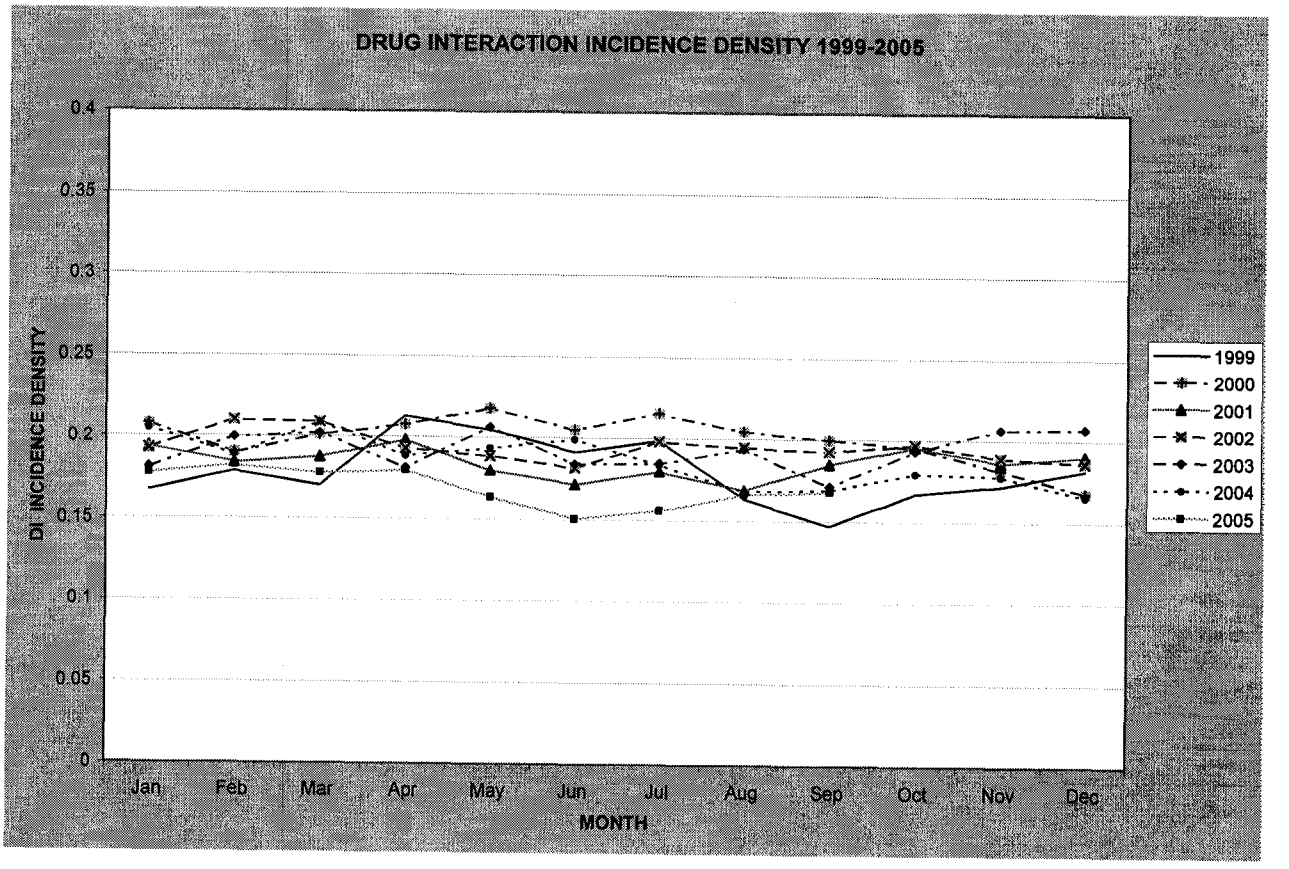
To test for a linear trend, the Spearman correlation coefficient between DDI Incidence Density and year of admission was found to be -0.25 which was not significant ($p=0.59$).

Exhibit 6: Drug-Drug Interaction Incidence Density by Year



Drug-drug interaction incidence density was defined as the total time with at least 1 DDI divided by the total hospitalization time. This is presented by year. The incidence density appears stable from 1999-2005.

Exhibit 7: Drug-Drug Interaction Incidence Density by Month



Drug-drug interaction incidence density is defined as the total interaction time divided by the total hospitalization time and represents the proportion of hospitalization time during which at least one interaction occurred. The DDI incidence density is shown separately for each year. The incidence density appears stable from 1999-2005. No obvious seasonal trends are apparent in any year.

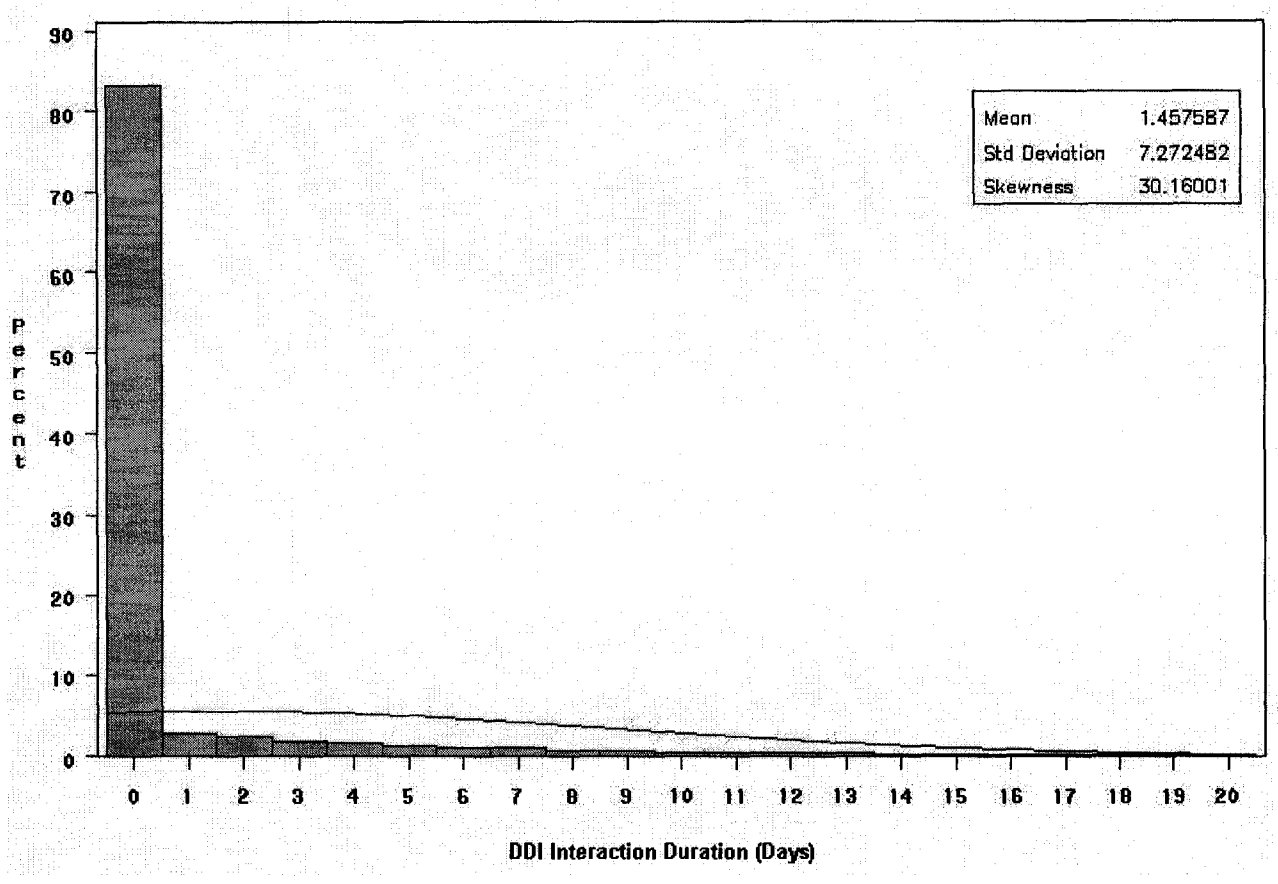
Exhibit 8: Drug-Drug Interaction Duration During Each Study Year

	Drug-Drug Interaction Duration (Days)								
	Mean	Std	Min	Max	P5	P25	P50	P75	P95
Year*									
1999	1.4	8.4	0.0	837.2	0.0	0.0	0.0	0.0	7.7
2000	1.6	8.1	0.0	336.8	0.0	0.0	0.0	0.0	8.4
2001	1.5	6.9	0.0	294.5	0.0	0.0	0.0	0.0	7.9
2002	1.5	6.7	0.0	282.8	0.0	0.0	0.0	0.0	8.6
2003	1.5	8.5	0.0	753.2	0.0	0.0	0.0	0.0	8.6
2004	1.4	6.1	0.0	244.2	0.0	0.0	0.0	0.0	7.9
2005	1.1	4.7	0.0	180.9	0.0	0.0	0.0	0.0	6.9

* January 1-September 30, 2005

Descriptive statistics for the drug-drug interaction duration in days are displayed by year. The unit of analysis is the hospitalizations. There was no significant linear trend (Spearman correlation -0.004, p=0.18).
(Std=Standard Deviation; Min=Minimum; Max=Maximum; P5=5th Percentile; P25=25th Percentile; P50=50th Percentile; P75=75th Percentile P95=95th Percentile)

Exhibit 9: Frequency Distribution of Drug-Drug Interaction Duration (Days)



The frequency of drug interaction duration in days is shown by the vertical bars. The solid line represents the line of normal distribution. This shows a discrepancy between the frequency of drug interaction duration and the line of normality due to the skewed frequency of drug interactions. The skewness is a measure of the tendency of the deviations from the mean to be larger in one direction than in the other (63). This "skewness" is represented in the summary statistics showing a low mean, large standard deviation and increased skewness.

Exhibit 10: Number of Drug-Drug Interactions by Interaction Category for 1999-2005

Interaction Category	Number of Drug-Drug Interactions	Drug-Drug Interactions(%total drug orders) 1999-2005)	Number of Drug- Drug Interactions per Hospitalization
1	98	0.00343	0.00070
2	22343	0.78134	0.15920
3	162760	5.69172	1.15968

* January 1-September 30, 2005

Drug Interaction Categories as defined by Hansten and Horne(35)

Category 1 - Drug combinations to be avoided.
Category 2 - Drug combinations that are usually avoided.
Category 3 - Drug combinations that should be altered to minimize risk.

Exhibit 11: Category 1 DDI Incidence Density

	Total Number of Category 1 DDI Interaction Days A	Total Hospitalization Days B	Category1 DDI Incidence Density Rate: A/B
Year			
1999	59.66	153454.86	0.00039
2000	90.82	173302.96	0.00052
2001	21.65	168966.03	0.00013
2002	21.80	163547.95	0.00013
2003	0.00	158461.88	0.00000
2004	30.70	160079.80	0.00019
2005	14.42	112731.88	0.00013
1999-2005	239.05	1090545.00	0.00022

* January 1-September 30, 2005

Category 1 interactions are those drug combinations that are recommended to be avoided by Hansten and Horne(35)

The above table lists the Category 1 incidence densities by hospitalization year. There appears to be a reduction in Category 1 incidence densities from 1999 to 2005 but there was no significant linear association, between Category 1 DDI incidence density and year of admission (Spearman correlation coefficient -0.69, p=0.12). Category 1 interactions are rare, accounting for 0.012-0.050% of hospitalization time.

Exhibit 12: Category 2 DDI Incidence Density

	Total Number of Category 2 DDI Interaction Days A	Total Hospitalization Days B	Category 2 DDI Incidence Density Rate: A/B
Year			
1999	1321.83	153454.86	0.009
2000	1813.37	173302.96	0.010
2001	2292.86	168966.03	0.014
2002	2648.84	163547.95	0.016
2003	2786.74	158461.88	0.018
2004	2631.60	160079.80	0.016
2005	1480.09	112731.88	0.013
1999-2005	14975.33	1090545.36	0.014

* January 1-September 30, 2005

Category 2 Interactions are those drug combinations that are usually avoided as recommended by Hansten and Horne. (35)

The above table lists the Category 2 incidence densities by hospitalization year. There was no significant linear association, between Category 2 DDI Incidence Density and year of admission (Spearman correlation coefficient of -0.61, p=0.09). These category 2 interactions account for only 0.9 to 1.8% of hospitalization time and are infrequent.

Exhibit 13: Category 3 DDI Incidence Density

	Total Number of Category 3 DDI Interaction Days A	Total Hospitalization Days B	Category 3 DDI Incidence Density Rate C=A/B
Year			
1999	26181.38	153454.86	0.171
2000	32682.71	173302.96	0.189
2001	28959.81	168966.03	0.171
2002	29101.67	163547.95	0.178
2003	27741.52	158461.88	0.175
2004	27067.34	160079.8	0.169
2005	17622.02	112731.88	0.156
1999-2005	189356.50	1090545.36	0.174

* January 1-September 30, 2005

Category 3 Interactions are those drug combinations that should be altered to minimize risk as recommended by Hansten and Horne. (35)

The above table lists the Category 3 incidence densities by hospitalization year. There was no significant linear association, between Category 3 DDI incidence density and year of admission (Spearman correlation coefficient of -0.54, p=0.22).

Exhibit 14: Most Frequent DDIs by Class of Interaction

Drug A	Drug B	Class Interaction	Number of DDIs 1999-2005
NITROGLYCERIN IN DEX	SILDENAFIL	1	7
RIFABUTIN	CLARITHROMYCIN	1	42
CLARITHROMYCIN	RIFABUTIN	1	57
SPIRONOLACTONE	POTASSIUM CHLORIDE	2	1435
METRONIDAZOLE	WARFARIN SODIUM	2	1886
ASPIRIN	WARFARIN SODIUM	2	12451
GLYBURIDE	WARFARIN SODIUM	3	5502
HEPARIN 25000U IN D	WARFARIN SODIUM	3	6844
DIGOXIN	FUROSEMIDE	3	7569

Exhibit **14 displays the three most frequent DDIs by class of interaction. Class 1 interactions are those interactions that are recommended to be avoided. Class 2 interactions are those interactions that are usually avoided and Class 3 interactions are those interactions that require dose adjustments or monitoring to minimize risk.**

Exhibit 15: Probability of Developing at Least One DDI by Hospital Length of Stay

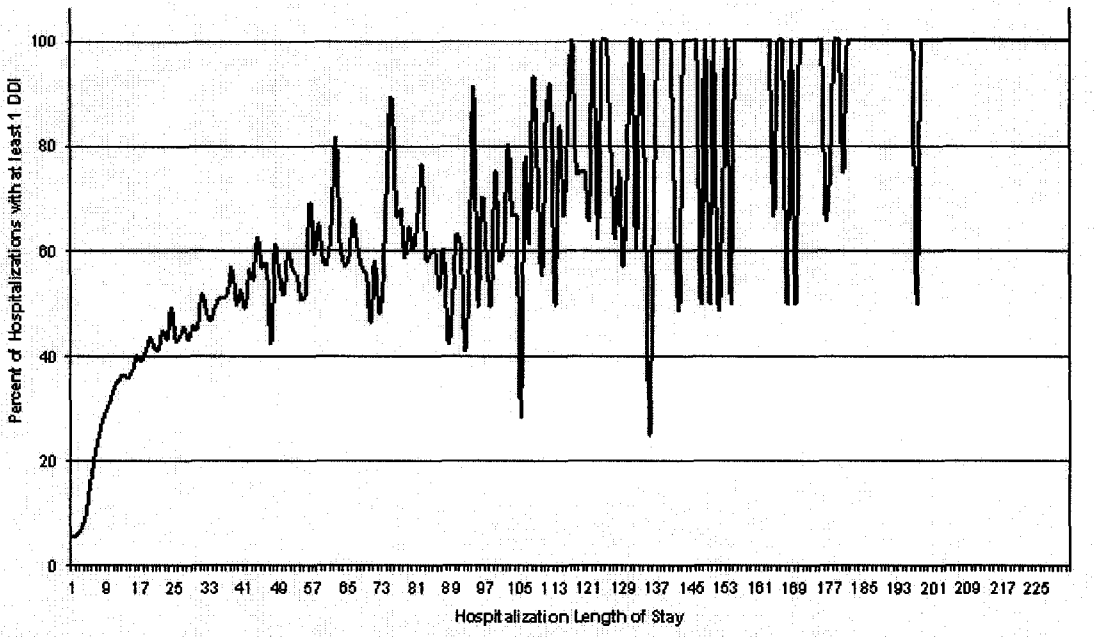


Exhibit 15 demonstrates the percent of hospitalizations with at least 1 DDI plotted against the hospital length of stay. As the length of stay increases, the percent of hospitalizations with at least 1 DDI increases and eventually approaches 100%.

Exhibit 16: Number of Drugs Ordered per Hospitalization by Year

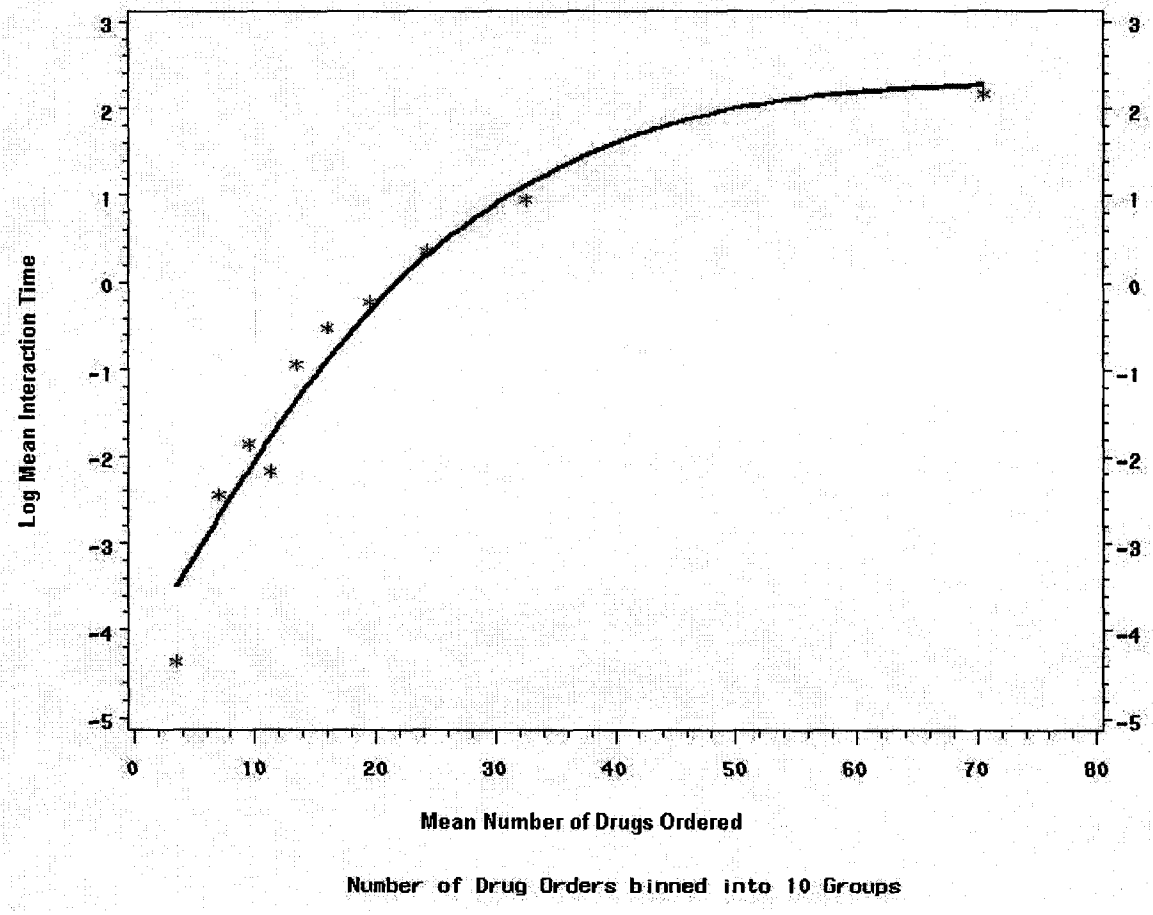
	Number of Drug Orders									
	Mean	Median	Std	Min	Max	P5	P25	P50	P75	P95
Year										
1999	18.49	13.00	21.04	0.00	512.00	2.00	9.00	13.00	21.00	52.00
2000	19.50	13.00	22.68	0.00	645.00	2.00	9.00	13.00	22.00	54.00
2001	19.61	14.00	21.53	0.00	476.00	2.00	10.00	14.00	23.00	54.00
2002	20.07	14.00	22.39	0.00	594.00	2.00	9.00	14.00	24.00	55.00
2003	21.85	15.00	24.43	0.00	610.00	3.00	11.00	15.00	26.00	59.00
2004	21.40	15.00	24.54	0.00	862.00	2.00	11.00	15.00	25.00	57.00
2005	20.89	16.00	21.26	0.00	516.00	2.00	11.00	16.00	25.00	55.00

* January 1-September 30, 2005

The summary statistics for the number of drugs ordered are displayed by year. The mean number of drugs ordered per hospitalization increases significantly roughout the study period (Spearman correlation coefficient of 0.075, $p<0.0001$).

(Std=Standard Deviation; Min=Minimum; Max=Maximum; P5=5th Percentile; P25=25th Percentile; P50=50th Percentile; P75=75th Percentile P95=95th Percentile)

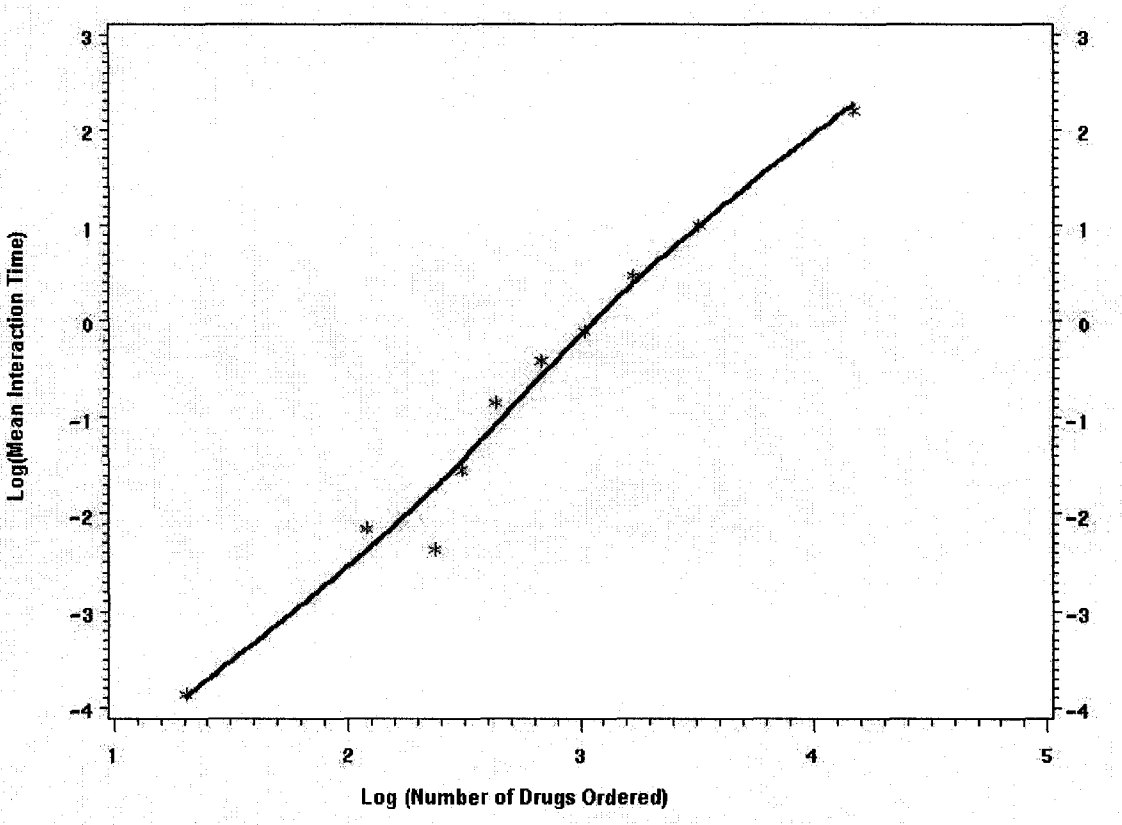
Exhibit 17: Log-means Plot of Mean Number of Drugs Ordered per Hospitalization



The log-means plot shows the relationship between the mean of the number of drugs ordered, binned into 10 groups (horizontal axis), and the log(mean interaction time)(vertical axis). There is a curvilinear and possible logarithmic relationship between the number of drugs ordered and the log(mean interaction time).

All log transformations were done with natural log-based calculations (ln).

Exhibit 18: Effect of Log Transformation on Log-means Plot of Mean Number of Drugs Ordered per Hospitalization



To transform the curvilinear curve of the log-means plot presented in Exhibit 17, the log(number of drugs ordered) was plotted against the log(mean interaction time). This resulted in straightening of the curve indicating that the log (number of drugs ordered) represents a better format for the Poisson regression model.

All log transformation were with natural log-based calculations (ln)

Exhibit 19: Patient Age

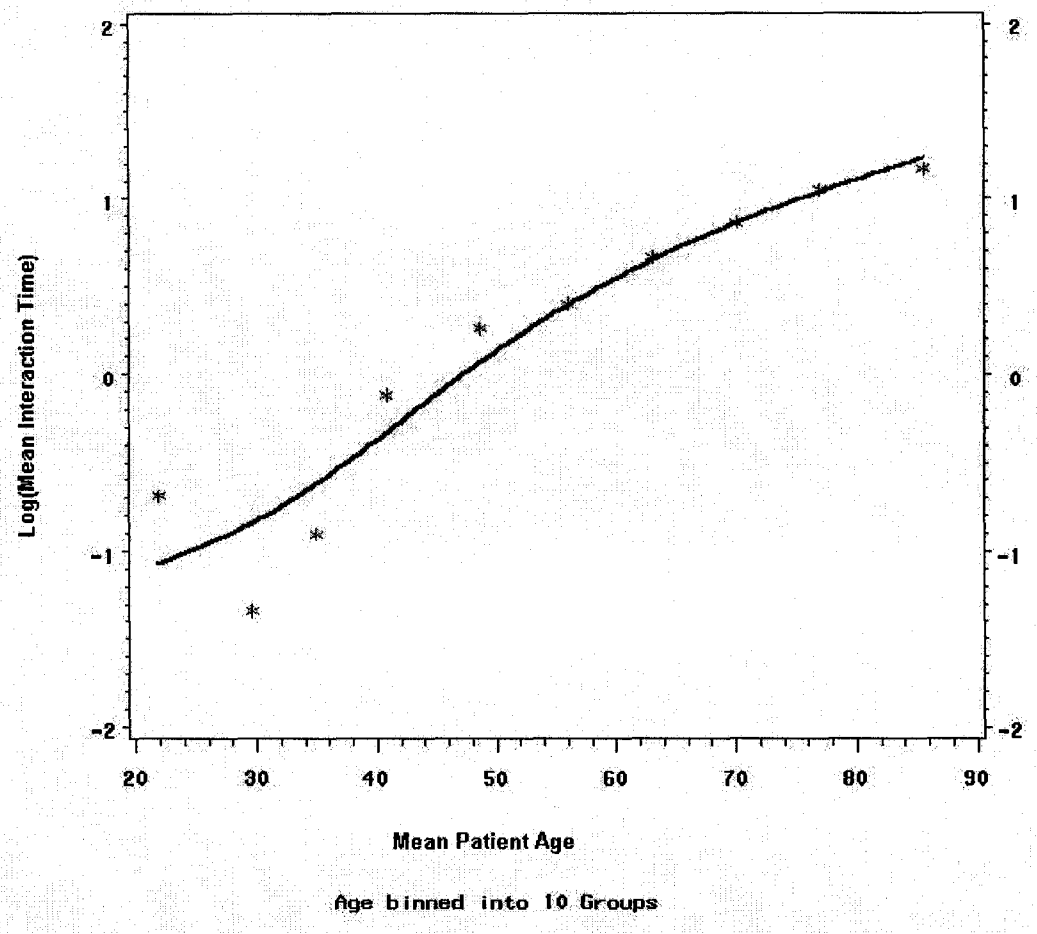
	hraAge									
	Mean	Median	Std	Min	Max	P5	P25	P50	P75	P95
Year										
1999	64.77	69.00	16.72	18.00	107.00	33.00	54.00	69.00	77.00	87.00
2000	65.44	69.00	16.43	18.00	104.00	33.00	55.00	69.00	78.00	87.00
2001	65.04	68.00	16.48	18.00	99.00	34.00	54.00	68.00	78.00	87.00
2002	65.51	68.00	16.28	18.00	104.00	35.00	55.00	68.00	78.00	87.00
2003	65.40	68.00	15.95	18.00	98.00	35.00	55.00	68.00	78.00	87.00
2004	64.93	67.00	16.22	18.00	103.00	35.00	54.00	67.00	78.00	87.00
2005	66.13	69.00	16.43	18.00	104.00	35.00	56.00	69.00	79.00	88.00

* January 1-September 30, 2005

Summary statistics for patient age are displayed by year. There appears to be a small increase in mean age throughout the study but there was no statistical evidence of a linear trend (Spearman coefficient of 0.008, p=0.19).

(Std=Standard Deviation; Min=Minimum; Max=Maximum; P5=5th Percentile; P25=25th Percentile; P50=50th Percentile; P75=75th Percentile P95=95th Percentile)

Exhibit 20: Log-Means Plot of Age



The log-means plot shows the relationship between the mean patient age, binned into 10 groups (horizontal axis) and the log(mean interaction time) (vertical axis). There initially appears to be a linear relationship with age as shown on the log-means plot. Closer inspection shows that the linear relationship may not be present in the lower ages as there is more scatter around the line.

All log transformations were done with natural log-based calculations (ln).

Exhibit 21: Length of Hospital Stay (Days) by Year

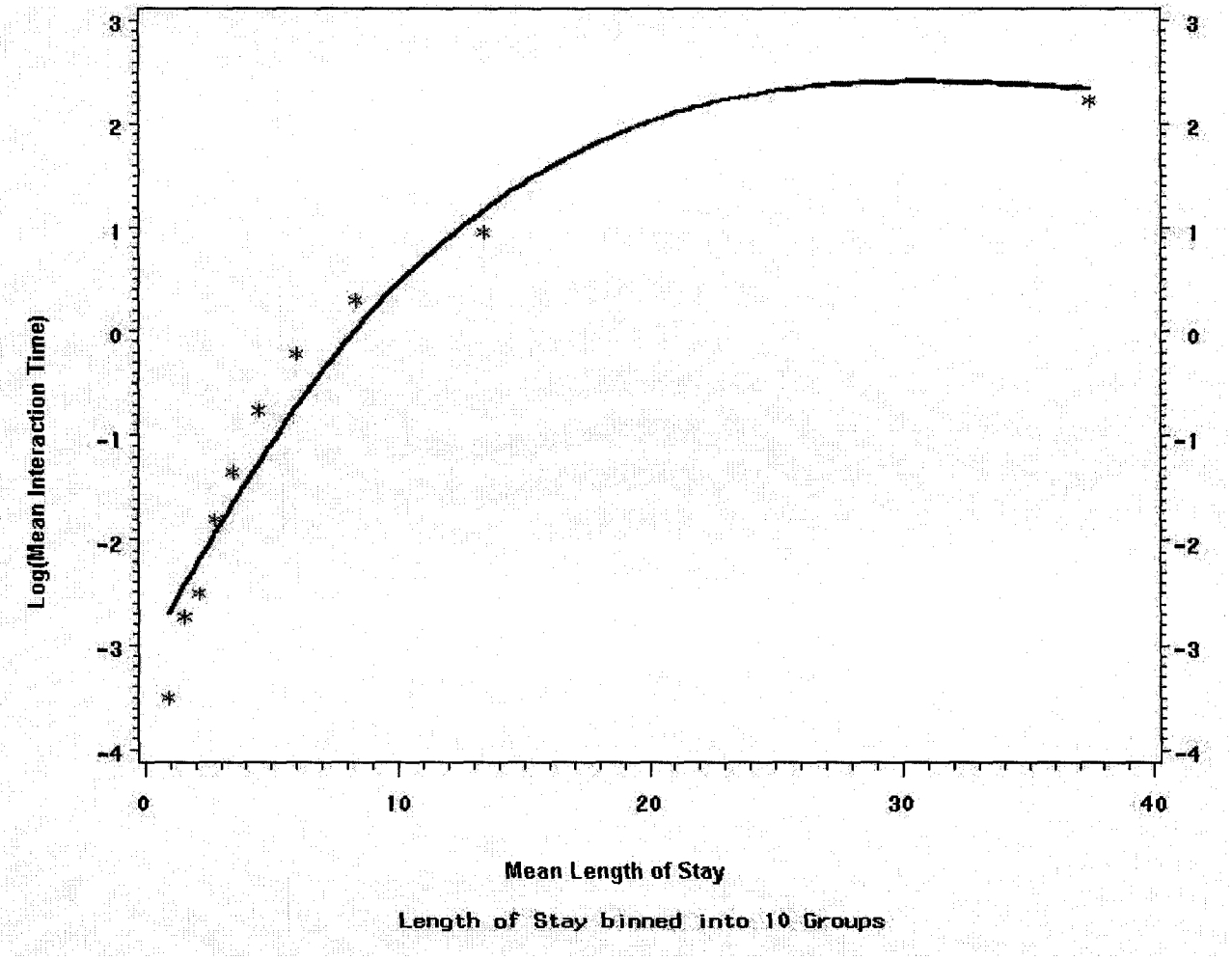
	Length of Stay									
	Mean	Median	Std	Min	Max	P5	P25	P50	P75	P95
Year										
1999	7.7	3.7	19.2	0.0	1113.6	0.8	2.0	3.7	7.7	27.8
2000	8.1	3.9	15.3	0.0	465.8	0.8	2.0	3.9	8.1	29.2
2001	8.0	3.9	14.4	0.0	539.1	0.8	2.1	3.9	8.0	28.6
2002	7.9	3.8	13.2	0.0	395.7	0.9	2.1	3.8	8.0	28.2
2003	7.8	3.8	14.5	0.0	806.5	0.8	2.0	3.8	8.1	27.9
2004	7.6	3.7	13.9	0.0	465.4	0.7	2.0	3.7	7.7	26.8
2005	7.0	3.7	10.2	0.0	202.5	0.8	2.1	3.7	7.7	23.8

* January 1-September 30, 2005

Summary statistics for mean length of stay are displayed for 1999-2005. There appears to be a reduced mean length of stay throughout the study; however the Spearman correlation coefficient of -0.003 was not significant (p=0.31) between length of stay and year of admission.

(Std=Standard Deviation; Min=Minimum; Max=Maximum; P5=5th Percentile; P25=25th Percentile; P50=50th Percentile; P75=75th Percentile P95=95th Percentile)

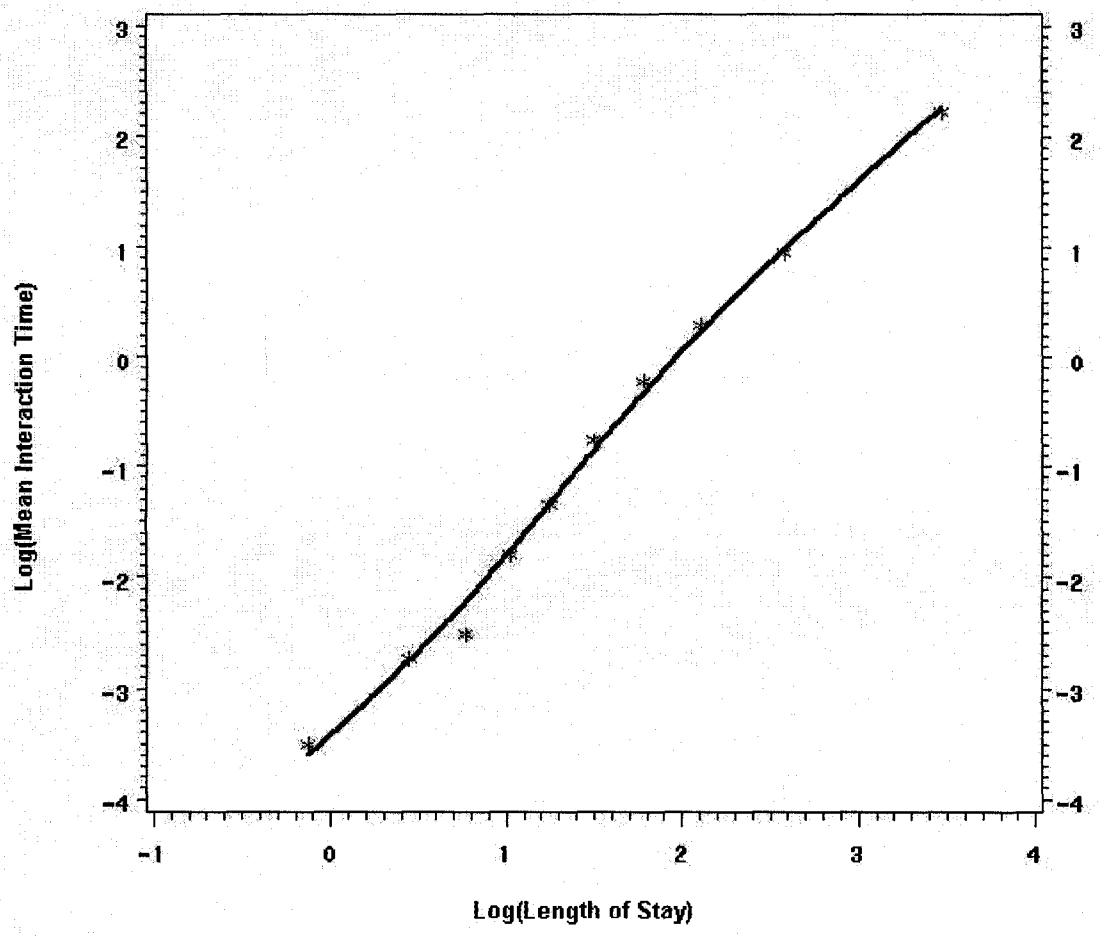
Exhibit 22: Log-Means Plot of Length of Stay



The log-means plot shows the relationship between the mean length of stay, binned into 10 groups (horizontal axis) and the log(mean interaction time)(vertical axis). This demonstrates a curvilinear or possible logarithmic relationship.

All log transformations were done with natural log-based calculations (ln).

Exhibit 23: Effect of Log Transformation on the Log-means Plot of Length of Stay



To transform the curvilinear curve of the log-means plot presented in Exhibit 22, the log(length of stay) was plotted against the log(mean interaction time) resulted in straightening of the curve, indicating that the log(length of stay) is a better format for the Poisson regression model.

All log transformation were with natural log-based calculations (ln)

Exhibit 24: Resource Intensity Weight

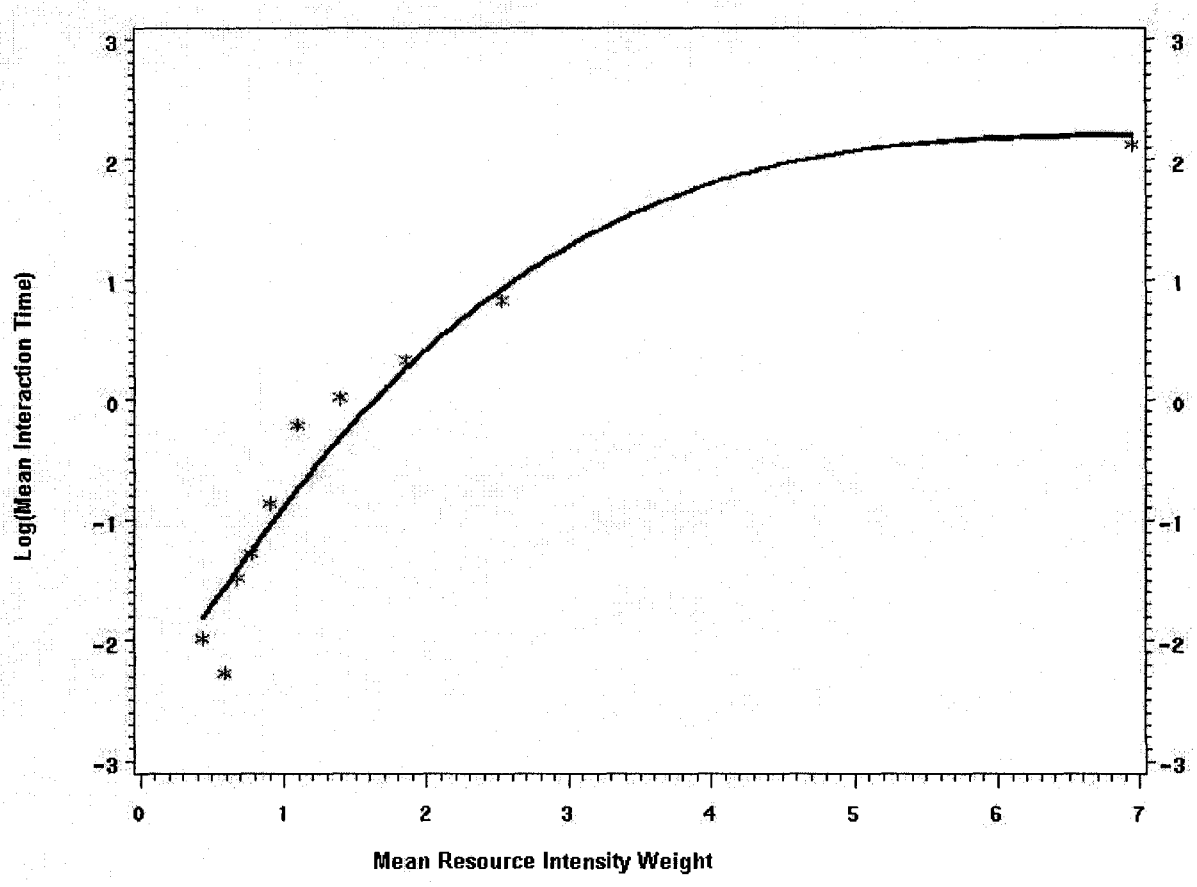
	Resource Intensity Weight									
	Mean	Median	Std	Min	Max	P5	P25	P50	P75	P95
Year										
1999	1.7	1.0	3.9	0.1	282.9	0.5	0.6	1.0	1.7	4.5
2000	1.9	1.0	3.5	0.1	109.0	0.5	0.7	1.0	2.0	5.6
2001	1.9	1.1	3.1	0.1	147.0	0.5	0.7	1.1	2.1	5.6
2002	1.8	1.0	2.4	0.1	65.2	0.4	0.7	1.0	2.0	5.3
2003	1.7	1.0	2.5	0.1	76.1	0.5	0.7	1.0	1.8	4.8
2004	1.6	1.0	2.5	0.1	93.5	0.5	0.7	1.0	1.7	4.4
2005	1.5	0.9	1.8	0.1	50.5	0.5	0.6	0.9	1.7	4.1

* January 1-September 30, 2005

Summary statistics for resource intensity weights are displayed for 1999-2005. The mean resource intensity weights appear to be higher in 2000/2001 (1.9) and are lowest in 2005 (1.5). There is evidence of a linear association with the Spearman correlation coefficient of -0.85 between RIW and year of admission, which is significant at the $p<0.0001$ level.

(Std=Standard Deviation; Min=Minimum; Max=Maximum; P5=5th Percentile; P25=25th Percentile; P50=50th Percentile; P75=75th Percentile P95=95th Percentile)

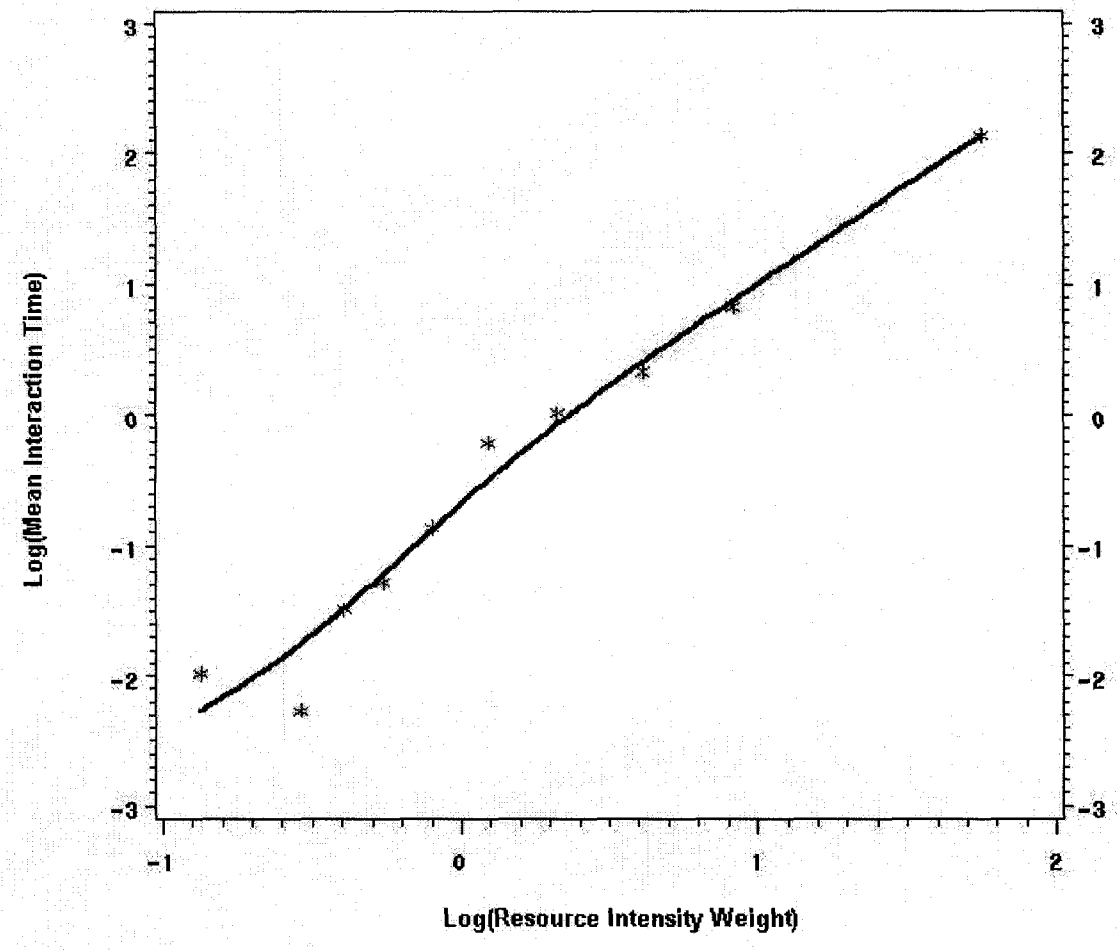
Exhibit 25: Log-means Plot of Resource Intensity Weight



The log-means plot shows the relationship between the mean resource intensity weight,binned into 10 groups (horizontal axis) and the log (mean interaction time)(vertical axis). The log-means plot of resource intensity weight demonstrates a curvilinear or possible logarithmic relationship.

All log transformations were done with natural log-based calculations (ln).

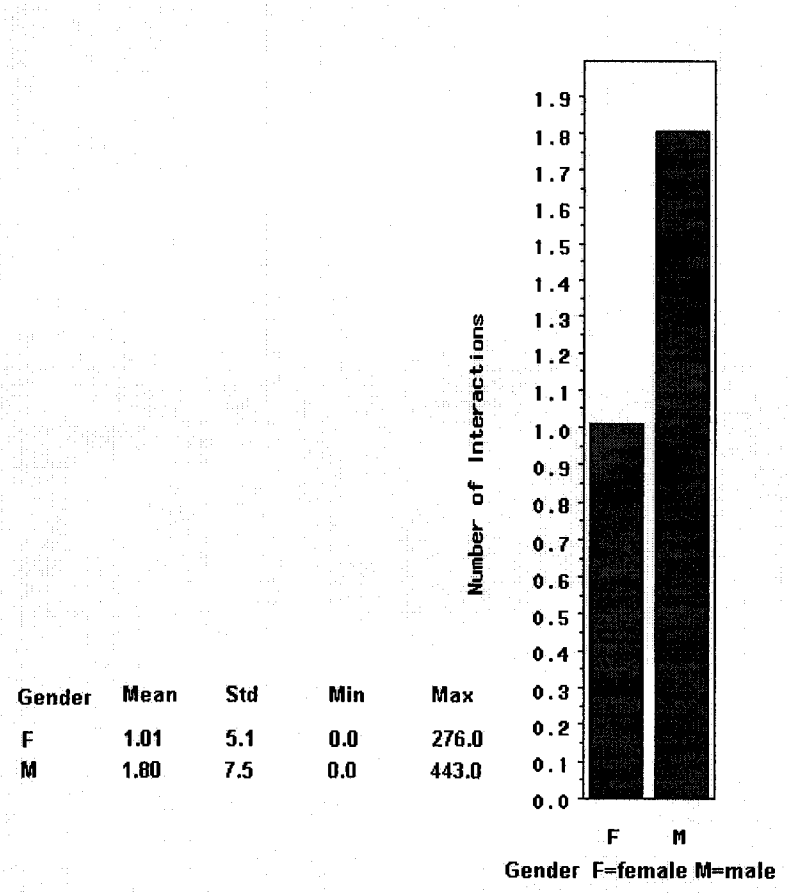
Exhibit 26: Effect of Log Transformation on the Log-means Plot of Resource Intensity Weight



To transform the curvilinear curve of the log-means plot presented in Exhibit 25, the log(RIW) was plotted against the log(mean interaction time). This resulted in straightening of the curve, indicating that the log(RIW) is a better format for the Poisson regression model.

All log transformation were with natural log-based calculations (ln)

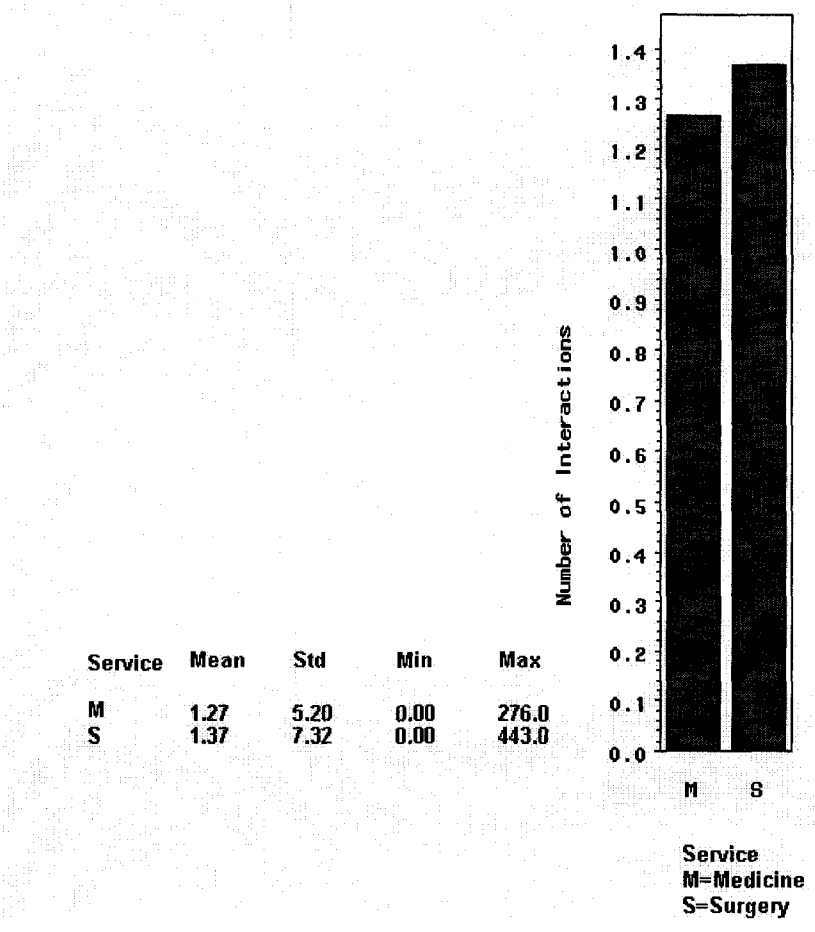
Exhibit 27: Number of DDIs by Gender



Gender	Mean	Std	Min	Max
F	1.01	5.1	0.0	276.0
M	1.80	7.5	0.0	443.0

The above vertical bar chart shows the mean number of DDIs per hospitalization by gender. The mean number of DDIs is higher in men than in women (1.80 vs 1.01).

Exhibit 28: Number of DDIs by Service

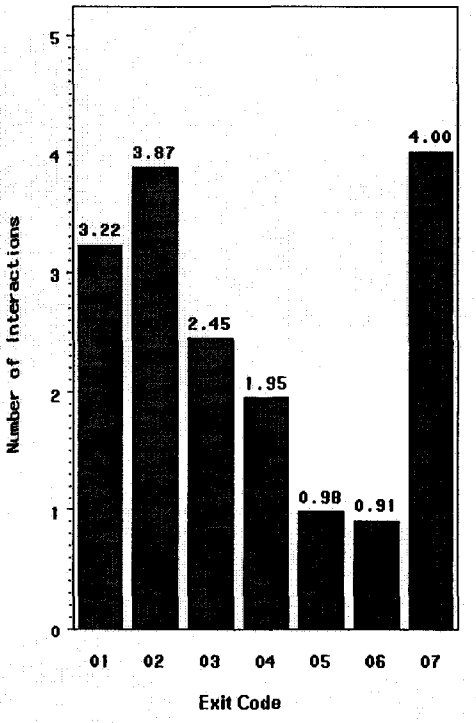


Service	Mean	Std	Min	Max
M	1.27	5.20	0.00	276.0
S	1.37	7.32	0.00	443.0

The vertical bar chart shows the mean number of DDIs per hospitalization by Service. The mean number of DDIs is higher in surgical services than medicine services (1.37 vs 1.27).

Exhibit 29: Number of DDIs by Disposition

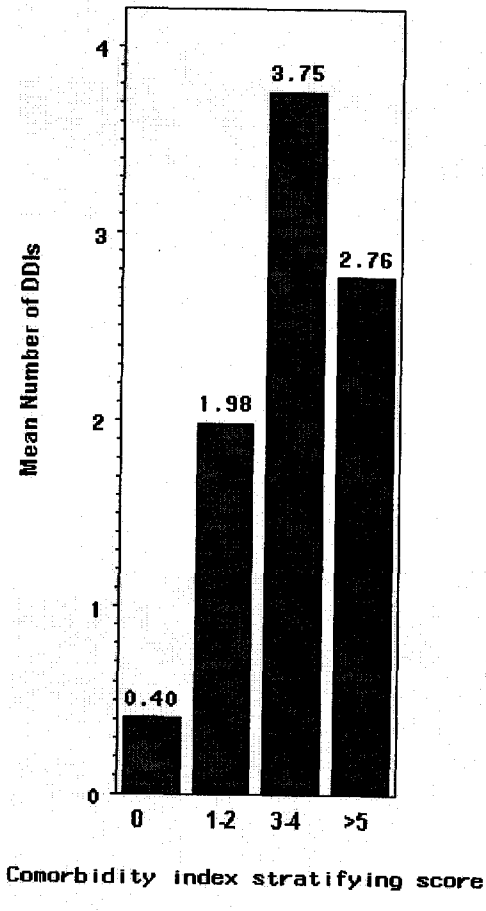
	Number of DDIs			
	Mean	Std	Min	Max
Disposition				
01 Transferred to an Acute Care Facility	3.22	9.87	0.00	184.0
02 Transferred to Long Term Care	3.87	13.56	0.00	443.0
03 Transferred to an Unspecified Facility	2.45	7.54	0.00	92.00
04 Discharged with Support Services	1.95	6.54	0.00	172.0
05 Discharged Home	0.98	4.83	0.00	276.0
06 Signed Out	0.91	3.97	0.00	55.00
07 Expired	4.00	13.13	0.00	294.0



The above vertical bars represent the number of DDIs of the seven Dispositions at the time the patient leaves the hospital. There is no obvious linear relationship present but there may be a difference between the categories if transfers (codes 01-03), discharged with services (04), discharges (codes 05-06) and expirations (code 07) are grouped together.

Exhibit 30: Number of DDIs by Charlson Comorbidity Index

	Number of DDIs			
	Mean	Std	Min	Max
Charlson Comorbidity Index				
0	0.40	2.86	0.00	262.0
1-2	1.98	7.96	0.00	443.0
3-4	3.75	10.12	0.00	209.0
≥5	2.76	8.84	0.00	252.0



Comorbidity Index is calculated as a sum of disease specific comorbidity weights defined by Charlson(49). The Charlson comorbidity index uses adjusted relative risks of mortality as weights and is shown in Appendix D.

The above figure and table show the mean Number of DDIs by comorbidity index. Category 3-4 has the highest number of DDIs at 3.75.

(Std=Standard Deviation; Min=Minimum; Max=Maximum)

Exhibit 31: Univariate Association of Predictor Variables with DDI Incidence Density

Predictor Variables	Categorical Level	Parameter Estimate	P	DDI Incidence Density Ratio	Confidence Intervals	
Age	18-30	Reference	Reference	Reference	Reference	Reference
	31-45	0.5507	<.0001	1.4160	1.3456	1.4901
	45-60	0.8636	<.0001	2.3717	2.2788	2.4684
	60-75	1.1542	<.0001	3.1714	3.0538	3.2935
	>75	1.2595	<.0001	3.5237	3.3932	3.6594
Gender (Male vs Female)		0.1891	<.0001	1.2082	1.1866	1.2301
Service (Medicine vs Surgery)		0.0517	<.0001	1.0531	1.0341	1.0724
	Discharged	Reference	Reference	Reference	Reference	Reference
Disposition	Discharged with Services	0.2196	<.0001	1.2050	1.2874	1.2050
	Transferred	0.5036	<.0001	1.6547	1.6159	1.6944
	Expired	0.5392	<.0001	1.7147	1.6679	1.7628
Comorbidity Index	0	Reference	Reference	Reference	Reference	Reference
	1-2	0.8091	<.0001	2.2460	2.1893	2.3041
	3-4	1.1846	<.0001	3.2693	3.1797	3.3615
	≥5	0.9365	<.0001	2.5510	2.4854	2.6183
log(Number of Drugs Ordered)		0.6045	<.0001	1.8302	1.8136	1.8471
log(Length of Stay)		0.3026	<.0001	1.3533	1.3439	1.3628
log(Resource Intensity Weight)		0.3111	<.0001	1.3649	1.3551	1.3749

Univariate Parameter Estimates and Incidence Density Ratios from Poisson Regression

log(Number of Drugs Ordered): the parameter estimates and incidence ratios shown are for every 1 natural log increase in the number of drugs ordered. This translates to an incidence density ratio of 2.6 for 5 drugs, 4.0 for 10 drugs and 6.1 for 20 drugs.

log(Length of Stay): the parameter estimates and incidence ratios shown are for every 1 natural log increase in the length of stay. This translates to an incidence density ratio of 1.8 for 7 days, 2.2 for14 days and 2.5 for 21 days.

log(Resource Intensity Weight): the parameter estimates and incidence ratios shown are for every 1 natural log increase in RIW. This translates to an incidence density ratio of 1.63 for a RIW of 5 and 2.0 for a RIW of 10.

All log transformation were with natural log-based calculations (ln)

Exhibit 32: Likelihood Ratio Statistics for Type III Analysis of Predictor Variables

LR Statistics For Type 3 Analysis						
Source	Num DF	Den DF	F Value	Pr > F	Chi-Square	Pr > ChiSq
Log(Number of Drugs Ordered)	1	140347	16432.4	<.0001	16432.4	<.0001
Log(Length of Stay)	1	140347	6977.9	<.0001	6977.9	<.0001
Log(Resource Intensity Weight)	1	140347	6501.8	<.0001	6501.8	<.0001
Comorbid Index	3	140333	2996.8	<.0001	8990.5	<.0001
Age Group	4	140344	1625.8	<.0001	6503.2	<.0001
Exit Code	3	140345	835.3	<.0001	2505.8	<.0001
Gender	1	140347	422.4	<.0001	422.4	<.0001
Hospital Service	1	140346	31.2	<.0001	31.2	<.0001

This table shows the likelihood ratio statistics for the **univariate** Poisson regression containing the eight significant predictor variables. All are significant at the $p<0.0001$ level.

All log transformation were with natural log-based calculations (ln)

Exhibit 33: Unadjusted Poisson Model-based DDI Incidence Density Rates

	Categorical Levels	Crude DDI Incidence Density Rate	95% Confidence Intervals	
Age (years)	18-30	0.0754	0.0723	0.0787
	31-45	0.1068	0.1038	0.1099
	46-59	0.1740	0.1705	0.1775
	60-75	0.2326	0.2290	0.2363
	>75	0.2585	0.2545	0.2625
Gender	Female	0.1720	0.1698	0.1741
	Male	0.2078	0.2051	0.2105
Service	Surgery	0.1822	0.1797	0.1847
	Medicine	0.1918	0.1896	0.1941
Disposition	Discharged	0.1603	0.1584	0.1621
	Discharged with Services	0.1996	0.1935	0.2059
	Transferred	0.2652	0.2598	0.2707
	Expired	0.2748	0.2680	0.2818
Comorbidity Index	0	0.0967	0.0948	0.0986
	1-2	0.2172	0.2137	0.2207
	3-4	0.3161	0.3100	0.3224
	≥5	0.2467	0.2425	0.2509
Log(Number of Drugs Ordered)		0.0374	0.0363	0.0384
Log(Length of Stay)		0.1028	0.1009	0.1046
Log(RIW)		0.1751	0.1735	0.1768

All log transformation were with natural log-based calculations (ln)

Crude DDI Incidence Density Rate: This represents the proportion of hospital time during which the patient is exposed to at least one DDI.

log(Number of Drugs Ordered): the incidence density rates shown are for every 1 natural log increase in the number of drugs ordered. This translates to a DDI incidence density of 0.06 for 5 drugs prescribed, 0.09 for 10 drugs prescribed and 0.11 for 20 drugs prescribed.

log(Length of Stay): the incidence density rates are shown are for every 1 natural log increase in the length of stay. This translates to a DDI incidence density of 0.20 for the first 7days hospitalized, 0.27 for the first 14 days and 0.31 for the first 21 days. For example, if a patient is admitted for 1 week, 20% of the time there will be at least one potential DDI.

log(Resource Intensity Weight): the incidence density rates are shown are for every 1 natural log increase in the resource intensity weight. This translates to a DDI incidence density of 0.28 for a RIW of 5. and 0.40 for a RIW of 10.

Exhibit 34: Percent Change in Intercept and Parameter Estimates Between Univariate and Multivariate Models

Predictor Variables	Categorical Level	Percent Change in Intercept	Percent Change in Parameter Estimate
Age (Years)		12.77	
	18-30		Reference
	31-45		75.03
	45-60		61.00
	60-75		48.93
	>75		35.61
Gender (Male vs Female)		-197.72	71.34
Service (Medicine vs Surgery)		-207.81	-672.34
Disposition		-186.26	
	Discharged		Reference
	Discharged with Services		154.69
	Transferred		157.23
	Expired		102.30
Comorbidity Index		-124.36	
	0		Reference
	1-2		64.73
	3-4		57.57
	≥5		71.72
log(Number of Drugs Ordered)		-34.68	-35.40
log(Length of Stay)		-103.32	134.34
log(Resource Intensity Weight)		-155.27	119.99

All log transformation were with natural log-based calculations (ln)

Exhibit 34 shows the percent change between the intercept and the parameter estimates between univariate and multivariate models. This demonstrates at least a 10% change in all estimates.

The percent change was determined using the following formula:

[(univariate estimate-multivariate estimate)/univariate estimate] x 100%.

Exhibit 35: Multivariate Association of Predictor Variables with DDI Incidence Density

LR Statistics For Type 3 Analysis						
Source	Num DF	Den DF	F Value	Pr > F	Chi-Square	Pr > ChiSq
Log(Number of Drugs Ordered)	1	140320	9355.84	<.0001	9355.84	<.0001
Hospital Service	1	140320	1404.77	<.0001	1404.77	<.0001
Age Group	4	140320	720.68	<.0001	2882.71	<.0001
Comorbid Index	3	140320	392.30	<.0001	1176.89	<.0001
Exit Code	3	140320	142.87	<.0001	428.62	<.0001
Log(Length of Stay)	1	140320	135.14	<.0001	135.14	<.0001
Log(Resource Intensity Weight)	1	140320	40.93	<.0001	40.93	<.0001
Gender	1	140320	36.94	<.0001	36.94	<.0001

This table shows the likelihood ratio statistics for the multivariate Poisson regression containing the eight significant predictor variables. All are significant at the $p<0.0001$ level.

All log transformation were with natural log-based calculations (ln)

Exhibit 36: Independent Association of Predictors with DDI Incidence Density

	Categoric al Levels	DDI Incidence Density Ratio	Chi-Square	Confidence Intervals	
Log(Number Drug		2.27	8836.4	2.23	2.30
Hospital Service (Surgery vs Medicine)		1.49	1392.8	1.46	1.52
Age	18-30	Reference	Reference	Reference	Reference
	31-45	1.15	29.53	1.09	1.21
	46-60	1.40	201.79	1.34	1.47
	61-75	1.80	659.95	1.72	1.89
	>75	2.25	1243.1	2.15	2.35
Comorbidity Index	0	Reference	Reference	Reference	Reference
	1-2	1.32	457.13	1.30	1.37
	3-4	1.65	1161.10	1.61	1.70
	≥5	1.29	330.47	1.26	1.33
Discharge Disposition	Discharge	Reference	Reference	Reference	Reference
	Discharge d with Services	0.89	53.62	0.86	0.92
	Transferr	0.99	1.03	0.96	1.01
	Expired	0.75	369.90	0.73	0.77
Log(Length of Stay)		0.90	135.19	0.89	0.92
Log(RIW)		0.94	40.91	0.92	0.96
Gender (Male vs		1.06	34.58	1.04	1.07

This table presents the incidence density ratios for all predictor variables in the multivariate model

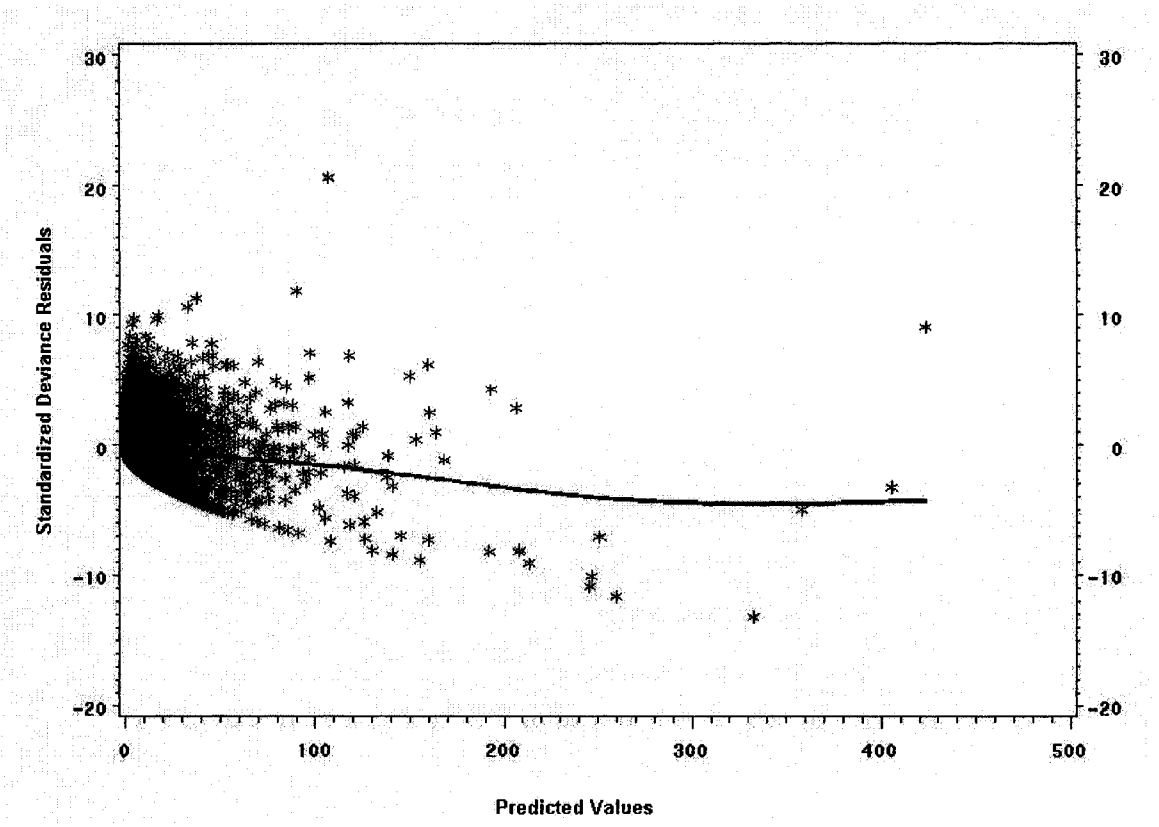
All log transformation were with natural log-based calculations (ln)

log(Number of Drugs Ordered): the incidence ratios shown are for every 1 natural log increase in the number of drugs ordered. This translates to an IDR of 3.7 for 5 drugs ordered, 6.6 for 10 drugs ordered and 11.7 for 20 drugs prescribed.

log(Length of Stay): the incidence ratios shown are for every 1 natural log increase in the length of stay. This translates to an IDR of 0.81 for a LOS of 7 days and 0.76 for 14 days.

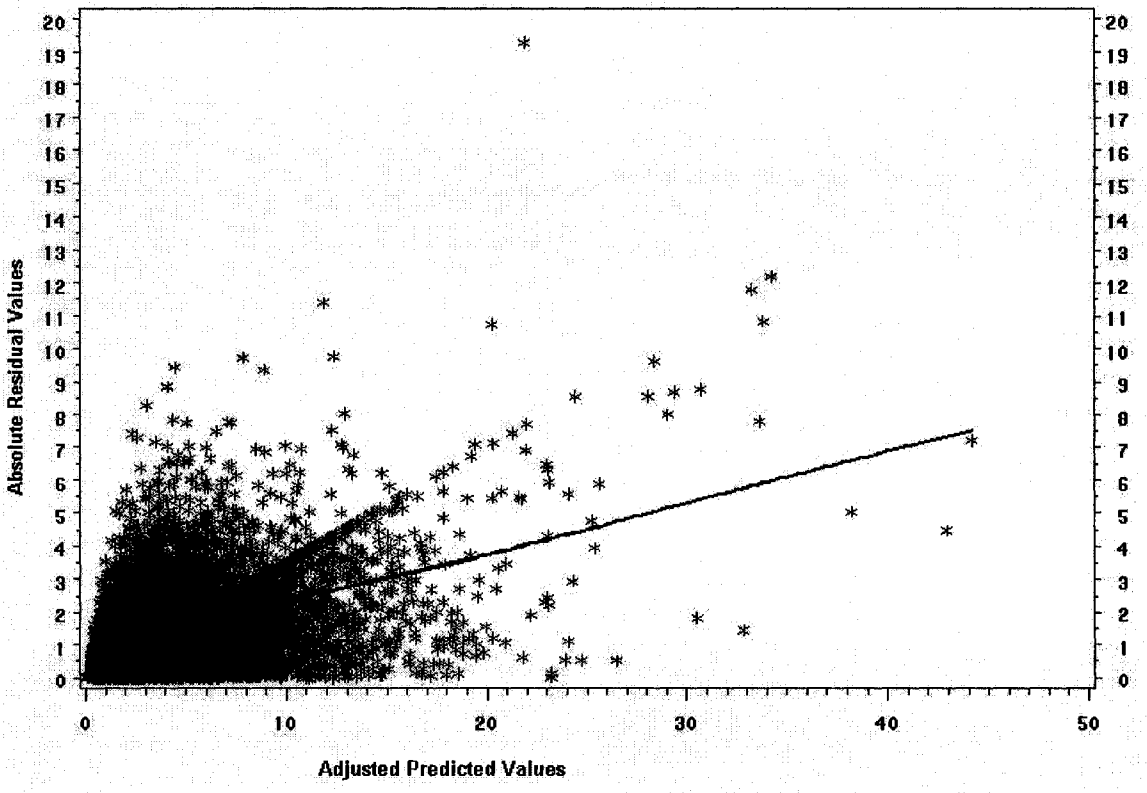
log(Resource Intensity Weight): the incidence ratios shown are for every 1 natural log increase in RIW. This translates to an IDR of 0.9 for a RIW of 5 and 0.87 for a RIW of 10.

Exhibit 37: Residual Plots (Standardized Deviance Residuals vs Predicted)



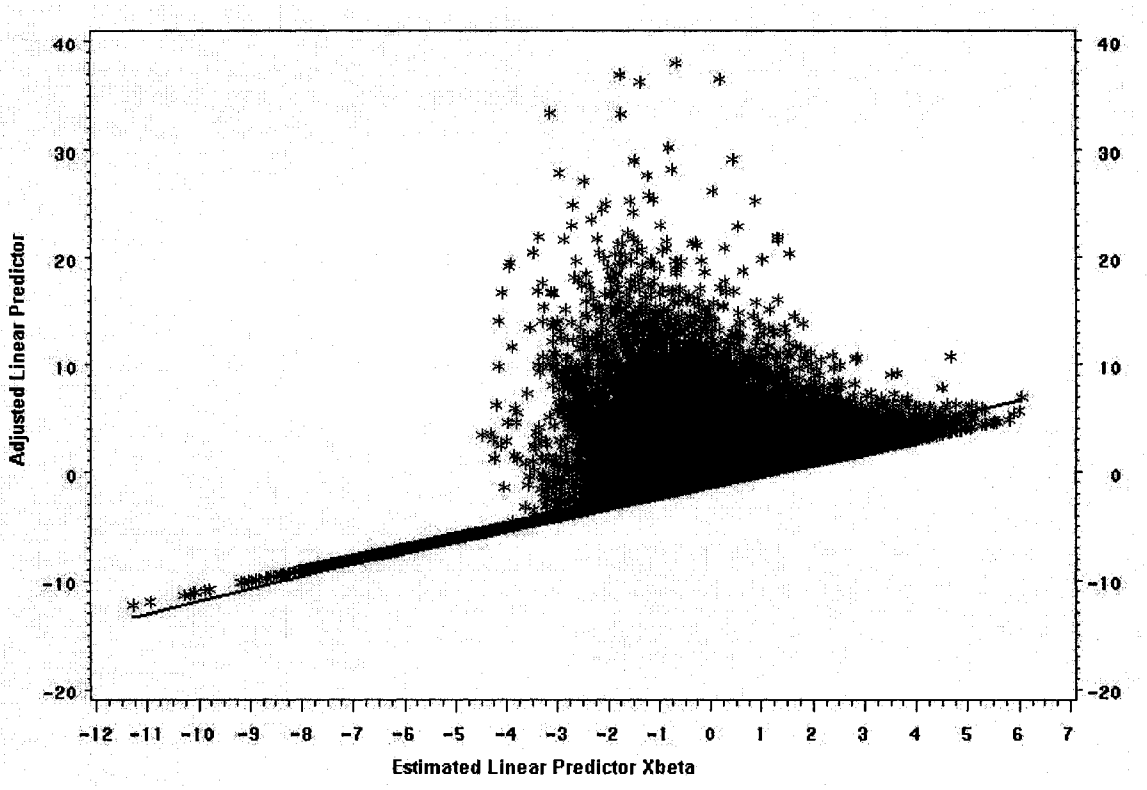
The plot of the standardized deviance residual against the predicted values shows a slight decrease in residual deviance with increasing predicted values. The funnel effect is also shown which indicates non-homoscedasticity with the variance differing as the predicted values increase. This may be due to either model misspecification or overdispersion.

Exhibit 38: Residual Plots (Absolute Residuals vs Adjusted Predictors)



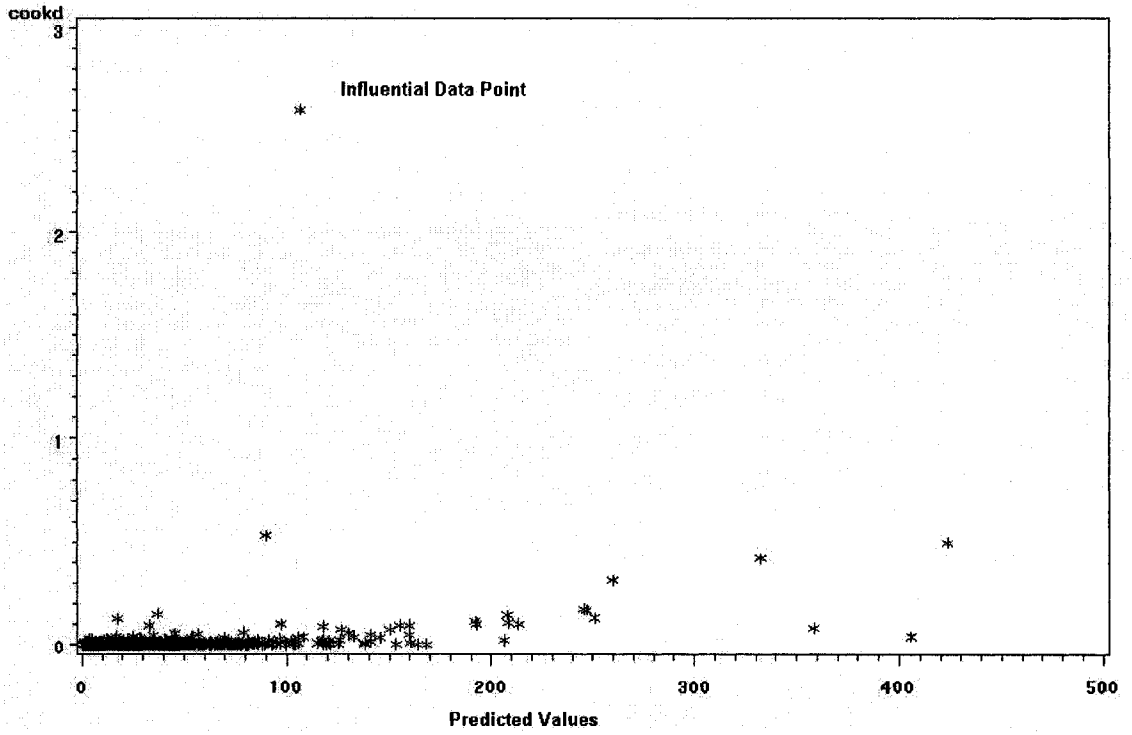
The plot of the absolute residuals against the adjusted predicted values shows a positive increase in the trend. This figure illustrates how the absolute values of the residuals can reveal problems that are not as obvious with the standardized deviance residual plots. This plot shows more of a funnel effect causing the smoothed line to have a positive slope. This suggests a non-constant variance that may result from either model misspecification or overdispersion.

Exhibit 39: Adjusted Linear Predictor vs Estimated Linear Predictor



The plot of the adjusted linear predictor by the estimated linear predictor clearly shows a linear trend. Therefore, the log link function seems appropriate for this model(53). If the line curved upwards, then the link function should be a higher order. If it curved down, then the link function should be a lower order.

Exhibit 40: Residual Diagnostics (Influential Observations)



There is one influential observation that is visible on the above plot of Cook's D vs. Predicted values. This encounters was for a long hospitalization (807 days), had numerous drug orders (58) and drug interactions (25). It does not represent the typical hospitalization and does not represent an acute care stay.

7 APPENDIX D: CHARLSON COMORBIDITY INDEX

The following table shows the assigned weights for the Charlson Comorbidity Index. The index is derived from the sum of the assigned weights.(49)

Assigned Weights for Diseases	Conditions
1	Myocardial Infarct Congestive Heart Failure Peripheral Vascular Disease Cerebrovascular Disease Dementia Chronic Lung Disease Connective Tissue Disease Ulcer Disease Mild Liver Disease Diabetes
2	Hemipelegia Moderate to Severe Renal Disease Diabetes with end organ damage Any tumour Lymphoma Leukemia
3	Moderate to Severe Liver Disease
6	Metastatic Solid Tumour AIDS

Percentage One-Year Mortality According to Severity and the Scores from the Weighted Index of Comorbidity

Severity and Reason for Admission	**0**	**1-2**	**3-4**	**>5**
Not to Mildy Ill				
Low Risk	7	14	29	60
High Risk	5	21	100	100
Moderately Ill				
Low Risk	7	19	38	91
High Risk	16	28	50	73
Severely Ill				
Low Risk	26	33	36	100
High Risk	38	58	94	100
Total	**12**	**26**	**52**	**85**

REFERENCES

(1) Agency for Healthcare Research and Quality. Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Evidence Report/Technology Assessment: Number 43. AHRQ . 1-7-0007.
Ref Type: Electronic Citation

(2) Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ 2004; 170(11):1678-1686.

(3) Bates DW, Boyle DL, Vander Vliet MB, Schneider J, Leape L. Relationship between medication errors and adverse drug events. J Gen Intern Med 1995; 10(4):199-205.

(4) WHO. Safety of Medicines: A guide to detecting and reporting adverse drug reactions. 2002.
Ref Type: Unpublished Work

(5) World Health Organization. Safety of Medicines
A guide to detecting and reporting
adverse drug reactions. 2002.
Ref Type: Unpublished Work

(6) Kohn LT. The Institute of Medicine. To Err is Human: Building a Safer health System. Corrigan JM, Molla SD, editors. 2000. National Academy Press.
Ref Type: Generic

(7) Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279(15):1200-1205.

(8) Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D et al. Incidence of adverse drug events and potential adverse drug events.

Implications for prevention. ADE Prevention Study Group. JAMA 1995; 274(1):29-34.

(9) Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA et al. The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group. JAMA 1997; 277(4):307-311.

(10) Burleson KW. Review of computer applications in institutional pharmacy--1975-1981. Am J Hosp Pharm 1982; 39(1):53-70.

(11) Hood JC, Miller JR. Use of computer drug-drug interaction program for detection of adverse drug reactions and related therapeutic problems. Drug Intell Clin Pharm 1979; 13(12):774-777.

(12) Greenlaw CW, Zellers DD. Computerized drug-drug interaction screening system. Am J Hosp Pharm 1978; 35(5):567-570.

(13) McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002; 36(9):1331-1336.

(14) Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ. Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing 2000; 29(1):35-39.

(15) Buajordet I, Ebbesen J, Erikssen J, Brors O, Hilberg T. Fatal adverse drug events: the paradox of drug treatment. J Intern Med 2001; 250(4):327-341.

(16) Hunziker T, Bruppacher R, Kuenzi UP, Maibach R, Braunschweig S, Halter F et al. Classification of ADRs: a proposal for harmonization and differentiation based on the experience of the Comprehensive Hospital Drug Monitoring Bern/St. Gallen, 1974-1993. Pharmacoepidemiol Drug Saf 2002; 11(2):159-163.

(17) Raschetti R, Morgutti M, Menniti-Ippolito F, Belisari A, Rossignoli A, Longhini P et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. Eur J Clin Pharmacol 1999; 54(12):959-963.

(18) Doucet J, Chassagne P, Trivalle C, Landrin I, Pauty MD, Kadri N et al. Drug-drug interactions related to hospital admissions in older adults: a prospective study of 1000 patients. J Am Geriatr Soc 1996; 44(8):944-948.

(19) Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug Saf 1993; 9(1):51-59.

(20) Prince BS, Goetz CM, Rihn TL, Olsky M. Drug-related emergency department visits and hospital admissions. Am J Hosp Pharm 1992; 49(7):1696-1700.

(21) Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003; 289(13):1652-1658.

(22) Egger T, Dormann H, Ahne G, Runge U, Neubert A, Criegee-Rieck M et al. Identification of adverse drug reactions in geriatric inpatients using a computerised drug database. Drugs Aging 2003; 20(10):769-776.

(23) Egger SS, Drewe J, Schlienger RG. Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003; 58(11):773-778.

(24) Gronroos PE, Irjala KM, Huupponen RK, Scheinin H, Forsstrom J, Forsstrom JJ. A medication database--a tool for detecting drug interactions in hospital. Eur J Clin Pharmacol 1997; 53(1):13-17.

(25) Chen YF, Avery AJ, Neil KE, Johnson C, Dewey ME, Stockley IH. Incidence and possible causes of prescribing potentially hazardous/contraindicated drug combinations in general practice. Drug Saf 2005; 28(1):67-80.

(26) Straubhaar B, Krahenbuhl S, Schlienger RG. The prevalence of potential drug-drug interactions in patients with heart failure at hospital discharge. Drug Saf 2006; 29(1):79-90.

(27) Wiltink EH. Medication control in hospitals: a practical approach to the problem of drug-drug interactions. Pharm World Sci 1998; 20(4):173-177.

(28) Huic M, Mucolic V, Vrhovac B, Francetic I, Bakran I, Giljanovic S. Adverse drug reactions resulting in hospital admission. Int J Clin Pharmacol Ther 1994; 32(12):675-682.

(29) Herr RD, Caravati EM, Tyler LS, Iorg E, Linscott MS. Prospective evaluation of adverse drug interactions in the emergency department. Ann Emerg Med 1992; 21(11):1331-1336.

(30) Tamai IY, Strome LS, Marshall CE, Mooradian AD. Analysis of drug-drug interactions among nursing home residents. Am J Hosp Pharm 1989; 46(8):1567-1569.

(31) Koepsell TD, Gurtel AL, Diehr PH, Temkin NR, Helfand KH, Gleser MA et al. The Seattle evaluation of computerized drug profiles: effects on prescribing practices and resource use. Am J Public Health 1983; 73(8):850-855.

(32) Karas S Jr. The potential for drug interactions. Ann Emerg Med 1981; 10(12):627-630.

(33) Glintborg B, Andersen SE, Dalhoff K. Drug-drug interactions among recently hospitalised patients--frequent but mostly clinically insignificant. Eur J Clin Pharmacol 2005; 61(9):675-681.

(34) Laine K, Forsstrom J, Gronroos P, Irjala K, Kailajarvi M, Scheinin M. Frequency and clinical outcome of potentially harmful drug metabolic interactions in patients hospitalized on internal and pulmonary medicine wards: focus on warfarin and cisapride. Ther Drug Monit 2000; 22(5):503-509.

(35) Hansten PD HJ. *Managing Clinically Important Drug Interactions.* Lippincott Williams and Wilkins, 2004.

(36) Schneider JK, Mion LC, Frengley JD. Adverse drug reactions in an elderly outpatient population. Am J Hosp Pharm 1992; 49(1):90-96.

(37) Beers MH, Storrie M, Lee G. Potential adverse drug interactions in the emergency room. An issue in the quality of care. Ann Intern Med 1990; 112(1):61-64.

(38) Gosney M, Tallis R. Prescription of contraindicated and interacting drugs in elderly patients admitted to hospital. Lancet 1984; 2(8402):564-567.

(39) Bacic V, V, Becirevic-Lacan M, Bozikov V, Birus M. Prescribing medication errors in hospitalised patients: a prospective study. Acta Pharm 2005; 55(2):157-167.

(40) Winterstein AG, Hatton RC, Gonzalez-Rothi R, Johns TE, Segal R. Identifying clinically significant preventable adverse drug events through a hospital's database of adverse drug reaction reports. Am J Health Syst Pharm 2002; 59(18):1742-1749.

(41) Mirco A, Campos L, Falcao F, Nunes JS, Aleixo A. Medication errors in an internal medicine department. Evaluation of a computerized prescription system. Pharm World Sci 2005; 27(4):351-352.

(42) Adson DE, Crow SJ, Meller WH, Magraw RM. Potential drug-drug interactions on a tertiary-care hospital consultation-liaison psychiatry service. Psychosomatics 1998; 39(4):360-365.

(43) Di Castri A, Jacquot JM, Hemmi P, Moati L, Rouy JM, Compan B et al. [Drug interactions: study of 409 prescriptions at the time of discharge from geriatric hospitalization]. Therapie 1995; 50(3):259-264.

(44) Cannon KT, Choi MM, Zuniga MA. Potentially inappropriate medication use in elderly patients receiving home health care: a retrospective data analysis. Am J Geriatr Pharmacother 2006; 4(2):134-143.

(45) Costa AJ. Potential drug interactions in an ambulatory geriatric population. Fam Pract 1991; 8(3):234-236.

(46) Hansten PD HJ. Drug Interactions Analysis and Management. October 2005. 5. Wolters Kluwer Health. Fact and Comparisons.
Ref Type: Serial (Book,Monograph)

(47) WHO. International Proprietary Names. WHO . 12-10-2007.
Ref Type: Electronic Citation

(48) WHO. WHO Collaborating Centre for Drug Statistics Methodology. WHO . 26-6-0007.
Ref Type: Electronic Citation

(49) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5):373-383.

(50) Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43(11):1130-1139.

(51) Schneeweiss S, Wang PS, Avorn J, Glynn RJ. Improved comorbidity adjustment for predicting mortality in Medicare populations. Health Serv Res 2003; 38(4):1103-1120.

(52) Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10):709-717.

(53) Patetta M. *Fitting Poisson Regression Models Using the GENMOD Procedure Course Notes.* SAS Institute Inc . 1-2-2005.
Ref Type: Electronic Citation

(54) Fox J. Regression Diagnostics: An Introduction. Newbury Park, CA: Sage University Paper Series on Quantitative Applications in the Social Sciences, series no 07-079, 1991.

(55) Pierce DA, Schafer DW. Residuals in Generalized Linear Models. Journal of AmericanStatistical Association 1986; 81:977-986.

(56) Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004; 351(6):543-551.

(57) National Prescription Drug Utilization Information System. Pharmaceutical Trends Overview Report. 1-6-2006.
Ref Type: Report

(58) Kohler GI, Bode-Boger SM, Busse R, Hoopmann M, Welte T, Boger RH. Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use. Int J Clin Pharmacol Ther 2000; 38(11):504-513.

(59) CIHI. Inpatient Hospitalizations and Average Length of Stay. 30-11-2005. CIHI. Analysis in Brief.
Ref Type: Report

(60) Domecq C, Naranjo CA, Ruiz I, Busto U. Sex-related variations in the frequency and characteristics of adverse drug reactions. Int J Clin Pharmacol Ther Toxicol 1980; 18(8):362-366.

(61) Pompei P, Charlson ME, Douglas RG, Jr. Clinical assessments as predictors of one year survival after hospitalization: implications for prognostic stratification. J Clin Epidemiol 1988; 41(3):275-284.

(62) Benson CA, Williams PL, Cohn DL, Becker S, Hojczyk P, Nevin T et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of Mycobacterium avium complex disease in patients with AIDS: A randomized, double-blind, placebo-controlled trial. The AIDS Clinical Trials Group 196/Terry Beirn Community Programs for Clinical Research on AIDS 009 Protocol Team. J Infect Dis 2000; 181(4):1289-1297.

(63) SAS Institute. SAS 9.1.3 Help and Documentation. SAS 9.1.3 . 2004. SAS Institute Inc.
Ref Type: Electronic Citation