# ANALYTICAL METHODS TO QUANTIFY RISK OF HARM FOR ALERT-OVERRIDDEN HIGH-RISK INTRAVENOUS MEDICATION INFUSIONS

by

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*I dedicate my dissertation work to my husband, Brian Tsang-Wei Lin, my parents, and my brother for their unwavering support and encouragement in these years.*

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# LIST OF ABBREVIATIONS

**A**

ADEs: Adverse Drug Events

AHP: Analytical Hierarchy Process

AHRQ: The Agency for Healthcare Research and Quality

AIC: Akaike Information Criterion

AICU: Adult Intensive Care Unit

AMSU: Adult Medical/Surgical Unit

**B**

BD: Bolus Dose

BDAR: Bolus Dose Administration Rate

BIC: Bayesian Information Criterion

**C**

CD: Continuous Dose

CR: Consistency Ratio

**D**

DERS: Dose Error Reduction System

**E**

EHRs: Electronic Health Records

**F**

FDA: The U.S. Food and Drug Administration

**H**

HardMax: Hard Maximum Drug Limit

**I**

IV: Intravenous

IP: Infusion Pump

ISMP: Institute for Safe Medication Practices

**K**

KPIs: Key Performance Indicators

**M**

MSE: Mean Square Error

MSPR: Mean Square Prediction Error

**N**

NCC MERP: The National Coordinating Council for Medication Error Reporting and Prevention

**R**

RCHE: The Regenstrief Center for Healthcare Engineering

REMEDI: The Regenstrief National Center for Medical Device Informatics

**S**

SIP: Smart Infusion Pump

SoftMax: Soft Maximum Drug Limit

# ABSTRACT

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The medication errors associated with intravenous (IV) administration may cause severe patient harm. To address this issue, smart infusion pumps now include a built-in dose error reduction system (DERS) to help ensure the safety of IV administration in clinical settings. However, a drug limit alert triggered by DERS may be overridden by the practitioners which can potentially cause patient harm, especially for high-risk medications. Most analytical measures used to estimate the associated risk of harm are frequency-based and only consider the overall drug performance rather than the severity impact from individual alerts. Unlike these other measures, the IV medication harm index attempts to quantify risk of harm for individual alerts. However, it is not known how well these measures describe the risk associated with alert-overridden scenarios. The goal of this research was (1) to quantitatively measure the risk for simulated individual alert-overridden infusions, (2) to compare these assessments against the risk scores obtained among four different analytical methods, and (3) to propose better risk quantification methods with a higher correlation to risk benchmarks than traditional measures, such as the IV Harm index.

In this study, 25 domain experts (20 pharmacists and 5 nurses) were recruited to assess the risk (adjusted for risk benchmarks) for representative scenarios created based on hospital alert data. Four analytical methods were applied to quantify risk for the scenarios: the linear mixed models (Method A), the IV harm index (Method B), Huang and Moh's matrix-based ranking method matrix-based method (Method C), and the analytical hierarchy process method, adjusted by linear mixed models (Method D). Method A used seven alert factors (identified as key risk factors) to build models for risk prediction, and Methods B and C used two out of seven factors to obtain risk scores. Method D used

pairwise comparison surveys to calculate the risk priorities. The quantified scores from the four methods were evaluated in comparison to the risk benchmarks.

Risk assessment results from the domain experts indicated that overdosing scenarios with continuous and bolus dose field limit types had significantly higher risks than those of bolus dose rate type. About the soft limit type, the expected risk in the group with a large soft maximum limit was significantly higher than the group with a small soft maximum limit. This significant difference could be found in the adult intensive care unit (AICU), but not in adult medical/surgical care unit (AMSU). The comparisons between four analytical methods and risk benchmarks showed that the risk scores from Method A ($\rho = 0.94$) and Method D ($\rho = 0.87$) were highly correlated to the risk benchmarks. The risk scores derived from Method B and Method C did not have a positive correlation with the benchmarks.

This study demonstrated that the traditional IV harm index should include more risk factors, along with their interaction effects, for increased correlation with risk benchmarks. Furthermore, the linear mixed models and the adjusted AHP method allow for better risk quantification methods where the quantified scores most correlated with the benchmarks. These methods can provide risk-based analytical support to evaluate alert overrides of four high-risk medications, propofol, morphine, insulin, and heparin in the settings of adult intensive care unit (AICU) and adult medical/surgical care unit (AMSU). We believe that healthcare systems can use these analytical methods to efficiently identify the riskiest medication-care unit combinations (e.g. propofol in AICU), and reduce medication error/harm associated with infusions to enhance patient safety.

Keywords: Intravenous (IV) infusions, Risk assessment, Medication safety, High-risk medications, Patient safety, Predictive models, Analytical methods

# CHAPTER 1. INTRODUCTION

Medication use processes include prescribing, transcribing, dispensing, administering, monitoring, etc. (ASHP, 2009), and medication errors might occur in any of these phases. Such errors may cause or lead to patient harm (Barker, Flynn, Pepper, Bates, & Mikeal, 2002). The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) has defined patient harm associated with medication errors as "death or temporary or permanent impairment of body function/structure requiring intervention," where intervention includes "monitoring the patient's condition, change in therapy, or active medical or surgical treatment" (NCC MERP, 2014). Harm can be of different degrees of magnitude. NCC MERP classified medication error and harm into nine categories from categories A to I (NCC MERP index) based on the severity of patient outcomes (NCC MERP, 2001). In addition, the Agency for Healthcare Research and Quality (AHRQ) did similar work in which they designed two versions of AHRQ's Harm scale with different categories between the extremes of no harm and death (T. Williams, Szekendi, Pavkovic, Clevenger, & Cerese, 2015). Of all the medication errors, the ones associated with intravenous (IV) administration have been identified as having the greatest potential for severe patient harm (IV infusion harm) (Eskew, Jacob, Buss, Warhurst, & Debord, 2002; Fields & Peterman, 2005; Hatcher, Sullivan, Hutchinson, Thurman, & Gaffney, 2004; Westbrook, Rob, Woods, & Parry, 2011; C. K. Williams & Maddox, 2005; Wilson & Sullivan, 2004).

Medication errors not only cause physical harm, but also translate to economic loss (Laswell, 2015). Studies have quantified the economic impact of medication error/harm in terms of costs of additional work and procedures, resources, required return visits, length of stays, etc. (Chang, Lawless, Newcomb, & Uhl, 2003; Rodriguez-Monguio, Otero, & Rovira, 2003). Furthermore, Pan et al. (2015) summarized the results from Hug's study (2012) showing that issues associated with preventable adverse drug events (ADEs) cost a hospital about $5.6 million (2014 U.S. dollars) annually. ADEs are defined as any medication error reaching to patients and causing a small or large injury resulting from IV medication infusion (Bates, Boyle, Vander Vliet, Schneider, & Leape, 1995; Leape & Kabcenell, 1998; Rodriguez-Monguio, Otero, & Rovira, 2003). Due to both physical and

economic impacts, great effort is needed to understand the infusion process and causes of the IV infusion errors to minimize the chance of these errors.

To ensure the safety of IV medication administration in clinical settings and avoid potentially catastrophic harm associated with medication errors, smart infusion pumps (SIPs) with a built-in software program, a dose-error reduction system (DERS), have been adopted by more than 70% of the healthcare systems in the United States as of 2012 (AAMI, 2016). A healthcare system can customize its drug limit settings defined in the drug limit library in DERS. Such a drug limit library includes the predetermined minimum and maximum drug limits (Hertzel & Sousa, 2009), and they can be preset for clinicians to monitor administration of the medications (Harding, 2012). When a nurse uses a smart IV pump to infuse a drug under the preset drug limits, a field limit alert will sound if the programmed parameters are below the minimum or above the maximum drug limits. The nurse can either choose to override or reprogram the infusion parameters in response to the alert. In particular, an alert-overridden infusion could potentially lead to some degrees of patient harm. For example, a nurse does not recognize the significance of a programming alert and then overrides it to administer insulin at an incorrect rate or dose, which results in severe harm to the patient. For such a situation, the IV pump technology with drug limit safety functions becomes useless in preventing that harm event (Scanlon, 2012). Note that all steps involved in IV drug administration, including the drug name, care area, programmed values, alert information, actions in response to alerts, etc., are usually recorded in the smart pump with some variation among different vendor pumps. This provides the clinicians and researchers with a tremendous amount of information to study various aspects of infusion pump use.

In many hospitals, medication safety teams, typically including pharmacists, nurses, and physicians, regularly use pump alert reports for reviewing drug infusion performance. Some common analysis tools such as (1) Key Performance Indicators (KPIs) (CareFusion, 2016), (2) Infusion Pump (IP) Safety Score (Carlson, Johnson, & Ensign, 2015), and (3) Regenstrief National Center for Medical Device Informatics (REMEDI), a web-based analytics tool, contributed by members of the community and supported by the Regenstrief Center for Healthcare Engineering (RCHE) of Purdue University, can be applied to evaluate infusion alerts associated with different actions taken, cancellations,

reprograms, and overrides. These drug performance measures and indicators are frequency-based (e.g. DERS compliance rate, alert overriding rate, override to reprogram ratio, etc.) and can only provide an aggregated view (frequency) of alert-overridden infusions, which we focus on this research, for a period of time. They do not consider that each alert-overridden infusion might cause a different level of severity of IV harm to patients, and they should be assessed individually first, and then aggregated (Sullivan, 2004; C. K. Williams et al., 2006).

As a way to assess potential IV harm for individual alerts, the IV Medication Harm Index Study Group (the patient safety experts) developed the "IV medication harm index" (Sullivan, 2004; C. K. Williams et al., 2006), which can be used to generate IV medication harm scores (range 3.5 - 14) for individual overridden alerts using the following factors: drug risk and overdose ratio (ratio means programming values (overdose) divided by the soft maximum drug limit), level of care/acuity, and detectability of ADEs. The greater sum of the harm scores indicates higher risk of IV harm. However, there are some possible limitations to using this IV medication harm index. One possible problem is that in some cases, the created discrete scale makes large jumps (i.e. from 3 to 6 or 6 to 9) for small changes of the continuous overdose ratio. Moreover, the quantified harm sub-scores associated with the factor "drug risk and overdose ratio" for all high-risk drugs are the same but different drugs can harm patients differently. Another potential limitation is that other factors such as drug limit types and total drug amounts patients receive are not considered, but they likely can cause various degrees of patient harm. Therefore, a better quantification method is greatly needed to improve the existing IV medication harm index and properly estimate *risk of harm*, defined as incorporating likelihood of potential degrees of IV harm (Cure, Zayas-Castro, & Fabri, 2014) of individual overridden alerts. Currently, in most healthcare systems, each alert-overridden infusion is not directly linked to clinical patient outcomes because infusion data (i.e. part of the treatment process) is not integrated with electronic health records (EHRs). When proposing or applying any method for risk quantification, the clinical patient outcomes associated with each overridden alert should be obtained to validate the quantified scores generated by the methods. Therefore, in this study, healthcare professionals were invited to participate in this research to assess *risk of harm* for the designed scenarios of alert-overridden infusions. Their assessments can be

used to calculate the expected risk, which was regarded as the benchmarks to validate the quantification results from the proposed or applied methods. Four high-risk drugs (propofol, morphine, insulin, and heparin) were selected for assessment in this research based on the Institute for Safe Medication Practices (ISMP) categories of medications (ISMP, 2007) and the therapeutic classes defined by San Diego Patient Safety Council (San Diego Patient Safety Council, 2014).

The goal of this research was to (1) apply four analytical methods that quantify risk for the designed individual alert-overridden infusions and (2) propose a proper risk quantification method. With the quantification method, how risk factors influence the overall risk can be observed. This method can be used for quantifying risk among individual alert-overridden infusions associated with four high-risk medications used in inpatient settings: propofol, morphine, insulin, and heparin. We aimed to (1) interview and analyze healthcare professionals' risk assessments (regarded as benchmarks) concerning the designed drug infusion scenarios, (2) apply several analytical methods to quantify risk for the designed individual alert-overridden infusions, (3) evaluate the quantified scores results derived from the analytical methods by comparing them with the benchmarks, (4) compare pros and cons and propose proper methods for risk quantification, and (5) provide a framework to apply the proposed methods to estimate *risk of harm* for individual overridden alerts associated with the four high-risk drugs. The contribution of this research is that it provides a risk-based analytical approach to support evaluating alert-overridden infusions that healthcare systems can use to efficiently identify the riskiest medication-care unit combinations (e.g. propofol in adult intensive care unit) using infusion alert data. These highlighted units will be regarded as the high-priority areas for the healthcare systems to improve nursing practices, workflow, and/or drug limit settings (Miller, 2016) based on root cause analysis (Taxis & Barber, 2003). By doing so, we believe healthcare systems can reduce medication error/harm associated with infusions and enhance patient safety.

This dissertation is structured as follows. In Chapter 2, we first describe the literature about medication errors and severity of IV harm, smart pumps and the safety features, and the common measures and their limitations for evaluating drug infusion performance. We also review the concept of expert risk judgment and some multi-criteria

decision-making methods that can be applied to this study. Chapter 3 lays out the research framework and hypotheses. The design of scenarios and survey questions, experimental design, and expected risk calculated from the healthcare professionals' risk assessments are detailed in Chapter 4. In Chapter 5, we apply different analytical methods to quantify risk of harm for individual alert overrides in high-risk IV medication infusions. We also validate the quantified scores derived from each analytical method, and the pros and cons of these methods are discussed in Chapter 6. Finally, conclusions are stated in Chapter 7.

# CHAPTER 2. LITERATURE REVIEW

In this chapter, we first introduce medication errors and how these errors can cause harm of various degrees during the IV medication infusion process. We then discuss safety features of smart infusion pumps which can help reduce the medication errors during an infusion process and methods of evaluating performance. One of the major issues is that when infusions with triggered alerts are overridden by nurses, the consequences potentially lead to severe patient harm, especially during the administration of high-risk medications. The final sections introduce several analysis tools which can be used to quantify or rank the risk of harm among the alert-overridden infusions.

## 2.1 Medication Errors and Severity of Harm

Medication errors can occur during any phase of the process which is associated with medication use (e.g. prescription, dispensing, transportation, and administration) (Lehmann & Kim, 2005). Medication errors have been classified into six categories (Table 1) (Moore & Balk, 2008). Previous studies have identified medication errors occurring during the administration phase as the most frequent type of mistakes in hospitals (Hicks, Cousins, & Williams, 2003). Such errors are also called intravenous (IV) medication errors. These IV medication errors are a common type of error identified in hospitals and can cause severe harm to patients. Over the past 20 years, the U.S. Food and Drug Administration (FDA) reported several hundred incidents involving IV medication administration, many of which have led to patient deaths (Husch et al., 2005).

Harm can be defined at different levels based on the severity or degree of patient outcomes. NCC MERP and AHRQ provided harm categories and scales to classify the harm magnitudes on patients. The application of the harm categories and scales can be found in the previous studies (Husch et al., 2005; Rozich, Haraden, & Resar, 2003; Shah et al., 2009; T. Williams et al., 2015). In this research, we focus on the IV medication errors, and the NCC MERP index was chosen for experts to assess the severity of harm for the alert-overridden scenarios, which are described in detail in Section 4-1.

Table 1: Categories of Medication Errors (Moore & Balk, 2008)

| Category | Error Type |
|---|---|
| **Dosing Errors** | Overdose |
| | Underdose |
| | Wrong dose strength |
| | Extra dose |
| | Omitted/Missed dose |
| **Drug Administration Errors** | Unordered/Unauthorized drug |
| | Wrong drug |
| | Wrong/No route |
| | Wrong technique |
| | Wrong form |
| **Drug Preparation Errors** | Wrong formulation/dilution |
| | Expired Drug |
| **Timing Errors** | Wrong time/frequency |
| **Prescription Errors** | Incomplete prescription |
| | Transcription error |
| | Illegible prescription |
| **Patient errors** | Drug reaction/allergy/interaction |
| | Wrong diagnosis |

## 2.2 Smart Infusion Pump and Their Safety Features

The Smart Infusion Pump (SIP) is a system that includes drug limit settings (also called guardrails) to ensure the safety of IV medication administration (Fields & Peterman, 2005; Ohashi, Dalleur, Dykes, & Bates, 2014). In hospitals, medication safety teams (pharmacists, nurses, and physicians) define drug limit settings which are then stored in a drug limit library linked to each smart pump. When nurses use smart infusion pumps (SIPs) to administer medications, they first program the parameters, for example, programming drug amounts, diluent volumes, and infusion duration, based on the drug prescriptions and the patients' therapy. If the programming values are above or below the drug limits, alerts will sound. If "Soft" alerts, (programming values are outside the soft limits) are triggered, nurses can either override, reprogram, or cancel alerts. However, "Hard" alerts (programming values are outside the hard limits) can only be either reprogrammed or canceled (Figure 1). During an IV medication administrative process, information associated with the process is recorded in the SIP system. This includes infusions

with/without alerts and/or alarms that may be triggered. The information and parameters can be obtained from the infusion and alert reports which are recorded in the SIP systems (a secure web-based hospital reporting tool). These reports are key information used by the safety team to evaluate drug infusion pump performance.

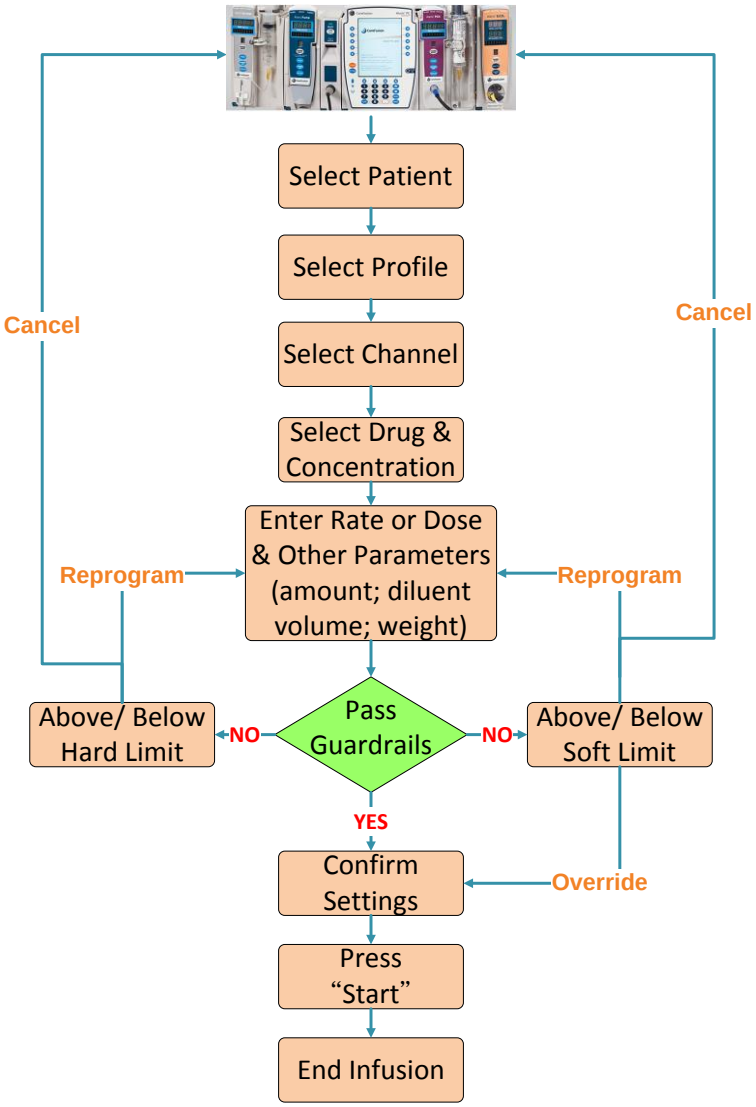



Figure 1: The Illustration of SIP Programming Process

As mentioned in the above paragraph, soft alerts can be overridden by nurses, leading to potential risk of harm, which is especially a concern for high-risk medications. To address this issue, this research focuses on risk quantification for high-risk infusion alerts with nurses' overriding responses. Previous studies have discussed many potential

factors causing nurses to override alerts (Grozdanovic, 2005; Kirwan, Kennedy, Taylor-Adams, & Lambert, 1997; Noroozi, Khakzad, Khan, MacKinnon, & Abbassi, 2013; Ohashi et al., 2014; Park & Lee, 2008; Tu, Lin, & Lin, 2015), and some of these factors are summarized in Table 2. The following section introduces common measures and their potential limitations for evaluating drug infusion pump performance using pump alert data.

Table 2: The Potential Factors Causing Overridden Alerts

| **Category** | **Factor** |
|---|---|
| (1) Individual | Experience/Training (nurse, pharmacist physicians) |
| | Stress, fatigue, and workload |
| | Nurse's confidence level for their infusion behavior |
| | Nurse's trust level for prescriptions |
| (2) Equipment and tool condition | The range of limit setting |
| | Pump interface design |
| (3) Environmental condition | Number of alarms |
| (4) Task, workflow, and procedure | Complexity of the procedures |
| (5) Supervision | Supervision for override |

## 2.3 Evaluation of Drug Infusion Performance

### 2.3.1 Evaluation Process of Drug Infusion Performance

In hospital systems, medication safety teams regularly extract alert reports from smart infusion pumps to evaluate drug infusion performance using analysis tools, such as Key Performance Indicators (KPIs) from BD Alaris™ pump vendor and Regenstrief National Center for Medical Device Informatics (REMEDI) system from Regenstrief Center for Healthcare Engineering at Purdue (Figure 2). These evaluations of drug infusion performance can lead to improvements in nurse practice, programming workflow, or drug limit settings. Regarding the improvement of drug limits, medication safety teams need to revise the limits which are stored in the drug limit library (Mansfield & Jarrett, 2013, 2015). After the revision of the drug limits, nurses need to start initial settings on the pumps for properly update the limits.

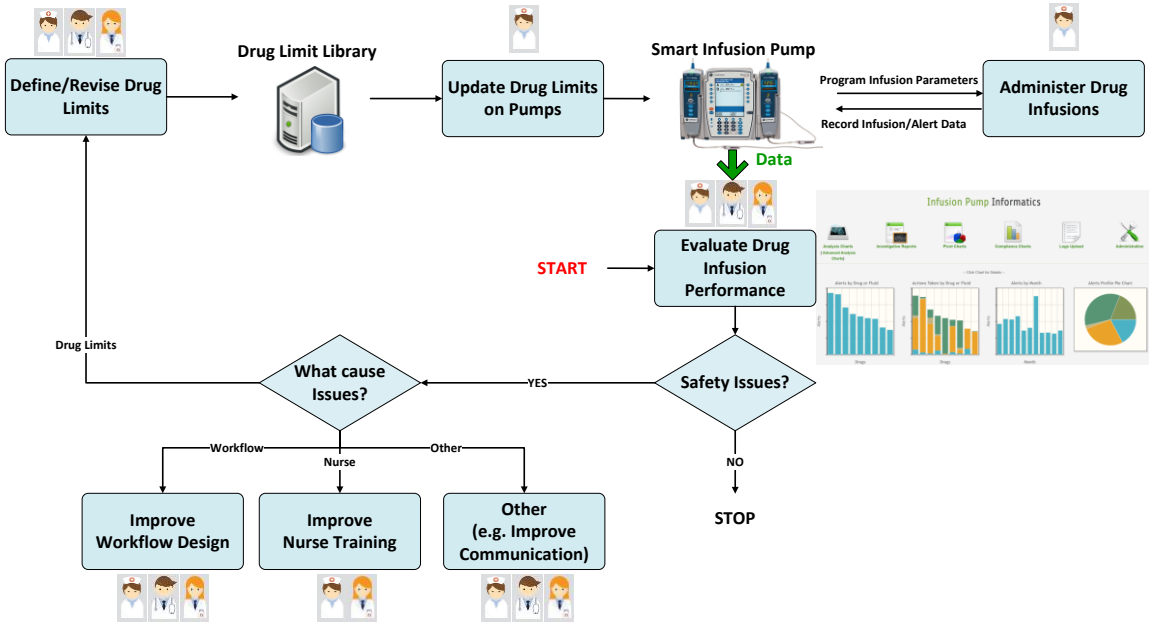



Figure 2: Evaluation Cycle of Drug Infusion Performance

### 2.3.2 Common Measures for Evaluating Drug Infusion Performance

Three typical analytical measures can be found in the literature for evaluation of drug infusion performance, which are Key Performance Indicators (KPIs) and Performance Scorecard (CareFusion, 2016), IV Medication Harm Index (Sullivan, 2004; C. K. Williams et al., 2006), and Infusion Pump (IP) Safety Score (Carlson et al., 2015). The KPIs and the IP Safety Score can only evaluate data during a specific period of time using aggregated views (defined as a global measure), such as total alert frequency, DERS compliance rate, and a number of soft/hard limit alerts. The key measures, the classification of individual or global assessments, and the drawbacks of these analytical measures are summarized in Table 3. For KPIs, only some measures account for risks of patient harm involved in the infusions, and most indicators are associated with the actual count of alert frequency, meaning some medications of low use or alert frequency with high safety risk might be overlooked.

Unlike the frequency-based measures mentioned above, the IV Harm Index was developed to assess and quantify risk for each individual alert (Sullivan, 2004; C. K. Williams et al., 2006). This harm index comprises three subscales that characterize the risk elements of the IV infusion harm: (1) the risk associated with the drug-dosing range being infused, (2) patient acuity (patient care type), and (3) detectability of an infusion-related ADE. The rule for quantifying the harm/risk scores for the three subscales is indicated in Table 4. The sum of the harm scores ranges from 3.5 to 14, and a sum equaling "11" or more was identified as "high risk" in the previous studies (Sullivan, 2004; C. K. Williams et al., 2006). In addition, its quantification methods for calculating sub-scores are not appropriate, and it might be easily changed the overall harm score (sum of the three subscales). For example, the subscale of 1.5 overdosing range with high-risk medication is "3", but the subscale of 1.6 overdosing range is "6". Moreover, its quantification settings of high overdosing ranges are not appropriate (e.g. times of limit =2.5 > 2.5 for the same risk-level medications were quantified as the same risk score) (Table 4). Therefore, this study applied several analytical methods, including some multi-criteria decision-making methods, for individual risk quantification. The application and validation of these methods involve expert judgment, which is discussed in the next section.

Table 3: Summary Table of Infusion Performance Measures

| Analysis Tool | Reference | Measures | Individual/ Global Levels | Issues |
|---|---|---|---|---|
| **Key Performance Indicators (KPIs)** | CareFusion (2016) | Total Guardrails Infusions/ Compliance Rate | Global | • Most KPIs are associated with the actual count of alert frequency<br>• Only global measures |
| | | Total Guardrails Alerts | | |
| | | Total Override Alerts | | |
| | | Total High-risk Override | | |
| | | Total Infusion Alarms | | |
| | | Total High-risk Drugs without Hard Limits | | |
| | | Quick Overridden Rate | | |
| **Infusion Pump Safety Score** | Carlson et al. (2015) | Basic Infusion Rate | Global | • Only global measures |
| | | Soft Limit Alert Rate | | |
| | | Hard Limit Alert Rate | | |
| **IV Medication Harm Index** | Sullivan (2004); Williams et al. (2006) | Drug Risk/ Overdose Magnitude Range | Individual & Global | • Cannot quantify the risk of under-dosing<br>• Quantification methods for calculating sub-scores are not appropriate<br>• Quantification settings of high overdosing ranges are not appropriate |
| | | Level of Care/ Acuity | | |
| | | Detectability | | |

Table 4: IV Medication Harm Index
(Sullivan, 2004; C. K. Williams et al., 2006)

**Subscale 1: Drug Risk/Overdosing Range (Score)**

| Drug | Low | Moderate | High |
|---|---|---|---|
| Low risk | 1-4 times (1.5) | 4.1-9.9 times (2) | ≥10 times (3) |
| Moderate risk | 1-2 times (2) | 2.1-4.9 times (4) | ≥5 times (6) |
| High risk | 1-1.5 times (3) | 1.6-2.4 times (6) | ≥2.5 times (9) |

**Subscale 2: Level of Care/Acuity**

| Level of Care | Description | Score |
|---|---|---|
| General | Medical, surgical, other | 1 |
| Intermediate | Non-ICU beds with telemetry | 1.2 |
| Adult ICU | - | 2 |
| PICU or NICU | Pediatric or Neonatal ICU | 3 |

**Subscale 3: Detectability**

Likely = 1
Unlikely = 2

Sum of score range = 3.5-14
High score = greater harm/risk

## 2.4 Risk and Expert Subjective Judgment

### 2.4.1 Risk Estimation

The process of risk analysis in healthcare includes risk identification and risk assessment phases (Cure et al., 2014). Risk estimation is the final step in the risk assessment phase and can generate the measure to assess the conditions of health, safety, and environment (Covello & Merkhofer, 1993). Risk is a two-dimensional measure, which includes both uncertainty and consequences (Aven, 2009). Subjective probabilities are often estimated using experts' subjective judgments during risk assessment process (Skjong & Wentworth, 2001). Some researchers suggest that the subjective probabilities, which are provided by experts should be adjusted using a non-linear function to more accurately measure the true probabilities (Tversky & Kahneman, 1992; Zhang & Maloney, 2012), as indicated in Figure 3. Estimates are also usually obtained from multiple experts which means the different estimates must be somehow combined or aggregated. The following section introduce some commonly methods for aggregating experts' subjective judgments.

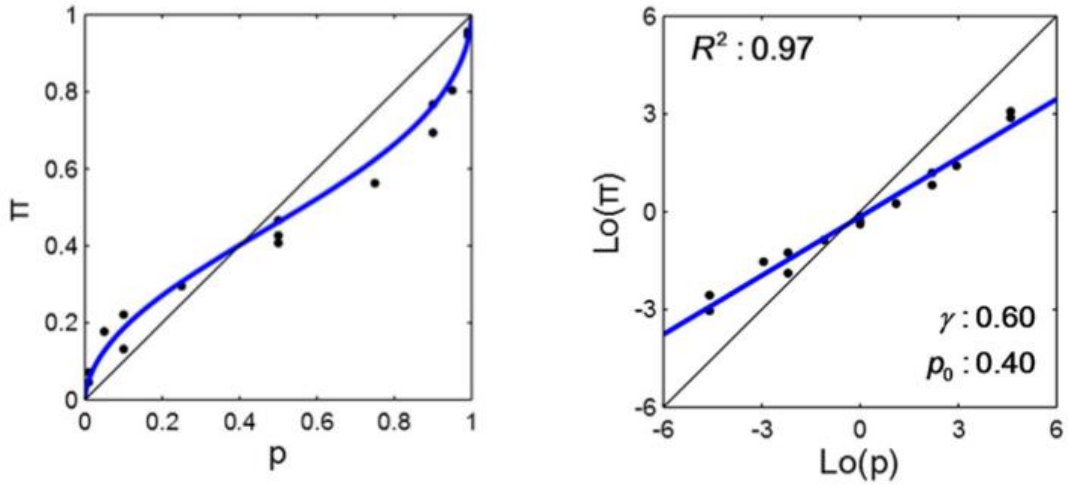



Figure 3: A Relationship between the True Probability and the Subjective Probability (Tversky & Kahneman, 1992)

### 2.4.2 Aggregation Methods of Expert Judgment

Winkler et al. (1992) stated that multiple experts' judgments should be aggregated because a combined distribution produces a better estimation than the individual distribution. This is similar to the psychological perspective that "two heads are better than one". There are two types of aggregations; one is *behavioral aggregation* and the other is *mathematical aggregation* (Ferson, 2005; Grozdanovic, 2005; Leung, Verga, & CSS OR Team, 2007; O'Hagan et al., 2006). There are several ways of aggregating experts' judgments. In *behavioral aggregation* methods, experts can estimate alone but have limited discussions for clarification purposes (e.g. Delphi method and nominal group technique); or they can meet as a group and discuss their estimates until they reach a consensus (e.g. consensus-group method). In *mathematical aggregation* methods, experts can estimate alone, with their opinions then aggregated mathematically (e.g. arithmetic (Eq. 2.1) or geometric mean (Eq. 2.2), and Bayesian method (Eq. 2.3)). The basic concept of the three mathematical aggregation methods are indicated as follows:

- Arithmetic mean aggregation

The first aggregation method is to calculate the arithmetic mean (average) of a set of values. Given a set of samples $\{x_i\}$, the arithmetic mean is

$$\bar{x} = \frac{1}{N} \sum_{i=1}^{N} x_i \tag{2.1}$$

- Geometric mean aggregation

The second one is an aggregated individual method (geometric mean), which will be applied to obtain the geometric mean of the four individual judgments. The geometric mean is defined as the $n^{th}$ root of the product of a set of n numbers $(x_1 \dots \dots \dots \dots x_n)$ defined as:

$$\left(\prod_{i=1}^{n} x_i\right)^{\frac{1}{n}} \tag{2.2}$$

- Bayesian aggregation

The third method is one of a common mathematical aggregation method, called Bayesian aggregation. The purpose of the mathematical aggregation is to specify the performance of the experts and combine or adjust the experts' individual probability values or distributions into one single value or distribution (Leung et al., 2007). Morris (1974) first proposed the concept of Bayesian methods, and Clemen and Winkler (1999) provided the extended work. The previous studies (French, 1983; Genest & Zidek, 1986) indicated that a Bayesian updating scheme is an appropriate method for the risk analysis situation. Suppose each of N experts is asked individually to assess some unknown quantity θ, the Bayesian model is indicated as follows:

$$\pi(\theta|E) \propto L(E|\theta)\,\pi(\theta) \tag{2.3}$$

where $\pi(\theta)$ is the prior probability function of the set $\theta$ and $\pi(\theta)$ reflects the analysts' prior state of knowledge about the unknown parameter. $E = \{x_1', x_2', \dots\dots\dots, x_N'\}$ is the set of the experts' evidence which are the values of experts' quantified estimation of interest $x$. $L(E|\theta)$ is the likelihood of the evidence $E$ conditional on the true value of the unknown quantity is $\theta$. $\pi(\theta|E)$ is the posterior probability functions of the set $\theta$ and it indicates the analysts' posterior state of knowledge about the unknown parameter $\theta$ conditional on they have received the set of experts' opinions. The experts' opinions can be used to update the knowledge on the values of theses parameters.

Considering the experimental design, data collection, and the recommendations from previous studies (Teknomo, 2006), the geometric mean (mathematical aggregation method) was selected to aggregate multiple experts' assessments in this study.

## 2.5 Multi-Criteria Decision-Making Methods

Decision making is a process that involves many criteria, which can be used to calculate relative priorities for a decision maker to make a better choice (Saaty, 2008). Many multi-criteria decision making (MCDM) approaches have been developed (Huang & Moh, 2016; Triantaphyllou, 2000), and these approaches have been applied to the healthcare area to support public health decision making (Baltussen & Niessen, 2006; Nobre, Trotta, & Gomes, 1999). Two approaches were selected in this study for the application of risk quantification. One is a new created non-linear non-weighted method also called the matrix-based ranking method, and the other is a widely used decision-making methodology, Analytical Hierarchy Process (AHP) Method (Saaty, 2008).

### 2.5.1 Matrix-based Ranking Method

The matrix-based ranking method is a multi-attribute decision-making method to rank the order of datasets (Huang & Moh, 2016). Given a comparison matrix for decision alternatives has been created, it can be proved that an almost-always primitive matrix, also called a non-negative square matrix, exists as a positive eigenvector of the matrix (Huang & Moh, 2016). This method has been applied to rank the hospitals using the performance scores. When applying this method, weights of decision criteria are not required, which is different from the weighted-sum method. The key procedures of applying this method is indicated as follows:

1) First, the comparison criteria should be identified. Then, the pairwise comparative strength vector is generated to form a comparison matrix. For example, Figure 4 shows an illustration concept of the application for risk score rankings. In this case, when comparing two alternatives, the one with higher degree value based on each comparison criteria obtains the performance score 0.25 (1 divided by 4 factors). If the two alternatives have equal degree values, each obtains 0.125. Therefore, the total performance scores for each alternative can be calculated, which comprise to a comparative strength vector. For example, in Figure 4, the risk levels of medications (degree value) for alternative A2 is higher than A4, so the performance score of A2 in the criteria is 0.25 and of A4 is 0.

2) After generating an overall comparison matrix, the 1st strength vector is derived given the evenly order "1" for all entries.
3) After the first iteration, the 2nd strength vector is derived by multiplying the comparison matrix and the 1st strength vector.
4) The iteration procedure will stop until all eigenvalues are positive, when the ranking results are cohesive and the strength vector uniqueness can be proved (Gakkai, 2000)

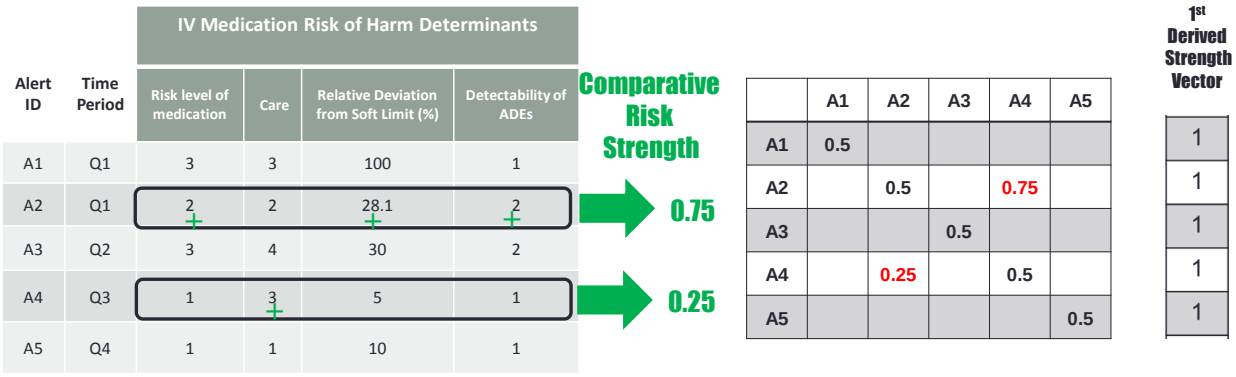



Figure 4: An Illustration of Overall Comparison Matrix Generation

### 2.5.2 Analytical Hierarchy Process (AHP) Method

This AHP method is a multi-criteria decision-making method (Liberatore & Nydick, 2008; Teknomo, 2006) used to derive relative weights for ranking the alternatives using the defined criteria and sub-criteria (Saaty, 2008; Saaty & Kearns, 1985). AHP methods have been applied to many important problems for decision-making, such as, ranking orders (priorities) for evaluating the service or quality (Prakash & Barua, 2016), for implementing the processes in a safety management system (Chan, Kwok, & Duffy, 2004), for safety risk assessment (Aminbakhsh, Gunduz, & Sonmez, 2013), and for medical and health care decision making (Liberatore & Nydick, 2008). The followings are the key steps to generate the priorities (Saaty, 2008; Teknomo, 2006):

1) Define the problem and construct the hierarchy including from the goal, decision criteria, to the alternatives.
2) Create a set of pairwise comparison matrices based on the pairwise surveys from the domain experts.

3) Use the comparison matrices to derive the normalized principle eigen vector (corresponding to the largest eigen value) also called priority vector. The priority vector is regarded as the relative weights in this level. The relative weights for the hierarchy levels are composited for the alternatives.
4) Calculate the consistency index and ratio to evaluate the subjective judgments from the experts.

# CHAPTER 3. RESEARCH FRAMEWORK AND HYPOTHESES

In this research, we designed representative infusion scenarios and collected healthcare professionals' risk assessment results. The results, including likelihood (probability) of each consequence level (degrees of harm), are combined, adjusted, and regarded as risk benchmarks which are compared to the quantified risk scores obtained using four different analytical methods (Figure 5). The proposed quantification methods that have a higher correlation with the risk score benchmarks can be used to support evaluating alert overrides in four high-risk drugs of propofol, morphine, insulin, and heparin, in the settings of adult medical and surgical care unit (AMSU) and adult intensive care unit (AICU).

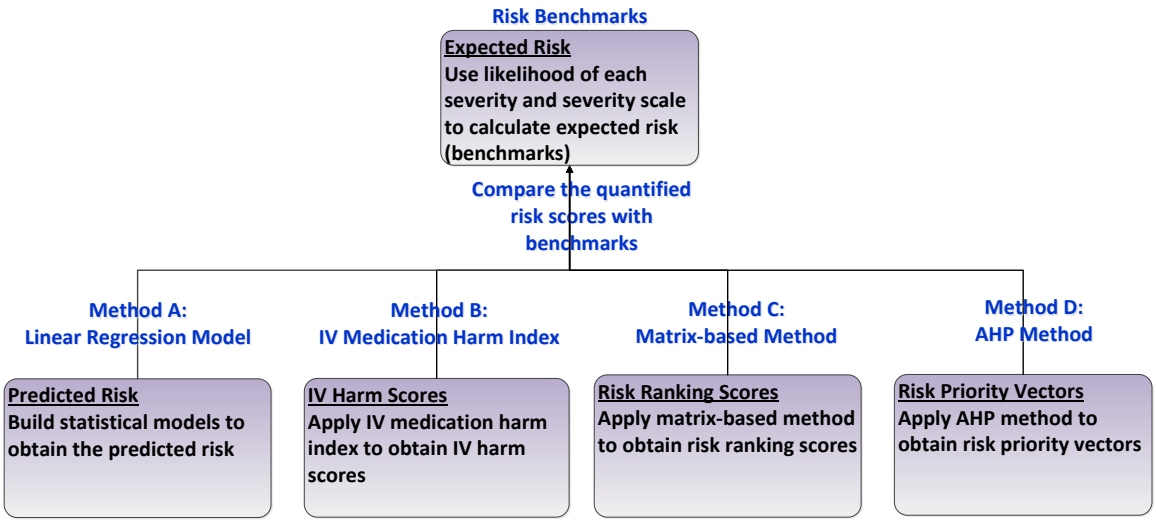



Figure 5: Research Framework

The research framework and the related hypotheses are described as follows:

## Risk Benchmarks

We created an abstract version of representative scenarios about alert-overridden infusions and invited medication safety experts to assess the risk of patient harm. In

general, risk is defined as "the chance of a specific adverse event happening that will have an impact on objectives" (Health Service Executive, 2009). In this study, we calculated expected risk of harm, defined as risk benchmarks, using the combination of likelihood and its severity (Health Service Executive, 2011). The larger risk benchmark means the higher risk of causing IV harm to patients. The detailed scenario and survey design, and the procedures of the risk assessment process for the healthcare professionals are shown in Chapter 4.

**Method A – Linear Predicted Risk vs. Risk Benchmarks**

Linear regression models are often used in statistics to describe how a linear combination of the potential predictors can be used to predict the outcome variables (Neter, Kutner, Nachtsheim, & Wasserman, 1996). In this study, we built linear regression models in which risk was the dependent variable and the key predictors (independent variable) were care area, medication, programming ratio (Sullivan, 2004; C. K. Williams et al., 2006), and other alert factors (e.g. drug limit types, infusion duration), which were selected from the infusion scenarios. Furthermore, the linear models were selected and validated using the model selection criteria (Neter et al., 1996). After selecting the final linear regression models, we used the models to generate the predicted risk for the infusion scenarios. The predicted risk was compared with the benchmarks. The detailed procedures are shown in Section 5.1. Accordingly, the following hypothesis is:

**Hypothesis 1: In all scenarios, the predicted risk calculated by the linear regression models is positively correlated with the risk benchmarks.**

$H_0$: $\rho \leq 0$ (Null hypothesis: the correlation is zero or negative)
$H_A$: $\rho > 0$ (Alternative hypothesis: the correlation is positive)

**Method B – IV Harm Scores vs. Risk Benchmarks**

IV Medication Harm Index has been applied to quantify the potential risk for individual alerts using three sub-risk scales: (1) the risk associated with the drug-dosing range being infused, (2) patient acuity (patient care type), and (3) detectability of an infusion-related ADE (Sullivan, 2004; C. K. Williams et al., 2006). The larger sum of IV harm scores indicates the higher risk of causing patient harm. This IV harm index was applied to obtain the IV harm scores for the infusion scenarios. The ham scores were

compared with the benchmarks. The detailed procedures are described in Section 5.2. Accordingly, the second hypothesis is:

**Hypothesis 2: In all scenarios, the IV harm scores obtained by the IV method harm index are positively correlated with the risk benchmarks.**

**Method C – Risk Ranking Scores vs. Risk Benchmarks**

Huang and Moh's matrix-based ranking method is a multi-criterion ranking method which can rank a group of data using the comparison criteria (Huang & Moh, 2016). In this study, the matrix-based method was applied to quantify the relative risk levels for individual alert-overridden scenarios using the defined comparison criteria. The risk ranking scores were compared with the benchmarks. The detailed procedures are described in Section 5.3. Accordingly, the third hypothesis is:

**Hypothesis 3: In all scenarios, the risk ranking scores generated by the matrix-based method are positively correlated with the risk benchmarks.**

**Method D – Risk Priority Vectors vs. Risk Benchmarks**

The analytic hierarchy process (AHP) method is a multi-criteria decision-making method, which can derive relative ratio scales, also called priority vectors, from the experts' pairwise comparisons (Saaty, 2008). The AHP method was applied to create the pairwise comparison matrices and to obtain the risk priorities for different infusion scenarios. The risk priorities were compared with the benchmarks. The detailed procedures are indicated in Section 5.4. Accordingly, the fourth hypothesis is:

**Hypothesis 4: The risk priorities for each scenario type, generated by the analytical hierarchy process (AHP) method are positively correlated with the risk benchmarks.**

In summary, the healthcare professionals conducted two types of surveys (A, D): the results from part I survey (A) were collected to obtain the risk benchmarks and to build the linear regression models; the results from part II survey (D) were collected and used to obtain the risk priority vectors. In addition, the IV harm index (B) and the matrix-based ranking method (C) were applied to quantify risk on the part I infusion scenarios. The quantified scores from the four analytical methods were compared with the benchmarks.

Finally, a framework of risk quantification for hospital alert-overridden infusions was created. The following diagram describes the relationship between Chapters 4, 5, and 6 (Figure 6).

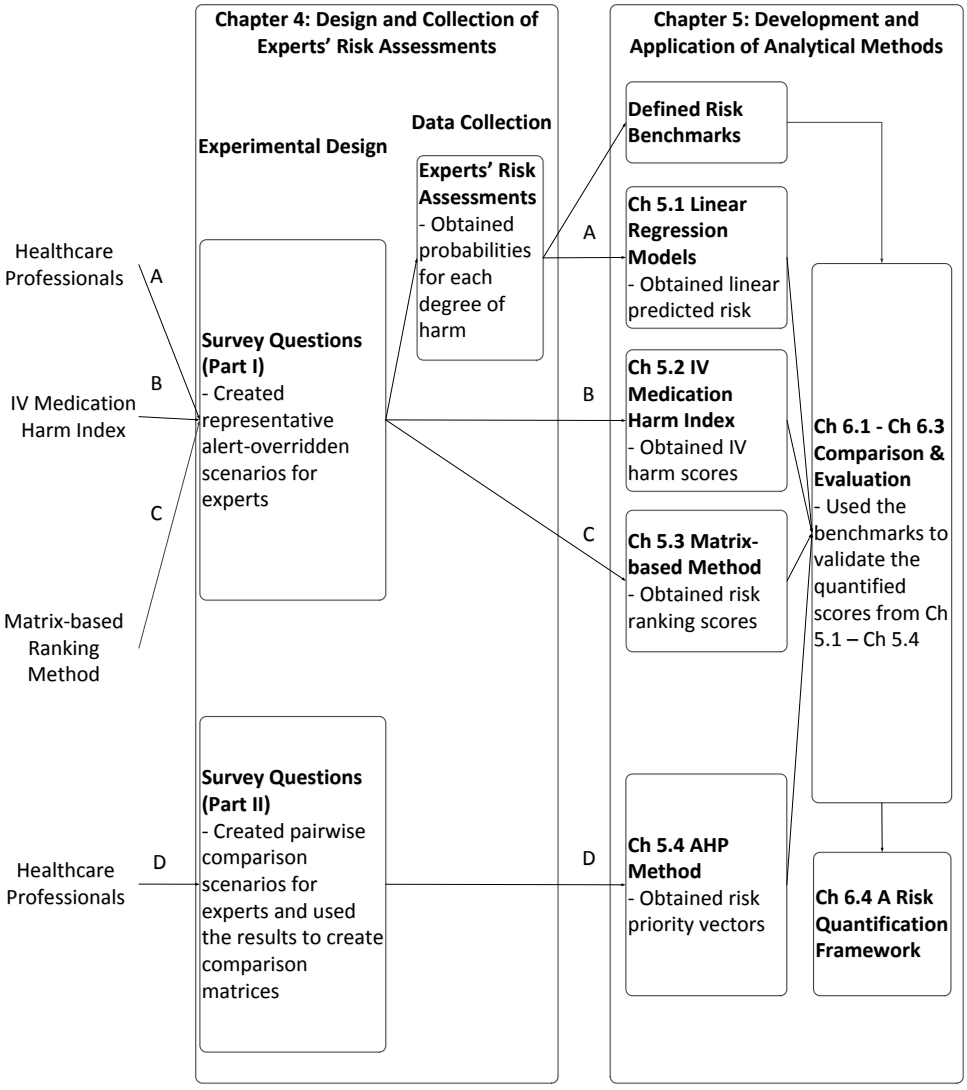



Figure 6: A Workflow between Chapter 4 and Chapter 6

# CHAPTER 4. EXPERIMENTAL DESIGN AND COLLECTION OF HEALTHCARE PROFESSIONALS' RISK ASSESSMENTS

The goal of this research was to propose analytical methods to estimate risk of IV harm for each alert-overridden infusion. In this chapter, we use healthcare professionals' risk assessments to estimate the expected risk of intravenous infusion harm for 270 simulated scenarios where infusions of high-risk medications exceed soft limits. These assessment results were adjusted, combined, and identified as the benchmarks to validate the quantification scores from the analytical methods.

## 4.1 Methods

### 4.1.1 Participants

The voluntary participants of IV harm risk assessment in this study included 20 pharmacists and 5 nurses who had experience working with intravenous (IV) infusions. Most of them were members of their hospitals' medication safety committees.

### 4.1.2 Scenario Design

We designed infusion scenarios with alert overrides using the combinations of programming information (i.e. infusion dose rate, drug amount, infusion duration, etc.) and corresponding drug limits. These specific values were based on an analysis of a dataset of 5-year's infusion alerts (from January 2010 to May 2015) obtained from one representative member of the Regenstrief National Center for Medical Device Informatics (REMEDI)[1]. We selected a dataset from one representative member (a health system) since drug limit

[1] Regenstrief National Center for Medical Device Informatics (REMEDI) system is a web-based analytics tool, contributed by members of the community and supported by the Regenstrief Center for Healthcare Engineering (RCHE) of Purdue University.

settings (the drugs in each care unit for the specific field limit type[2]) vary across hospital systems. Table 5 shows the definition of the field limit type associated with continuous and bolus infusion types (CareFusion Corporation, 2015). In this study, we focused on overridden alerts associated with four high-risk medications defined by ISMP, namely, propofol, morphine, insulin, and heparin, used in the settings of adult intensive care unit (AICU) and adult medical and surgical care unit (AMSU). The targeted alerts were then classified into 30 scenario types (with higher frequency of alert overrides) based on the programming and alert information (Table 6). Figure 7 shows scenario design structure and information. Within each scenario type, four numerical variables identified as the 3rd layer scenario factors were provided: (1) total dose (drug amount) patient received, (2) infusion duration, (3) infusion rate ((1) divided by (2)), and (4) ratio of programming rate/dose to the SoftMax (Table 5). Furthermore, each scenario type was composed of nine different sub-scenarios (Figure 7) according to each of the three level of the 3rd layer scenario factors (Figure 8).

Table 5: Continuous and Bolus Infusion Type and Field Limit Type

| | **Continuous Infusion** | **Bolus Infusion** |
|---|---|---|
| **Infusion Parameters** | Enter infusion rate and total volume<br>*Infusion duration will be automatically calculated by given infusion rate and total continuous drug amount (total volume and concentration) | Enter infusion drug amount and infusion duration (min)<br>*Infusion rate will be automatically calculated by given drug amount and infusion duration (min) |
| **Field Limit Type** | Continuous Dose (CD) | Bolus Dose (BD), Bolus Dose Administration Rate (BDAR) |
| **An Example of Field Limit in AMSU for Morphine** | CD: 50 mg/h | BD: 10 mg<br>BDAR: 5 mg/min |
| **Field Limit Alert** | An alert can be triggered when a programming continuous dose rate is outside the CD filed limit type | An alert can be triggered when a programming bolus dose/dose rate is outside the BD or BDAR filed limit type |

[2] The field limit types in Becton Dickinson Alaris™ System include continuous does rate (CD), bolus dose (BD), and bolus dose rate (BDAR), which have different units. The continuous infusion by entering infusion rate and total volume could trigger CD field limit type, and the bolus infusion by entering infusion drug amount and duration (min) could trigger either BD or BDAR type.

Table 6: 30 Scenario Types and Information

| | 1st Layer Scenario Factor | | | 2nd Layer Scenario Factor | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Scenario Type (S) | Care Area | Medication | Field Limit Type | Soft Max Drug Limit | Hard Max Drug Limit | Drug Limit Unit | Conc* | Conc* Unit | Alert Frequency |
| 1 | AICU | propofol | CD | 51 | 80 | mcg/kg.min | 10 | mg/mL | 2236 |
| 2 | AICU | propofol | CD | 51 | - | mcg/kg.min | 10 | mg/mL | - |
| 3 | AICU | propofol | CD | 100 | 150 | mcg/kg.min | 10 | mg/mL | 1208 |
| 4 | AICU | propofol | CD | 100 | - | mcg/kg.min | 10 | mg/mL | - |
| 5 | AICU | propofol | BD | 20 | - | mg | 10 | mg/mL | 12119 |
| 6 | AICU | propofol | BDAR | 10.1 | 25 | mg/min | 10 | mg/mL | 2106 |
| 7 | AICU | morphine | CD | 20 | - | mg/h | 1 | mg/mL | 642 |
| 8 | AICU | morphine | CD | 20 | 54 | mg/h | 1 | mg/mL | - |
| 9 | AICU | morphine | CD | 50 | - | mg/h | 5 | mg/mL | 41 |
| 10 | AICU | morphine | BD | 25 | - | mg | 1 | mg/mL | 15 |
| 11 | AICU | morphine | BDAR | 5 | - | mg/min | 1 | unit/mL | 65 |
| 12 | AICU | insulin | CD | 35 | 49 | unit/h | 1 | unit/mL | 1206 |
| 13 | AICU | insulin | CD | 35 | - | unit/h | 1 | unit/mL | - |
| 14 | AICU | insulin | CD | 81 | 121 | unit/h | 1 | unit/mL | 361 |
| 15 | AICU | insulin | CD | 81 | - | unit/h | 1 | unit/mL | - |
| 16 | AICU | insulin | BD | 10 | 20 | unit | 1 | unit/mL | 336 |
| 17 | AICU | heparin | CD | 2601 | 3500 | unit/h | 100 | unit/mL | 7974 |
| 18 | AICU | heparin | CD | 2601 | - | unit/h | 100 | unit/mL | - |
| 19 | AICU | heparin | CD | 4501 | 6001 | unit/h | 100 | unit/mL | 495 |
| 20 | AICU | heparin | CD | 4501 | - | unit/h | 100 | unit/mL | - |
| 21 | AMSU | morphine | CD | 10 | 20 | mg/h | 1 | mg/mL | 1022 |
| 22 | AMSU | morphine | CD | 30 | 50 | mg/h | 5 | mg/mL | 76 |
| 23 | AMSU | morphine | BD | 5 | 10 | mg | 1 | mg/mL | 137 |
| 24 | AMSU | morphine | BDAR | 2 | 5 | mg/min | 1 | mg/mL | 255 |
| 25 | AMSU | morphine | BDAR | 4 | 10 | mg/min | 5 | mg/mL | 10 |

Table 6 continued

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 26 | AMSU | insulin | CD | 35 | 49 | unit/h | 1 | unit/mL | 28 |
| 27 | AMSU | insulin | CD | 81 | 121 | unit/h | 1 | unit/mL | 22 |
| 28 | AMSU | insulin | BD | 10 | 20 | unit | 1 | unit/mL | 90 |
| 29 | AMSU | heparin | CD | 2500 | 3500 | unit/h | 100 | unit/mL | 3179 |
| 30 | AMSU | heparin | CD | 4501 | 6001 | unit/h | 100 | unit/mL | 46 |

*Conc: Concentration; "-": NA

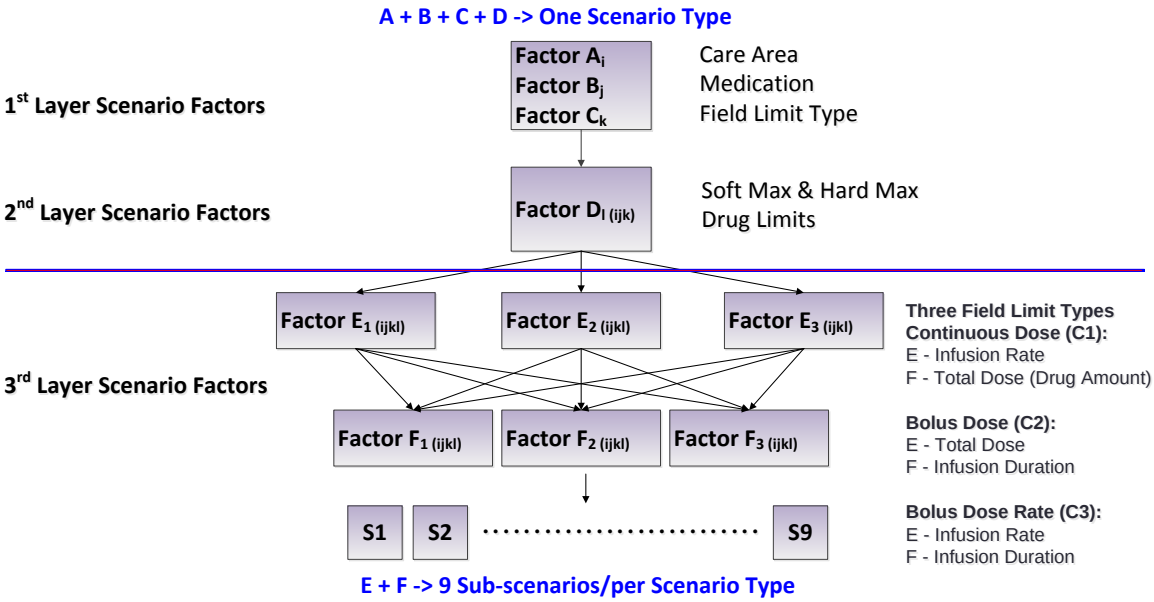



Figure 7: Scenario Design Structure

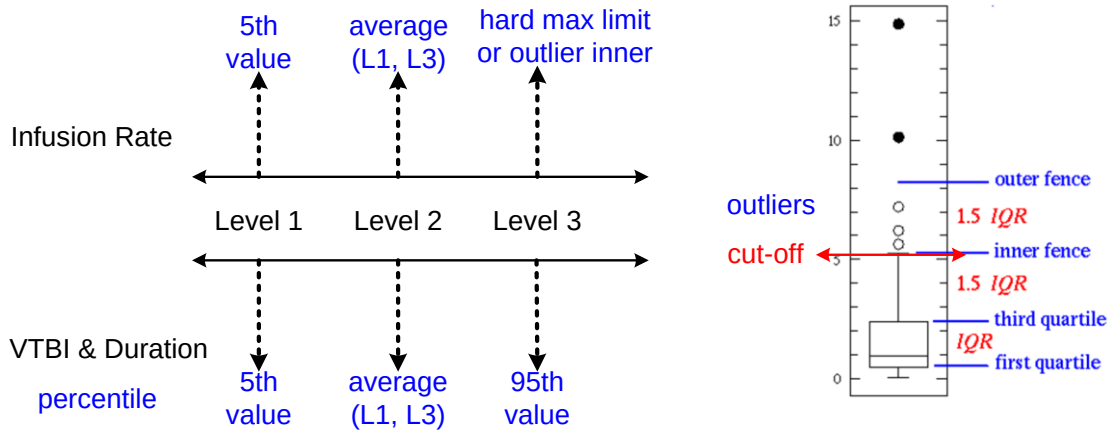



Figure 8: Three Levels Design for the Numerical Variables

### 4.1.3 Experimental Design

Our 30 infusion scenario types were designed as unbalanced scenario combinations based on the principle of incomplete factorial design (Collins, Dziak, & Li, 2009), incoporating the typical and most frequent scenarios observed in pump alerts. Because of the unbalanced combinations, the number of scenario types and the sample size that we used to test the factor effects were different as shown in Table 7. Since it was inpractical to have any study participant to review and assess all 270 survey questions (30 types x 9 sub-scenarios), we applied an Incomplete Block Design (IBD) in which the individual difference was treated as a blocking factor that controlled the sources of variation and eliminated the effect on the statistical comparisons among treatments (Hinkelmann, 2011; Montgomery, 2012). Statistical software packages, R and JMP® (SAS institute), were used to create model matrices and generate D-optimal criteria for evaluating and comparing various designs (Goos, 2012). We followed the selected IBD to assign the specific three scenario types, including nine sub-scenarios per type, for each of the 25 participants. Each scenario type was repeated two or three times based on the IBD. A total of 675 (25 x 3 x 9) assessments were collected.

The experimental design with the scenario effects can be illustrated using the following statistical model (Montgomery, 2012):

$$y_{ijk} = \mu + \tau_i + \beta_j + \cdots + (\tau\beta)_{ij} + \cdots + \delta_k + \varepsilon_{ijk} \quad (4.1)$$

where $\tau_i$ represents the first effect from factor A, $\beta_j$ represents the second effect from factor B, $(\tau\beta)_{ij}$ is the interaction effect from factors A and B, $\delta_k$ is the block effect, and $\varepsilon_{ijk}$ is the NID $(0, \sigma^2)$ error component.

Table 7: Scenario Combinations and Sample Size for Testing Factor Effects

| **Factor Effect** | **Scenario Type** | **Number of Scenario Types** | **Sample Size** |
|---|---|---|---|
| Field limit type | S1-S11, S21-S25 | 16 | 333 |
| Soft limit type | S1-S4, S7-S9, S12-S15, S17-S22, S26-S27, S29-S30 | 21 | 468 |
| Hard limit type | S1-S4, S7-S9, S12-S15, S17-S20 | 15 | 306 |
| Care area and medication | S7-S9, S12-S15, S17-S22, S26-S27, S29-S30 | 17 | 396 |

### 4.1.4 Survey and Procedures

This research was given an exempt status from the Purdue University Institutional Review Board (IRB Protocol #: 1703018925). In the surveys, we described the scenarios and questions, also presented the risk rating tables for the participants (Figure 9). This risk rating table was designed using a two-dimensional rating scale, probability (likelihood) and its severity impact (ordinal linguistic scale: No harm, Minor, Moderate, Major, and Extreme harm map to the NCC MERP index (NCC MERP, 2001)). As part of the surveys, we further created pairwise comparison questions for the AHP risk quantification. The procedures and the comparison surveys are explained in Section 5.3. The surveys progressed over a face-to-face interview or a conference call with about two hours for each participant. All responses were kept anonymous and secured.

## Alert and Pump Information

**AICU - Propofol**
**Field Limit Type: Continuous Dose**

**Soft Max:** 100 mcg/kg.min
**Hard Max:** NA

| *Scenario I - Infusion Information* | *Total Amount Patient Received* |
|---|---|
| **Dose (Dose Rate):** 130 mcg/kg.min | **Drug Amount:** 590 mg (59 mL) |
| **Ratio =** $\frac{\textit{Dose (Dose Rate)}}{\textit{Soft Max (100 mcg/ kg.min)}}$ **= 1.3** | |
| **Volume Rate:** 0.9 mL/min (54 mL/h) (Concentration: 10 mg/mL) | |

## Alert-overridden Scenario

In **ACIU**, a 35-year-old male patient (70 kg) was prescribed **propofol** via **continuous** IV infusion at **130 mcg/kg.min**. A soft alert was triggered by the Soft Max drug limit at a dose of **100 mcg/kg.min**. The patient received **590 mg (59 mL) after 1.1 hours.** The nurse chose to **OVERRIDE** this alert. Any harm to the patient?

**QUESTION 1:**

**What is your expected severity of IV infusion harm in this scenario?**

Please consider **ALL conditions of non-anesthesia patients** and select the potential severity of IV harm, which maps on to the NCC MERP category index as shown in the rating table. **Mark** the estimated probability (in percentage) of **EACH** possible severity of IV harm. The sum of the probabilities does not need to be equal to 100%.

**[NOTE]:**

**"In many cases, you may not have all the clinical information you may want to make a sound care decision or assessment. It is important to use your best judgement to identify the expected level of harm given the limited information presented in the scenario."**

**NCC Category - Harm Definition**

C - No detectable harm
D - No detectable harm; Minimum temporary harm
E - Moderate/Serious temporary harm
F, G - Serious temporary harm; Minimum/Moderate/Serious permanent harm
H, I - Serious temporary/permanent harm; Death

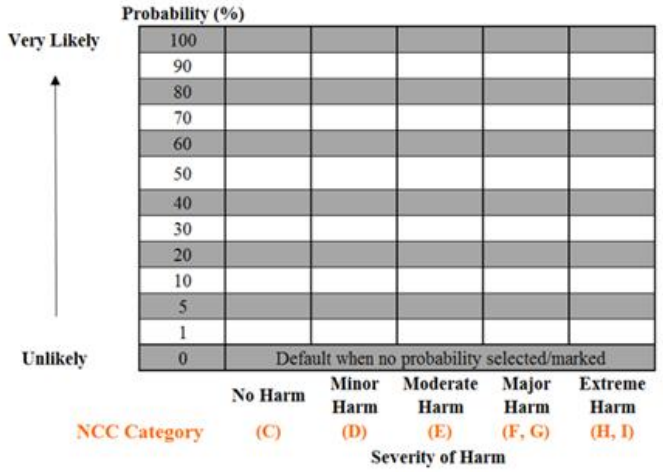



Figure 9: An Example of Survey Design

### 4.1.5 Measures

We used subjective assessments, which are vectors in the form of five probabilities associated with a severity of harm, to calculate the *risk of harm*. Specifically, we applied the Absolute Probability Judgment (APJ) method (Grozdanovic, 2005) for the participants to answer the survey questions and provided an estimated absolute probability value.

In this study, we calculated the risk measure using the summation of the product of the probability and the severity of harm with the non-linear transformation suggested by previous studies (Chang et al., 2003; Tversky & Kahneman, 1992; Zhang & Maloney, 2012). Therefore, the subjective probabilities ($p$) in this study were adjusted as $p'$ using a non-linear transformation:

$$Lo(p') = \frac{1}{\gamma} \times Lo(p) - \frac{1-\gamma}{\gamma} \times Lo(p_0) \quad (4.2)$$

where $p'$ indicates true probability, $p$ indicates the subjective probability, $\gamma$ and $p_0$ were respectively selected as 0.6 and 0.4 (Tversky & Kahneman, 1992), and

$$Lo(probability) = log \frac{probability}{1-probability} \quad (4.3)$$

is the log odds (Barnard, 1949) or logit function (Berkson, 1944).

And the severity of harm was quantified using exponential growth using the order of magnitudes for five degrees of harm ($10^0$, $10^1$, $10^2$, $10^3$, $10^4$) due to the non-linear severity impact proposed by the literature (Chang et al., 2003).

### 4.1.6 Analytical Approach

Descriptive statistics, including sample size (n), sample mean (M), and standard deviation of the samples (SD) within each group, were reviewed. It was noted that the sample means could be affected by individual differences among the assessors and the potential risk factors. Participants who tended to assess with higher ratings could lead to greater sample means. Thus, for each hypothesis associated with the factor effect testing, the least squared means (LS mean)[3] were estimated using analysis of variance (ANOVA)

[3] Least square means are means for groups that are adjusted for means of other factors in the model. In this study, we adjusted the difference among the individuals in each group.

with a random block[4] in the lmerTest Package of R software, to control for the assessment impact by individual difference (Kuznetsova, Brockhoff, & Christensen, 2017). The post hoc tests with Tukey adjustment were further conducted to test the risk difference among the levels of risk factors.

## 4.2 Results

In this section, we tested the potential risk factor effects of field limit type, soft and hard maximum drug limit type, and care area-medication combination on expected risk of IV harm.

### 4.2.1 Field Limit Type

The data selected from the simulated scenario types associated with morphine and propofol was used to test the effect of field limit type, continuous dose (CD), bolus dose (BD), and bolus dose rate (BDAR). Table 8 shows the sample mean and LS mean estimated by a mixed model, in which the expected risk of field limit type is the lowest in BDAR, followed by BD and CD. There was a significant difference across these three levels of field limit type ($F(2, 219) = 42.58$, $p < 0.001$). The post hoc test showed that overdosed infusions triggered by CD and BD field limits had significantly higher risk perceived by clinicians than by BDAR ($p < 0.001$, see Table 9), while the continuous dose and bolus dose did not differ on risk ($p = 0.73$).

Table 8: Descriptive Analysis and LS Mean for Expected Risk of Field Limit Type

| **Field limit type** | ***n*** | ***M*** | ***SD*** | ***LSmean*** | ***SE*** | ***df*** | ***group*** |
|---|---|---|---|---|---|---|---|
| BDAR | 90 | 1.080 | 0.675 | 0.036 | 0.283 | 34.67 | a |
| BD | 63 | 1.785 | 1.346 | 2.134 | 0.251 | 30.51 | b |
| CD | 180 | 1.879 | 1.119 | 2.281 | 0.237 | 22.31 | b |

Note. LS mean = least squared mean; df = Satterthwaite approximation for degrees of freedom; group = expected risk was significantly different in a and b groups identified using post hoc test

[4] The ANOVA analysis with a random block (type III sums of squares with Satterthwaite approximation for degrees of freedom) was conducted with a mixed-effects model using R software, with the treatments treated as a fixed effect and the blocks, the individuals blocked in the experimental design, treated as a random effect.

Table 9: Post Hoc Rest for Field Limit Type

| **Contrast** | ***estimate*** | ***SE*** | ***df*** | ***t.ratio*** | ***p.value*** |
|---|---|---|---|---|---|
| BD - BDAR | 2.098 | 0.233 | 267.61 | 8.987 | <0.001*** |
| BD - CD | -0.147 | 0.195 | 298.79 | -0.757 | 0.730 |
| BDAR - CD | -2.246 | 0.281 | 156.25 | -7.985 | <0.001*** |

### 4.2.2 Soft Maximum Drug Limit Type

The data selected from the simulated scenario types associated with continuous dose for all four medications was used to test the effect of soft maximum drug limit (soft max) type. Table 10 shows that the means of expected risk in the group with large soft max were significantly larger than those of the small soft max ($F(1, 464) = 15.45$, $p < 0.001$).

Table 10: The Descriptive Analysis and LS Mean for Expected Risk of Softmax Limit Type

| **Soft limit type** | ***n*** | ***M*** | ***SD*** | ***LSmean*** | ***SE*** | ***df*** | ***group*** |
|---|---|---|---|---|---|---|---|
| Small | 243 | 1.555 | 1.090 | 1.437 | 0.144 | 27.48 | a |
| Large | 225 | 1.865 | 1.168 | 1.857 | 0.147 | 29.20 | b |

### 4.2.3 Hard Maximum Drug Limit Type

The simulated scenarios of drug infusions in AICU using continuous dose were selected to test the effect of hard maximum drug limit (hard max) type. The descriptive analysis for the hard max type showed that the means of expected risk for the scenarios with (*M*ean = 1.58, *SD* = 1.22) and without (*M*ean = 1.62, *SD* = 1.11) hard limit were similar, and no significant main effect of hard max type was found ($F(1, 288) = 3.08$, $p = 0.080$). The interaction effect between hard max and soft max types was not significant ($F(1, 147) = 3.16$, $p = 0.078$). Also, the interaction between hard max type and medication was found to have no significant effect ($F(3, 118) = 1.37$, $p = 0.256$).

### 4.2.4 Care Area and Medication

The data selected from the simulated scenario types associated with continuous dose for heparin, insulin, and morphine was used to test the main effects of care area and

medication. Table 11 shows the descriptive analysis for each combination of care area and medication. In addition, the results by the two-way ANOVA indicated that there was no significant difference on risk between the Adult Intensive Care Unit (AICU) and the Adult Medical/Surgical Care Unit (AMSU) ($F(1, 89) = 0.45$, $p = 0.121$), neither was among the three medications ($F(2, 224) = 2.54$, $p = 0.08$). There was no significant interaction between the impact of care area and medication ($F(2, 80) = 1.20$, $p = 0.306$). Therefore, we further tested the effects of care area and medication with each of the following variables, soft limit type, hard limit type, drug amount level, and dose rate level, using a three-way ANOVA. The results showed that soft limit type and the drug amount levels had interactions with the care area as explained below.

Table 11: Descriptive Analysis of the Combinations of Care Area and Mediation

| **Care Area** | **Medication** | ***n*** | ***M*** | ***SD*** |
|---|---|---|---|---|
| AICU | Heparin | 108 | 1.365 | 1.257 |
| AMSU | Heparin | 54 | 1.846 | 0.857 |
| AICU | Insulin | 72 | 1.789 | 1.058 |
| AMSU | Insulin | 54 | 1.544 | 1.166 |
| AICU | Morphine | 54 | 1.836 | 1.353 |
| AMSU | Morphine | 54 | 2.311 | 1.011 |

Note. AICU = Adult Intensive Care Unit; AMSU = Adult Medical/Surgical

The first three-way ANOVA (care area, medication, and soft limit type) showed that there was no significant care area effect ($F(1, 58) = 1.41$, $p = 0.24$) and medication effect ($F(2, 144) = 2.73$, $p = 0.07$) on risk, but there was a significant difference between the groups of small and large soft limit types ($F(1, 183) = 6.59$, $p = 0.01$). Furthermore, the descriptive analysis and the estimated LS mean for the four scenario combinations (care area-soft limit type combination) are shown in Table 12. There was a significant interaction between care area and soft limit type ($F(1, 173) = 5.46$, $p = 0.02$). The post hoc analysis showed that only the contrast between AICU-large soft max and AICU-small soft max was significant (*t ratio* = 4.31, $p < 0.001$). The expected risk for the group of AICU-Soft small is the lowest, followed by the groups of AMSU-Soft small and AMSU-Soft large, and the highest expected risk is the group of AICU-Soft large (see Table 12 and Figure 10).

Table 12: Descriptive Analysis and LS Mean for the Combinations of Care Area and Soft Limit Type

| Care Area | Soft limit type | *n* | *M* | *SD* | *LSmean* | *SE* | *df* | *group* |
|---|---|---|---|---|---|---|---|---|
| AICU | Small | 126 | 1.438 | 1.101 | 1.297 | 0.173 | 37.52 | a |
| AMSU | Small | 81 | 1.876 | 1.135 | 1.699 | 0.206 | 60.15 | ab |
| AMSU | Large | 81 | 1.925 | 0.989 | 1.756 | 0.208 | 60.08 | ab |
| AICU | Large | 108 | 1.798 | 1.361 | 2.002 | 0.177 | 40.27 | b |

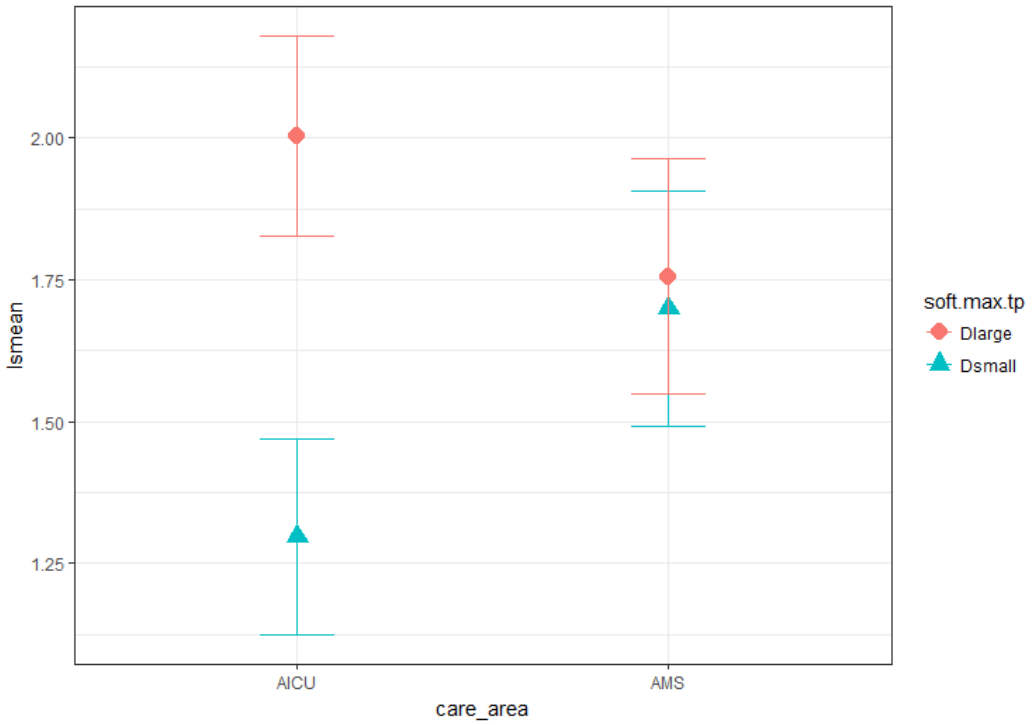



Figure 10: The Expected Risk for the Interaction between Care Area and Soft Limit Type

The second three-way ANOVA (care area, medication, and drug amount levels) showed that there was no significant care area effect ($F(1, 143) = 3.21$, $p = 0.08$). However, the expected risk was significantly different among the three medication groups ($F(2, 264) = 4.16$, $p = 0.017$) and among three drug amount levels ($F(2, 354) = 148.61$, $p < 0.001$). Table 13 shows the descriptive analysis and the estimated LS means for the six scenario combinations (care area-drug amount level combination). There was a significant interaction between care area and drug amount level ($F(2, 354) = 5.16$, $p = 0.006$). The

post hoc analysis indicated that expected risk for the six combinations can be classified into four different groups as shown in Table 13 and Figure 11.

Table 13: Descriptive Analysis and LS Mean for the Combinations of Care Area and Drug Amount Level

| **Care Area** | **Drug amount level** | ***n*** | ***M*** | ***SD*** | ***LSmean*** | ***SE*** | ***df*** | ***group*** |
|---|---|---|---|---|---|---|---|---|
| AICU | 1 | 78 | 0.559 | 0.706 | 0.591 | 0.156 | 38.05 | a |
| AMSU | 1 | 54 | 1.161 | 0.979 | 1.002 | 0.172 | 52.74 | a |
| AICU | 2 | 78 | 1.806 | 1.057 | 1.838 | 0.156 | 38.05 | b |
| AMSU | 2 | 54 | 2.108 | 0.906 | 1.950 | 0.172 | 52.74 | bc |
| AMSU | 3 | 54 | 2.431 | 0.868 | 2.273 | 0.172 | 52.74 | cd |
| AICU | 3 | 78 | 2.449 | 1.074 | 2.481 | 0.156 | 38.05 | d |

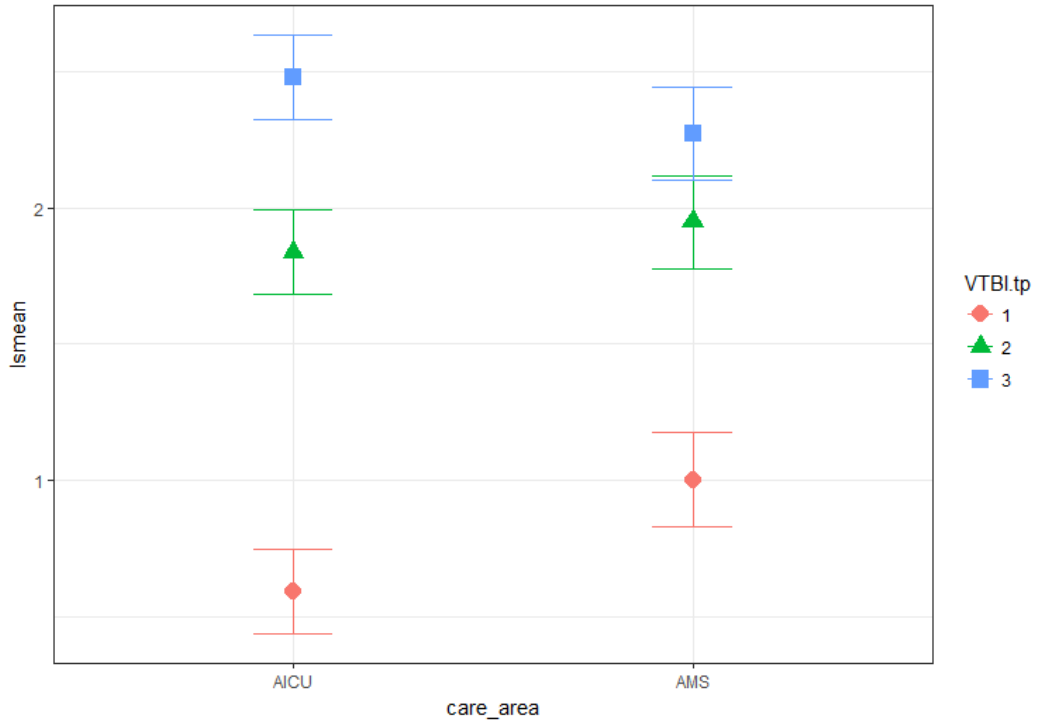



Figure 11: The Expected Risk for the Interaction between Care Area and Drug Amount Level

## 4.3 Discussion

### 4.3.1 Field Limit Type

The factor of field limit type (CD, BD, and BDAR) had significant effect on the expected risk. Specifically, the effects of CD and BD led to significantly higher risk than that of BDAR, while there was no difference between CD and BD. A possible reason that leads to different expected risk between CD and BDAR is the infusion duration. Note that a nurse needs to enter infusion dose rate and total volume when selecting the continuous infusion, so the infusion duration will be generated (see Table 5). The range of infusion duration for CD scenarios could be short (a few minutes) or long (a few hours), and that for BDAR scenarios was within minutes. Obviously, the longer overdose situations without clinicians' check-in (CD) could cause patients a higher risk of harm.

To compare BD and BDAR, although the units of field limit setup for BD and BDAR differed (i.e. drug amount and infusion rate, respectively), the total dose infused to patients for BDAR could be calculated given the infusion duration. In this study, the design of drug amounts of morphine for BD scenarios were 29, 49 and 68 mg, and the infusion rates for BDAR scenarios were 6, 10 and 14 mg per minute with the infusion duration of 1, 2 and 3 miniutes. Therefore, for BDAR, the drug amount could be low at 6 mg or high at 42 mg, , most of which had drug amount less than that in BD scenarios. Thus it was reasonable that BD scenarios had higher expected risk than BDAR. Furthremore, the participating pharmacists and nurses indicated that, the higher overdosing drug amounts, such as morhpine, could lead to greater risk of harm for general populations who cannot tolerant hight dose. Their opinions can also explain why the overall risk of BD scenarios were higher than BDAR. This is consistent with previous research findings that showed, compared to other infusion types, bolus dose (BD) infusions have higher risk of incurring mediation errors (Westbrook et al., 2011) and severe patient harm (Cassano-Piché, Fan, Sabovitch, Masino, & Easty, 2012; Giuliano, 2018) due to programming errors. Therefore, we suggest that for infusions , the start key on smart pumps should be disabled in Dose Error Reduction System if a BD overdosing alert has been triggered. The nurse cannot override this alert type from a patient sfaty standpoint, except in special circumstances.

### 4.3.2 Soft and Hard Maximum Drug Limit Type

The factor of soft maximum drug limit type (small/large) had significant effect on the expected risk, where the higher risk of potential patient harm was found for those alert-overridden scenarios with large soft maximum limits. In general, for any care area-medication combination case, the large soft maximum limit usually is intended for patients who have special health conditions or those who need specific therapies. Therefore, infusions of overridden alerts of large soft max limit correspond to the higher dose rate or total dose, which present higher risk for adverse events, especially to critically ill patients (Cullen et al., 1997; Rothschild et al., 2005). This could be the main reason why the experts rated the scenarios with large soft maximum limits with higher risk than those with small soft maximum limits.

For the hard maximum limit, the expected risk had no difference between the scenarios with and without hard limit. Most of the pharmacists and nurses who participated in this study review infusion alert resports frequently. According to our observation during the interviews, many of them could easily estimate the thresholds of drug amount and the infusion rate for the specific care area-medication combination, which could affect the risk of harm they perceived on patients whether the hard limits were provided. In other words, these pharmacists and nurses used forward reasoning approach to validate assumptions based on the scenarios they interpreted (Phansalkar, Hoffman, Hurdle, & Patel, 2009). It explains that providing hard limit did not have an impact on the experts' ratings, since most experts did not refer to the limit.

### 4.3.3 Care Area and Medication

The significant interaction between care area and soft maximum limit indicated that, in AICU, there was higher risk of harm to the patient if a nurse overdoses with the infusion over a large soft maximum limit than versus a small soft maximum limit. However, such difference in risk does not exist in AMSU. One possible reason could be that AICU patients are sicker than those in AMSU. A larger overdose of drug infusions understandably may cause more serious patient harm in AICU.

Our analysis also showed the significant interaction between care area and drug amount, and risk was different among the infusion cases with three levels of drug amount in AICU: higher total drug amount causes higher risk, followed by moderate and lower drug amount. In AMSU, higher and moderate drug amount led to significantly higher risk than lower drug amount, and there was no difference between higher and moderate drug amount. The finding in AMSU was not consistent with what was proposed in the IV mediation harm index (Sullivan, 2004; C. K. Williams et al., 2006), where the increase of the drug amount levels cause higher risk of harm. These results encourage clinicians to carefully check the infusions parameters, especially for infusing high-risk drugs in AICU.

### 4.3.4 Limitation

There are some limitations to this study. First, the patient in each scenario was assumed to be a 35-year-old male weighing 70 kg. By doing so, we did not consider the impacts of the patients' age, gender, and body weight (S. Pan, Zhu, Chen, Xia, & Zhou, 2016). Secondly, the patient's conditions and physician's orders were not provided in the scenario design. The expert participants were asked to consider all possible patient conditions and provide the likelihoods of each degree of harm given the limited information. Lastly, the effect of pharmacist's and nurse's roles was not considered and the number of each was not balanced (5 nurses, 20 pharmacists). A hospital medication safety team typically includes these two healthcare professional roles, so their perspectives are both important in this study. Future research may focus on studying the effect of pharmacist's and nurse's roles and experience on their assessed risk of IV harm.

**Summary:**

In Chapter 4, we obtained the expected risk for simulated high-risk IV Infusions and found that field limit and soft maximum limit types could affect expected risk based on healthcare professionals' perspectives. The expected risk calculated and adjusted from the domain experts' risk assessments were regarded as risk benchmarks (APPENDIX B, Column "Benchmarks") for validating four risk quantification methods in the following chapters.

# CHAPTER 5: DEVELOPMENT AND APPLICATION OF ANALYTICAL METHODS

This research applied different analytical methods to obtain risk/relative risk scores for the simulated alert-overridden infusion scenarios, which were described in Chapter 4.1. The quantified risk/relative risk scores derived from the different methods were compared with the risk benchmarks (i.e. the expected risk assigned by the experts for each scenario), and are calculated as the likelihood of degree of harm from the healthcare professionals multiplied by the nonlinear severity impact that was quantified using exponential growth. The quantification method with the results closest to the benchmarks was selected and regarded as a proper risk quantification method. This method can help estimate the relative risk of individual alert-overridden infusions associated with the four high-risk medications studied here, which are propofol, morphine, insulin, and heparin, to support evaluating drug infusion performance. In Sections 5.1 to 5.4, we describe the procedures in detail for deriving risk and relative risk scores and calculate the scores of each applied method That is: the linear regression model (Section 5.1), the IV medication harm index (Section 5.2), Huang and Moh's matrix-based ranking method (Section 5.3), and the analytical hierarchy process (AHP) method (Section 5.4).

## 5.1 Development of Linear Regression Models for Risk Prediction

### 5.1.1 Methods

#### *Study Design*

We applied stepwise *AIC* regression for feature selection (i.e. the key important predictors) of the study data, which reduced the set of potential predictor variables to the most important ones using *AIC* criteria. This set of selected variables was used to build the candidate models. We finally conducted K-fold cross validation to validate and selecte final models. Also, we conducted ANOVA and Post Hoc Tests to investigate the important risk factors and the least-square means difference among the levels of the factors from the perspective of the selected final models, which are multi-variate linear regression models.

After the final models were validated, we used these models to calculate the predicted risk for all simulated IV medication infusion scenarios.

***Outcome Variable***

The outcome variable was the expected risk of IV harm obtained from the previous risk assessment study in Chapter 4, which we also refer to as the risk benchmarks used to create and validate the risk predictive models in this research. The expected risk is defined as a sum of each likelihood for the degrees of harm multiplied by the corresponding quantified scales of severity impacts. In the previous study, we assumed an exponential growth for five degree of harm ($10^0, 10^1, 10^2, 10^3, 10^4$) due to nonlinear severity impacts (Chang et al., 2003). In addition, we adjusted the probabilities subjectively estimated by the healthcare professionals ($p$), to the true probability ($p'$) using the following non-linear function suggested by Tversky and Kahneman (1992) when humans make decision under uncertainty:

$$Lo(p') = \frac{1}{\gamma} \times Lo(p) - \frac{1-\gamma}{\gamma} \times Lo(p_0) \quad (5.1)$$

where $p'$ indicates true probability, $p$ indicates subjective probability, $\gamma$ and $p_0$ were respectively selected as 0.6 and 0.4 (Tversky & Kahneman, 1992), and $Lo(probability)$ is the log odds (Barnard, 1949).

***Predictor Variables***

According to the study design mentioned in Chapter 4, there were three-layer scenario factors and one blocking factor, which were assigned as 10 variables ($X_1$ - $X_{10}$), in addition to the patient information (Table 14). When building linear regression models, the variables $X_4$ and $X_5$, soft and hard maximum drug limits, were defined as categorical variables (drug limit types), since we were interested in the effect of small or large soft limits and were also interested in the effect of that whether providing hard limits could have an impact on the outcome variables. The levels for the categorical variables are indicated in Table 14 . In addition, the variables $X_8$ and $X_9$ were selected only on the 3rd layer because there is a linear relationship between the variables $X_6$, $X_7$, and $X_8$, ($X_6 = X_7/X_8$), so only two variables are needed to create the models. However, the ranges and units of infusion rate ($X_6$) and dose ($X_7$) for different medications varied. Therefore, the

ratio of the soft maximum drug limit ($X_9$), which can be the ratio of infusion rate or dose depending on the variable field limit type ($X_3$), was selected to represent $X_6$ and $X_7$.

Table 14: Scenario Information and Selected Main Independent Variables

| **Scenario Information** | **Variable Code** | **Main Independent Variable** | **Levels of Categorical Variable** | **Categorical or Numerical Variable** |
|---|---|---|---|---|
| Patient<br>(35-year-old male patient, 70 kg) | | | | |
| **Layer I** | | | | |
| Care Area | $X_1$ | V | AICU, AMSU | Categorical |
| Medication | $X_2$ | V | P, M, I, H | Categorical |
| Field Limit Alert Type | $X_3$ | | CD, BD, BDAR | Categorical |
| **Layer II (nested by Layer I)** | | | | |
| Soft Maximum Limit | $X_4$ | V | Small/Large, Soft Drug Limit Type | Categorical |
| Hard Maximum Limit | $X_5$ | V | Hard Drug Limit Type: Hard Limit Provided Y/N | Categorical |
| Concentration | | | | Numerical |
| **Layer III (nested by Layer I & II)** | | | | |
| Infusion Rate (Rate) | $X_6$ | | | Numerical |
| Total Dose Patient Receive (Dose) | $X_7$ | | | Numerical |
| Infusion Duration (Duration) | $X_8$ | V | | Numerical |
| Ratio of (Rate or Dose)/Soft Max | $X_9$ | V | | Numerical |
| **Blocking Factor** | | | | |
| Participant | $X_{10}$ | V | Participant ID | |

Note. P: propofol; M: morphine; I: insulin; H: heparin

***Development of Risk Predictive Models Using Linear Regression Model***

We applied a generalized linear mixed model (GLMM), an extension of the generalized linear model (GLM), to predict the expected risk since the predictors consist of the usual fixed effects and the random effect (Breslow & Clayton, 1993; Jiang, 2007). In this research, the participant factor was treated as a random effect that had an expected value of zero in the population. There were three phases to build a linear mixed model, which were data preparation in phase 1, reduction of predictor variables in phase 2, and model validation and model selection in phase 3.

*Phase 1: Data Collection and Preparation*

After defining the outcome and predictor variables, we classified data into three sub-groups based on three field limit types, continuous dose (CD), bolus dose (BD), and bolus dose administration rate (BDAR) groups for building three types of linear regress models. Three reasons led to the grouping: (1) the range of $X_8$ for CD group is larger than BD and BDAR groups; (2) there is no different level of $X_4$ being designed for the data in the BD group, so this variable is not relevant for creating models for the BD group; (3) the drug limit settings for BD and BDAR are different, which $X_9$ for BD means infusion dose, but meaning infusion rate for BDAR. In other words, the larger $X_8$ means smaller infusion rate with fixed dose for BD, but meaning larger infusion dose with fixed rate for BDAR, so the data in these two groups should be separated.

*Phase 2: Reduction of Predictor Variables*

Due to a large number of potential independent variables in the pool, including main X variables and their interaction effects, the number of possible models is large. Evaluating all the possible alternatives is not a simple task (Neter et al., 1996). Therefore, we applied a stepwise *AIC* regression for selecting predictor variables, which is an automatic procedure to fit and compare the regression models sequentially using the Akaike information criterion (*AIC*) (Neter et al., 1996). Further, we selected the backward stepwise regression (Draper & Smith, 2014) to sequentially subset the predictor variables, also called a backward elimination search procedure, for the CD, BD, and BDAR groups. In the beginning of the stepwise procedure, all potential X variables, was involved. At each step, one variable would be subtracted, which made the regression model with a minimum *AIC* value in comparison to others at this step. Note that a lower *AIC* indicates a better

fitting performance, and the procedure was repeated until no further X variables can be dropped. We selected three candidate regression models with three minimum *AIC* values for each group, including the subset of the predictor X variables.

*Phase 3: Model Validation and Model Selection*

We conducted the K-fold cross validation to validate the candidate models and select the final model. In the beginning, we need to choose a proper number of folds of data splits for each field limit type since the datasets of each field limit type, CD, BD, and BDAR, for building linear regression models are small (less than 500 samples). Then, we used the selected K-fold cross validation results to evaluate and compare the performance of the candidate models. Referring to K-fold cross validation, also called repeated K times cross validation, the data is first split into K number of roughly equal folds (Neter et al., 1996). The K-1 folds were used as the training dataset to build a model and the other Kth fold was used as the testing dataset to examine the predictive capability, which uses the model fitted from the training dataset to predict the outcomes of the testing dataset. The sample size of the training dataset is equal to or larger than the testing dataset. The measure for the actual predictive capability is denoted by the mean squared prediction error, *MSPR*. The smaller *MSPR* means the higher predictive capability (Neter et al., 1996).

$$MSPR = \sum_{i=1}^{n^*}(Y_i - \widehat{Y_{\iota(\iota)}})^2/n^* \quad (5.2)$$

Where: $Y_i$ is the observed response and $\widehat{Y_{\iota(\iota)}}$ is the predicted value obtained for the i-th validation case; $n^*$ is the sample size of validation dataset

In addition, for each candidate model, both training and testing ith case datasets can fit two types of regression models, which are defined as a training type model and a testing type model in this research. Within each K-fold split, the variation of goodness of fit measures, $R^2_{adj}$ values, obtained from the two types of fitting models for all candidate models were initially examined. The smaller variation of $R^2_{adj}$ values within the repeated K-times cross validation means that the fitting performance within the repeated times of the K-folds data split for both types of models are more consistent. The processes of choosing proper K-folds to split training and testing datasets for reviewing the cross-validation results and selecting final models are as follows: (1) We assigned the number of total folds as 2, 3, 4, etc. until the number, N, where the sample size of the testing datasets for the N-folds is larger than the number of parameters, (2) initially targeted the number of

folds with smaller variation of $R^2_{adj}$ values (i.e. 3- or 4-folds), and (3) chose the specific number of total folds, K, with the minimum *MSPR* value and regarded it as proper K-folds.

After the specific number of folds, K, was selected for each field limit type, the measures of actual prediction capability, the *MSPR* values, from a validation method were reviewed to assess the validity of the candidate regression models built by the training datasets. We selected the models with the minimum *MSPR* as the final models. We further used the fitting performance criteria, which included Akaike information criterion (*AIC*), Bayesian information criterion (*BIC*), mean squared errors (*MSE*), and adjusted R-square ($R^2_{adj}$), to confirm the selected final models built by the entire datasets. Compared to the other candidate models, the overall performance of using model-selection criteria, *MSPR*, *AIC*, *BIC*, *MSE*, and $R^2_{adj}$, for the final selected model should be the best. We also conducted Analysis of Variance (ANOVA) and the post hoc tests using the final models to investigate which risk factors (X variables) have significant impacts on expected risk, which were regarded as strong predictors for the multi-variate linear mixed regression models.

### 5.1.2 Model Selection and Validation

***Phase 1: Data Collection and Preparation***

We classified the data into three sub-groups and built models based on each field limit type. These three groups were continuous dose (CD), bolus dose (BD), and bolus dose administration rate (BDAR). The total number of data points in CD group are 468, 117 in BD, and 90 in BDAR. These main variables and the interactions among these variables were initially to create three types of full models. We reviewed the fitting performance using $R^2$ values for the full models of CD, BDAR (Eq. 5.3). $X_4$ was not involved in the full model of BD (Eq. 5.4) due to its one level design for this field limit type. There was a maximum $R^2$ for BD full model ($R^2$ = 0.91), following for BDAR ($R^2$ = 0.84), then for CD ($R^2$ = 0.76). The full models are indicated as follows:

$$Y \sim \underbrace{X_1 \times X_2 \times X_4 \times X_5 \times X_8 \times X_9}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \tag{5.3}$$

$$Y \sim \underbrace{X_1 \times X_2 \times X_5 \times X_8 \times X_9}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \tag{5.4}$$

***Phase 2: Reduction of Potential Predictor Variables***

In phase 2, we ran stepwise *AIC* regressions and selected predictor variables to build the candidate models. According to the stepwise *AIC* results, we built three candidate models for each group using the subset of the predictors with three minimum *AIC* values (Table 15, Table 16, and Table 17).

Table 15: Three Candidate Models for the CD Group

| | |
|---|---|
| Model 1 | $Y \sim X_1 + X_2 + X_4 + X_5 + X_8 + X_9 + X_1 \times X_2 + X_1 \times X_4 + X_4 \times X_5 + X_4 \times X_8 + X_1 \times X_2 \times X_4 + X_1 \times X_2 \times X_8 + X_1 \times X_4 \times X_8 + X_4 \times X_8 \times X_9 + X_{10}$ |
| Model 2 | $Y \sim X_1 + X_2 + X_4 + X_5 + X_8 + X_9 + X_1 \times X_2 + X_1 \times X_4 + X_4 \times X_5 + X_4 \times X_8 + X_1 \times X_2 \times X_4 + X_1 \times X_2 \times X_8 + X_1 \times X_4 \times X_8 + X_4 \times X_8 \times X_9 + \boldsymbol{X_1 \times X_2 \times X_4 \times X_9} + X_{10}$ |
| Model 3 | $Y \sim X_1 + X_2 + X_4 + X_5 + X_8 + X_9 + X_1 \times X_2 + X_1 \times X_4 + X_4 \times X_5 + X_4 \times X_8 + X_1 \times X_2 \times X_4 + X_1 \times X_2 \times X_8 + X_1 \times X_4 \times X_8 + \boldsymbol{X_2 \times X_4 \times X_5} + X_4 \times X_8 \times X_9 + \boldsymbol{X_1 \times X_2 \times X_4 \times X_9} + X_{10}$ |

Table 16: Three Candidate Models for the BD Group

| | |
|---|---|
| Model 1 | $Y \sim X_1 + X_2 + X_5 + X_8 + X_9 + X_2 \times X_9 + X_5 \times X_9 + X_{10}$ |
| Model 2 | $Y \sim X_1 + X_2 + X_5 + X_8 + X_9 + X_2 \times X_9 + \boldsymbol{X_5 \times X_8} + X_5 \times X_9 + X_{10}$ |
| Model 3 | $Y \sim X_1 + X_2 + X_5 + X_8 + X_9 + \boldsymbol{X_1 \times X_8} + X_2 \times X_9 + \boldsymbol{X_5 \times X_8} + X_5 \times X_9 + X_{10}$ |

Table 17: Three Candidate Models for the BDAR Group

| | |
|---|---|
| Model 1 | $Y \sim X_2 + X_4 + X_8 + X_9 + X_4 \times X_8 + X_4 \times X_9 + X_5 \times X_8 + X_5 \times X_9 + X_{10}$ |
| Model 2 | $Y \sim X_2 + X_4 + X_8 + X_9 + X_4 \times X_8 + X_4 \times X_9 + X_5 \times X_8 + X_5 \times X_9 + \boldsymbol{X_8 \times X_9} + X_{10}$ |
| Model 3 | $Y \sim X_2 + X_4 + X_8 + X_9 + \boldsymbol{X_2 \times X_9} + X_4 \times X_8 + X_4 \times X_9 + X_5 \times X_8 + X_5 \times X_9 + X_{10}$ |

***Phase 3: Model Validation and Model Selection***

In phase 3, we chose proper K-folds to split the dataset and conduct K-folds cross-validation for the candidate models, then selected the final models using the model prediction capability and fitting performance criteria. The number of folds to split data for the CD field limit type is 2 to 8, for BD is 2 to 7, and for BDAR is 2 to 5, which are the initial input number of folds. The total sample size of the training and testing datasets for

the CD group is 468, and Figure 12 shows the sample size of the two datasets across the K-folds split. For example, when using 3 folds to split data, it means that 312 datasets (468 x 2/3) were used as the training dataset and 156 (468 x 1/3) as the testing dataset. According to the boxplot of $R^2_{adj}$ values for two model types shown in Figure 13, the variation of $R^2_{adj}$ for the 2- to 4-folds are smaller in comparison to the 5- to 8- folds. Since the average *MSPR* of the 4-folds, including all candidate models, is minimum among 2- to 4-folds data splits (Table 18), we selected 4-folds split to conduct cross-validation across the three CD candidate models. We regarded model 2 as the final model since it has the minimum average *MSPR* value. It also has the best overall model fitting performance, with the minimum *AIC*, *MSE*, and the maximum $R^2_{adj}$ across all three candidate models (Table 19). The selected final model for the continuous dose infusion is expressed in Eq. 3.5 (

Table 20).

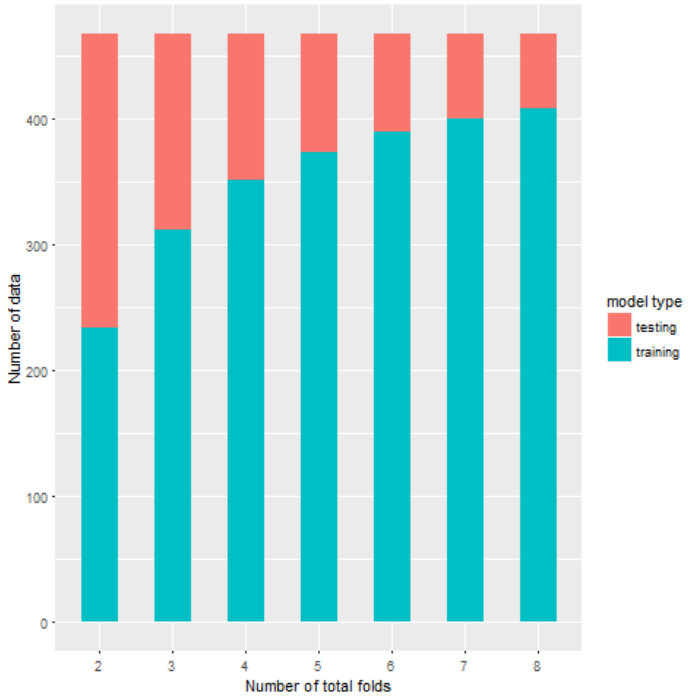



Figure 12: The Stacked Bar Plot of Number of Training (Green) and Testing (Red) Datasets for Different Folds – CD Group

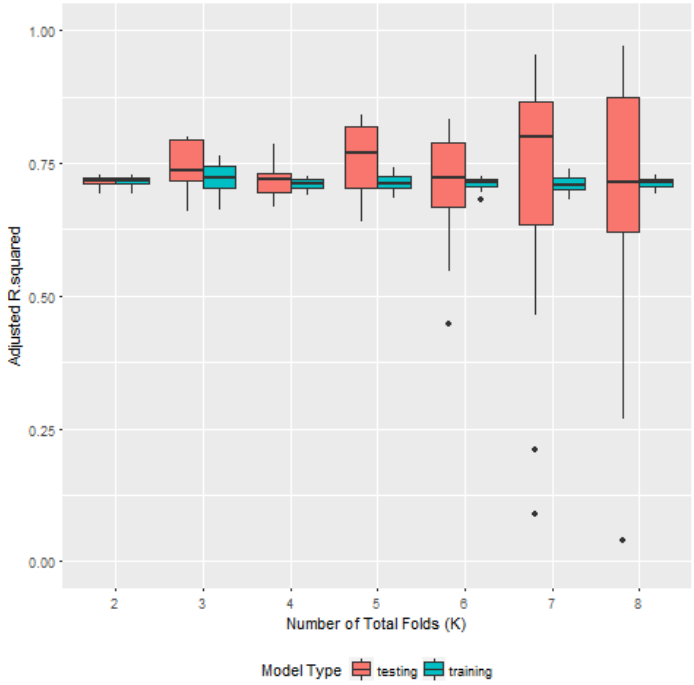



Figure 13: The Boxplot of $R^2_{adj}$ Values for Different Folds – CD Group
The Training Model is Green and Testing Model is Red

Table 18: The average MSPR for CD, BD, and BDAR Groups

| Field Limit Alert Type | Total N | Ave. *MSPR* for Different K-Folds split | | | Selected K-folds |
|---|---|---|---|---|---|
| | | 2-folds | 3-folds | 4-folds | |
| CD | 468 | 0.523 | 0.528 | **0.453** | 4-folds |
| BD | 117 | 0.251 | **0.191** | 0.203 | 3-folds |
| BDAR | 90 | 0.140 | 0.147 | **0.136** | 4-folds |

Note. The minimum average *MSPR* was marked in bold within each field limit alert type.

Table 19: The Performance Criteria for the Candidate Models – CD Group
The Values with Best Individual Performance are Marked in Bold

| Candidate model | 4-folds ave. *MSPR* | Number of parameters | *AIC* | *BIC* | *MSE* | $R^2_{adj}$ |
|---|---|---|---|---|---|---|
| Model 1 | 0.455 | 30 | 1185.244 | **1309.698** | 0.395 | 0.695 |
| **Model 2*** | **0.441** | 43 | **1154.427** | 1332.811 | **0.369** | **0.715** |
| Model 3 | 0.463 | 48 | 1159.719 | 1358.845 | 0.372 | 0.713 |

Note. The minimum average *MSPR*, the minimum *AIC*, *BIC*, *MSER*, and the maximum $R^2_{adj}$ among the candidate models were marked in bold. *Final selected model.

$$Y \sim \underbrace{X_1 + X_2 + X_4 + X_5 + X_8 + X_9 + X_1 * X_2 + X_1 * X_4 + X_4 * X_5 + X_4 * X_8}_{fixed\ effect} +$$

$$\underbrace{X_1 * X_2 * X_4 + X_1 * X_2 * X_8 + X_1 * X_4 * X_8 + X_4 * X_8 * X_9 + X_1 * X_2 * X_4 * X_9}_{fixed\ effect} +$$

$$\underbrace{X_{10}}_{random\ effect} \tag{3.5}$$

Table 20: Variable Terms and Estimated Coefficients of the CD Final Model

| **Random effects** | **Estimate** |
|---|---|
| $X_{10}$ (Participants) | 0.524 |
| Residual | 0.385 |
| **Fixed effects** | **Estimate** |
| (Intercept) | -0.545 |
| $X_1$(AMSU) | -0.123 |
| $X_2$(Insulin) | -0.495 |
| $X_2$(Morphine) | -0.496 |
| $X_2$(Propofol) | 0.003 |
| $X_4$(SoftMax-Dsmall) | -1.894 |
| $X_5$(HardMax-Y) | -0.276 |
| $X_8$(InfusionDuration) | 0.006 |
| $X_9$(Ratio-Rate/SoftMax) | 0.436 |
| $X_1$(AMSU)*$X_2$(Insulin) | 1.347 |
| $X_1$(AMSU)*$X_2$(Morphine) | 3.048 |
| $X_1$(AMSU)*$X_4$(SoftMax-Dsmall) | 2.187 |
| $X_4$(SoftMax-Dsmall)*$X_5$(HardMax-Y) | 0.842 |
| $X_4$(SoftMax-Dsmall)*$X_8$(InfusionDuration) | -0.010 |
| $X_1$(AICU)*$X_2$(Insulin)*$X_4$(SoftMax-Dsmall) | 2.350 |
| $X_1$(AMSU)*$X_2$(Insulin)*$X_4$(SoftMax-Dsmall) | -7.197 |
| $X_1$(AICU)*$X_2$(Morphine)*$X_4$(SoftMax-Dsmall) | 2.424 |
| $X_1$(AMSU)*$X_2$(Morphine)*$X_4$(SoftMax-Dsmall) | -0.976 |
| $X_1$(AICU)*$X_2$(Propofol)*$X_4$(SoftMax-Dsmall) | 2.504 |
| $X_1$(AICU)*$X_2$(Heparin)*$X_8$(InfusionDuration) | 0.000 |
| $X_1$(AMSU)*$X_2$(Heparin)*$X_8$(InfusionDuration) | -0.004 |
| $X_1$(AICU)*$X_2$(Insulin)*$X_8$(InfusionDuration) | 0.012 |
| $X_1$(AMSU)*$X_2$(Insulin)*$X_8$(InfusionDuration) | -0.003 |

Table 20 continued

| | |
|---|---|
| $X_1$(AICU)*$X_2$(Morphine)*$X_8$(InfusionDuration) | -0.001 |
| $X_1$(AMSU)*$X_2$(Morphine)*$X_8$(InfusionDuration) | -0.006 |
| $X_1$(AMSU)*$X_4$(SoftMax-Dsmall)*X8(InfusionDuration) | 0.005 |
| $X_4$(SoftMax-Dlarge)*$X_8$(InfusionDuration)*$X_9$(Ratio-Rate/SoftMax) | 0.001 |
| $X_4$(SoftMax-Dsmall)*$X_8$(InfusionDuration)*$X_9$(Ratio-Rate/SoftMax) | 0.006 |
| $X_1$(AICU)*$X_2$(Heparin)*$X_4$(SoftMax-Dlarge)*$X_9$(Ratio-Rate/SoftMax) | 0.836 |
| $X_1$(AMSU)*$X_2$(Heparin)*$X_4$(SoftMax-Dlarge)*$X_9$(Ratio-Rate/SoftMax) | 1.337 |
| $X_1$(AICU)*$X_2$(Insulin)*$X_4$(SoftMax-Dlarge)*$X_9$(Ratio-Rate/SoftMax) | 1.054 |
| $X_1$(AMSU)*$X_2$(Insulin)*$X_4$(SoftMax-Dlarge)*$X_9$(Ratio-Rate/SoftMax) | 0.580 |
| $X_1$(AICU)*$X_2$(Morphine)*$X_4$(SoftMax-Dlarge)*$X_9$(Ratio-Rate/SoftMax) | 0.575 |
| $X_1$(AMSU)*$X_2$(Morphine)*$X_4$(SoftMax-Dlarge)*$X_9$(Ratio-Rate/SoftMax) | -0.576 |
| $X_1$(AICU)*$X_2$(Propofol)*$X_4$(SoftMax-Dlarge)*$X_9$(Ratio-Rate/SoftMax) | 0.979 |
| $X_1$(AICU)*$X_2$(Heparin)*$X_4$(SoftMax-Dsmall)*$X_9$(Ratio-Rate/SoftMax) | 1.526 |
| $X_1$(AMSU)*$X_2$(Heparin)*$X_4$(SoftMax-Dsmall)*$X_9$(Ratio-Rate/SoftMax) | 0.203 |
| $X_1$(AICU)*$X_2$(Insulin)*$X_4$(SoftMax-Dsmall)*$X_9$(Ratio-Rate/SoftMax) | 0.069 |
| $X_1$(AMSU)*$X_2$(Insulin)*$X_4$(SoftMax-Dsmall)*$X_9$(Ratio-Rate/SoftMax) | 4.694 |
| $X_1$(AICU)*$X_2$(Morphine)*$X_4$(SoftMax-Dsmall)*$X_9$(Ratio-Rate/SoftMax) | -0.108 |
| $X_1$(AMSU)*$X_2$(Morphine)*$X_4$(SoftMax-Dsmall)*$X_9$(Ratio-Rate/SoftMax) | -0.708 |

Note. The estimates for the reference level of each categorical variable were zero (not included in the table) using the statistical software *R*; $\beta_1 X_1 = \beta_{AICU} I(X_1 = AICU) + \beta_{AMSU} I(X_1 = AMSU)$; $\beta_{48} X_4 * X_8 = \gamma_{8,Dsmall} RatioI(X_4 = Dsmall) + \gamma_{8,Dlarge} RatioI(X_4 = Dlarge)$

We followed the same procedures for analyzing the BD and BDAR datasets. For the BD group, the variation of $R^2_{adj}$ for the 2- to 4-folds are smaller in comparison to the 5- to 7- folds (Figure 14). Also, the average *MSPR* for the 3-folds, including all candidate models, is minimum among 2- to 4-folds (Table 18). Therefore, a 3-folds cross-validation was conducted to evaluate the three BD candidate models. Table 21 shows that the average *MSPR* across the 3 models are the same, so the overall fitting performance criteria for comparing the regression models was further examined to help select the final model. The overall fitting performance for model 1 was the best, which was regarded as the final model. The selected final model for the bolus dose infusion is expressed in Eq. 3.6 (Table 22).

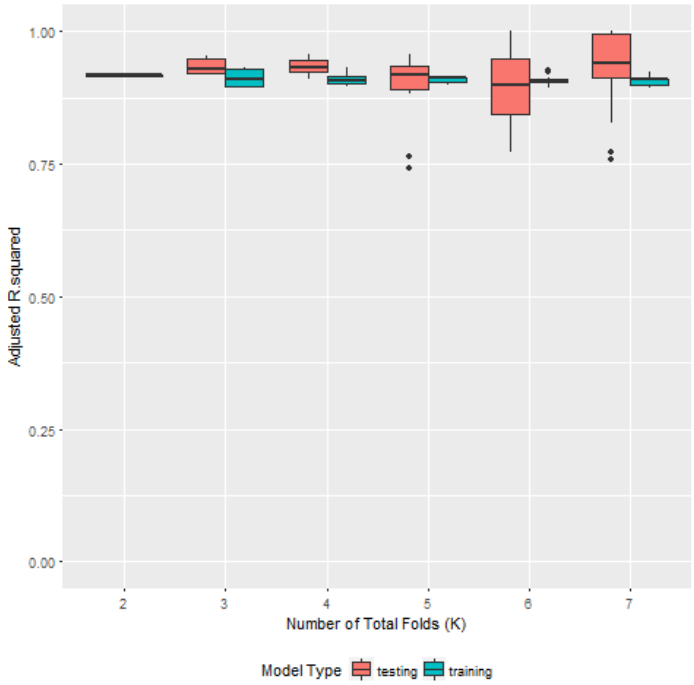



Figure 14: The Boxplot of $R^2_{adj}$ Values for Different Folds – BD Group
The Training Model is Green and Testing Model is Red

Table 21: The Performance Criteria for the Candidate models – BD Group
The Values with Best Individual Performance are Marked in Bold

| Candidate model | 3-folds ave. *MSPR* | Number of parameters | *AIC* | *BIC* | *MSE* | $R^2_{adj}$ |
|---|---|---|---|---|---|---|
| **Model 1*** | **0.193** | 12 | **170.034** | **203.181** | **0.130** | **0.907** |
| Model 2 | **0.190** | 13 | 175.007 | 210.915 | **0.129** | **0.907** |
| Model 3 | **0.192** | 14 | 179.894 | 218.564 | **0.131** | **0.906** |

Note. The minimum average *MSPR*, the minimum *AIC*, *BIC*, *MSER*, and the maximum $R^2_{adj}$ among the candidate models were marked in bold. *Final selected model

$$Y \sim \underbrace{X_1 + X_2 + X_5 + X_8 + X_9 + X_2 * X_9 + X_5 * X_9}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \quad (3.6)$$

Table 22: Variable Terms and Estimated Coefficients of the BD Final Model

| **Random effects** | **Estimate** |
|---|---|
| $X_{10}$ (Participants) | 0.409 |
| Residual | 0.137 |
| **Fixed effects** | **Estimate** |
| (Intercept) | 2.531 |
| $X_1$(AMSU) | 0.519 |
| $X_2$(Morphine) | -0.477 |
| $X_2$(Propofol) | -2.298 |
| $X_5$(HardMax-Y) | -2.837 |
| $X_8$(InfusionDuration) | -0.079 |
| $X_9$(Ratio-Dose/SoftMax) | 0.369 |
| $X_2$(Morphine)*$X_9$(Ratio-Dose/SoftMax) | 0.609 |
| $X_2$(Propofol)*$X_9$(Ratio-Dose/SoftMax) | -0.003 |
| $X_5$(HardMax-Y)*$X_9$(Ratio-Dose/SoftMax) | 0.251 |

For the BDAR group, the variation of $R^2_{adj}$ for the 2- and 4-folds is smaller in comparison to the 3- and 5- folds since there are some outliers presented in the 3- and 5-folds (Figure 15). In addition, the average *MSPR* of the 4-folds split, including all candidate models, is smaller than the average *MSPR* of the 2-folds split (Table 18). Therefore, we conducted 4-folds cross-validation to evaluate the three BDAR candidate models. We regarded model 1 as the final model with the minimum average *MSPR* value. Also, the overall model fitting performance for model 1 is the best, including the minimum *AIC*, *BIC*, *MSE*, and the maximum $R^2_{adj}$ across the three candidate models (Table 23). The selected final model for the bolus dose rate of infusion is expressed in Eq. 3.7 (Table 24).

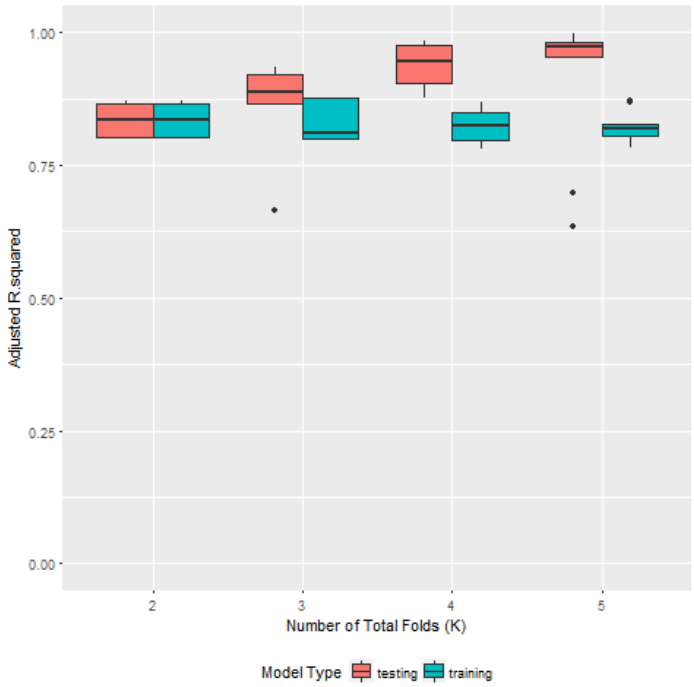



Figure 15: The Boxplot of $R^2_{adj}$ Values for Different Folds – BDAR Group
The Training Model is Green and Testing Model is Red

Table 23: The Performance Criteria for the Candidate models – BDAR Group
The Values with Best Individual Performance are Marked in Bold

| Candidate model | 4-folds ave. *MSPR* | Number of parameters | *AIC* | *BIC* | *MSE* | $R^2_{adj}$ |
|---|---|---|---|---|---|---|
| **Model 1*** | **0.129** | 14 | **102.335** | **137.332** | **0.083** | **0.817** |
| Model 2 | 0.139 | 15 | 107.193 | 144.690 | **0.084** | **0.816** |
| Model 3 | 0.139 | 15 | 107.193 | 144.690 | **0.084** | **0.816** |

Note. The minimum average *MSPR*, the minimum *AIC*, *BIC*, *MSER*, and the maximum $R^2_{adj}$ among the candidate models were marked in bold. *Final selected model.

$$Y \sim \underbrace{X_2 + X_4 + X_8 + X_9 + X_4 * X_8 + X_4 * X_9 + X_8 * X_5 + X_9 * X_5}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \quad (3.7)$$

Table 24: Variable Terms and Estimated Coefficients of the BDAR Final Model

| **Random effects** | **Estimate** |
|---|---|
| $X_{10}$ (Participants) | 0.143 |
| Residual | 0.087 |
| **Fixed effects** | **Estimate** |
| (Intercept) | -0.849 |
| $X_2$(Propofol) | 0.322 |
| $X_4$(SoftMax-Dlarge) | -0.220 |
| $X_4$(SoftMax-Dsmall) | 0.403 |
| $X_8$(InfusionDuration) | 0.286 |
| $X_9$(Ratio-Rate/SoftMax) | 0.856 |
| $X_4$(SoftMax-Dlarge)*$X_8$(InfusionDuration) | -0.476 |
| $X_4$(SoftMax-Dsmall)*$X_8$(InfusionDuration) | -0.118 |
| $X_4$(SoftMax-Dlarge)*$X_9$(Ratio-Rate/SoftMax) | 0.276 |
| $X_4$(SoftMax-Dsmall)*$X_9$(Ratio-Rate/SoftMax) | -0.150 |
| $X_8$(InfusionDuration)*$X_5$(HardMax-Y) | 0.335 |
| $X_9$(Ratio-Rate/SoftMax)*$X_5$(HardMax-Y) | -0.343 |

### *ANOVA and Post Hoc Tests for the Final Regression Models*

*Continuous Dose*

Table 25 shows the ANOVA table using the final CD regression model, and the significant effects were considered as the strong risk predictors for this continuous dose filed limit alerts. The positive estimate of the model (0.436) and the significant effect of $X_9$, on the expected risk for the CD group indicated that the increase of ratio of soft max drug limit, meaning the increase of infusion dose for CD field limits (Su et al., 2018), can increase the expected risk of IV harm.

In addition, the effects of $X_2$, $X_1$*$X_2$, and $X_1$*$X_2$*$X_4$ were significant on the expected risk showing that the effects of medication ($X_2$) under each care area group ($X_1$) or under each combination of care area ($X_1$) and soft max limit type ($X_4$) were different. We conducted post hoc test for $X_1$*$X_2$ and the $X_1$*$X_2$*$X_4$ effect to estimate the least-square means of expected risk (Table 26), an estimated marginal means of the groups, and the difference of the least-square means (LS means). The results of the $X_1$*$X_2$ showed that in

AICU, the expected risk of insulin overdose was significantly higher than that of propofol and heparin ($p < 0.001$), and the expected risks of propofol and heparin were significantly higher than that of morphine ($p < 0.001$). On the other hand, in AMSU, the expected overdose risks of insulin, heparin, and morphine were similar. Furthermore, we observed the LS means difference of the expected risk between small and large soft maximum limit types under each combination of care area and medication using the post hoc test of $X_1*X_2*X_4$ interaction effect. The results showed that the expected risk of the large soft limit group is significantly higher than the small soft limit group for heparin ($p = 0.006$) and propofol ($p = 0.009$) in AICU, and for insulin in both AICU ($p < 0.001$) and AMS ($p = 0.05$) (Figure 16). In this study, we used the high-order interaction variables to increase the model fitting performance.

Table 25: ANOVA Table – CD Group

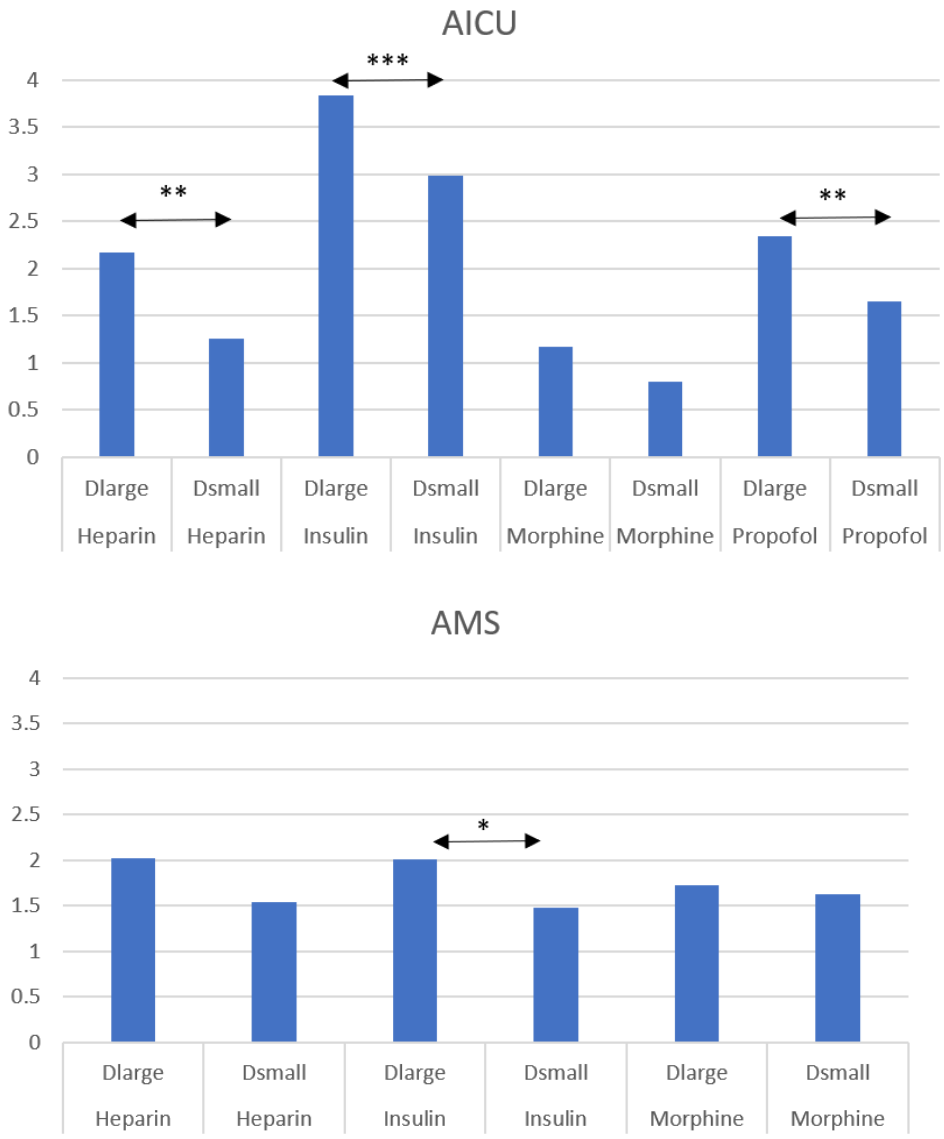
| Effect | Sum Sq | Mean Sq | DF | DenDF | F.value | Pr(>F) |
|---|---|---|---|---|---|---|
| $X_1$ | 0.07 | 0.07 | 1 | 419 | 0.18 | 0.672 |
| $X_2$ | 5.58 | 1.86 | 3 | 411 | 4.83 | **0.003** |
| $X_4$ | 0.52 | 0.52 | 1 | 403 | 1.34 | 0.248 |
| $X_5$ | 0.72 | 0.72 | 1 | 314 | 1.87 | 0.172 |
| $X_8$ | 0.59 | 0.59 | 1 | 402 | 1.53 | 0.217 |
| $X_9$ | 8.16 | 8.16 | 1 | 402 | 21.20 | **<0.001** |
| $X_1*X_2$ | 4.91 | 2.45 | 2 | 420 | 6.38 | **0.002** |
| $X_1*X_4$ | 1.48 | 1.48 | 1 | 404 | 3.84 | 0.051 |
| $X_4*X_5$ | 2.73 | 2.73 | 1 | 202 | 7.11 | **0.008** |
| $X_4*X_8$ | 4.88 | 4.88 | 1 | 402 | 12.68 | **<0.001** |
| $X_1*X_2*X_4$ | 5.22 | 1.04 | 5 | 408 | 2.71 | **0.020** |
| $X_1*X_2*X_8$ | 31.12 | 6.22 | 6 | 402 | 16.18 | **<0.001** |
| $X_1*X_4*X_8$ | 8.57 | 8.57 | 1 | 402 | 22.27 | **<0.001** |
| $X_4*X_8*X_9$ | 10.09 | 5.05 | 2 | 402 | 13.11 | **<0.001** |
| $X_1*X_2*X_4*X_9$ | 16.00 | 1.23 | 13 | 402 | 3.20 | **<0.001** |

Note. $X_1$: AICU, AMSU; $X_2$: heparin, insulin, morphine, propofol; $X_4$: soft maximum limit is large or small; $X_5$: hard maximum limit provided Y/N

Table 26: Least Squares Means (LS mean) of $X_1$* $X_2$ Interaction Effect – CD Group

| $X_1$ | $X_2$ | Estimated LS mean | Std. Error | DF | t-value | Lower CI | Upper CI |
|---|---|---|---|---|---|---|---|
| AICU | Heparin | 1.71 | 0.22 | 52 | 7.71 | 1.27 | 2.16 |
| AMSU | Heparin | 1.78 | 0.28 | 78 | 6.4 | 1.23 | 2.34 |
| AICU | Insulin | 3.40 | 0.27 | 73 | 12.87 | 2.88 | 3.93 |
| AMSU | Insulin | 1.74 | 0.22 | 48 | 8.06 | 1.31 | 2.18 |
| AICU | Morphine | 0.99 | 0.25 | 62 | 3.92 | 0.48 | 1.49 |
| AMSU | Morphine | 1.67 | 0.25 | 54 | 6.68 | 1.17 | 2.18 |
| AICU | Propofol | 2.00 | 0.22 | 45 | 9.28 | 1.56 | 2.43 |
| AMSU | Propofol | NA | NA | NA | NA | NA | NA |

Note. LS mean: means for groups that are adjusted the individual difference




Note. Significant codes: '***' $p \leq 0.001$; '**' $0.001 < p \leq 0.01$; '*' $0.01 < p \leq 0.05$

Figure 16: LS mean of Soft Limit Type in Different Combination of Care Area and Medication

*Bolus Dose*

The significant effects of the ANOVA table were regarded as the strong risk predictors for the final BD regression model (Table 27). The negative estimate of $X_8$ (-0.079) indicated the decrease of infusion rate with fixed dose for the BD field limits can decrease the expected risk. Also, the post hoc test of $X_5$ effect showed that the expected risk for the BD alert overrides without hard maximum drug limits was higher than the cases

with hard drug limits ($p$ = 0.017). The significant $X_2$*$X_9$ interaction effect indicated that when increasing ratio of soft max drug limit, $X_9$, (infusion dose for BD field limits setting), the increase trend of the expected risk was different for the four medications (heparin, insulin, morphine, and propofol). The further post hoc test showed that the expected risk for the alert overrides associated with morphine was significantly higher than propofol ($p$ = 0.002), and that insulin overrides have higher risk than propofol overrides ($p$ = 0.026).

*Bolus Dose Administration Rate*

The significant predictor variables of the BDAR model are shown in Table 28. The significant $X_4$*$X_8$ and $X_4$*$X_9$ interaction effects indicated that when increasing infusion duration, $X_8$, or ratio of soft max drug limit, $X_9$, (infusion rate for BDAR field limits), the increase trend of the expected risk for the different levels of soft limit type were different. The increase of infusion duration or infusion rate increased the expected risk due to the positive estimates of the regression models ($X_8$ is 0.286, $X_9$ is 0.856).

Table 27: ANOVA Table – BD Group

| Effect | Sum Sq | Mean Sq | DF | DenDF | F.value | Pr(>F) |
|---|---|---|---|---|---|---|
| $X_1$ | 0.13 | 0.13 | 1 | 8 | 0.95 | 0.358 |
| $X_2$ | 0.87 | 0.43 | 2 | 17 | 3.16 | 0.069 |
| $X_5$ | 1.29 | 1.29 | 1 | 14 | 9.39 | **0.008** |
| $X_8$ | 1.27 | 1.27 | 1 | 99 | 9.27 | **0.003** |
| $X_9$ | 12.67 | 12.67 | 1 | 99 | 92.50 | **<0.001** |
| $X_2$*$X_9$ | 2.39 | 1.19 | 2 | 99 | 8.70 | **<0.001** |
| $X_5$*$X_9$ | 0.13 | 0.13 | 1 | 99 | 0.93 | 0.338 |

Note. $X_1$: AICU, AMSU; $X_2$: insulin, morphine, propofol; $X_5$: hard maximum limit provided Y/N

Table 28: ANOVA Table – BDAR Group

| Effect | Sum Sq | Mean Sq | DF | DenDF | F.value | Pr(>F) |
|---|---|---|---|---|---|---|
| $X_2$ | 0.02 | 0.02 | 1 | 49 | 0.29 | 0.596 |
| $X_4$ | 0.21 | 0.11 | 2 | 75 | 1.21 | 0.303 |
| $X_8$ | 1.07 | 1.07 | 1 | 72 | 12.28 | **0.001** |
| $X_9$ | 7.42 | 7.42 | 1 | 72 | 85.06 | **<0.001** |
| $X_4$*$X_8$ | 0.56 | 0.28 | 2 | 72 | 3.19 | **0.047** |
| $X_4$*$X_9$ | 0.69 | 0.35 | 2 | 72 | 3.96 | **0.023** |
| $X_8$*$X_5$ | 0.27 | 0.27 | 1 | 72 | 3.09 | 0.083 |
| $X_9$*$X_5$ | 0.25 | 0.25 | 1 | 72 | 2.91 | 0.093 |

Note. $X_1$: AICU, AMSU; $X_2$: morphine, propofol; $X_4$: soft maximum limit is regular, large or small; $X_5$: hard maximum limit provided Y/N

### 5.1.3 Discussion

The combinations of the main and interaction effects of expected risk, which were regarded as predictors to create the final models, were different for three field limit types (CD, BD, and BDAR). High-order interactions were included as predictors for the CD final risk predictive model but not the BD and BDAR models. The adjusted R-square value was 0.7 for the CD model, while that was higher for BDAR (0.8) and BD (0.9). A possible reason is that much was unknown in the simulated infusion scenarios, such as patient conditions and prescriptions from physicians (Su et al., 2018). In addition, patients may be on continuous dose infusions (CD) for a few hours. Since patient conditions could change during the infusion, predicting risk for hours (CD type model) can be more difficult and less accurate than that for just minutes behind (BD and BDAR types models). For better fitting performance and predictive capability of the CD models, the variables with high-order interactions were considered as predictors after stepwise *AIC* procedures. On the other hand, if more patient clinical information associate with drug infusions, such as physician's orders, DRG codes (Diagnosis Related Group), or Current Procedural Terminology (CPT[5]) code, is available, we can include more potential model predictors, replacing the high-order predictors, to improve the current model in future research.

[5] CPT® codes are a medical code set maintained by the American Medical Association. These codes are for medical professionals report medical, surgical, radiology, laboratory, diagnostic procedures, and services. https://www.ama-assn.org/practice-management/cpt-current-procedural-terminology?-process-how-code-becomes-code=

According to the ANOVA results, the effect of $X_9$, the ratio of soft maximum drug limit, was regarded as a strong predictor for the final models of three field limit types. Based on different field limit settings (Su et al., 2018), where higher ratio of soft maximum drug limit, for the CD and BDAR types being corresponding with larger infusion rate and for the BD type being corresponding with larger infusion drug amount, could lead to higher risk of harm on patients. The finding was consistent with that of the IV harm index (Sullivan, 2004; C. K. Williams et al., 2006). On the other hand, we found that the effect of $X_5$, infusions with/without hard maximum hard limits, was a strong predictor only for the BD model. When BD field limit alerts were triggered and being overridden, the clinician intended to overdose the soft maximum drug limits within a few minutes, which created a very high-risk condition for the patient, especially if it's a high-risk drug. Therefore, we suggested that the hospital system should set up hard maximum drug limits for the BD field limits of high-risk medications to reduce risk of harm when conducting a bolus dose infusion.

The risk-based models we developed in this study for three different field limit types were more complex than the IV harm index since our models consider not only the main key risk factors, but also the expected risk that could vary across different combinations of the risk factors using interaction effects. There are some limitations to our risk-based models. First, the outcome variable, risk benchmark, was defined using the adjusted likelihoods assessed from the experts multiplied by the quantified severity, since pump alert reports currently do not link to the clinical patient outcomes in most hospital systems. If some small datasets in which the overridden alerts link to the patient outcomes can be obtained, we could map the clinical outcomes to the NCC MERP index (Rozich et al., 2003) and use these new data and outcomes to validate and improve our current models, which we could address in future research. Second, the proposed models can only quantify risk for the alert overrides associated with the four high-risk medications (propofol, morphine, insulin, and heparin) in AICU or AMSU settings. Third, the risk-based models were created based on the drug limit settings and alert datasets in a large teaching hospital. Some validations and revision for the models might be needed when applying to other alert datasets.

**Summary:**

We presented three types of risk predictive models for different field limit alerts (continuous dose, bolus dose, bolus dose administration rate), which can be used to demonstrate the important risk factors for predicting expected risk of IV harm considering multiple independent variables. According to the experimental design, the linear predicted risk for all 270 infusion scenarios (30 scenario types x 9 sub-scenarios) was estimated and shown in APPENDIX B (Column "Predicted Risk-A"). We could further use the predicted risk to compare with the risk benchmarks. The comparison results are shown in Section 6.2.

## 5.2 Application of the IV Medication Harm Index

### 5.2.1 Data Preparation and Pre-processing

In this study, we focused on alert-overridden infusions associated with four high-risk medications, which were propofol, morphine, insulin, and heparin. When applying the IV harm index (Table 4) to quantify risk for the overridden alerts, each alert should be quantified based on the sub-scales, (1) risk levels of medication, (2) levels of patient care unit, (3) the programming ratio (ratio of programming values to the maximum/minimum drug limits), and (4) the detectability of ADEs. The sub-scales of (1), (2), and (4) could be quantified by experts' opinions and their clinical knowledge.

We only focused on four high-risk medications in AICU and AMSU for this risk assessment study. More important or frequently checked drugs in various care areas can be addressed in future research. We invited the Group I experts to help us quantify the sub-scales for the frequently checked drugs in the representative care units. This data preparation is not only for the current study, but also for the future research. For the data preparation, first, we downloaded the REMEDI user activity records from September 2011 - November 2015. We computed the investigation frequency by medication and sorted from the highest to the lowest investigation frequency. Thus, the top 24 frequently checked medications were selected.

We acquired some experts from Group 1 (4 pharmacists and 1 nurse) to assess the risk-level of each medication. These experts also assessed the detectability of an infusion-related ADE of each medication in the four levels of patient care units. Table 29 shows the risk-level and the detectability of an infusion-related ADE associated with the top 24 frequently checked medications. We collected alert data with different available time frames from the six hospitals (Table 30). We used R software to identify the unique patient care units (defined as profiles in the alert data) with the most alert, and, we acquired Group 1 experts to map each profile to the four levels of patient care units (Table 31).The summary results exclude the profiles "respiratory care", "outpatient infusion center", "general pediatrics", and "general nursery and infant" due to the various expert detectability assessments or the alert data mixed with the other profiles (e.g. pediatric

hematology/oncology alerts are mixed with general pediatrics alerts and they cannot be identified and separated).

Table 29: Risk Levels and Detectability of ADEs of Top 24 Checked Medications Based on Experts' Assessment

| Order | Frequency | Drug Name | Risk level of IV Medication (Low-, Moderate, or High-risk) | Detectability of ADEs (drug in different level of care) the easiest (lower risk: 1 ) → the hardest (higher risk: 3) | | | |
|---|---|---|---|---|---|---|---|
| | | | | General Care | Intermediate Care | Adult Intensive Care | Pediatric & Neonatal Intensive Care |
| | | | | **The profiles in each level of care are indicated in the previous slide | | | |
| 1 | 1937 | propofol | High | 2 | 2 | 1 | 1 |
| 2 | 1823 | HYDROmorphone | High | 3 | 2 | 1 | 1 |
| 3 | 1035 | heparin | High | 3 | 3 | 3 | 2 |
| 4 | 974 | VANCOmycin | Moderate | 2 | 2 | 2 | 2 |
| 5 | 651 | morphine | High | 3 | 2 | 1 | 1 |
| 6 | 548 | potassium chloride | High | 3 | 2 | 1 | 1 |
| 7 | 508 | FENTanyl | High | 3 | 2 | 1 | 1 |
| 8 | 499 | insulin | High | 3 | 3 | 2 | 2 |
| 9 | 455 | ampicillin | Low | 3 | 3 | 2 | 2 |
| 10 | 441 | oxytocin | Low | 3 | 2 | 1 | 1 |
| 11 | 395 | piperacillin/tazo | Low | 2 | 2 | 1 | 1 |
| 12 | 351 | dexmedetomidine | High | 3 | 3 | 2 | 2 |
| 13 | 284 | LORazepam | Moderate | 3 | 2 | 2 | 2 |
| 14 | 272 | NORepinephrine | Moderate | 3 | 2 | 2 | 2 |
| 15 | 208 | magnesium sulfate | High | 3 | 2 | 1 | 1 |
| 16 | 207 | GENTAmicin | Moderate | 2 | 2 | 2 | 2 |
| 17 | 188 | bevacizumab | High | 3 | 3 | 2 | 2 |
| 18 | 171 | rituximab | High | 3 | 3 | 2 | 2 |
| 19 | 161 | PACLitaxel | High | 3 | 3 | 2 | 2 |
| 20 | 158 | ceftriaxone | Low | 2 | 2 | 1 | 1 |
| 21 | 150 | niCARdipine | Moderate | 3 | 2 | 2 | 2 |
| 22 | 139 | calcium gluconate | Moderate | 2 | 2 | 1 | 1 |
| 23 | 126 | Argatroban | High | 3 | 3 | 3 | 2 |
| 24 | 81 | penicillin G K | Low | 2 | 2 | 1 | 1 |

Table 30: Different Available Time Frames of the Six Hospitals

| **IPI member** | **Available time frame** |
|---|---|
| Community Health Network | July 2010 – Aug. 2015 |
| Eskenazi Hospital | Jan. 2011 - Aug. 2015 |
| Indiana University Health | Dec. 2009 - May 2015 |
| Nebraska Medicine | April 2011 - Aug. 2015 |
| St. Vincent Indianapolis | Mar. 2014 - July 2015 |
| University of Wisconsin Hospital | Dec. 2009 - May 2015 |

Table 31: Summary of Profile Names Grouped under each Level of Care

| General Care | Intermediate Care | Adult Intensive Care | Pediatric & Neonatal Intensive Care |
|---|---|---|---|
| **Profile names in each level of care** | | | |
| Adult Med/Surg | Adult Heme/Onc | Acuity Adaptable | NICU |
| Cardiac Diagnostics | Cardiology | Adult ICU | PICU |
| ECHO/Nuclear Med | ED | Cath IR | |
| Epidural | Hospice | Critical Care/ED | |
| Family Beginnings | IMC/Cardiac | Intensive Care | |
| Heart Center | Med Surg/ Telemetry | IR Thrombolysis | |
| L&D (OB care unit) | Telemetry | | |
| LDRP | | | |
| MedCheck Infusion | | | |
| Postpartum | | | |
| Progressive Care | | | |
| Seton General | | | |

### 5.2.2 Calculation of IV Harm Scores for All 270 Simulated Infusion Scenarios

IV harm scores were then estimated for the 270 infusion scenarios discussed earlier in Chapter 4. Four steps were followed to calculate the IV harm scores for all simulated IV medication infusion scenarios as discussed below:

**Step 1: Quantify sub-risk score (I) based on the risk-levels associated with medication-and-programming ratio**

The harm index was applied to obtain the sub-scores (I) based on the programming ratio of each simulated alert-overridden scenarios. We focused on the high-risk medication group since propofol, morphine, insulin, and heparin are all high-risk medications. The sub-risk scores (I) were quantified as 3, 6, or 9 based on the degrees of the range of programming ratio.

**Step 2: Quantify sub-risk score (II) based on the risk levels associated with patient care unit**

The way to quantify sub-risk score (II) is the same as the definition mentioned in Table 4. The patient care units designed in the scenarios can be identified in four levels (Table 31), which can map to the sub-risk score (II). The range of sub-risk score II is from 1 to 2.

**Step 3: Quantify sub-risk score (III) based on the risk levels associated with detectability of an infusion-related ADE**

The previous studies only showed the detectability of ADEs of some medications (Sullivan, 2004; C. K. Williams et al., 2006). In this study, the detectability of ADEs for the four high-risk medications in AICU and AMSU was assessed by Group I experts. Therefore, the sub-risk score (III) for each alert-overridden infusion can be obtained. The range of sub-risk score (III) is from 1 to 3.

**Step 4: Compute the sum of risk score for all scenarios**

The sum of risk scores for each scenario was computed using the summation of the results from steps 1 to 3. The range of overall risk score is from 5 to 13. According to the experimental design, the IV harm scores for all 270 infusion scenarios were calculated and shown in APPENDIX B (Column "IV Harm Scores"). The IV harm scores were then compared with the risk benchmarks (see Section 6.2).

## 5.3 Application of The Matrix-based Ranking Method

Matrix-based risk ranking scores (see Section 2.5.1) were calculated for the same 270 infusion scenarios discussed earlier. Five steps were followed to calculate the risk ranking scores for all simulated IV medication infusion scenarios as discussed below:

**Step 1: Define IV medication risk factors**

We defined four IV medication risk of harm factors based on the IV Medication Harm Index (Sullivan, 2004; C. K. Williams et al., 2006). These factors were: (1) risk levels of medication [F1], (2) risk levels of patient care unit [F2], (3) detectability of an infusion-related ADE [F3], and (4) programming ratio (programming value to the drug limit). When

applying this matrix-based method, we transferred "programming ratio" into "relative deviation from programming values to the drug limits (%)" [F4] for easily representing the programming values of overdose and underdose.

**Step 2: Define comparison criteria and create alert risk factor metrics**

A Group I expert was invited to define the relative degree of risk to generate comparison criteria for each risk factor. Based on these domain expert inputs, the following alert risk factor metrics were created (Table 32). The experts defined three relative risk of harm levels for medications (F1 risk factor), from low, moderate, to high risk levels. Regards F2 factor, it was defined as four risk levels. Also, for F3 factor, they gave three relative risk levels, from the lowest (the easiest to detect adverse drug events) to the highest risk (the hardest). For F4 factor, they defined four risk levels, from the lower risk where infusions alerts were triggered by upper bound drug limit (overdose) with the programming values close to soft drug limits, to the higher risk where alerts were triggered by lower bound drug limit (underdose) with programming values far from soft limits.

Table 32: Alert Risk Factor Metrics

| IV Medication Risk of Harm Factors | Lower Risk (Good) → Moderate Risk (Bad) → Higher Risk (Very Bad) | | | |
|---|---|---|---|---|
| F1: Risk Level of IV Medication | Low | Moderate | High | |
| F2: Level of Care Unit | General Care | Intermediate Care | Adult Intensive Care | Pediatric & Neonatal Intensive Care |
| F3: Detectability of Adverse Drug Events (ADEs) | Easy | Moderate | Hard | |
| F4: Relative Deviation from Programming Values to Soft Limits (%) | Smaller (Upper Bound) → Large Number (UB) → Smaller (Lower Bound) → Large Number (LB) | | | |

**Step 3: Select alert-overridden infusions data and create risk datasets**

We selected 5-year alert-overridden infusion data from one hospital in the IPI database, and the top 24 frequently checked medications (Table 29). In addition, according to the previous assessment from the Group I experts, for all alert entities, we identified the

relative degree of risk under the first three factors defined in Step 1. For the fourth factor, we identified it as above or below the limits and also recorded their relative deviation values (programming values to limits). Consequently, the alert-overridden risk dataset was created, which was illustrated in Section 2.5.

**Step 4: Select representative alert-overridden cases and establish a risk ranking scale**

A risk scale dataset (RSD) was specified by first selecting 1,050 overridden infusions as representative infusion cases (685 were selected from the risk datasets and 365 were created). This RSD, including all representative programming ranges, was used to generate an overall comparison matrix. The matrix-based algorithm was applied to generate the ranking score from 1 (riskiest) to 1050 (the lowest risk) for these representative cases, and these scores were normalized to establish a new scale from 100 (riskiest) to 1 (least risky) for estimating the ranking scores of other infusion scenarios. The RSD (overall comparison matrix) with the ranking scores (normalized from 100 to 1) associated with the four performance scores of the risk criteria (F1-F4) are shown in Appendix C.

**Step 5: Estimate matrix-based risk ranking scores for all scenarios**

The last step was to use the RSD to estimate the risk ranking scores for all 270 infusion scenarios (new dataset) mentioned earlier in Chapter 4. This was done by comparing their performance scores on the four criteria (F1-F4) against those from the RSD. Following are some sequencing rules: (1) we assigned the performance scores of each risk criteria (i.e. F1: risk levels of medication from 1 to 3, F2: care unit level from 1 to 4, F3: detectability of ADEs from 1 to 3, and F4: programming values from small to large) for the 270 infusion scenarios (Table 32); (2) For each scenario in the new dataset, we mapped a set of the four performance scores to the representative infusion cases in RSD. The risk ranking scores for the new dataset were obtained directly from 100 (riskiest) to 1 (least risky) for the same mapping infusion cases. Table 33 shows an example of the mapping from the RSD. If the performance score set was (2, 2, 1, 200), the corresponding risk ranking score was 993. If the performance score set did not completely match the RSD, such as a set of (2, 2, 1, 240), the linear interpolation method considering the adjacent two performance scores (F4 of 200 and 300) would be used. For such case, the corresponding risk ranking score was 988.2 (993 x 0.6 + 981 x 0.4).

Table 33: An Example of RSD

| Est. Values | F1 Risk level IV Med | F2: Level of Care | F3: Detect of ADEs | F4_Processed Exceeding Limits (Adjusted) | Risk Ranking Score |
|---|---|---|---|---|---|
| 0.6926 | 2 | 2 | 1 | 100 | 1002 |
| 0.6817 | 2 | 2 | 1 | 200 | 993 |
| 0.6704 | 2 | 2 | 1 | 300 | 981 |

According to the experimental design, the 270 matrix-based risk ranking scores for all simulated infusion scenarios were estimated (Column "Matrix-based Risk Rankings" in APPENDIX B). The matrix-based risk ranking scores were used to compare with the risk benchmarks, and the comparison results were indicated in Section 6.2.

## 5.4 Application of the AHP Method

As part of the survey discussed earlier in section 4.1.4, after each expert participant assessed risk for one scenario type, the participants were asked to make pairwise comparisons to compare the relative impact on overall risk of IV harm among the six risk factors (Question 2 in Appendix D). They were also asked to compare which designed levels of infusion rate/programming ratio (Question 3 in Appendix D) and which designed levels of total drug amount patient received were more risky (Question 4 in Appendix D). Their survey responses were used to create a set of comparison matrices for the corresponding AHP structures. Each pairwise comparison survey regarding one scenario type was used to create one AHP structure, and a total of 30 AHP structures were created based on the total of 30 scenario types. The survey responses from multiple experts to the same scenario type were aggregated using the geometric mean method (Saaty, 2008; Teknomo, 2006). The following procedures indicate the steps to applying the AHP method for obtaining the risk priority vector of each scenario type.

### 5.4.1 Calculation of AHP Risk Priorities for All 270 Simulated Infusion Scenarios

There are four steps to calculate the AHP Risk Priorities for all simulated IV medication infusion scenarios:

**Step 1: Construct each AHP structure for each scenario type**

The goal of the AHP structure called level 0 is to obtain the relative risk levels among the 9 sub-scenarios for each scenario type (Figure 17). There are 6 risk factors: (1) care area, (2) medication, (3) field limit type combined with the soft maximum limits (SoftMax), (4) hard limit type, (5) infusion rate/total dose combined with the ratio of the SoftMax, and (6) total dose/infusion duration. The specific Factors 5 and 6 were selected depending on the field limit types (CD, BD, and BDAR): Factor 5 is infusion rate for CD and BDAR, and total dose for BD; Factor 6 is total dose for CD, and infusion duration for BD and BDAR. The specific levels of factors from (1) to (4) and the corresponding information of factors (5) and (6) are regarded as level 1 of the AHP structure. The last level, level 2, consists of the 9 sub-scenarios.

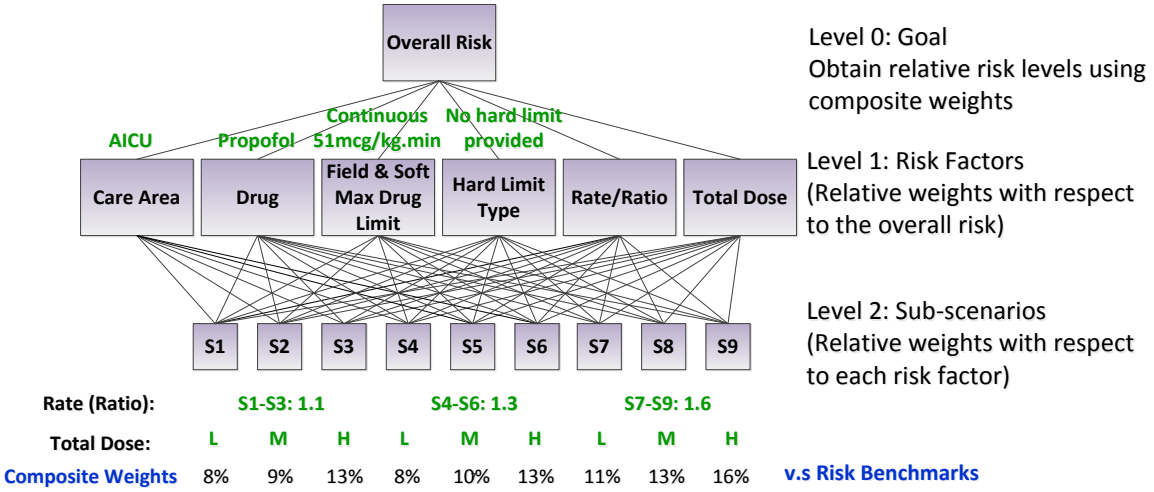



Figure 17: An Example of the AHP Structure

**Step 2: Construct pairwise comparison matrix**

In level 1, for each expert participant, we created one 6-by-6 pairwise comparison matrix (Figure 18) corresponding to 15 pairwise responses between the specific 6 factors with respect to the overall risk (Figure 19). The pairwise responses using linguistic variables were mapped on to the numerical scales (Saaty, 2008). Furthermore, in level 2, we created six 9-by-9 pairwise comparison matrices with respect to the specific six factors. For both levels 1 and 2, the overall comparison matrix of the several matrices from multiple expert participants was constructed using the weighted geometric mean method (Teknomo,

2006). We used the weighted geometric mean method because some of the expert participants' *Consistency Ratio (CR)* corresponding to their comparison results are larger than the threshold, 10%. There is a limitation in this research that the same respondents cannot be asked again to adjust their subjective responses. However, two or three experts provided the pairwise responses for each scenario type. Therefore, the expert participants with lower *Consistency Ratio (CR)*, which means their responses are more consistent, were assigned the higher aggregated weights in each specific AHP structure.

| Matrix | | CareArea | Medication | FieldLimitTp & SoftMax | HardMaxTp | InfusionRate (Ratio) | TotalDose |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| CareArea | 1 | - | 1/3 | 1 | 1/3 | 1/5 | 1/5 |
| Medication | 2 | 3 | - | 3 | 1/3 | 1/5 | 1/5 |
| FieldLimitTp & SoftMax | 3 | 1 | 1/3 | - | 1/3 | 1/5 | 1/5 |
| HardMaxTp | 4 | 3 | 3 | 3 | - | 1/5 | 1/5 |
| InfusionRate (Ratio) | 5 | 5 | 5 | 5 | 5 | - | 1/3 |
| TotalDose | 6 | 5 | 5 | 5 | 5 | 3 | - |

Figure 18: An Example of the Pairwise Comparison Matrix

| | | Criteria | | more important ? | Scale |
|---|---|---|---|---|---|
| i | j | A | B | A or B | (1-9) |
| 1 | 2 | CareArea | Medication | B | 3 |
| 1 | 3 | | FieldLimitTp & SoftMax | | 1 |
| 1 | 4 | | HardMaxTp | B | 3 |
| 1 | 5 | | InfusionRate (Ratio) | B | 5 |
| 1 | 6 | | TotalDose | B | 5 |
| 1 | 7 | | | | |
| 1 | 8 | | | | |
| 2 | 3 | Medication | FieldLimitTp & SoftMax | A | 3 |
| 2 | 4 | | HardMaxTp | B | 3 |
| 2 | 5 | | InfusionRate (Ratio) | B | 5 |
| 2 | 6 | | TotalDose | B | 5 |
| 2 | 7 | | | | |
| 2 | 8 | | | | |
| 3 | 4 | FieldLimitTp & SoftMax | HardMaxTp | B | 3 |
| 3 | 5 | | InfusionRate (Ratio) | B | 5 |
| 3 | 6 | | TotalDose | B | 5 |
| 3 | 7 | | | | |
| 3 | 8 | | | | |
| 4 | 5 | HardMaxTp | InfusionRate (Ratio) | B | 5 |
| 4 | 6 | | TotalDose | B | 5 |
| 4 | 7 | | | | |
| 4 | 8 | | | | |
| 5 | 6 | InfusionRate (Ratio) | TotalDose | B | 3 |

Figure 19: An Example of the Pairwise Response

**Step 3: Calculate the normalized eigen vectors and combine to obtain the overall composite weights**

The two types of normalized Eigen vectors for both level 1 (type I) and level 2 (type II) were calculated using the overall comparison matrices. The type I Eigen vector is regarded as the relative weights of the specific six risk factors with respect to the overall risk and the type II vector is regarded as the relative weights of the nine sub-scenarios with respect to the specific risk factor. The overall composite weights were calculated by the summation of the multiplication of the two types of vectors. The overall composite weights are also called normalized risk priority, in which the sum of all elements in the risk priority vector is 100%.

For each scenario type, we aggregated normalized Eigen vectors from multiple experts for each type I and type II using the online tool, "A New AHP Excel Template with Multiple Inputs with 2017-10-11 version (Goepel, 2013)". The aggregated type I and type II normalized Eigen vectors were used to calculate the overall composite weights for each

scenario type, defined as the AHP risk priorities (see APPENDIX E). For example, in scenario type 1, the type I normalized Eigen vector (level 1), the relative weights of the six risk factors (0.0602, 0.1193, 0.1161, 0.1148, 0.2083, 0.3812), was multiplied by the type II normalized Eigen vectors (level 2), the relative weights of the nine sub-scenarios with respect to each risk factor. The overall sum of the composite weights were calculated and regarded as risk priorities for each scenario.

**Step 4: Calculate adjusted AHP risk priorities using LLMs for all scenarios**

In order to compare the AHP risk priorities with the risk benchmarks among all simulated scenarios (Section 6.2), we further adjusted the aggregated risk priorities by multiplying the average predicted risk of each scenario type, which was derived from the linear mixed models (Method A). The calculated risk priorities were indicated in APPENDIX B (Column "Adjusted AHP Risk Priorities"). For example, one scenario type of original risk priorities (0.0628, 0.0823, 0.1406, 0.0.0734, 0.0930, 0.1513, 0.0997, 0.1193, and 0.1776) multiplied by the mean predicted risk (0.861 for scenario type 1) was adjusted as a new set of AHP risk priorities (0.0541, 0.0709, 0.1211, 0.0632, 0.0801, 0.1303, 0.0858, 0.1027, 0.1529).

# CHAPTER 6. ANALYTICAL METHOD COMPARISON AND EVALUATION

In Chapter 5, we described the detailed procedures of development of the risk prediction model using a generalized linear mixed model, LMMs, (Method A) and procedures of applications to risk quantification using the IV medication harm index (Method B), Huang and Moh's matrix-based ranking method (Method C), and the adjusted AHP method (Method D, adjusted by LLMs). We also calculated the quantified scores using each method (APPENDIX B). In the following sections in this chapter, we first describe the criteria used to compare and evaluate the four analytical risk quantification methods. Then, we present the comparison results and the pros and cons for each of the these analytical methods. In addition, we provide a conceptual framework of application of the proposed methods for real alert data, and how the analysis could be addressed in future research.

## 6.1 Evaluation Criteria for the Four Analytical Methods

According to the experimental designs in Chapter 4, there were 675 expected risk scores collected from 270 simulated IV infusion scenarios since each scenario were assessed by two or three domain experts. In the first phase, for each scenario, we used the geometric mean to aggregate the expected risk scores obtained from multiple experts, and the 270 aggregated risk scores were regarded as risk benchmarks. In the second phase, we used scatter plots to show the relations between the quantified scores and the risk benchmarks. Then, we compared risk benchmarks with the quantified scores from each analytical method (A-D), using the evaluation criteria of person's correlation coefficient ($\rho$) and distance of min-max normalized risk scores (*Dist*). The *Dist* measure was defined as the absolute distance between the min-max normalization of risk benchmarks and of the quantified scores. The min-max normalized values ranged from 0 to 1. The smaller *Dist* using paired t-test means that the quantified scores were closer with the benchmarks. We finally proposed the analytical risk quantification methods with greater positive correlation coefficients and the smaller *Dist* measures.

## 6.2 Comparisons of Risk Benchmarks with Linear Predicted risk, IV Harm Scores, and Risk Ranking Scores, and Adjusted AHP Risk Priorities

The relationships between the risk benchmarks and the quantified scores calculated for the 270 risk scenarios (APPENDIX B) as shown below in Figure 20, Figure 21, Figure 22, and Figure 23. Figure 20 and Figure 23 show strong linear relationships between the risk benchmarks and the quantified scores (Methods A and D). There was no linear relationship between the risk benchmarks and the quantified scores (Methods B and C) (Figure 21 and Figure 22) .

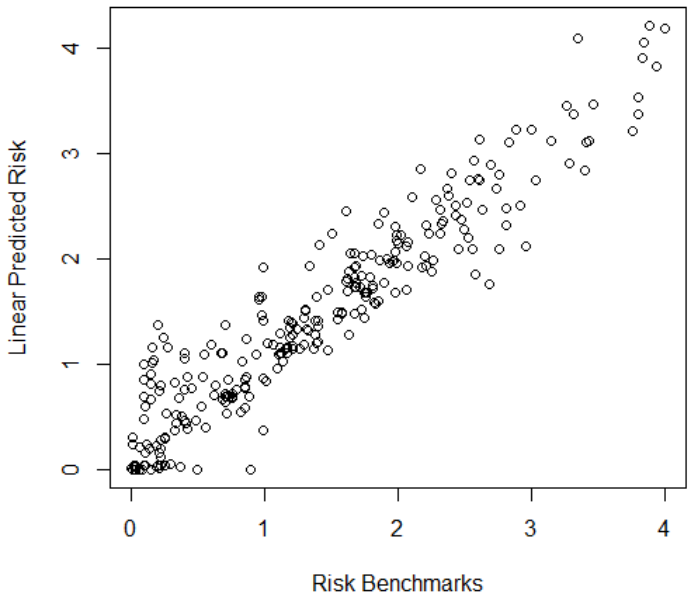



Figure 20: The Relationship between Benchmarks and Linear Predicted Risk (Method A) for the 270 risk scenarios

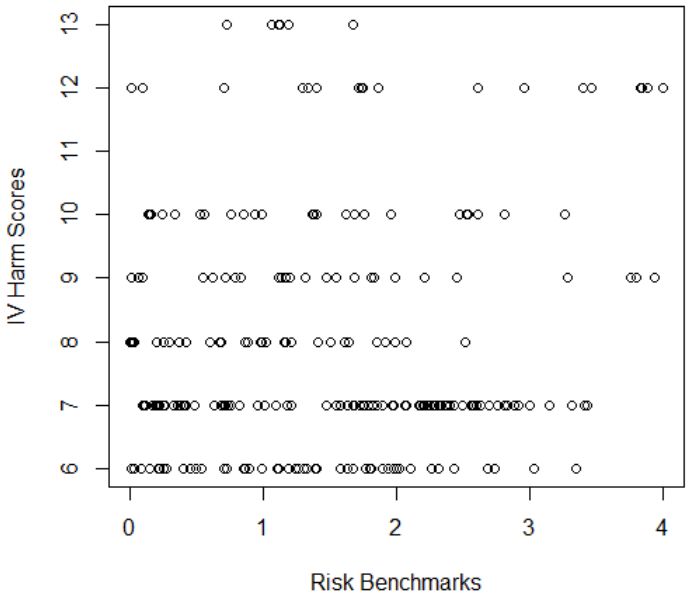



Figure 21: The Relationship between Benchmarks and IV Harm Scores (Method B) for the 270 risk scenarios

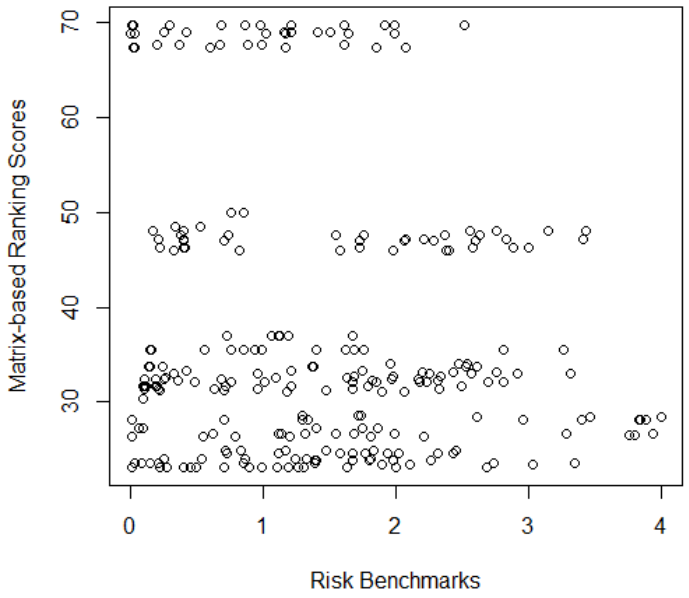



Figure 22: The Relationship between Benchmarks and Risk Ranking Scores (Method C) for the 270 risk scenarios

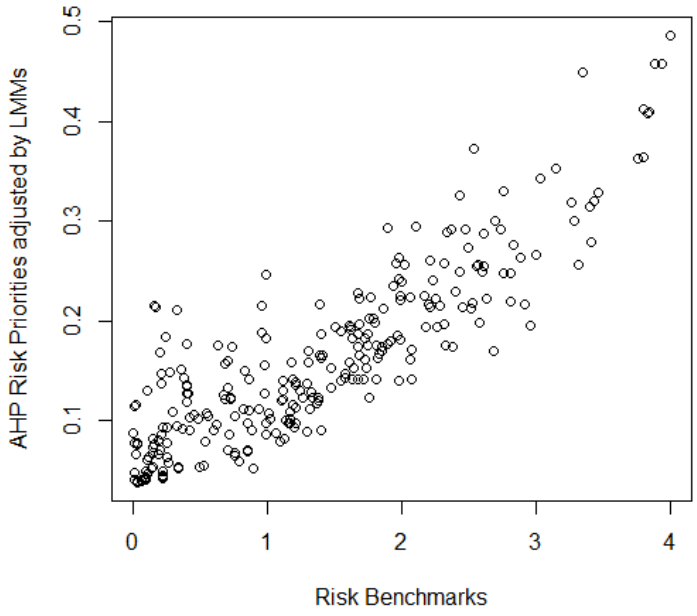



Figure 23: The Relationship between Benchmarks and Adjusted AHP Risk Priorities (Method D) for the 270 risk scenarios

The statistical significance of the relationships between the risk benchmarks and the quantified scores were validated the results above. According to the results of the correlation coefficient tests (Table 34), there were positive correlations between the benchmarks and the predicted risk for Method A ($\rho$ = 0.943; Hypothesis 1 was supported) and between the benchmarks and the adjusted risk priorities from Method D ($\rho$ = 0.869; Hypothesis 4 was supported). However, there was no linear relationship between the benchmarks and the IV harm scores from Method B ($\rho$ = 0.071; Hypothesis 2 was not supported) and negative relationship between the benchmarks and the matrix-based ranking scores from Method C ($\rho$ = -0.129; Hypothesis 3 was not supported). It also should be noted that the *Dist* measures show that Method A was the best risk quantification method where mean *Dist* of 0.0602 was the smallest, followed by Method D, as shown in Table 34. The results are consistent with the paired t-test comparing *Dist* measures generated from each analytical method (Table 35). The estimated *Dist* measure for Method A was significantly smaller than that for Method B ($t$ = -17.699, $p < 0.001$) and smaller than that from Method C ($t$ = -17.531, $p < 0.001$). Same results could be found for Method D with significant smaller *Dist* measure than Method B and C.

Table 34: Correlation Coefficient ($\rho$) and *Dist* Measures for Four Methods

| **Method** | **Quantified Score (vs. Benchmarks)** | **Pearson's Correlation Coefficient ($\rho$)** | **Mean Distance of Min-max Normalized Risk Scores *(Dist)*** |
|---|---|---|---|
| Method A: Linear Mixed Models (LMMs) | Linear Predicted Risk | 0.943*** | 0.0602 |
| Method B: IV Harm Index | IV Harm Score | 0.071 | 0.2876 |
| Method C: Matrix-based Risk Ranking Method | Risk Ranking Scores | -0.129* | 0.3380 |
| Method D: AHP Risk Priorities Adjusted by LMMs | Adjusted AHP Risk Priorities | 0.869*** | 0.1149 |

Note. *Correlation is significant at the 0.05 level (two-tailed); number of data (n): 270; Significant codes: '***' $p \leq 0.001$; '**' $0.001 < p \leq 0.01$; '*' $0.01 < p \leq 0.05$

Table 35: Paired t-test of *Dist* Measures from the Four Methods

| **Contrast** | ***Estimates Mean Difference*** | ***df*** | ***t*** | ***p-value*** |
|---|---|---|---|---|
| Method A - Method B | -0.2273 | 269 | -17.699 | <0.001 |
| Method A - Method C | -0.2777 | 269 | -17.531 | <0.001 |
| Method A - Method D | -0.0547 | 269 | -8.8915 | <0.001 |
| Method B - Method C | -0.0504 | 269 | -2.4416 | 0.015 |
| Method D - Method B | -0.1726 | 269 | -13.117 | <0.001 |
| Method D - Method C | -0.2230 | 269 | -13.752 | <0.001 |

## 6.3 Discussion

Of the quantified risk scores by the four analytical methods, which were the generalized linear mixed model, LMMs, (Method A), the IV medication harm index (Method B), Huang and Moh's matrix-based ranking method (Method C), and the adjusted AHP method (Method D, adjusted by LLMs), the scores from Method A were most correlated and closest to the risk benchmarks, followed by the risk scores from Method D. The IV harm scores from Method B and the ranking scores from Method C did not have a positive correlation with the benchmarks. Also, the overall *Dist* measures from Methods B and C were larger than Methods A and D, which indicated that the quantified scores from Methods B and C were different from the benchmarks. A possible main reason is that both Methods A and D used the seven factors (care area, medication, field limit type, soft maximum limit type, hard maximum limit type, ratio of programming rate/dose to the Soft Max, and infusion duration) in the scenarios to predict/quantify risk. The main and interaction effects of these factors were considered and validated as important risk factors by linear mixed models that had impacts on the risk benchmarks. However, Methods B and C only applied two (care area and programming ratio) out of the seven factors along with the detectability of adverse drug events (ADEs) (Sullivan, 2004; C. K. Williams et al., 2006) that was not in the designed scenarios, to obtain the IV harm scores and the ranking scores for all scenarios. Therefore, applying fewer key risk factors and an additional factor irrelevant to the scenarios led to lower correlation with the benchmarks.

For the IV harm index, we observed that in certain scenarios that the IV harm scores from this method were more correlated with the benchmarks when we subset the data into smaller groups. For example, when we selected a fixed level of infusion duration and then divided the cases into three groups corresponding to field limit types for continuous dose (CD), bolus dose (BD), and bolus dose administration rate (BDAR). A positive correlation was found for both BD and BDAR groups, in which small positive correlation ($\rho$ = 0.25) for BD and strong positive correlation ($\rho$ = 0.73) for BDAR. In the CD group, we found that there were various increase trends of the benchmarks versus IV harm scores for each combination of medication and care area (APPENDIX F). Although some studies have applied the IV harm index to quantify risk (Crass & Vanderveen, 2010; Sullivan, 2004; C. K. Williams et al., 2006) for assessing the IV medication infusion alerts, the findings also

suggest that the IV harm index should be modified by considering more risk factors (e.g. field limit type) and their interaction effects (different increasing trends for risk), especially medications combined with care areas.

Regarding the matrix-based method, we modified the risk categories of the IV harm index to define comparison criteria and create alert risk factor metrics. As we mentioned above, more risk factors and the combination of the risk effects should be adjusted. However, the domain experts would be challenged to define comparison criteria for either of these additional or combined factors. Method C is not an appropriate method to quantify risk for alert overrides in IV medication infusions for this domain area even though this kind of multi-criteria decision making approaches have been applied to support making decisions in public health domains (Baltussen & Niessen, 2006; Nobre et al., 1999).

For the AHP method, we adjusted the original risk priorities to conduct appropriate comparisons across all 270 infusion scenarios. The positive linear relationship between the adjusted AHP risk priorities and the benchmarks ($\rho = 0.87$) suggests that the AHP method adjusted by the linear mixed models (Method) might be an option to quantify risk for the real overridden alerts properly. In this study, the average predicted risk of each scenario type was selected to adjust the AHP risk priorities for proper cross comparisons. The priorities for the 9 sub-scenarios were multiplied by one value, which could keep the original relative weights among the sub-scenarios. More appropriate adjustment methods could be considered in future research.

According to the discussion above, some pros and cons for the four analytical methods are summarized in Table 36. The linear mixed models and the AHP supported by the linear mixed models performed better in comparison with the IV harm index and the matrix-based ranking methods. The IV harm and the matrix-based methods could be improved if more key risk factors are considered. Note that some additional tasks should be conducted when applying the linear mixed models and the adjusted AHP method to quantify risk for new alert datasets from the hospital systems where their drug limit settings are different with the limits used for the scenario designs (Bates, Vanderveen, Seger, Yamaga, & Rothschild, 2005). For example, identifying soft limit types (small or large for linear models) or applying a linear interpolation method to estimate the risk priorities (for the adjusted AHP method) would be needed.

Table 36: Comparison Summary of the Four Analytical Methods

| **Method** | **PROS** | **CONS** |
|---|---|---|
| Linear Mixed Model (Method A) | -Higher correlation with the benchmarks<br>-Main and interaction effects were involved in the models<br>-Models were cross-validated | -Additional tasks (i.e. identify small/large soft limits) are needed for applying to new alerts with different drug limit settings<br>-Additional surveys might be needed for other combinations of medication and care area |
| AHP + Linear Mixed Model (Method D) | -Higher correlation with the benchmarks | -Conducting pairwise comparison surveys was time-consuming<br>-Many AHP structures and priority vectors were generated<br>-A linear interpolation is needed to estimate risk priorities for new alerts<br>-Additional pairwise surveys might be needed for other combinations of medication and care area |
| IV Harm Index (Method B) | The harm scores are easy to be derived | -Poor correlation with the benchmarks<br>-The quantified scores were discrete: small overdosing change could lead to different harm scores; different overdose ratios in the same overdosing range were quantified as the same scores |
| Matrix-based Ranking Method (Method C) | The ranking scores are flexible to be adjusted if more information collected | -Poor correlation with the benchmarks<br>-The comparison criteria were hard to define for additional risk factors, or combinations of them<br>-Ranking scores were relative, so a small value difference could have large ranking difference<br>-Selecting different representative cases could lead to different ranking scores |

### 6.4 A Framework of Risk Quantification for Individual Alert Overrides

The linear mixed models and the AHP method combined with the linear models have been proposed in the previous sections for proper risk quantification methods. In this section, a framework about how to apply these methods to quantify risk for real alert datasets is indicated as follows (Figure 24 and Figure 25):

In the linear mixed models (Figure 24), first, the information of the key risk factors from the new alert datasets is the input of the linear models. Then, the proper corresponding models are selected for each individual alert based on the three field limit types, CD, BD, and BDAR, to obtain the expected risk. Next, the expected risk can be mapped on to the five degrees of harm and also the NCC MERP index. Note that, when applying the CD and BDAR models to the new alerts with different soft maximum drug limit settings, we need to pre-process and classify the soft alert limits into small or large limit types.

In addition, for applying the AHP method (Figure 25), first, each new input alert is mapped on to the corresponding scenario type. Furthermore, the relevant risk priority for this alert, $R_{ij}$, can be estimated using the linear interpolation method, in which the two continuous variables depending on the field limit types, dose rate, infusion dose, or infusion duration, are compared with three levels of the two variables for pairwise comparisons. Then, the priority multiplied by the mean of the predicted risk in the relevant scenario type can be adjusted, which is regarded as, $R'_{ij}$, for a proper comparison with other alerts in the new dataset.

In this study, we describe the frameworks for the two proposed methods. The quantification of the real alerts is not included in this study and can be addressed in future research.

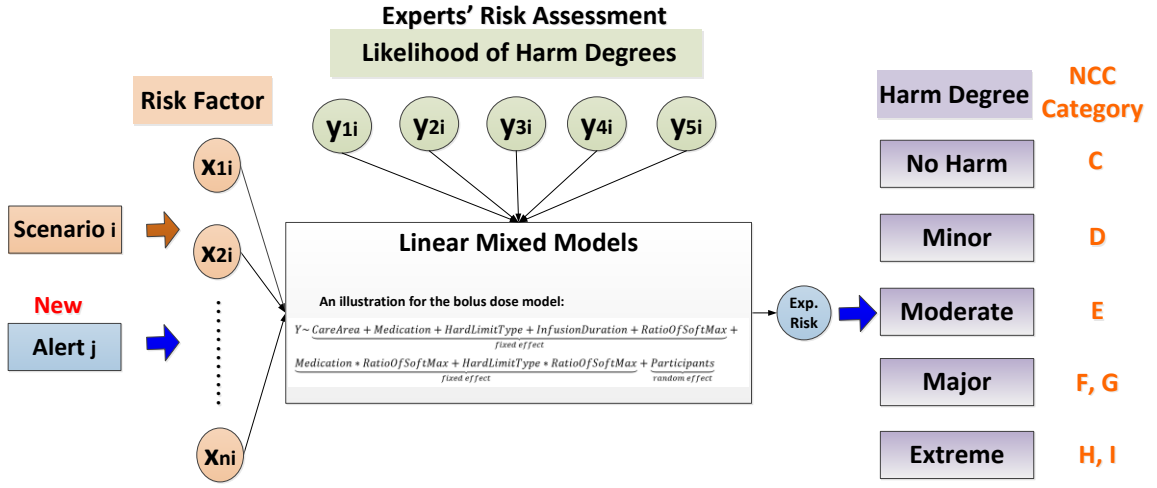



Figure 24: A Framework for Applying Linear Mixed Models for Risk Quantification

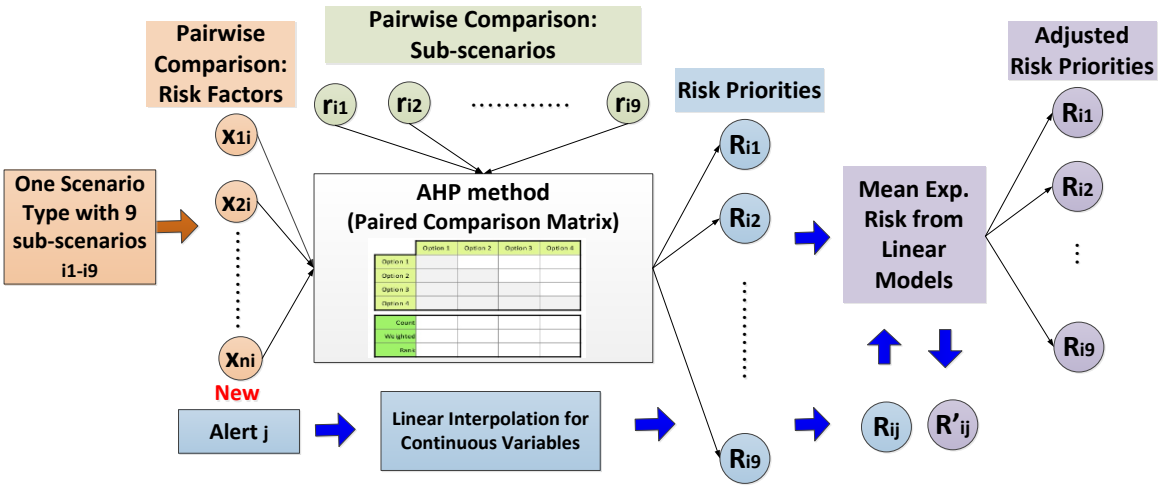



Figure 25: A Framework for Applying the AHP Combined with Linear Mixed Models for Risk Quantification

# CHAPTER 7. CONCLUSION

The objectives of this research were to apply four analytical methods that quantified risk of IV harm for the simulated individual alert-overridden infusions and to propose the proper methods in which the quantified scores are highly correlated with the risk benchmarks. The benchmarks were calculated by the non-linear transferred likelihoods, suggested in previous studies (Tversky & Kahneman, 1992; Zhang & Maloney, 2012), and the severity impacts. The severity impacts were quantified using the increase of n orders of magnitude, multiplying a quantity by $10^n$, since the direct and indirect costs associated with different degrees of harm increased non-linearly (Chang et al., 2003). The design and quantification of expected risk of IV harm for alert overrides in the simulated high-risk IV infusions were prepared as the first journal article as shown in APPENDIX G.

This research demonstrated that the linear mixed regression models (Method A) built for three field limit types of continuous dose, bolus dose, and bolus dose administration rate, were the best risk quantification methods with the highest correlation with risk benchmarks compared to the other three methods. We summarized the development of the regression models including model selection and validation and prepared as a second journal article (APPENDIX H). Compared to Method A, the application of the IV harm index (Method B) and the matrix-based ranking method (Method C) for risk quantification were less accurate as they fail to consider key risk factors, along with their interaction effects. For Method D, we further adjusted the risk priorities using the original values multiplied by the averaged predicted risk of each scenario type from Method A. There was a positive correlation between the adjusted AHP scores with the benchmarks. The adjusted AHP method could be an option for risk quantification.

This study also provides a risk quantification framework for real alert-overridden infusions associated with the four high-risk drugs. Some additional adjustments are needed when applying the proposed methods to the pump alert datasets in hospitals, which have different drug limits in comparison to the limit designs in this study.

The limitations of this research include the aspects of patient, domain expert, and data. For each scenario, the patient was assumed as a 35-year-old male weighting 70 kg,

patient condition was not considered, and the effect of domain experts' occupations (pharmacists and nurses) were considered. About the data, the smart pump alert data was not connected to patient outcomes, and the database was from only one large teaching hospital. The proposed risk quantification models can only be applied to the conditions of four high-risk medications and two care units.

With the quantified risk scores for the individual alerts during a specific period of time (risk-based approach), the results for each medication-care unit can be aggregated (frequency-based approach) either using a sum of the risk scores or calculating the frequency of degrees of harm using the NCC MERP index. The risk quantified scores from the proposed methods can be regarded as an indicator of drug infusion performance, which can be composited with the current indicators (i.e. DERS compliance rate) for evaluating performance using an aggregated view (Mansfield & Jarrett, 2013). The medication-care units with the higher sum of risk scores (or the higher frequency of major and extreme harm) and other lower performance indicators will be highlighted as the high-priority areas for a proper improvement in the healthcare systems.

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# APPENDIX A. AN EXAMPLE OF THE STEPWISE AIC PROCEDURES FOR THE BOLUS DOSE GROUP

| STEP | ACTION | VAR_ BESTAIC | RESULT_ BESTAIC | STRING_BESTAIC |
|---|---|---|---|---|
| 0 | None | Full | 165.712 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X8*X9 X2*X8*X9 X5*X8*X9 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 X1*X2*X8*X9 X2*X5*X8*X9 X1*X5*X8*X9 X1*X2*X5*X9 X1*X2*X5*X8*X9 |
| 1 | Drop | X1*X2*X5*X8*X9 | 165.712 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X8*X9 X2*X8*X9 X5*X8*X9 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 X1*X2*X8*X9 X2*X5*X8*X9 X1*X5*X8*X9 X1*X2*X5*X9 |
| 2 | Drop | X1*X2*X5*X9 | 165.712 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X8*X9 X2*X8*X9 X5*X8*X9 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 X1*X2*X8*X9 X2*X5*X8*X9 X1*X5*X8*X9 |
| 3 | Drop | X1*X5*X8*X9 | 165.712 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 |

| | | | | |
|---|---|---|---|---|
| | | | | X1*X8*X9 X2*X8*X9 X5*X8*X9 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 X1*X2*X8*X9 X2*X5*X8*X9 |
| 4 | Drop | X2*X5*X8*X9 | 165.712 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X8*X9 X2*X8*X9 X5*X8*X9 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 X1*X2*X8*X9 |
| 5 | Drop | X1*X2*X8*X9 | 165.712 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X8*X9 X2*X8*X9 X5*X8*X9 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 |
| 6 | Drop | X2*X8*X9 | 163.483 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X8*X9 X5*X8*X9 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 |
| 7 | Drop | X1*X8*X9 | 162.692 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X5*X8*X9 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 |
| 8 | Drop | X5*X8*X9 | 162.336 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X5*X9 X2*X5*X9 X1*X2*X9 X1*X2*X5*X8 |

| | | | | |
|---|---|---|---|---|
| 9 | Drop | X1*X2*X5*X8 | 162.336 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X5*X9 X2*X5*X9 X1*X2*X9 |
| 10 | Drop | X1*X2*X9 | 162.336 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X5*X9 X2*X5*X9 |
| 11 | Drop | X2*X5*X9 | 162.336 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 X1*X5*X9 |
| 12 | Drop | X1*X5*X9 | 162.336 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 |
| 13 | Drop | X1*X9 | 161.943 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 X1*X2*X8 |
| 14 | Drop | X1*X2*X8 | 161.943 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X2*X5 X1*X5*X8 X2*X5*X8 |
| 15 | Drop | X2*X5*X8 | 161.943 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X2*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X2*X5 X1*X5*X8 |
| 16 | Drop | X2*X8 | 156.126 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X1*X8 X8*X9 X5*X9 X2*X9 X1*X2*X5 X1*X5*X8 |
| 17 | Drop | X8*X9 | 155.894 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X1*X8 X5*X9 X2*X9 X1*X2*X5 X1*X5*X8 |

| | | | | |
|---|---|---|---|---|
| 18 | Drop | X1*X5*X8 | 155.894 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X1*X8 X5*X9 X2*X9 X1*X2*X5 |
| 19 | Drop | X1*X8 | 153.007 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X8 X5*X9 X2*X9 X1*X2*X5 |
| 20 | Drop | X5*X8 | 150.034 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X9 X2*X9 X1*X2*X5 |
| 21 | Drop | X1*X2*X5 | 150.034 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X1*X5 X5*X9 X2*X9 |
| 22 | Drop | X1*X5 | 150.034 | X1 X2 X5 X8 X9 X1*X2 X2*X5 X5*X9 X2*X9 |
| 23 | Drop | X2*X5 | 150.034 | X1 X2 X5 X8 X9 X1*X2 X5*X9 X2*X9 |
| 24 | Drop | X1*X2 | 150.034 | X1 X2 X5 X8 X9 X5*X9 X2*X9 |
| 25 | Drop | X9 | 150.034 | X1 X2 X5 X8 X5*X9 X2*X9 |

# APPENDIX B. BENCHMARKS AND QUANTIFIED SCORES FOR ALL 270 INFUSION SCENARIOS

| Scenario | | Sub-Scenarios | Care Area | Drug | Field Limit Type | Soft Max Type | Hard Max Type | Benchmarks | Predicted Risk-A | IV Harm Scores-B | Matrix-based Risk Rankings-C | Adjusted AHP Risk Priorities -D |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | Type | | | | | | | | | | | |
| 1 | 1 | 1 | AICU | Propofol | CD | Dsmall | 1 | 0.4962 | 0.0105 | 6 | 23.118 | 0.0541 |
| 2 | 1 | 2 | AICU | Propofol | CD | Dsmall | 1 | 0.7042 | 0.6923 | 6 | 23.118 | 0.0709 |
| 3 | 1 | 3 | AICU | Propofol | CD | Dsmall | 1 | 1.1081 | 1.0972 | 6 | 23.118 | 0.1211 |
| 4 | 1 | 4 | AICU | Propofol | CD | Dsmall | 1 | 0.2504 | 0.3004 | 6 | 23.976 | 0.0632 |
| 5 | 1 | 5 | AICU | Propofol | CD | Dsmall | 1 | 0.5339 | 0.8894 | 6 | 23.976 | 0.0801 |
| 6 | 1 | 6 | AICU | Propofol | CD | Dsmall | 1 | 1.2435 | 1.3455 | 6 | 23.976 | 0.1303 |
| 7 | 1 | 7 | AICU | Propofol | CD | Dsmall | 1 | 0.7199 | 0.5392 | 9 | 24.866 | 0.0858 |
| 8 | 1 | 8 | AICU | Propofol | CD | Dsmall | 1 | 1.1664 | 1.1657 | 9 | 24.866 | 0.1027 |
| 9 | 1 | 9 | AICU | Propofol | CD | Dsmall | 1 | 1.4768 | 1.7087 | 9 | 24.866 | 0.1529 |
| 10 | 2 | 1 | AICU | Propofol | CD | Dsmall | 0 | 0.4562 | 0.7797 | 6 | 23.118 | 0.1056 |
| 11 | 2 | 2 | AICU | Propofol | CD | Dsmall | 0 | 1.2624 | 1.1584 | 6 | 23.118 | 0.1239 |
| 12 | 2 | 3 | AICU | Propofol | CD | Dsmall | 0 | 1.3011 | 1.5151 | 6 | 23.118 | 0.1700 |
| 13 | 2 | 4 | AICU | Propofol | CD | Dsmall | 0 | 0.8647 | 0.8846 | 6 | 23.976 | 0.1111 |
| 14 | 2 | 5 | AICU | Propofol | CD | Dsmall | 0 | 1.3228 | 1.3272 | 6 | 23.976 | 0.1294 |
| 15 | 2 | 6 | AICU | Propofol | CD | Dsmall | 0 | 1.8071 | 1.7474 | 6 | 23.976 | 0.1755 |
| 16 | 2 | 7 | AICU | Propofol | CD | Dsmall | 0 | 0.8274 | 1.0382 | 9 | 24.866 | 0.1497 |
| 17 | 2 | 8 | AICU | Propofol | CD | Dsmall | 0 | 1.8306 | 1.5785 | 9 | 24.866 | 0.1678 |
| 18 | 2 | 9 | AICU | Propofol | CD | Dsmall | 0 | 2.4472 | 2.0955 | 9 | 24.866 | 0.2139 |
| 19 | 3 | 1 | AICU | Propofol | CD | Dlarge | 1 | 1.1894 | 1.3534 | 6 | 23.143 | 0.1423 |
| 20 | 3 | 2 | AICU | Propofol | CD | Dlarge | 1 | 2.6801 | 1.7616 | 6 | 23.143 | 0.1707 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | 3 | 3 | AICU | Propofol | CD | Dlarge | 1 | 1.9956 | 2.1476 | 6 | 23.143 | 0.2400 |
| 22 | 3 | 4 | AICU | Propofol | CD | Dlarge | 1 | 1.3907 | 1.6439 | 6 | 23.857 | 0.1655 |
| 23 | 3 | 5 | AICU | Propofol | CD | Dlarge | 1 | 2.2586 | 1.9862 | 6 | 23.857 | 0.1939 |
| 24 | 3 | 6 | AICU | Propofol | CD | Dlarge | 1 | 1.9729 | 2.3145 | 6 | 23.857 | 0.2633 |
| 25 | 3 | 7 | AICU | Propofol | CD | Dlarge | 1 | 1.6758 | 1.9321 | 6 | 24.571 | 0.2285 |
| 26 | 3 | 8 | AICU | Propofol | CD | Dlarge | 1 | 2.0186 | 2.2288 | 6 | 24.571 | 0.2567 |
| 27 | 3 | 9 | AICU | Propofol | CD | Dlarge | 1 | 2.4298 | 2.5145 | 6 | 24.571 | 0.3261 |
| 28 | 4 | 1 | AICU | Propofol | CD | Dlarge | 0 | 0.2756 | 1.1593 | 6 | 23.143 | 0.1482 |
| 29 | 4 | 2 | AICU | Propofol | CD | Dlarge | 0 | 1.3004 | 1.5297 | 6 | 23.143 | 0.1592 |
| 30 | 4 | 3 | AICU | Propofol | CD | Dlarge | 0 | 1.6290 | 1.8919 | 6 | 23.143 | 0.1826 |
| 31 | 4 | 4 | AICU | Propofol | CD | Dlarge | 0 | 1.3957 | 1.4211 | 6 | 23.857 | 0.1636 |
| 32 | 4 | 5 | AICU | Propofol | CD | Dlarge | 0 | 1.6698 | 1.7394 | 6 | 23.857 | 0.1746 |
| 33 | 4 | 6 | AICU | Propofol | CD | Dlarge | 0 | 1.8032 | 2.0508 | 6 | 23.857 | 0.1978 |
| 34 | 4 | 7 | AICU | Propofol | CD | Dlarge | 0 | 1.7722 | 1.6886 | 6 | 24.571 | 0.2243 |
| 35 | 4 | 8 | AICU | Propofol | CD | Dlarge | 0 | 1.9370 | 1.9690 | 6 | 24.571 | 0.2353 |
| 36 | 4 | 9 | AICU | Propofol | CD | Dlarge | 0 | 2.3109 | 2.2425 | 6 | 24.571 | 0.2585 |
| 37 | 5 | 1 | AICU | Propofol | BD | D | 0 | 0.0380 | 0.0100 | 6 | 23.5 | 0.0384 |
| 38 | 5 | 2 | AICU | Propofol | BD | D | 0 | 0.0380 | 0.0106 | 6 | 23.5 | 0.0390 |
| 39 | 5 | 3 | AICU | Propofol | BD | D | 0 | 0.0898 | 0.0112 | 6 | 23.5 | 0.0406 |
| 40 | 5 | 4 | AICU | Propofol | BD | D | 0 | 0.0666 | 0.0117 | 9 | 27.185 | 0.0401 |
| 41 | 5 | 5 | AICU | Propofol | BD | D | 0 | 0.0696 | 0.2168 | 9 | 27.185 | 0.0408 |
| 42 | 5 | 6 | AICU | Propofol | BD | D | 0 | 0.0959 | 0.4905 | 9 | 27.185 | 0.0424 |
| 43 | 5 | 7 | AICU | Propofol | BD | D | 0 | 0.1012 | 0.6966 | 12 | 30.284 | 0.0413 |
| 44 | 5 | 8 | AICU | Propofol | BD | D | 0 | 0.1012 | 0.8586 | 12 | 30.284 | 0.0420 |
| 45 | 5 | 9 | AICU | Propofol | BD | D | 0 | 0.0975 | 1.0084 | 12 | 30.284 | 0.0435 |
| 46 | 6 | 1 | AICU | Propofol | BDAR | D | 1 | 0.7276 | 0.8554 | 6 | 24.518 | 0.1222 |
| 47 | 6 | 2 | AICU | Propofol | BDAR | D | 1 | 1.1170 | 1.1683 | 6 | 24.518 | 0.1222 |
| 48 | 6 | 3 | AICU | Propofol | BDAR | D | 1 | 1.5824 | 1.4802 | 6 | 24.518 | 0.1477 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 6 | 4 | AICU | Propofol | BDAR | D | 1 | 1.1170 | 1.1138 | 9 | 26.63 | 0.1399 |
| 50 | 6 | 5 | AICU | Propofol | BDAR | D | 1 | 1.5443 | 1.4258 | 9 | 26.63 | 0.1399 |
| 51 | 6 | 6 | AICU | Propofol | BDAR | D | 1 | 1.6859 | 1.7373 | 9 | 26.63 | 0.1654 |
| 52 | 6 | 7 | AICU | Propofol | BDAR | D | 1 | 1.4019 | 1.3714 | 12 | 27.302 | 0.1877 |
| 53 | 6 | 8 | AICU | Propofol | BDAR | D | 1 | 1.7487 | 1.6830 | 12 | 27.302 | 0.1877 |
| 54 | 6 | 9 | AICU | Propofol | BDAR | D | 1 | 1.8578 | 1.9943 | 12 | 27.302 | 0.2132 |
| 55 | 7 | 1 | AICU | Morphine | CD | Dsmall | 0 | 0.0137 | 0.0065 | 6 | 23.143 | 0.0412 |
| 56 | 7 | 2 | AICU | Morphine | CD | Dsmall | 0 | 0.8919 | 0.0085 | 6 | 23.143 | 0.0522 |
| 57 | 7 | 3 | AICU | Morphine | CD | Dsmall | 0 | 0.9851 | 0.3854 | 6 | 23.143 | 0.0862 |
| 58 | 7 | 4 | AICU | Morphine | CD | Dsmall | 0 | 0.0076 | 0.0084 | 9 | 26.286 | 0.0479 |
| 59 | 7 | 5 | AICU | Morphine | CD | Dsmall | 0 | 0.7854 | 0.7593 | 9 | 26.286 | 0.0589 |
| 60 | 7 | 6 | AICU | Morphine | CD | Dsmall | 0 | 1.2036 | 1.4051 | 9 | 26.286 | 0.0929 |
| 61 | 7 | 7 | AICU | Morphine | CD | Dsmall | 0 | 0.0076 | 0.3173 | 12 | 28.061 | 0.0779 |
| 62 | 7 | 8 | AICU | Morphine | CD | Dsmall | 0 | 1.2979 | 1.1934 | 12 | 28.061 | 0.0890 |
| 63 | 7 | 9 | AICU | Morphine | CD | Dsmall | 0 | 1.3384 | 1.9393 | 12 | 28.061 | 0.1228 |
| 64 | 8 | 1 | AICU | Morphine | CD | Dsmall | 1 | 0.2219 | 0.7994 | 6 | 23.143 | 0.0929 |
| 65 | 8 | 2 | AICU | Morphine | CD | Dsmall | 1 | 0.4063 | 1.1172 | 6 | 23.143 | 0.1278 |
| 66 | 8 | 3 | AICU | Morphine | CD | Dsmall | 1 | 0.9876 | 1.4223 | 6 | 23.143 | 0.2464 |
| 67 | 8 | 4 | AICU | Morphine | CD | Dsmall | 1 | 0.5510 | 1.0993 | 9 | 26.286 | 0.1072 |
| 68 | 8 | 5 | AICU | Morphine | CD | Dsmall | 1 | 1.8092 | 1.7211 | 9 | 26.286 | 0.1421 |
| 69 | 8 | 6 | AICU | Morphine | CD | Dsmall | 1 | 2.2078 | 2.3234 | 9 | 26.286 | 0.2607 |
| 70 | 8 | 7 | AICU | Morphine | CD | Dsmall | 1 | 0.7100 | 1.3787 | 12 | 28.061 | 0.1604 |
| 71 | 8 | 8 | AICU | Morphine | CD | Dsmall | 1 | 2.9540 | 2.1210 | 12 | 28.061 | 0.1955 |
| 72 | 8 | 9 | AICU | Morphine | CD | Dsmall | 1 | 3.3930 | 2.8436 | 12 | 28.061 | 0.3141 |
| 73 | 9 | 1 | AICU | Morphine | CD | Dlarge | 0 | 1.3880 | 1.2063 | 6 | 23.5 | 0.2171 |
| 74 | 9 | 2 | AICU | Morphine | CD | Dlarge | 0 | 2.7369 | 2.6675 | 6 | 23.5 | 0.2918 |
| 75 | 9 | 3 | AICU | Morphine | CD | Dlarge | 0 | 3.3398 | 4.0934 | 6 | 23.5 | 0.4489 |
| 76 | 9 | 4 | AICU | Morphine | CD | Dlarge | 0 | 1.9918 | 1.9670 | 9 | 26.629 | 0.2258 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 77 | 9 | 5 | AICU | Morphine | CD | Dlarge | 0 | 3.2849 | 2.9130 | 9 | 26.629 | 0.3005 |
| 78 | 9 | 6 | AICU | Morphine | CD | Dlarge | 0 | 3.9354 | 3.8383 | 9 | 26.629 | 0.4577 |
| 79 | 9 | 7 | AICU | Morphine | CD | Dlarge | 0 | 2.6131 | 2.7546 | 12 | 28.351 | 0.2544 |
| 80 | 9 | 8 | AICU | Morphine | CD | Dlarge | 0 | 3.4591 | 3.4773 | 12 | 28.351 | 0.3291 |
| 81 | 9 | 9 | AICU | Morphine | CD | Dlarge | 0 | 3.9960 | 4.1852 | 12 | 28.351 | 0.4863 |
| 82 | 10 | 1 | AICU | Morphine | BD | D | 0 | 1.8986 | 2.4392 | 6 | 23.357 | 0.2931 |
| 83 | 10 | 2 | AICU | Morphine | BD | D | 0 | 2.1057 | 2.5965 | 6 | 23.357 | 0.2948 |
| 84 | 10 | 3 | AICU | Morphine | BD | D | 0 | 3.0262 | 2.7538 | 6 | 23.357 | 0.3436 |
| 85 | 10 | 4 | AICU | Morphine | BD | D | 0 | 3.7521 | 3.2214 | 9 | 26.543 | 0.3624 |
| 86 | 10 | 5 | AICU | Morphine | BD | D | 0 | 3.7914 | 3.3787 | 9 | 26.543 | 0.3637 |
| 87 | 10 | 6 | AICU | Morphine | BD | D | 0 | 3.7960 | 3.5360 | 9 | 26.543 | 0.4129 |
| 88 | 10 | 7 | AICU | Morphine | BD | D | 0 | 3.8239 | 3.9058 | 12 | 28.157 | 0.4075 |
| 89 | 10 | 8 | AICU | Morphine | BD | D | 0 | 3.8411 | 4.0630 | 12 | 28.157 | 0.4092 |
| 90 | 10 | 9 | AICU | Morphine | BD | D | 0 | 3.8801 | 4.2203 | 12 | 28.157 | 0.4584 |
| 91 | 11 | 1 | AICU | Morphine | BDAR | D | 0 | 0.1477 | 0.0072 | 6 | 23.5 | 0.0817 |
| 92 | 11 | 2 | AICU | Morphine | BDAR | D | 0 | 0.2087 | 0.1592 | 6 | 23.5 | 0.0862 |
| 93 | 11 | 3 | AICU | Morphine | BDAR | D | 0 | 0.8561 | 0.5882 | 6 | 23.5 | 0.0974 |
| 94 | 11 | 4 | AICU | Morphine | BDAR | D | 0 | 0.6177 | 0.7183 | 9 | 26.714 | 0.0960 |
| 95 | 11 | 5 | AICU | Morphine | BDAR | D | 0 | 1.1414 | 1.0317 | 9 | 26.714 | 0.1005 |
| 96 | 11 | 6 | AICU | Morphine | BDAR | D | 0 | 1.3119 | 1.3330 | 9 | 26.714 | 0.1117 |
| 97 | 11 | 7 | AICU | Morphine | BDAR | D | 0 | 1.2933 | 1.4492 | 12 | 28.546 | 0.1378 |
| 98 | 11 | 8 | AICU | Morphine | BDAR | D | 0 | 1.7100 | 1.7437 | 12 | 28.546 | 0.1423 |
| 99 | 11 | 9 | AICU | Morphine | BDAR | D | 0 | 1.7323 | 2.0359 | 12 | 28.546 | 0.1535 |
| 100 | 12 | 1 | AICU | Insulin | CD | Dsmall | 1 | 0.3308 | 0.3724 | 7 | 46.012 | 0.0955 |
| 101 | 12 | 2 | AICU | Insulin | CD | Dsmall | 1 | 1.5763 | 1.4934 | 7 | 46.012 | 0.1426 |
| 102 | 12 | 3 | AICU | Insulin | CD | Dsmall | 1 | 2.3823 | 2.6120 | 7 | 46.012 | 0.1744 |
| 103 | 12 | 4 | AICU | Insulin | CD | Dsmall | 1 | 0.4018 | 0.4694 | 7 | 46.996 | 0.1360 |
| 104 | 12 | 5 | AICU | Insulin | CD | Dsmall | 1 | 1.7245 | 1.5189 | 7 | 46.996 | 0.1831 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 105 | 12 | 6 | AICU | Insulin | CD | Dsmall | 1 | 2.2877 | 2.5684 | 7 | 46.996 | 0.2149 |
| 106 | 12 | 7 | AICU | Insulin | CD | Dsmall | 1 | 0.3843 | 0.5136 | 7 | 47.643 | 0.1429 |
| 107 | 12 | 8 | AICU | Insulin | CD | Dsmall | 1 | 1.5421 | 1.4944 | 7 | 47.643 | 0.1900 |
| 108 | 12 | 9 | AICU | Insulin | CD | Dsmall | 1 | 2.6245 | 2.4721 | 7 | 47.643 | 0.2218 |
| 109 | 13 | 1 | AICU | Insulin | CD | Dsmall | 0 | 0.8201 | 0.5500 | 7 | 46.012 | 0.1123 |
| 110 | 13 | 2 | AICU | Insulin | CD | Dsmall | 0 | 1.9733 | 1.6897 | 7 | 46.012 | 0.1406 |
| 111 | 13 | 3 | AICU | Insulin | CD | Dsmall | 0 | 2.3998 | 2.8122 | 7 | 46.012 | 0.2290 |
| 112 | 13 | 4 | AICU | Insulin | CD | Dsmall | 0 | 0.7076 | 0.6510 | 7 | 46.996 | 0.1326 |
| 113 | 13 | 5 | AICU | Insulin | CD | Dsmall | 0 | 2.0584 | 1.7154 | 7 | 46.996 | 0.1609 |
| 114 | 13 | 6 | AICU | Insulin | CD | Dsmall | 0 | 2.6012 | 2.7686 | 7 | 46.996 | 0.2494 |
| 115 | 13 | 7 | AICU | Insulin | CD | Dsmall | 0 | 0.7425 | 0.6967 | 7 | 47.643 | 0.1747 |
| 116 | 13 | 8 | AICU | Insulin | CD | Dsmall | 0 | 1.7621 | 1.6908 | 7 | 47.643 | 0.2029 |
| 117 | 13 | 9 | AICU | Insulin | CD | Dsmall | 0 | 2.3657 | 2.6720 | 7 | 47.643 | 0.2914 |
| 118 | 14 | 1 | AICU | Insulin | CD | Dlarge | 1 | 0.4135 | 0.4395 | 7 | 46.336 | 0.1269 |
| 119 | 14 | 2 | AICU | Insulin | CD | Dlarge | 1 | 1.7212 | 1.8516 | 7 | 46.336 | 0.1617 |
| 120 | 14 | 3 | AICU | Insulin | CD | Dlarge | 1 | 2.9966 | 3.2283 | 7 | 46.336 | 0.2659 |
| 121 | 14 | 4 | AICU | Insulin | CD | Dlarge | 1 | 0.2098 | 0.7488 | 7 | 47.23 | 0.1370 |
| 122 | 14 | 5 | AICU | Insulin | CD | Dlarge | 1 | 2.0772 | 1.9402 | 7 | 47.23 | 0.1716 |
| 123 | 14 | 6 | AICU | Insulin | CD | Dlarge | 1 | 2.8284 | 3.1170 | 7 | 47.23 | 0.2760 |
| 124 | 14 | 7 | AICU | Insulin | CD | Dlarge | 1 | 0.1736 | 1.0503 | 7 | 48.068 | 0.2141 |
| 125 | 14 | 8 | AICU | Insulin | CD | Dlarge | 1 | 2.7546 | 2.0928 | 7 | 48.068 | 0.2487 |
| 126 | 14 | 9 | AICU | Insulin | CD | Dlarge | 1 | 3.1444 | 3.1298 | 7 | 48.068 | 0.3531 |
| 127 | 15 | 1 | AICU | Insulin | CD | Dlarge | 0 | 0.4013 | 0.4683 | 7 | 46.336 | 0.1197 |
| 128 | 15 | 2 | AICU | Insulin | CD | Dlarge | 0 | 2.5817 | 1.8553 | 7 | 46.336 | 0.1985 |
| 129 | 15 | 3 | AICU | Insulin | CD | Dlarge | 0 | 2.8825 | 3.2286 | 7 | 46.336 | 0.2640 |
| 130 | 15 | 4 | AICU | Insulin | CD | Dlarge | 0 | 0.4013 | 0.7644 | 7 | 47.23 | 0.1351 |
| 131 | 15 | 5 | AICU | Insulin | CD | Dlarge | 0 | 2.2073 | 1.9436 | 7 | 47.23 | 0.2138 |
| 132 | 15 | 6 | AICU | Insulin | CD | Dlarge | 0 | 3.4094 | 3.1175 | 7 | 47.23 | 0.2793 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 133 | 15 | 7 | AICU | Insulin | CD | Dlarge | 0 | 0.4013 | 1.0602 | 7 | 48.068 | 0.1765 |
| 134 | 15 | 8 | AICU | Insulin | CD | Dlarge | 0 | 2.5595 | 2.0956 | 7 | 48.068 | 0.2552 |
| 135 | 15 | 9 | AICU | Insulin | CD | Dlarge | 0 | 3.4277 | 3.1302 | 7 | 48.068 | 0.3208 |
| 136 | 16 | 1 | AICU | Insulin | BD | D | 1 | 0.2252 | 0.1254 | 7 | 46.286 | 0.0429 |
| 137 | 16 | 2 | AICU | Insulin | BD | D | 1 | 0.2252 | 0.2097 | 7 | 46.286 | 0.0442 |
| 138 | 16 | 3 | AICU | Insulin | BD | D | 1 | 0.2252 | 0.2907 | 7 | 46.286 | 0.0459 |
| 139 | 16 | 4 | AICU | Insulin | BD | D | 1 | 0.3432 | 0.4454 | 10 | 48.476 | 0.0525 |
| 140 | 16 | 5 | AICU | Insulin | BD | D | 1 | 0.3432 | 0.5246 | 10 | 48.476 | 0.0537 |
| 141 | 16 | 6 | AICU | Insulin | BD | D | 1 | 0.5259 | 0.6037 | 10 | 48.476 | 0.0554 |
| 142 | 16 | 7 | AICU | Insulin | BD | D | 1 | 0.7555 | 0.6946 | 10 | 50 | 0.0678 |
| 143 | 16 | 8 | AICU | Insulin | BD | D | 1 | 0.8583 | 0.7735 | 10 | 50 | 0.0690 |
| 144 | 16 | 9 | AICU | Insulin | BD | D | 1 | 0.8524 | 0.8523 | 10 | 50 | 0.0707 |
| 145 | 17 | 1 | AICU | Heparin | CD | Dsmall | 1 | 0.2012 | 0.0457 | 8 | 67.665 | 0.0713 |
| 146 | 17 | 2 | AICU | Heparin | CD | Dsmall | 1 | 0.8857 | 0.7026 | 8 | 67.665 | 0.0904 |
| 147 | 17 | 3 | AICU | Heparin | CD | Dsmall | 1 | 1.6085 | 1.7880 | 8 | 67.665 | 0.1585 |
| 148 | 17 | 4 | AICU | Heparin | CD | Dsmall | 1 | 0.2590 | 0.0518 | 8 | 69.016 | 0.0786 |
| 149 | 17 | 5 | AICU | Heparin | CD | Dsmall | 1 | 1.1596 | 1.1484 | 8 | 69.016 | 0.0977 |
| 150 | 17 | 6 | AICU | Heparin | CD | Dsmall | 1 | 1.4071 | 2.1417 | 8 | 69.016 | 0.1657 |
| 151 | 17 | 7 | AICU | Heparin | CD | Dsmall | 1 | 0.2956 | 0.0575 | 8 | 69.786 | 0.1092 |
| 152 | 17 | 8 | AICU | Heparin | CD | Dsmall | 1 | 0.9786 | 1.4694 | 8 | 69.786 | 0.1282 |
| 153 | 17 | 9 | AICU | Heparin | CD | Dsmall | 1 | 1.6091 | 2.4583 | 8 | 69.786 | 0.1963 |
| 154 | 18 | 1 | AICU | Heparin | CD | Dsmall | 0 | 0.3731 | 0.0349 | 8 | 67.665 | 0.0921 |
| 155 | 18 | 2 | AICU | Heparin | CD | Dsmall | 0 | 0.6727 | 1.1137 | 8 | 67.665 | 0.1267 |
| 156 | 18 | 3 | AICU | Heparin | CD | Dsmall | 0 | 0.9907 | 1.9231 | 8 | 67.665 | 0.1827 |
| 157 | 18 | 4 | AICU | Heparin | CD | Dsmall | 0 | 0.4228 | 0.3868 | 8 | 69.016 | 0.1039 |
| 158 | 18 | 5 | AICU | Heparin | CD | Dsmall | 0 | 1.2055 | 1.3888 | 8 | 69.016 | 0.1383 |
| 159 | 18 | 6 | AICU | Heparin | CD | Dsmall | 0 | 1.5000 | 2.2471 | 8 | 69.016 | 0.1944 |
| 160 | 18 | 7 | AICU | Heparin | CD | Dsmall | 0 | 0.6827 | 0.6785 | 8 | 69.786 | 0.1219 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 161 | 18 | 8 | AICU | Heparin | CD | Dsmall | 0 | 0.9845 | 1.6451 | 8 | 69.786 | 0.1564 |
| 162 | 18 | 9 | AICU | Heparin | CD | Dsmall | 0 | 2.5134 | 2.5449 | 8 | 69.786 | 0.2125 |
| 163 | 19 | 1 | AICU | Heparin | CD | Dlarge | 1 | 0.0199 | 0.0343 | 8 | 67.358 | 0.0660 |
| 164 | 19 | 2 | AICU | Heparin | CD | Dlarge | 1 | 0.5984 | 1.1945 | 8 | 67.358 | 0.0912 |
| 165 | 19 | 3 | AICU | Heparin | CD | Dlarge | 1 | 1.8493 | 2.3387 | 8 | 67.358 | 0.1703 |
| 166 | 19 | 4 | AICU | Heparin | CD | Dlarge | 1 | 0.0338 | 0.0392 | 8 | 68.952 | 0.0772 |
| 167 | 19 | 5 | AICU | Heparin | CD | Dlarge | 1 | 1.0215 | 1.2050 | 8 | 68.952 | 0.1026 |
| 168 | 19 | 6 | AICU | Heparin | CD | Dlarge | 1 | 1.9867 | 2.2333 | 8 | 68.952 | 0.1816 |
| 169 | 19 | 7 | AICU | Heparin | CD | Dlarge | 1 | 0.0264 | 0.0436 | 8 | 69.714 | 0.1164 |
| 170 | 19 | 8 | AICU | Heparin | CD | Dlarge | 1 | 0.8643 | 1.2442 | 8 | 69.714 | 0.1418 |
| 171 | 19 | 9 | AICU | Heparin | CD | Dlarge | 1 | 1.9886 | 2.1765 | 8 | 69.714 | 0.2209 |
| 172 | 20 | 1 | AICU | Heparin | CD | Dlarge | 0 | 0.0323 | 0.0090 | 8 | 67.358 | 0.0775 |
| 173 | 20 | 2 | AICU | Heparin | CD | Dlarge | 0 | 1.1633 | 1.1098 | 8 | 67.358 | 0.0980 |
| 174 | 20 | 3 | AICU | Heparin | CD | Dlarge | 0 | 2.0729 | 2.1636 | 8 | 67.358 | 0.1423 |
| 175 | 20 | 4 | AICU | Heparin | CD | Dlarge | 0 | 0.0060 | 0.0186 | 8 | 68.952 | 0.0878 |
| 176 | 20 | 5 | AICU | Heparin | CD | Dlarge | 0 | 1.1633 | 1.1188 | 8 | 68.952 | 0.1085 |
| 177 | 20 | 6 | AICU | Heparin | CD | Dlarge | 0 | 1.6428 | 2.0628 | 8 | 68.952 | 0.1528 |
| 178 | 20 | 7 | AICU | Heparin | CD | Dlarge | 0 | 0.0110 | 0.2461 | 8 | 69.714 | 0.1155 |
| 179 | 20 | 8 | AICU | Heparin | CD | Dlarge | 0 | 1.2079 | 1.1523 | 8 | 69.714 | 0.1362 |
| 180 | 20 | 9 | AICU | Heparin | CD | Dlarge | 0 | 1.9176 | 2.0086 | 8 | 69.714 | 0.1805 |
| 181 | 21 | 1 | AMS | Morphine | CD | Dsmall | 1 | 0.2065 | 1.3734 | 7 | 31.714 | 0.1690 |
| 182 | 21 | 2 | AMS | Morphine | CD | Dsmall | 1 | 1.7857 | 1.8325 | 7 | 31.714 | 0.2029 |
| 183 | 21 | 3 | AMS | Morphine | CD | Dsmall | 1 | 2.4896 | 2.2819 | 7 | 31.714 | 0.2732 |
| 184 | 21 | 4 | AMS | Morphine | CD | Dsmall | 1 | 0.2438 | 1.2642 | 10 | 33.808 | 0.1841 |
| 185 | 21 | 5 | AMS | Morphine | CD | Dsmall | 1 | 2.5221 | 2.2108 | 10 | 33.808 | 0.2179 |
| 186 | 21 | 6 | AMS | Morphine | CD | Dsmall | 1 | 2.6131 | 3.1373 | 10 | 33.808 | 0.2883 |
| 187 | 21 | 7 | AMS | Morphine | CD | Dsmall | 1 | 0.1599 | 1.1664 | 10 | 35.483 | 0.2150 |
| 188 | 21 | 8 | AMS | Morphine | CD | Dsmall | 1 | 2.8032 | 2.3281 | 10 | 35.483 | 0.2487 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 189 | 21 | 9 | AMS | Morphine | CD | Dsmall | 1 | 3.2550 | 3.4644 | 10 | 35.483 | 0.3190 |
| 190 | 22 | 1 | AMS | Morphine | CD | Dlarge | 1 | 1.6763 | 2.0614 | 7 | 32.133 | 0.1865 |
| 191 | 22 | 2 | AMS | Morphine | CD | Dlarge | 1 | 2.8063 | 2.4833 | 7 | 32.133 | 0.2192 |
| 192 | 22 | 3 | AMS | Morphine | CD | Dlarge | 1 | 2.6893 | 2.9009 | 7 | 32.133 | 0.3002 |
| 193 | 22 | 4 | AMS | Morphine | CD | Dlarge | 1 | 2.1972 | 2.0292 | 7 | 33.11 | 0.2168 |
| 194 | 22 | 5 | AMS | Morphine | CD | Dlarge | 1 | 2.4309 | 2.4219 | 7 | 33.11 | 0.2495 |
| 195 | 22 | 6 | AMS | Morphine | CD | Dlarge | 1 | 2.7520 | 2.8106 | 7 | 33.11 | 0.3305 |
| 196 | 22 | 7 | AMS | Morphine | CD | Dlarge | 1 | 1.9522 | 1.9849 | 10 | 34.087 | 0.2585 |
| 197 | 22 | 8 | AMS | Morphine | CD | Dlarge | 1 | 2.4754 | 2.3735 | 10 | 34.087 | 0.2912 |
| 198 | 22 | 9 | AMS | Morphine | CD | Dlarge | 1 | 2.5348 | 2.7578 | 10 | 34.087 | 0.3722 |
| 199 | 23 | 1 | AMS | Morphine | BD | D | 1 | 0.4849 | 0.4725 | 7 | 32.133 | 0.1018 |
| 200 | 23 | 2 | AMS | Morphine | BD | D | 1 | 0.7595 | 0.6801 | 7 | 32.133 | 0.1046 |
| 201 | 23 | 3 | AMS | Morphine | BD | D | 1 | 1.0153 | 0.8442 | 7 | 32.133 | 0.1081 |
| 202 | 23 | 4 | AMS | Morphine | BD | D | 1 | 1.3682 | 1.1541 | 10 | 33.808 | 0.1173 |
| 203 | 23 | 5 | AMS | Morphine | BD | D | 1 | 1.3825 | 1.2879 | 10 | 33.808 | 0.1200 |
| 204 | 23 | 6 | AMS | Morphine | BD | D | 1 | 1.3825 | 1.4184 | 10 | 33.808 | 0.1237 |
| 205 | 23 | 7 | AMS | Morphine | BD | D | 1 | 1.6196 | 1.6942 | 10 | 35.483 | 0.1908 |
| 206 | 23 | 8 | AMS | Morphine | BD | D | 1 | 1.6196 | 1.8194 | 10 | 35.483 | 0.1936 |
| 207 | 23 | 9 | AMS | Morphine | BD | D | 1 | 1.6821 | 1.9435 | 10 | 35.483 | 0.1971 |
| 208 | 24 | 1 | AMS | Morphine | BDAR | Dsmall | 1 | 0.1900 | 0.0359 | 7 | 31.714 | 0.0801 |
| 209 | 24 | 2 | AMS | Morphine | BDAR | Dsmall | 1 | 0.7206 | 0.6999 | 7 | 31.714 | 0.0860 |
| 210 | 24 | 3 | AMS | Morphine | BDAR | Dsmall | 1 | 1.2144 | 1.2911 | 7 | 31.714 | 0.0980 |
| 211 | 24 | 4 | AMS | Morphine | BDAR | Dsmall | 1 | 0.5633 | 0.4045 | 10 | 35.483 | 0.1056 |
| 212 | 24 | 5 | AMS | Morphine | BDAR | Dsmall | 1 | 0.9393 | 1.0964 | 10 | 35.483 | 0.1115 |
| 213 | 24 | 6 | AMS | Morphine | BDAR | Dsmall | 1 | 1.7611 | 1.6399 | 10 | 35.483 | 0.1235 |
| 214 | 24 | 7 | AMS | Morphine | BDAR | Dsmall | 1 | 0.7250 | 0.7074 | 13 | 37.034 | 0.1238 |
| 215 | 24 | 8 | AMS | Morphine | BDAR | Dsmall | 1 | 1.1212 | 1.2971 | 13 | 37.034 | 0.1297 |
| 216 | 24 | 9 | AMS | Morphine | BDAR | Dsmall | 1 | 1.6704 | 1.8298 | 13 | 37.034 | 0.1418 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 217 | 25 | 1 | AMS | Morphine | BDAR | Dlarge | 1 | 0.1027 | 0.1596 | 7 | 32.343 | 0.0605 |
| 218 | 25 | 2 | AMS | Morphine | BDAR | Dlarge | 1 | 0.1909 | 0.2361 | 7 | 32.343 | 0.0662 |
| 219 | 25 | 3 | AMS | Morphine | BDAR | Dlarge | 1 | 0.2514 | 0.3108 | 7 | 32.343 | 0.0937 |
| 220 | 25 | 4 | AMS | Morphine | BDAR | Dlarge | 1 | 0.7582 | 0.7218 | 10 | 35.483 | 0.0647 |
| 221 | 25 | 5 | AMS | Morphine | BDAR | Dlarge | 1 | 0.8554 | 0.7946 | 10 | 35.483 | 0.0703 |
| 222 | 25 | 6 | AMS | Morphine | BDAR | Dlarge | 1 | 0.9943 | 0.8674 | 10 | 35.483 | 0.0978 |
| 223 | 25 | 7 | AMS | Morphine | BDAR | Dlarge | 1 | 1.1236 | 1.1172 | 13 | 37.034 | 0.0827 |
| 224 | 25 | 8 | AMS | Morphine | BDAR | Dlarge | 1 | 1.0585 | 1.1899 | 13 | 37.034 | 0.0884 |
| 225 | 25 | 9 | AMS | Morphine | BDAR | Dlarge | 1 | 1.1857 | 1.2626 | 13 | 37.034 | 0.1158 |
| 226 | 26 | 1 | AMS | Insulin | CD | Dsmall | 1 | 0.2101 | 0.0243 | 7 | 31.428 | 0.1477 |
| 227 | 26 | 2 | AMS | Insulin | CD | Dsmall | 1 | 0.6343 | 0.8064 | 7 | 31.428 | 0.1760 |
| 228 | 26 | 3 | AMS | Insulin | CD | Dsmall | 1 | 0.9572 | 1.6134 | 7 | 31.428 | 0.2161 |
| 229 | 26 | 4 | AMS | Insulin | CD | Dsmall | 1 | 0.6830 | 1.1082 | 7 | 32.372 | 0.1574 |
| 230 | 26 | 5 | AMS | Insulin | CD | Dsmall | 1 | 1.9696 | 1.9954 | 7 | 32.372 | 0.1860 |
| 231 | 26 | 6 | AMS | Insulin | CD | Dsmall | 1 | 2.1716 | 2.8525 | 7 | 32.372 | 0.2260 |
| 232 | 26 | 7 | AMS | Insulin | CD | Dsmall | 1 | 0.9569 | 1.6473 | 7 | 32.97 | 0.1883 |
| 233 | 26 | 8 | AMS | Insulin | CD | Dsmall | 1 | 2.9096 | 2.5185 | 7 | 32.97 | 0.2168 |
| 234 | 26 | 9 | AMS | Insulin | CD | Dsmall | 1 | 3.3096 | 3.3728 | 7 | 32.97 | 0.2568 |
| 235 | 27 | 1 | AMS | Insulin | CD | Dlarge | 1 | 0.2247 | 0.0507 | 7 | 31.193 | 0.0492 |
| 236 | 27 | 2 | AMS | Insulin | CD | Dlarge | 1 | 0.7029 | 0.7226 | 7 | 31.193 | 0.0710 |
| 237 | 27 | 3 | AMS | Insulin | CD | Dlarge | 1 | 1.4738 | 1.1353 | 7 | 31.193 | 0.1336 |
| 238 | 27 | 4 | AMS | Insulin | CD | Dlarge | 1 | 0.2618 | 0.5390 | 7 | 32.485 | 0.0576 |
| 239 | 27 | 5 | AMS | Insulin | CD | Dlarge | 1 | 1.0956 | 0.9618 | 7 | 32.485 | 0.0794 |
| 240 | 27 | 6 | AMS | Insulin | CD | Dlarge | 1 | 1.6300 | 1.2799 | 7 | 32.485 | 0.1420 |
| 241 | 27 | 7 | AMS | Insulin | CD | Dlarge | 1 | 0.4174 | 0.8901 | 7 | 33.364 | 0.0910 |
| 242 | 27 | 8 | AMS | Insulin | CD | Dlarge | 1 | 1.2101 | 1.1829 | 7 | 33.364 | 0.1127 |
| 243 | 27 | 9 | AMS | Insulin | CD | Dlarge | 1 | 1.7509 | 1.4468 | 7 | 33.364 | 0.1754 |
| 244 | 28 | 1 | AMS | Insulin | BD | D | 1 | 0.1062 | 0.0432 | 7 | 31.714 | 0.0473 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 245 | 28 | 2 | AMS | Insulin | BD | D | 1 | 0.1008 | 0.0481 | 7 | 31.714 | 0.0499 |
| 246 | 28 | 3 | AMS | Insulin | BD | D | 1 | 0.1222 | 0.2520 | 7 | 31.714 | 0.0638 |
| 247 | 28 | 4 | AMS | Insulin | BD | D | 1 | 0.1367 | 0.2067 | 10 | 33.808 | 0.0519 |
| 248 | 28 | 5 | AMS | Insulin | BD | D | 1 | 0.1460 | 0.6732 | 10 | 33.808 | 0.0545 |
| 249 | 28 | 6 | AMS | Insulin | BD | D | 1 | 0.1441 | 0.9065 | 10 | 33.808 | 0.0684 |
| 250 | 28 | 7 | AMS | Insulin | BD | D | 1 | 0.1494 | 0.8139 | 10 | 35.483 | 0.0737 |
| 251 | 28 | 8 | AMS | Insulin | BD | D | 1 | 0.1553 | 1.0235 | 10 | 35.483 | 0.0763 |
| 252 | 28 | 9 | AMS | Insulin | BD | D | 1 | 1.4028 | 1.2132 | 10 | 35.483 | 0.0902 |
| 253 | 29 | 1 | AMS | Heparin | CD | Dsmall | 1 | 0.1035 | 0.6091 | 7 | 31.312 | 0.1299 |
| 254 | 29 | 2 | AMS | Heparin | CD | Dsmall | 1 | 1.6678 | 1.4818 | 7 | 31.312 | 0.1422 |
| 255 | 29 | 3 | AMS | Heparin | CD | Dsmall | 1 | 2.3276 | 2.3342 | 7 | 31.312 | 0.1752 |
| 256 | 29 | 4 | AMS | Heparin | CD | Dsmall | 1 | 0.3562 | 0.6813 | 7 | 32.301 | 0.1511 |
| 257 | 29 | 5 | AMS | Heparin | CD | Dsmall | 1 | 1.8198 | 1.5879 | 7 | 32.301 | 0.1635 |
| 258 | 29 | 6 | AMS | Heparin | CD | Dsmall | 1 | 2.3173 | 2.4777 | 7 | 32.301 | 0.1964 |
| 259 | 29 | 7 | AMS | Heparin | CD | Dsmall | 1 | 0.3309 | 0.8294 | 7 | 32.97 | 0.2106 |
| 260 | 29 | 8 | AMS | Heparin | CD | Dsmall | 1 | 2.2555 | 1.8915 | 7 | 32.97 | 0.2231 |
| 261 | 29 | 9 | AMS | Heparin | CD | Dsmall | 1 | 2.5631 | 2.9393 | 7 | 32.97 | 0.2559 |
| 262 | 30 | 1 | AMS | Heparin | CD | Dlarge | 1 | 1.1834 | 1.4210 | 7 | 31.04 | 0.1581 |
| 263 | 30 | 2 | AMS | Heparin | CD | Dlarge | 1 | 1.8950 | 1.7804 | 7 | 31.04 | 0.1775 |
| 264 | 30 | 3 | AMS | Heparin | CD | Dlarge | 1 | 2.0625 | 2.1307 | 7 | 31.04 | 0.2242 |
| 265 | 30 | 4 | AMS | Heparin | CD | Dlarge | 1 | 1.8559 | 1.5989 | 7 | 32.132 | 0.1750 |
| 266 | 30 | 5 | AMS | Heparin | CD | Dlarge | 1 | 2.1817 | 1.9225 | 7 | 32.132 | 0.1944 |
| 267 | 30 | 6 | AMS | Heparin | CD | Dlarge | 1 | 2.2322 | 2.2391 | 7 | 32.132 | 0.2411 |
| 268 | 30 | 7 | AMS | Heparin | CD | Dlarge | 1 | 1.6793 | 1.7772 | 7 | 32.691 | 0.2223 |
| 269 | 30 | 8 | AMS | Heparin | CD | Dlarge | 1 | 1.9809 | 2.0725 | 7 | 32.691 | 0.2419 |
| 270 | 30 | 9 | AMS | Heparin | CD | Dlarge | 1 | 2.3384 | 2.3625 | 7 | 32.691 | 0.2885 |

# APPENDIX C. RISK SCALE DATASET (OVERALL COMPARISON MATRIX)

| EST. VALUES | F1 RISK LEVEL IV MED | F2: LEVEL OF CARE | F3: DETECT OF ADES | F4_PROCESSED EXCEEDING LIMITS (ADJUSTED) | RISK RANKING SCORE |
|---|---|---|---|---|---|
| 0.0988 | 3 | 4 | 3 | 1000090 | 1 |
| 0.1058 | 3 | 4 | 3 | 1000080 | 2 |
| 0.1131 | 3 | 4 | 3 | 1000070 | 3 |
| 0.1203 | 3 | 4 | 3 | 1000060 | 4 |
| 0.1270 | 3 | 4 | 3 | 1000050 | 5 |
| 0.1342 | 3 | 4 | 3 | 1000040 | 6 |
| 0.1412 | 3 | 4 | 3 | 1000030 | 7 |
| 0.1496 | 3 | 4 | 3 | 1000020 | 8 |
| 0.1514 | 3 | 3 | 3 | 1000099 | 9 |
| 0.1518 | 3 | 3 | 3 | 1000095 | 10 |
| 0.1553 | 3 | 3 | 3 | 1000090 | 11 |
| 0.1572 | 3 | 4 | 3 | 1000010 | 12 |
| 0.1623 | 3 | 3 | 3 | 1000080 | 13 |
| 0.1649 | 3 | 4 | 3 | 1000001 | 14 |
| 0.1696 | 3 | 3 | 3 | 1000070 | 15 |
| 0.1758 | 3 | 4 | 2 | 1000090 | 16 |
| 0.1768 | 3 | 3 | 3 | 1000060 | 17 |
| 0.1790 | 2 | 4 | 3 | 1000090 | 18 |
| 0.1802 | 3 | 4 | 3 | 5000 | 19 |
| 0.1828 | 3 | 4 | 2 | 1000080 | 20 |
| 0.1835 | 3 | 3 | 3 | 1000050 | 21 |
| 0.1860 | 2 | 4 | 3 | 1000080 | 22 |
| 0.1901 | 3 | 4 | 2 | 1000070 | 23 |
| 0.1907 | 3 | 3 | 3 | 1000040 | 24 |
| 0.1933 | 2 | 4 | 3 | 1000070 | 25 |
| 0.1934 | 3 | 4 | 3 | 3000 | 26 |
| 0.1974 | 3 | 4 | 2 | 1000060 | 27 |
| 0.1977 | 3 | 3 | 3 | 1000030 | 28 |
| 0.2006 | 2 | 4 | 3 | 1000060 | 29 |
| 0.2040 | 3 | 4 | 2 | 1000050 | 30 |
| 0.2061 | 3 | 3 | 3 | 1000020 | 31 |
| 0.2071 | 3 | 4 | 3 | 2000 | 32 |
| 0.2072 | 2 | 4 | 3 | 1000050 | 33 |
| 0.2113 | 3 | 4 | 2 | 1000040 | 34 |
| 0.2137 | 3 | 3 | 3 | 1000010 | 35 |
| 0.2145 | 2 | 4 | 3 | 1000040 | 36 |
| 0.2182 | 3 | 4 | 2 | 1000030 | 37 |
| 0.2189 | 3 | 4 | 3 | 1500 | 38 |

| | | | | | |
|---|---|---|---|---|---|
| 0.2192 | 3 | 2 | 3 | 1000090 | 39 |
| 0.2214 | 3 | 3 | 3 | 1000001 | 40 |
| 0.2214 | 2 | 4 | 3 | 1000030 | 41 |
| 0.2262 | 3 | 2 | 3 | 1000080 | 42 |
| 0.2267 | 3 | 4 | 2 | 1000020 | 43 |
| 0.2299 | 2 | 4 | 3 | 1000020 | 44 |
| 0.2323 | 3 | 3 | 2 | 1000090 | 45 |
| 0.2332 | 3 | 4 | 3 | 1000 | 46 |
| 0.2335 | 3 | 2 | 3 | 1000070 | 47 |
| 0.2342 | 3 | 4 | 2 | 1000010 | 48 |
| 0.2355 | 2 | 3 | 3 | 1000090 | 49 |
| 0.2367 | 3 | 3 | 3 | 5000 | 50 |
| 0.2374 | 2 | 4 | 3 | 1000010 | 51 |
| 0.2393 | 3 | 3 | 2 | 1000080 | 52 |
| 0.2407 | 3 | 2 | 3 | 1000060 | 53 |
| 0.2414 | 3 | 3 | 3 | 4895 | 54 |
| 0.2417 | 3 | 4 | 3 | 900 | 55 |
| 0.2420 | 3 | 4 | 2 | 1000001 | 56 |
| 0.2420 | 3 | 3 | 3 | 4309.425 | 57 |
| 0.2425 | 2 | 3 | 3 | 1000080 | 58 |
| 0.2433 | 3 | 3 | 3 | 3900 | 59 |
| 0.2452 | 2 | 4 | 3 | 1000001 | 60 |
| 0.2460 | 3 | 3 | 3 | 3230 | 61 |
| 0.2466 | 3 | 3 | 2 | 1000070 | 62 |
| 0.2474 | 3 | 2 | 3 | 1000050 | 63 |
| 0.2498 | 2 | 3 | 3 | 1000070 | 64 |
| 0.2499 | 3 | 3 | 3 | 3000 | 65 |
| 0.2515 | 3 | 4 | 3 | 800 | 66 |
| 0.2539 | 3 | 3 | 2 | 1000060 | 67 |
| 0.2546 | 3 | 2 | 3 | 1000040 | 68 |
| 0.2557 | 3 | 3 | 3 | 2700 | 69 |
| 0.2560 | 2 | 4 | 2 | 1000090 | 70 |
| 0.2562 | 3 | 3 | 3 | 2566.666667 | 71 |
| 0.2571 | 2 | 3 | 3 | 1000060 | 72 |
| 0.2572 | 3 | 4 | 2 | 5000 | 73 |
| 0.2604 | 2 | 4 | 3 | 5000 | 74 |
| 0.2605 | 3 | 3 | 2 | 1000050 | 75 |
| 0.2614 | 3 | 4 | 3 | 700 | 76 |
| 0.2616 | 3 | 2 | 3 | 1000030 | 77 |
| 0.2630 | 2 | 4 | 2 | 1000080 | 78 |
| 0.2636 | 3 | 3 | 3 | 2000 | 79 |
| 0.2637 | 2 | 3 | 3 | 1000050 | 80 |
| 0.2656 | 3 | 4 | 1 | 1000090 | 81 |
| 0.2663 | 1 | 4 | 3 | 1000090 | 82 |
| 0.2678 | 3 | 3 | 2 | 1000040 | 83 |
| 0.2680 | 3 | 3 | 3 | 1900 | 84 |

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| 0.2701 | 3 | 2 | 3 | 1000020 | 85 |
| 0.2703 | 2 | 4 | 2 | 1000070 | 86 |
| 0.2704 | 3 | 4 | 2 | 3000 | 87 |
| 0.2710 | 2 | 3 | 3 | 1000040 | 88 |
| 0.2722 | 3 | 4 | 3 | 600 | 89 |
| 0.2726 | 3 | 4 | 1 | 1000080 | 90 |
| 0.2733 | 1 | 4 | 3 | 1000080 | 91 |
| 0.2736 | 2 | 4 | 3 | 3000 | 92 |
| 0.2747 | 3 | 3 | 2 | 1000030 | 93 |
| 0.2754 | 3 | 3 | 3 | 1500 | 94 |
| 0.2765 | 3 | 4 | 1 | 1000076 | 95 |
| 0.2776 | 2 | 4 | 2 | 1000060 | 96 |
| 0.2776 | 3 | 2 | 3 | 1000010 | 97 |
| 0.2779 | 2 | 3 | 3 | 1000030 | 98 |
| 0.2799 | 3 | 4 | 1 | 1000070 | 99 |
| 0.2799 | 3 | 3 | 3 | 1400 | 100 |
| 0.2806 | 1 | 4 | 3 | 1000070 | 101 |
| 0.2822 | 3 | 4 | 3 | 500 | 102 |
| 0.2832 | 3 | 3 | 2 | 1000020 | 103 |
| 0.2835 | 3 | 4 | 1 | 1000062.4 | 104 |
| 0.2841 | 3 | 1 | 3 | 1000098.958 | 105 |
| 0.2841 | 3 | 4 | 2 | 2000 | 106 |
| 0.2842 | 2 | 4 | 2 | 1000050 | 107 |
| 0.2847 | 3 | 3 | 3 | 1100 | 108 |
| 0.2853 | 3 | 2 | 3 | 1000001 | 109 |
| 0.2864 | 2 | 3 | 3 | 1000020 | 110 |
| 0.2873 | 2 | 4 | 3 | 2000 | 111 |
| 0.2877 | 3 | 1 | 3 | 1000090 | 112 |
| 0.2879 | 1 | 4 | 3 | 1000060 | 113 |
| 0.2897 | 3 | 3 | 3 | 1000 | 114 |
| 0.2907 | 3 | 3 | 2 | 1000010 | 115 |
| 0.2915 | 2 | 4 | 2 | 1000040 | 116 |
| 0.2918 | 3 | 4 | 3 | 400 | 117 |
| 0.2938 | 3 | 4 | 1 | 1000050 | 118 |
| 0.2939 | 2 | 3 | 3 | 1000010 | 119 |
| 0.2945 | 1 | 4 | 3 | 1000050 | 120 |
| 0.2959 | 3 | 4 | 2 | 1500 | 121 |
| 0.2962 | 3 | 2 | 2 | 1000090 | 122 |
| 0.2979 | 3 | 1 | 3 | 1000079.975 | 123 |
| 0.2982 | 3 | 3 | 3 | 900 | 124 |
| 0.2985 | 3 | 3 | 2 | 1000001 | 125 |
| 0.2985 | 2 | 4 | 2 | 1000030 | 126 |
| 0.2991 | 2 | 4 | 3 | 1500 | 127 |
| 0.2994 | 2 | 2 | 3 | 1000090 | 128 |
| 0.3006 | 3 | 2 | 3 | 5000 | 129 |
| 0.3011 | 3 | 4 | 1 | 1000040 | 130 |

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| 0.3017 | 2 | 3 | 3 | 1000001 | 131 |
| 0.3018 | 1 | 4 | 3 | 1000040 | 132 |
| 0.3020 | 3 | 1 | 3 | 1000070 | 133 |
| 0.3029 | 3 | 4 | 3 | 300 | 134 |
| 0.3032 | 3 | 2 | 2 | 1000080 | 135 |
| 0.3038 | 3 | 3 | 2 | 15000 | 136 |
| 0.3064 | 2 | 2 | 3 | 1000080 | 137 |
| 0.3069 | 2 | 4 | 2 | 1000020 | 138 |
| 0.3080 | 3 | 3 | 3 | 800 | 139 |
| 0.3080 | 3 | 4 | 1 | 1000030 | 140 |
| 0.3088 | 1 | 4 | 3 | 1000030 | 141 |
| 0.3092 | 3 | 1 | 3 | 1000060 | 142 |
| 0.3095 | 3 | 3 | 2 | 5864.2 | 143 |
| 0.3102 | 3 | 4 | 2 | 1000 | 144 |
| 0.3105 | 3 | 2 | 2 | 1000070 | 145 |
| 0.3125 | 2 | 3 | 2 | 1000090 | 146 |
| 0.3134 | 2 | 4 | 3 | 1000 | 147 |
| 0.3137 | 2 | 2 | 3 | 1000070 | 148 |
| 0.3138 | 3 | 2 | 3 | 3000 | 149 |
| 0.3142 | 3 | 4 | 3 | 200 | 150 |
| 0.3145 | 2 | 4 | 2 | 1000010 | 151 |
| 0.3165 | 3 | 4 | 1 | 1000020 | 152 |
| 0.3169 | 2 | 3 | 3 | 5000 | 153 |
| 0.3172 | 1 | 4 | 3 | 1000020 | 154 |
| 0.3173 | 3 | 3 | 2 | 4958.2 | 155 |
| 0.3178 | 3 | 2 | 2 | 1000060 | 156 |
| 0.3179 | 3 | 3 | 3 | 700 | 157 |
| 0.3187 | 3 | 4 | 2 | 900 | 158 |
| 0.3193 | 3 | 1 | 3 | 1000049.988 | 159 |
| 0.3196 | 2 | 3 | 2 | 1000080 | 160 |
| 0.3199 | 3 | 3 | 2 | 3952.75 | 161 |
| 0.3210 | 2 | 2 | 3 | 1000060 | 162 |
| 0.3219 | 2 | 4 | 3 | 900 | 163 |
| 0.3221 | 3 | 3 | 1 | 1000090 | 164 |
| 0.3222 | 2 | 4 | 2 | 1000001 | 165 |
| 0.3228 | 1 | 3 | 3 | 1000090 | 166 |
| 0.3231 | 3 | 1 | 3 | 1000040 | 167 |
| 0.3241 | 3 | 4 | 1 | 1000010 | 168 |
| 0.3244 | 3 | 2 | 2 | 1000050 | 169 |
| 0.3248 | 1 | 4 | 3 | 1000010 | 170 |
| 0.3251 | 3 | 4 | 3 | 100 | 171 |
| 0.3268 | 2 | 3 | 2 | 1000070 | 172 |
| 0.3275 | 3 | 2 | 3 | 2000 | 173 |
| 0.3276 | 2 | 2 | 3 | 1000050 | 174 |
| 0.3285 | 3 | 4 | 2 | 800 | 175 |
| 0.3287 | 3 | 3 | 3 | 600 | 176 |

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| 0.3291 | 3 | 3 | 1 | 1000080 | 177 |
| 0.3298 | 1 | 3 | 3 | 1000080 | 178 |
| 0.3301 | 2 | 3 | 3 | 3000 | 179 |
| 0.3305 | 3 | 3 | 2 | 2997.7 | 180 |
| 0.3317 | 3 | 2 | 2 | 1000040 | 181 |
| 0.3317 | 2 | 4 | 3 | 800 | 182 |
| 0.3318 | 3 | 4 | 1 | 1000001 | 183 |
| 0.3325 | 1 | 4 | 3 | 1000001 | 184 |
| 0.3332 | 3 | 1 | 3 | 1000029.994 | 185 |
| 0.3336 | 3 | 3 | 2 | 2490 | 186 |
| 0.3341 | 2 | 3 | 2 | 1000060 | 187 |
| 0.3349 | 2 | 2 | 3 | 1000040 | 188 |
| 0.3364 | 3 | 3 | 1 | 1000070 | 189 |
| 0.3371 | 1 | 3 | 3 | 1000070 | 190 |
| 0.3375 | 2 | 4 | 2 | 5000 | 191 |
| 0.3375 | 3 | 4 | 3 | 10 | 192 |
| 0.3384 | 3 | 4 | 2 | 700 | 193 |
| 0.3386 | 3 | 1 | 3 | 1000020 | 194 |
| 0.3387 | 3 | 2 | 2 | 1000030 | 195 |
| 0.3387 | 3 | 3 | 3 | 500 | 196 |
| 0.3393 | 3 | 2 | 3 | 1500 | 197 |
| 0.3407 | 2 | 3 | 2 | 1000050 | 198 |
| 0.3416 | 2 | 4 | 3 | 700 | 199 |
| 0.3419 | 2 | 2 | 3 | 1000030 | 200 |
| 0.3433 | 1 | 4 | 2 | 1000090 | 201 |
| 0.3437 | 3 | 3 | 1 | 1000060 | 202 |
| 0.3438 | 2 | 3 | 3 | 2000 | 203 |
| 0.3444 | 1 | 3 | 3 | 1000060 | 204 |
| 0.3458 | 2 | 4 | 1 | 1000090 | 205 |
| 0.3461 | 3 | 3 | 2 | 1898 | 206 |
| 0.3470 | 3 | 4 | 1 | 5000 | 207 |
| 0.3471 | 3 | 2 | 2 | 1000020 | 208 |
| 0.3477 | 1 | 4 | 3 | 5000 | 209 |
| 0.3480 | 2 | 3 | 2 | 1000040 | 210 |
| 0.3483 | 3 | 3 | 3 | 400 | 211 |
| 0.3492 | 3 | 4 | 2 | 600 | 212 |
| 0.3493 | 3 | 1 | 3 | 1000009.991 | 213 |
| 0.3503 | 2 | 2 | 3 | 1000020 | 214 |
| 0.3503 | 3 | 3 | 1 | 1000050 | 215 |
| 0.3504 | 1 | 4 | 2 | 1000080 | 216 |
| 0.3507 | 2 | 4 | 2 | 3000 | 217 |
| 0.3510 | 1 | 3 | 3 | 1000050 | 218 |
| 0.3524 | 2 | 4 | 3 | 600 | 219 |
| 0.3529 | 2 | 4 | 1 | 1000080 | 220 |
| 0.3536 | 3 | 2 | 3 | 1000 | 221 |
| 0.3547 | 3 | 2 | 2 | 1000010 | 222 |

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| 0.3550 | 2 | 3 | 2 | 1000030 | 223 |
| 0.3556 | 2 | 3 | 3 | 1500 | 224 |
| 0.3569 | 3 | 3 | 2 | 1400 | 225 |
| 0.3576 | 3 | 3 | 1 | 1000040 | 226 |
| 0.3576 | 1 | 4 | 2 | 1000070 | 227 |
| 0.3577 | 3 | 1 | 3 | 1000000.012 | 228 |
| 0.3579 | 2 | 2 | 3 | 1000010 | 229 |
| 0.3582 | 3 | 1 | 3 | 24900 | 230 |
| 0.3583 | 1 | 3 | 3 | 1000040 | 231 |
| 0.3583 | 3 | 1 | 3 | 20100 | 232 |
| 0.3588 | 3 | 1 | 3 | 17042.85714 | 233 |
| 0.3593 | 3 | 4 | 2 | 500 | 234 |
| 0.3594 | 3 | 1 | 3 | 13135.29412 | 235 |
| 0.3594 | 3 | 3 | 3 | 300 | 236 |
| 0.3601 | 2 | 4 | 1 | 1000070 | 237 |
| 0.3603 | 3 | 4 | 1 | 3000 | 238 |
| 0.3604 | 3 | 1 | 3 | 9900 | 239 |
| 0.3605 | 3 | 3 | 2 | 1150 | 240 |
| 0.3610 | 1 | 4 | 3 | 3000 | 241 |
| 0.3614 | 3 | 1 | 3 | 8900 | 242 |
| 0.3619 | 3 | 1 | 3 | 8272.093023 | 243 |
| 0.3621 | 3 | 2 | 3 | 900 | 244 |
| 0.3624 | 3 | 2 | 2 | 1000001 | 245 |
| 0.3625 | 2 | 4 | 3 | 500 | 246 |
| 0.3630 | 3 | 1 | 3 | 6958.823529 | 247 |
| 0.3634 | 2 | 3 | 2 | 1000020 | 248 |
| 0.3644 | 2 | 4 | 2 | 2000 | 249 |
| 0.3647 | 3 | 1 | 2 | 1000090 | 250 |
| 0.3649 | 1 | 4 | 2 | 1000060 | 251 |
| 0.3653 | 1 | 3 | 3 | 1000030 | 252 |
| 0.3653 | 3 | 1 | 3 | 5438.461538 | 253 |
| 0.3656 | 2 | 2 | 3 | 1000001 | 254 |
| 0.3667 | 3 | 3 | 2 | 1000 | 255 |
| 0.3674 | 2 | 4 | 1 | 1000060 | 256 |
| 0.3678 | 2 | 3 | 2 | 1000010.022 | 257 |
| 0.3679 | 2 | 1 | 3 | 1000090 | 258 |
| 0.3684 | 3 | 3 | 1 | 1000028.529 | 259 |
| 0.3689 | 3 | 4 | 2 | 400 | 260 |
| 0.3691 | 3 | 1 | 3 | 5000 | 261 |
| 0.3699 | 2 | 3 | 3 | 1000 | 262 |
| 0.3706 | 3 | 3 | 2 | 920 | 263 |
| 0.3707 | 3 | 3 | 3 | 200 | 264 |
| 0.3715 | 1 | 4 | 2 | 1000050 | 265 |
| 0.3717 | 3 | 1 | 2 | 1000080 | 266 |
| 0.3719 | 3 | 2 | 3 | 800 | 267 |
| 0.3721 | 2 | 4 | 3 | 400 | 268 |

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| 0.3730 | 3 | 3 | 1 | 1000020 | 269 |
| 0.3737 | 1 | 3 | 3 | 1000020 | 270 |
| 0.3740 | 3 | 4 | 1 | 2000 | 271 |
| 0.3740 | 2 | 4 | 1 | 1000050 | 272 |
| 0.3747 | 1 | 4 | 3 | 2000 | 273 |
| 0.3749 | 2 | 1 | 3 | 1000080 | 274 |
| 0.3761 | 2 | 4 | 2 | 1500 | 275 |
| 0.3764 | 2 | 2 | 2 | 1000090 | 276 |
| 0.3767 | 3 | 1 | 3 | 3702.816901 | 277 |
| 0.3769 | 3 | 1 | 3 | 3500 | 278 |
| 0.3775 | 3 | 1 | 3 | 3437.681159 | 279 |
| 0.3776 | 3 | 2 | 2 | 5000 | 280 |
| 0.3784 | 2 | 3 | 3 | 900 | 281 |
| 0.3785 | 3 | 1 | 3 | 3112.12 | 282 |
| 0.3788 | 1 | 4 | 2 | 1000040 | 283 |
| 0.3790 | 3 | 1 | 2 | 1000070 | 284 |
| 0.3799 | 3 | 4 | 2 | 300 | 285 |
| 0.3806 | 3 | 3 | 1 | 1000010 | 286 |
| 0.3808 | 2 | 2 | 3 | 5000 | 287 |
| 0.3813 | 1 | 3 | 3 | 1000010 | 288 |
| 0.3813 | 2 | 4 | 1 | 1000040 | 289 |
| 0.3816 | 3 | 3 | 3 | 100 | 290 |
| 0.3818 | 3 | 2 | 3 | 700 | 291 |
| 0.3822 | 2 | 3 | 2 | 1000000.062 | 292 |
| 0.3822 | 2 | 1 | 3 | 1000070 | 293 |
| 0.3831 | 2 | 4 | 3 | 300 | 294 |
| 0.3835 | 2 | 2 | 2 | 1000080 | 295 |
| 0.3850 | 3 | 3 | 2 | 800 | 296 |
| 0.3857 | 2 | 3 | 2 | 9890 | 297 |
| 0.3857 | 3 | 4 | 1 | 1500 | 298 |
| 0.3858 | 1 | 4 | 2 | 1000030 | 299 |
| 0.3860 | 3 | 2 | 1 | 1000090 | 300 |
| 0.3862 | 2 | 3 | 2 | 8900 | 301 |
| 0.3863 | 3 | 1 | 2 | 1000060 | 302 |
| 0.3864 | 1 | 4 | 3 | 1500 | 303 |
| 0.3865 | 3 | 1 | 3 | 2900 | 304 |
| 0.3867 | 1 | 2 | 3 | 1000090 | 305 |
| 0.3873 | 2 | 3 | 2 | 7900 | 306 |
| 0.3873 | 3 | 1 | 3 | 2800 | 307 |
| 0.3877 | 2 | 3 | 2 | 7400 | 308 |
| 0.3877 | 3 | 3 | 3 | 49.975 | 309 |
| 0.3881 | 3 | 1 | 3 | 2700 | 310 |
| 0.3882 | 2 | 3 | 2 | 6900 | 311 |
| 0.3882 | 2 | 3 | 3 | 800 | 312 |
| 0.3883 | 2 | 4 | 1 | 1000030 | 313 |
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| 0.3890 | 1 | 3 | 3 | 1000001 | 315 |
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| 0.3895 | 2 | 1 | 3 | 1000060 | 317 |
| 0.3896 | 2 | 3 | 2 | 5900 | 318 |
| 0.3900 | 3 | 1 | 3 | 2400 | 319 |
| 0.3903 | 2 | 3 | 2 | 5400 | 320 |
| 0.3904 | 2 | 4 | 2 | 1000 | 321 |
| 0.3907 | 2 | 2 | 2 | 1000070 | 322 |
| 0.3909 | 3 | 2 | 2 | 3000 | 323 |
| 0.3912 | 3 | 4 | 2 | 200 | 324 |
| 0.3913 | 3 | 1 | 3 | 2230 | 325 |
| 0.3917 | 3 | 1 | 3 | 2100 | 326 |
| 0.3919 | 3 | 3 | 1 | 1000000.048 | 327 |
| 0.3922 | 3 | 1 | 3 | 2005.263158 | 328 |
| 0.3926 | 3 | 2 | 3 | 600 | 329 |
| 0.3929 | 3 | 1 | 2 | 1000050 | 330 |
| 0.3930 | 3 | 2 | 1 | 1000080 | 331 |
| 0.3938 | 1 | 2 | 3 | 1000080 | 332 |
| 0.3940 | 3 | 3 | 3 | 10 | 333 |
| 0.3941 | 2 | 2 | 3 | 3000 | 334 |
| 0.3942 | 1 | 4 | 2 | 1000020 | 335 |
| 0.3944 | 2 | 4 | 3 | 200 | 336 |
| 0.3949 | 3 | 3 | 1 | 9900 | 337 |
| 0.3949 | 3 | 3 | 2 | 700 | 338 |
| 0.3958 | 3 | 3 | 1 | 8900 | 339 |
| 0.3961 | 2 | 1 | 3 | 1000050 | 340 |
| 0.3966 | 3 | 3 | 1 | 8021.96 | 341 |
| 0.3967 | 2 | 4 | 1 | 1000020 | 342 |
| 0.3970 | 3 | 3 | 1 | 7468.18 | 343 |
| 0.3977 | 3 | 3 | 1 | 6900 | 344 |
| 0.3980 | 2 | 2 | 2 | 1000060 | 345 |
| 0.3980 | 3 | 3 | 1 | 6429.42 | 346 |
| 0.3981 | 2 | 3 | 2 | 4900 | 347 |
| 0.3981 | 2 | 3 | 3 | 700 | 348 |
| 0.3989 | 3 | 3 | 3 | 5 | 349 |
| 0.3990 | 3 | 3 | 1 | 5954.54 | 350 |
| 0.3990 | 2 | 4 | 2 | 900 | 351 |
| 0.3994 | 2 | 3 | 2 | 4162.4 | 352 |
| 0.3995 | 3 | 3 | 1 | 5450 | 353 |
| 0.3999 | 1 | 3 | 2 | 1000090 | 354 |
| 0.4000 | 3 | 4 | 1 | 1000 | 355 |
| 0.4002 | 3 | 1 | 2 | 1000040 | 356 |
| 0.4003 | 3 | 2 | 1 | 1000070 | 357 |
| 0.4004 | 3 | 1 | 3 | 1900 | 358 |
| 0.4006 | 2 | 3 | 2 | 3900 | 359 |
| 0.4007 | 1 | 4 | 3 | 1000 | 360 |

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| 0.4010 | 1 | 2 | 3 | 1000070 | 361 |
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| 0.4018 | 1 | 4 | 2 | 1000010 | 363 |
| 0.4019 | 3 | 1 | 3 | 1800 | 364 |
| 0.4021 | 3 | 4 | 2 | 100 | 365 |
| 0.4022 | 2 | 3 | 2 | 3452 | 366 |
| 0.4022 | 3 | 1 | 3 | 1700 | 367 |
| 0.4026 | 3 | 2 | 3 | 500 | 368 |
| 0.4028 | 2 | 3 | 2 | 3233.333333 | 369 |
| 0.4030 | 3 | 1 | 3 | 1600 | 370 |
| 0.4034 | 2 | 1 | 3 | 1000040 | 371 |
| 0.4036 | 2 | 3 | 2 | 3025 | 372 |
| 0.4036 | 1 | 3 | 2 | 1000085 | 373 |
| 0.4042 | 1 | 3 | 3 | 5000 | 374 |
| 0.4043 | 2 | 4 | 1 | 1000010 | 375 |
| 0.4046 | 3 | 2 | 2 | 2000 | 376 |
| 0.4046 | 2 | 2 | 2 | 1000050 | 377 |
| 0.4053 | 2 | 4 | 3 | 100 | 378 |
| 0.4057 | 2 | 3 | 1 | 1000089.976 | 379 |
| 0.4069 | 1 | 3 | 2 | 1000080 | 380 |
| 0.4072 | 3 | 1 | 2 | 1000030 | 381 |
| 0.4076 | 3 | 2 | 1 | 1000060 | 382 |
| 0.4077 | 3 | 3 | 1 | 4900 | 383 |
| 0.4078 | 2 | 2 | 3 | 2000 | 384 |
| 0.4078 | 3 | 1 | 3 | 1500 | 385 |
| 0.4083 | 1 | 2 | 3 | 1000060 | 386 |
| 0.4086 | 3 | 4 | 1 | 900 | 387 |
| 0.4086 | 3 | 3 | 1 | 4461.64 | 388 |
| 0.4088 | 2 | 4 | 2 | 800 | 389 |
| 0.4089 | 2 | 3 | 3 | 600 | 390 |
| 0.4093 | 1 | 4 | 3 | 900 | 391 |
| 0.4094 | 2 | 3 | 1 | 1000080 | 392 |
| 0.4095 | 1 | 4 | 2 | 1000001 | 393 |
| 0.4102 | 3 | 3 | 1 | 3900 | 394 |
| 0.4104 | 2 | 1 | 3 | 1000030 | 395 |
| 0.4107 | 3 | 3 | 1 | 3898.578199 | 396 |
| 0.4113 | 2 | 3 | 2 | 2900 | 397 |
| 0.4115 | 3 | 3 | 1 | 3472.96 | 398 |
| 0.4119 | 2 | 2 | 2 | 1000040 | 399 |
| 0.4120 | 2 | 4 | 1 | 1000001 | 400 |
| 0.4123 | 3 | 2 | 3 | 400 | 401 |
| 0.4123 | 3 | 1 | 3 | 1400 | 402 |
| 0.4138 | 3 | 1 | 3 | 1303.506667 | 403 |
| 0.4142 | 3 | 2 | 1 | 1000050 | 404 |
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| 0.4149 | 2 | 3 | 2 | 2400 | 406 |

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| 0.4152 | 3 | 1 | 3 | 1200 | 408 |
| 0.4156 | 3 | 1 | 2 | 1000020 | 409 |
| 0.4158 | 3 | 3 | 2 | 500 | 410 |
| 0.4163 | 3 | 2 | 2 | 1500 | 411 |
| 0.4166 | 2 | 3 | 1 | 1000070 | 412 |
| 0.4168 | 2 | 3 | 2 | 2033.34 | 413 |
| 0.4171 | 3 | 1 | 3 | 1100 | 414 |
| 0.4175 | 1 | 3 | 3 | 3000 | 415 |
| 0.4176 | 1 | 3 | 2 | 1000069.868 | 416 |
| 0.4177 | 2 | 4 | 3 | 10 | 417 |
| 0.4181 | 3 | 2 | 3 | 350 | 418 |
| 0.4184 | 3 | 4 | 1 | 800 | 419 |
| 0.4187 | 2 | 4 | 2 | 700 | 420 |
| 0.4188 | 2 | 1 | 3 | 1000020 | 421 |
| 0.4189 | 2 | 2 | 2 | 1000030 | 422 |
| 0.4190 | 2 | 3 | 3 | 500 | 423 |
| 0.4191 | 1 | 4 | 3 | 800 | 424 |
| 0.4195 | 2 | 2 | 3 | 1500 | 425 |
| 0.4209 | 3 | 3 | 1 | 2900 | 426 |
| 0.4214 | 1 | 3 | 2 | 1000060 | 427 |
| 0.4215 | 3 | 2 | 1 | 1000040 | 428 |
| 0.4221 | 3 | 1 | 3 | 1000 | 429 |
| 0.4222 | 1 | 2 | 3 | 1000040 | 430 |
| 0.4232 | 3 | 1 | 2 | 1000010 | 431 |
| 0.4233 | 3 | 2 | 3 | 300 | 432 |
| 0.4239 | 2 | 3 | 1 | 1000060 | 433 |
| 0.4244 | 3 | 3 | 1 | 2400 | 434 |
| 0.4248 | 1 | 4 | 2 | 5000 | 435 |
| 0.4253 | 2 | 3 | 2 | 1900 | 436 |
| 0.4254 | 3 | 3 | 2 | 400 | 437 |
| 0.4264 | 2 | 1 | 3 | 1000010 | 438 |
| 0.4271 | 2 | 3 | 2 | 1700 | 439 |
| 0.4273 | 2 | 4 | 1 | 5000 | 440 |
| 0.4273 | 2 | 2 | 2 | 1000020 | 441 |
| 0.4277 | 2 | 3 | 2 | 1606.666 | 442 |
| 0.4280 | 1 | 3 | 2 | 1000050 | 443 |
| 0.4283 | 3 | 4 | 1 | 700 | 444 |
| 0.4285 | 3 | 2 | 1 | 1000030 | 445 |
| 0.4286 | 2 | 3 | 3 | 400 | 446 |
| 0.4290 | 1 | 4 | 3 | 700 | 447 |
| 0.4292 | 1 | 2 | 3 | 1000030 | 448 |
| 0.4294 | 2 | 4 | 2 | 600 | 449 |
| 0.4305 | 2 | 3 | 1 | 1000050 | 450 |
| 0.4306 | 3 | 2 | 2 | 1000 | 451 |
| 0.4306 | 3 | 1 | 3 | 900 | 452 |

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| 0.4309 | 3 | 1 | 2 | 1000001 | 453 |
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| 0.4327 | 2 | 3 | 2 | 1500 | 455 |
| 0.4332 | 1 | 4 | 1 | 1000090 | 456 |
| 0.4338 | 2 | 2 | 3 | 1000 | 457 |
| 0.4341 | 2 | 1 | 3 | 1000001 | 458 |
| 0.4343 | 3 | 3 | 1 | 1900.266509 | 459 |
| 0.4346 | 3 | 2 | 3 | 200 | 460 |
| 0.4348 | 3 | 3 | 1 | 1900 | 461 |
| 0.4349 | 2 | 2 | 2 | 1000010 | 462 |
| 0.4353 | 1 | 3 | 2 | 1000040 | 463 |
| 0.4365 | 3 | 3 | 2 | 300 | 464 |
| 0.4369 | 3 | 2 | 1 | 1000020 | 465 |
| 0.4372 | 2 | 3 | 2 | 1400 | 466 |
| 0.4376 | 1 | 2 | 3 | 1000020 | 467 |
| 0.4378 | 2 | 3 | 1 | 1000040 | 468 |
| 0.4380 | 1 | 4 | 2 | 3000 | 469 |
| 0.4390 | 3 | 4 | 1 | 600 | 470 |
| 0.4392 | 3 | 2 | 2 | 900 | 471 |
| 0.4395 | 2 | 4 | 2 | 500 | 472 |
| 0.4396 | 2 | 3 | 3 | 300 | 473 |
| 0.4397 | 1 | 4 | 3 | 600 | 474 |
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| 0.4402 | 1 | 4 | 1 | 1000080 | 476 |
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| 0.4420 | 2 | 3 | 2 | 1100 | 480 |
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| 0.4425 | 2 | 3 | 2 | 1011.111111 | 483 |
| 0.4426 | 2 | 2 | 2 | 1000001 | 484 |
| 0.4429 | 1 | 3 | 3 | 1500 | 485 |
| 0.4441 | 3 | 2 | 2 | 860 | 486 |
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| 0.4449 | 2 | 1 | 2 | 1000090 | 489 |
| 0.4452 | 1 | 2 | 3 | 1000010 | 490 |
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| 0.4461 | 3 | 3 | 1 | 1470.75 | 492 |
| 0.4461 | 3 | 1 | 2 | 5000 | 493 |
| 0.4468 | 1 | 3 | 2 | 1000024.986 | 494 |
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| 0.4477 | 3 | 3 | 2 | 200 | 496 |
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| 0.4493 | 2 | 1 | 3 | 5000 | 500 |
| 0.4497 | 3 | 3 | 1 | 1200 | 501 |
| 0.4498 | 1 | 4 | 3 | 500 | 502 |
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| 0.4509 | 2 | 3 | 3 | 200 | 504 |
| 0.4514 | 1 | 1 | 3 | 1000099 | 505 |
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| 0.4520 | 2 | 1 | 2 | 1000080 | 507 |
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| 0.4522 | 3 | 2 | 1 | 1000001 | 509 |
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| 0.4537 | 3 | 3 | 2 | 110 | 512 |
| 0.4542 | 2 | 4 | 1 | 2000 | 513 |
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| 0.4555 | 2 | 3 | 2 | 900 | 520 |
| 0.4565 | 3 | 3 | 1 | 1000 | 521 |
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| 0.4586 | 3 | 3 | 2 | 100 | 526 |
| 0.4587 | 3 | 4 | 1 | 400 | 527 |
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| 0.4602 | 2 | 4 | 2 | 300 | 533 |
| 0.4608 | 2 | 3 | 1 | 1000010 | 534 |
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| 0.4618 | 2 | 3 | 3 | 100 | 538 |
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| 0.4658 | 1 | 3 | 3 | 900 | 549 |
| 0.4659 | 1 | 1 | 3 | 1000076.768 | 550 |
| 0.4660 | 2 | 4 | 1 | 1500 | 551 |
| 0.4660 | 1 | 3 | 2 | 1000001 | 552 |
| 0.4663 | 2 | 2 | 1 | 1000090 | 553 |
| 0.4665 | 2 | 1 | 2 | 1000060 | 554 |
| 0.4675 | 3 | 2 | 1 | 5000 | 555 |
| 0.4682 | 1 | 2 | 3 | 5000 | 556 |
| 0.4686 | 1 | 4 | 1 | 1000040 | 557 |
| 0.4688 | 3 | 1 | 1 | 1000070 | 558 |
| 0.4695 | 1 | 1 | 3 | 1000070 | 559 |
| 0.4696 | 3 | 2 | 2 | 600 | 560 |
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| 0.4698 | 2 | 3 | 2 | 793.3002481 | 562 |
| 0.4705 | 1 | 4 | 3 | 300 | 563 |
| 0.4708 | 1 | 2 | 2 | 1000080 | 564 |
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| 0.4711 | 3 | 1 | 3 | 500 | 567 |
| 0.4715 | 2 | 4 | 2 | 200 | 568 |
| 0.4728 | 2 | 2 | 3 | 600 | 569 |
| 0.4731 | 3 | 1 | 2 | 2000 | 570 |
| 0.4732 | 2 | 3 | 1 | 19900 | 571 |
| 0.4733 | 2 | 2 | 1 | 1000080 | 572 |
| 0.4741 | 3 | 2 | 2 | 580 | 573 |
| 0.4742 | 2 | 3 | 3 | 10 | 574 |
| 0.4743 | 2 | 3 | 1 | 12402.32252 | 575 |
| 0.4748 | 2 | 3 | 1 | 9902.089379 | 576 |
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| 0.4752 | 2 | 3 | 2 | 700 | 578 |
| 0.4756 | 1 | 3 | 3 | 800 | 579 |
| 0.4761 | 3 | 1 | 1 | 1000060 | 580 |
| 0.4763 | 2 | 1 | 3 | 2000 | 581 |
| 0.4768 | 2 | 1 | 2 | 1000049.984 | 582 |
| 0.4777 | 1 | 4 | 2 | 1000 | 583 |
| 0.4781 | 1 | 2 | 2 | 1000070 | 584 |
| 0.4782 | 3 | 3 | 2 | 0.036 | 585 |
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| 0.4796 | 1 | 4 | 1 | 1000028 | 587 |
| 0.4797 | 3 | 3 | 1 | 784.643 | 588 |
| 0.4797 | 3 | 2 | 2 | 500 | 589 |
| 0.4799 | 1 | 1 | 3 | 1000059.964 | 590 |

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| 0.4802 | 2 | 4 | 1 | 1000 | 591 |
| 0.4804 | 1 | 4 | 1 | 1000021.087 | 592 |
| 0.4804 | 2 | 1 | 2 | 1000040 | 593 |
| 0.4806 | 2 | 2 | 1 | 1000070 | 594 |
| 0.4807 | 3 | 2 | 1 | 3000 | 595 |
| 0.4808 | 3 | 1 | 3 | 400 | 596 |
| 0.4810 | 3 | 4 | 1 | 200 | 597 |
| 0.4813 | 1 | 3 | 2 | 5000 | 598 |
| 0.4814 | 1 | 2 | 3 | 3000 | 599 |
| 0.4817 | 1 | 4 | 3 | 200 | 600 |
| 0.4824 | 2 | 4 | 2 | 100 | 601 |
| 0.4827 | 3 | 1 | 1 | 1000050 | 602 |
| 0.4829 | 2 | 2 | 3 | 500 | 603 |
| 0.4834 | 1 | 1 | 3 | 1000050 | 604 |
| 0.4843 | 2 | 1 | 2 | 1000030.093 | 605 |
| 0.4848 | 3 | 3 | 1 | 700 | 606 |
| 0.4848 | 2 | 2 | 2 | 2000 | 607 |
| 0.4848 | 3 | 1 | 2 | 1500 | 608 |
| 0.4853 | 1 | 2 | 2 | 1000060 | 609 |
| 0.4855 | 1 | 3 | 3 | 700 | 610 |
| 0.4859 | 2 | 3 | 2 | 600 | 611 |
| 0.4862 | 3 | 4 | 1 | 150 | 612 |
| 0.4863 | 1 | 4 | 2 | 900 | 613 |
| 0.4866 | 1 | 3 | 1 | 1000090.023 | 614 |
| 0.4878 | 2 | 2 | 1 | 1000060 | 615 |
| 0.4879 | 2 | 3 | 1 | 4900 | 616 |
| 0.4880 | 2 | 1 | 3 | 1500 | 617 |
| 0.4882 | 1 | 4 | 1 | 1000012.664 | 618 |
| 0.4886 | 2 | 3 | 1 | 4515.333333 | 619 |
| 0.4888 | 2 | 4 | 1 | 900 | 620 |
| 0.4893 | 3 | 2 | 2 | 400 | 621 |
| 0.4894 | 2 | 3 | 1 | 4110.526316 | 622 |
| 0.4900 | 3 | 1 | 1 | 1000040 | 623 |
| 0.4902 | 3 | 3 | 1 | 620 | 624 |
| 0.4904 | 2 | 3 | 1 | 3900 | 625 |
| 0.4911 | 2 | 3 | 1 | 3723.68034 | 626 |
| 0.4918 | 3 | 1 | 3 | 300 | 627 |
| 0.4920 | 3 | 4 | 1 | 100 | 628 |
| 0.4920 | 1 | 2 | 2 | 1000050 | 629 |
| 0.4925 | 2 | 2 | 3 | 400 | 630 |
| 0.4927 | 1 | 4 | 3 | 100 | 631 |
| 0.4928 | 2 | 3 | 1 | 3232.910819 | 632 |
| 0.4943 | 1 | 1 | 3 | 1000039.985 | 633 |
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| 0.4948 | 2 | 4 | 2 | 10 | 637 |
| 0.4951 | 1 | 2 | 3 | 2000 | 638 |
| 0.4960 | 2 | 3 | 2 | 500 | 639 |
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| 0.4962 | 1 | 3 | 3 | 600 | 641 |
| 0.4966 | 2 | 2 | 2 | 1500 | 642 |
| 0.4970 | 3 | 1 | 1 | 1000030 | 643 |
| 0.4977 | 1 | 1 | 3 | 1000030 | 644 |
| 0.4981 | 3 | 1 | 3 | 203 | 645 |
| 0.4986 | 2 | 4 | 1 | 800 | 646 |
| 0.4991 | 3 | 1 | 2 | 1000 | 647 |
| 0.4992 | 2 | 1 | 2 | 1000019.992 | 648 |
| 0.4992 | 1 | 2 | 2 | 1000040 | 649 |
| 0.5001 | 1 | 3 | 1 | 1000079.971 | 650 |
| 0.5004 | 3 | 2 | 2 | 300 | 651 |
| 0.5017 | 2 | 2 | 1 | 1000040 | 652 |
| 0.5020 | 1 | 1 | 3 | 1000025.403 | 653 |
| 0.5023 | 2 | 1 | 3 | 1000 | 654 |
| 0.5025 | 2 | 3 | 1 | 2757.000796 | 655 |
| 0.5027 | 1 | 1 | 3 | 1000020.04 | 656 |
| 0.5036 | 2 | 2 | 3 | 300 | 657 |
| 0.5040 | 1 | 3 | 1 | 1000070 | 658 |
| 0.5043 | 3 | 4 | 1 | 10 | 659 |
| 0.5047 | 2 | 3 | 1 | 2400 | 660 |
| 0.5050 | 1 | 4 | 3 | 10 | 661 |
| 0.5054 | 3 | 1 | 1 | 1000020 | 662 |
| 0.5056 | 3 | 3 | 1 | 500 | 663 |
| 0.5056 | 2 | 3 | 2 | 400 | 664 |
| 0.5057 | 2 | 3 | 1 | 2299.783817 | 665 |
| 0.5060 | 1 | 4 | 2 | 700 | 666 |
| 0.5061 | 3 | 2 | 1 | 1500 | 667 |
| 0.5062 | 2 | 3 | 1 | 2122.447796 | 668 |
| 0.5062 | 1 | 2 | 2 | 1000030 | 669 |
| 0.5063 | 1 | 3 | 3 | 500 | 670 |
| 0.5068 | 2 | 1 | 2 | 1000009.028 | 671 |
| 0.5069 | 1 | 2 | 3 | 1500 | 672 |
| 0.5077 | 3 | 1 | 2 | 900 | 673 |
| 0.5078 | 1 | 3 | 1 | 1000060.017 | 674 |
| 0.5082 | 1 | 3 | 2 | 2000 | 675 |
| 0.5085 | 2 | 4 | 1 | 700 | 676 |
| 0.5087 | 2 | 2 | 1 | 1000030 | 677 |
| 0.5094 | 3 | 1 | 3 | 100.9765625 | 678 |
| 0.5104 | 3 | 4 | 1 | 0.334448161 | 679 |
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| 0.5130 | 3 | 1 | 1 | 1000010 | 683 |
| 0.5146 | 1 | 4 | 1 | 5000 | 684 |
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| 0.5156 | 2 | 3 | 1 | 1899.680851 | 688 |
| 0.5159 | 1 | 3 | 3 | 400 | 689 |
| 0.5163 | 2 | 1 | 2 | 16564.60587 | 690 |
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| 0.5171 | 2 | 2 | 1 | 1000020 | 694 |
| 0.5172 | 2 | 3 | 1 | 1627.277778 | 695 |
| 0.5175 | 3 | 1 | 2 | 800 | 696 |
| 0.5175 | 1 | 1 | 3 | 1000007.692 | 697 |
| 0.5179 | 1 | 3 | 1 | 1000050 | 698 |
| 0.5191 | 2 | 1 | 2 | 8272.093023 | 699 |
| 0.5192 | 2 | 4 | 1 | 600 | 700 |
| 0.5194 | 2 | 2 | 2 | 900 | 701 |
| 0.5200 | 1 | 3 | 2 | 1500 | 702 |
| 0.5201 | 3 | 3 | 1 | 399.9864462 | 703 |
| 0.5204 | 3 | 2 | 1 | 1000 | 704 |
| 0.5207 | 2 | 1 | 3 | 800 | 705 |
| 0.5207 | 3 | 1 | 1 | 1000001 | 706 |
| 0.5211 | 1 | 2 | 3 | 1000 | 707 |
| 0.5213 | 3 | 3 | 1 | 304.04 | 708 |
| 0.5215 | 2 | 1 | 2 | 6106.896552 | 709 |
| 0.5221 | 2 | 3 | 2 | 220 | 710 |
| 0.5222 | 1 | 2 | 2 | 1000010 | 711 |
| 0.5225 | 2 | 3 | 1 | 1500 | 712 |
| 0.5226 | 3 | 2 | 2 | 100 | 713 |
| 0.5246 | 1 | 1 | 3 | 1000000.7 | 714 |
| 0.5247 | 2 | 2 | 1 | 1000010 | 715 |
| 0.5251 | 1 | 3 | 1 | 1000040 | 716 |
| 0.5258 | 2 | 2 | 3 | 100 | 717 |
| 0.5264 | 3 | 1 | 3 | 10 | 718 |
| 0.5268 | 1 | 4 | 2 | 500 | 719 |
| 0.5270 | 1 | 3 | 3 | 300 | 720 |
| 0.5274 | 3 | 1 | 2 | 700 | 721 |
| 0.5274 | 1 | 1 | 3 | 10185.71429 | 722 |
| 0.5277 | 2 | 3 | 1 | 1399.916504 | 723 |
| 0.5278 | 1 | 4 | 1 | 3000 | 724 |
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| 0.5287 | 2 | 3 | 1 | 1236.734694 | 726 |
| 0.5290 | 1 | 1 | 2 | 1000094.995 | 727 |
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| 0.5292 | 2 | 2 | 2 | 800 | 729 |
| 0.5293 | 2 | 4 | 1 | 500 | 730 |
| 0.5297 | 1 | 2 | 3 | 900 | 731 |
| 0.5299 | 1 | 2 | 2 | 1000001 | 732 |
| 0.5305 | 2 | 1 | 2 | 4900 | 733 |
| 0.5306 | 2 | 1 | 3 | 700 | 734 |
| 0.5314 | 2 | 3 | 1 | 1100.057422 | 735 |
| 0.5322 | 3 | 3 | 1 | 210 | 736 |
| 0.5323 | 2 | 1 | 2 | 4066.666667 | 737 |
| 0.5324 | 2 | 2 | 1 | 1000001 | 738 |
| 0.5327 | 3 | 1 | 3 | 0.046666667 | 739 |
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| 0.5335 | 2 | 3 | 2 | 116.6666667 | 741 |
| 0.5342 | 1 | 3 | 2 | 1000 | 742 |
| 0.5348 | 2 | 1 | 1 | 1000090 | 743 |
| 0.5350 | 3 | 2 | 2 | 10 | 744 |
| 0.5353 | 1 | 1 | 2 | 1000089.983 | 745 |
| 0.5355 | 1 | 3 | 1 | 1000028.571 | 746 |
| 0.5360 | 3 | 1 | 1 | 5000 | 747 |
| 0.5364 | 1 | 4 | 2 | 400 | 748 |
| 0.5367 | 1 | 1 | 3 | 5000 | 749 |
| 0.5381 | 3 | 1 | 2 | 600 | 750 |
| 0.5381 | 2 | 2 | 3 | 10 | 751 |
| 0.5383 | 1 | 3 | 3 | 200 | 752 |
| 0.5388 | 3 | 2 | 1 | 800 | 753 |
| 0.5389 | 2 | 4 | 1 | 400 | 754 |
| 0.5391 | 2 | 2 | 2 | 700 | 755 |
| 0.5393 | 1 | 1 | 2 | 1000080 | 756 |
| 0.5395 | 1 | 2 | 3 | 800 | 757 |
| 0.5396 | 2 | 1 | 2 | 3000 | 758 |
| 0.5401 | 3 | 2 | 2 | 4 | 759 |
| 0.5405 | 1 | 3 | 1 | 1000020 | 760 |
| 0.5413 | 2 | 1 | 3 | 600 | 761 |
| 0.5415 | 1 | 4 | 1 | 2000 | 762 |
| 0.5418 | 2 | 1 | 1 | 1000080 | 763 |
| 0.5423 | 3 | 3 | 1 | 155 | 764 |
| 0.5428 | 1 | 3 | 2 | 900 | 765 |
| 0.5435 | 3 | 3 | 1 | 110 | 766 |
| 0.5448 | 2 | 1 | 2 | 2757.868383 | 767 |
| 0.5452 | 1 | 2 | 2 | 5000 | 768 |
| 0.5453 | 2 | 3 | 1 | 900 | 769 |
| 0.5461 | 2 | 1 | 2 | 2500 | 770 |
| 0.5466 | 1 | 1 | 2 | 1000070 | 771 |
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| 0.5482 | 3 | 1 | 2 | 500 | 775 |
| 0.5487 | 3 | 2 | 1 | 700 | 776 |
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| 0.5492 | 1 | 3 | 3 | 100 | 778 |
| 0.5492 | 3 | 1 | 1 | 3000 | 779 |
| 0.5494 | 1 | 2 | 3 | 700 | 780 |
| 0.5498 | 2 | 2 | 2 | 600 | 781 |
| 0.5499 | 1 | 1 | 3 | 3000 | 782 |
| 0.5500 | 2 | 3 | 1 | 861.5277778 | 783 |
| 0.5500 | 2 | 4 | 1 | 300 | 784 |
| 0.5507 | 1 | 1 | 2 | 1000060.004 | 785 |
| 0.5513 | 2 | 3 | 2 | 10 | 786 |
| 0.5514 | 2 | 1 | 3 | 500 | 787 |
| 0.5520 | 1 | 3 | 1 | 1000007.692 | 788 |
| 0.5526 | 1 | 3 | 2 | 800 | 789 |
| 0.5533 | 1 | 4 | 1 | 1500 | 790 |
| 0.5533 | 2 | 1 | 2 | 2000 | 791 |
| 0.5536 | 1 | 2 | 1 | 1000090 | 792 |
| 0.5541 | 3 | 3 | 1 | 50 | 793 |
| 0.5547 | 1 | 1 | 3 | 2862.962963 | 794 |
| 0.5551 | 2 | 3 | 1 | 800 | 795 |
| 0.5563 | 2 | 1 | 1 | 1000060 | 796 |
| 0.5578 | 3 | 1 | 2 | 400 | 797 |
| 0.5579 | 2 | 3 | 2 | 0.046313449 | 798 |
| 0.5584 | 1 | 2 | 2 | 3000 | 799 |
| 0.5585 | 2 | 1 | 2 | 1899.652023 | 800 |
| 0.5588 | 1 | 3 | 1 | 1000000.709 | 801 |
| 0.5588 | 1 | 4 | 2 | 200 | 802 |
| 0.5594 | 3 | 2 | 1 | 600 | 803 |
| 0.5599 | 2 | 2 | 2 | 500 | 804 |
| 0.5601 | 1 | 2 | 3 | 600 | 805 |
| 0.5605 | 1 | 1 | 2 | 1000050 | 806 |
| 0.5606 | 1 | 2 | 1 | 1000080 | 807 |
| 0.5608 | 3 | 3 | 1 | 10 | 808 |
| 0.5609 | 2 | 1 | 2 | 1566.666667 | 809 |
| 0.5609 | 2 | 2 | 1 | 3000 | 810 |
| 0.5610 | 2 | 1 | 3 | 400 | 811 |
| 0.5613 | 2 | 4 | 1 | 200 | 812 |
| 0.5616 | 1 | 3 | 3 | 10 | 813 |
| 0.5625 | 1 | 3 | 2 | 700 | 814 |
| 0.5629 | 3 | 1 | 1 | 2000 | 815 |
| 0.5629 | 2 | 1 | 1 | 1000050 | 816 |
| 0.5634 | 3 | 1 | 2 | 370.34 | 817 |
| 0.5636 | 1 | 1 | 3 | 2000 | 818 |
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| 0.5675 | 1 | 4 | 1 | 1000 | 820 |

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| 0.5677 | 3 | 3 | 1 | 0.04 | 821 |
| 0.5677 | 1 | 1 | 2 | 1000040 | 822 |
| 0.5679 | 1 | 2 | 1 | 1000070 | 823 |
| 0.5689 | 3 | 1 | 2 | 300 | 824 |
| 0.5695 | 3 | 2 | 1 | 500 | 825 |
| 0.5695 | 2 | 2 | 2 | 400 | 826 |
| 0.5697 | 1 | 4 | 2 | 100 | 827 |
| 0.5700 | 2 | 3 | 1 | 650 | 828 |
| 0.5702 | 1 | 2 | 3 | 500 | 829 |
| 0.5702 | 2 | 1 | 1 | 1000040 | 830 |
| 0.5711 | 1 | 3 | 1 | 5000 | 831 |
| 0.5715 | 1 | 1 | 3 | 1530 | 832 |
| 0.5716 | 2 | 1 | 2 | 1233.733418 | 833 |
| 0.5721 | 2 | 1 | 3 | 300 | 834 |
| 0.5721 | 1 | 2 | 2 | 2000 | 835 |
| 0.5722 | 2 | 4 | 1 | 100 | 836 |
| 0.5732 | 1 | 3 | 2 | 600 | 837 |
| 0.5737 | 2 | 1 | 2 | 1148 | 838 |
| 0.5746 | 2 | 2 | 1 | 2000 | 839 |
| 0.5746 | 3 | 1 | 1 | 1500 | 840 |
| 0.5750 | 2 | 1 | 2 | 1011.111111 | 841 |
| 0.5751 | 1 | 2 | 1 | 1000060 | 842 |
| 0.5757 | 2 | 3 | 1 | 600 | 843 |
| 0.5761 | 1 | 4 | 1 | 900 | 844 |
| 0.5772 | 2 | 1 | 1 | 1000030 | 845 |
| 0.5780 | 1 | 3 | 2 | 566.6666667 | 846 |
| 0.5782 | 1 | 1 | 2 | 1000028.571 | 847 |
| 0.5791 | 3 | 2 | 1 | 400 | 848 |
| 0.5798 | 1 | 2 | 3 | 400 | 849 |
| 0.5799 | 1 | 1 | 3 | 1400 | 850 |
| 0.5802 | 3 | 1 | 2 | 200 | 851 |
| 0.5806 | 2 | 2 | 2 | 300 | 852 |
| 0.5808 | 1 | 1 | 3 | 1316.665 | 853 |
| 0.5818 | 1 | 2 | 1 | 1000050 | 854 |
| 0.5821 | 1 | 4 | 2 | 10 | 855 |
| 0.5822 | 1 | 1 | 3 | 1233.335 | 856 |
| 0.5831 | 1 | 1 | 2 | 1000020 | 857 |
| 0.5833 | 1 | 3 | 2 | 500 | 858 |
| 0.5833 | 2 | 1 | 3 | 200 | 859 |
| 0.5834 | 1 | 1 | 3 | 1150 | 860 |
| 0.5839 | 1 | 2 | 2 | 1500 | 861 |
| 0.5843 | 1 | 3 | 1 | 3000 | 862 |
| 0.5846 | 2 | 4 | 1 | 10 | 863 |
| 0.5853 | 3 | 1 | 2 | 150 | 864 |
| 0.5856 | 2 | 1 | 1 | 1000020 | 865 |
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| 0.5859 | 1 | 4 | 1 | 800 | 867 |
| 0.5864 | 2 | 2 | 1 | 1500 | 868 |
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| 0.5889 | 3 | 1 | 1 | 1000 | 870 |
| 0.5890 | 1 | 2 | 1 | 1000040 | 871 |
| 0.5902 | 3 | 2 | 1 | 300 | 872 |
| 0.5907 | 1 | 1 | 2 | 1000010 | 873 |
| 0.5909 | 1 | 2 | 3 | 300 | 874 |
| 0.5911 | 3 | 1 | 2 | 100 | 875 |
| 0.5919 | 2 | 2 | 2 | 200 | 876 |
| 0.5920 | 1 | 3 | 1 | 2400 | 877 |
| 0.5929 | 1 | 3 | 2 | 400 | 878 |
| 0.5932 | 2 | 1 | 1 | 1000010 | 879 |
| 0.5943 | 2 | 1 | 3 | 100 | 880 |
| 0.5954 | 2 | 3 | 1 | 400 | 881 |
| 0.5955 | 1 | 1 | 2 | 1000001.01 | 882 |
| 0.5958 | 1 | 4 | 1 | 700 | 883 |
| 0.5960 | 1 | 2 | 1 | 1000030 | 884 |
| 0.5975 | 3 | 1 | 1 | 900 | 885 |
| 0.5977 | 2 | 1 | 2 | 800 | 886 |
| 0.5980 | 1 | 3 | 1 | 2000 | 887 |
| 0.5982 | 1 | 2 | 2 | 1000 | 888 |
| 0.5982 | 1 | 1 | 3 | 900 | 889 |
| 0.5999 | 2 | 1 | 3 | 50 | 890 |
| 0.6006 | 2 | 1 | 3 | 16.66666667 | 891 |
| 0.6006 | 2 | 2 | 1 | 1000 | 892 |
| 0.6009 | 2 | 1 | 1 | 1000001 | 893 |
| 0.6015 | 3 | 2 | 1 | 200 | 894 |
| 0.6022 | 1 | 2 | 3 | 200 | 895 |
| 0.6028 | 2 | 2 | 2 | 100 | 896 |
| 0.6034 | 1 | 1 | 3 | 816.665 | 897 |
| 0.6034 | 3 | 1 | 2 | 10 | 898 |
| 0.6040 | 1 | 3 | 2 | 300 | 899 |
| 0.6045 | 1 | 2 | 1 | 1000020 | 900 |
| 0.6053 | 1 | 3 | 1 | 1566.699629 | 901 |
| 0.6065 | 2 | 3 | 1 | 300 | 902 |
| 0.6066 | 1 | 4 | 1 | 600 | 903 |
| 0.6066 | 2 | 1 | 3 | 10 | 904 |
| 0.6067 | 1 | 2 | 2 | 900 | 905 |
| 0.6073 | 3 | 1 | 1 | 800 | 906 |
| 0.6076 | 2 | 1 | 2 | 700 | 907 |
| 0.6092 | 2 | 2 | 1 | 900 | 908 |
| 0.6097 | 1 | 3 | 2 | 212.5 | 909 |
| 0.6120 | 1 | 2 | 1 | 1000010 | 910 |
| 0.6124 | 3 | 2 | 1 | 100 | 911 |
| 0.6131 | 1 | 1 | 3 | 733.335 | 912 |

| | | | | | |
|---|---|---|---|---|---|
| 0.6131 | 1 | 2 | 3 | 100 | 913 |
| 0.6133 | 2 | 1 | 2 | 614.2857143 | 914 |
| 0.6137 | 1 | 1 | 2 | 5000 | 915 |
| 0.6152 | 2 | 2 | 2 | 10 | 916 |
| 0.6162 | 2 | 1 | 1 | 5000 | 917 |
| 0.6165 | 1 | 2 | 2 | 800 | 918 |
| 0.6166 | 1 | 4 | 1 | 500 | 919 |
| 0.6172 | 3 | 1 | 1 | 700 | 920 |
| 0.6178 | 2 | 3 | 1 | 200 | 921 |
| 0.6179 | 1 | 3 | 1 | 1150 | 922 |
| 0.6190 | 2 | 2 | 1 | 800 | 923 |
| 0.6197 | 1 | 2 | 1 | 1000001 | 924 |
| 0.6221 | 1 | 1 | 1 | 1000090 | 925 |
| 0.6234 | 2 | 1 | 2 | 524.6478873 | 926 |
| 0.6239 | 1 | 1 | 3 | 608.335 | 927 |
| 0.6248 | 3 | 2 | 1 | 10 | 928 |
| 0.6255 | 1 | 2 | 3 | 10 | 929 |
| 0.6262 | 1 | 3 | 2 | 100 | 930 |
| 0.6262 | 1 | 4 | 1 | 400 | 931 |
| 0.6264 | 1 | 2 | 2 | 700 | 932 |
| 0.6279 | 3 | 1 | 1 | 600 | 933 |
| 0.6287 | 2 | 3 | 1 | 100 | 934 |
| 0.6289 | 2 | 2 | 1 | 700 | 935 |
| 0.6291 | 1 | 1 | 1 | 1000080 | 936 |
| 0.6294 | 2 | 1 | 1 | 3000 | 937 |
| 0.6311 | 1 | 1 | 2 | 2900 | 938 |
| 0.6326 | 1 | 3 | 1 | 900 | 939 |
| 0.6334 | 1 | 3 | 2 | 11.11111111 | 940 |
| 0.6346 | 1 | 1 | 2 | 2400 | 941 |
| 0.6350 | 1 | 2 | 1 | 5000 | 942 |
| 0.6359 | 2 | 3 | 1 | 11.11111111 | 943 |
| 0.6364 | 1 | 1 | 1 | 1000070 | 944 |
| 0.6372 | 1 | 2 | 2 | 600 | 945 |
| 0.6373 | 1 | 4 | 1 | 300 | 946 |
| 0.6380 | 3 | 1 | 1 | 500 | 947 |
| 0.6380 | 2 | 1 | 2 | 400 | 948 |
| 0.6387 | 1 | 1 | 3 | 500 | 949 |
| 0.6397 | 2 | 2 | 1 | 600 | 950 |
| 0.6406 | 1 | 1 | 2 | 2000 | 951 |
| 0.6424 | 1 | 3 | 1 | 800 | 952 |
| 0.6431 | 2 | 1 | 1 | 2000 | 953 |
| 0.6436 | 1 | 1 | 1 | 1000060 | 954 |
| 0.6472 | 1 | 2 | 2 | 500 | 955 |
| 0.6476 | 3 | 1 | 1 | 400 | 956 |
| 0.6482 | 1 | 2 | 1 | 3000 | 957 |
| 0.6483 | 1 | 1 | 3 | 400 | 958 |

| | | | | | |
|---|---|---|---|---|---|
| 0.6486 | 1 | 4 | 1 | 200 | 959 |
| 0.6491 | 2 | 1 | 2 | 300 | 960 |
| 0.6497 | 2 | 2 | 1 | 500 | 961 |
| 0.6503 | 1 | 1 | 1 | 1000050 | 962 |
| 0.6523 | 1 | 3 | 1 | 700 | 963 |
| 0.6524 | 1 | 1 | 2 | 1500 | 964 |
| 0.6549 | 2 | 1 | 1 | 1500 | 965 |
| 0.6556 | 2 | 1 | 2 | 200.0278242 | 966 |
| 0.6569 | 1 | 2 | 2 | 400 | 967 |
| 0.6573 | 1 | 3 | 1 | 650 | 968 |
| 0.6575 | 1 | 1 | 1 | 1000040 | 969 |
| 0.6587 | 3 | 1 | 1 | 300 | 970 |
| 0.6593 | 2 | 2 | 1 | 400 | 971 |
| 0.6594 | 1 | 1 | 3 | 300 | 972 |
| 0.6595 | 1 | 4 | 1 | 100 | 973 |
| 0.6619 | 1 | 2 | 1 | 2000 | 974 |
| 0.6631 | 1 | 3 | 1 | 600 | 975 |
| 0.6645 | 1 | 1 | 1 | 1000030 | 976 |
| 0.6667 | 1 | 1 | 2 | 1000 | 977 |
| 0.6679 | 1 | 2 | 2 | 300 | 978 |
| 0.6691 | 2 | 1 | 1 | 1000 | 979 |
| 0.6700 | 3 | 1 | 1 | 200 | 980 |
| 0.6704 | 2 | 2 | 1 | 300 | 981 |
| 0.6707 | 1 | 1 | 3 | 200 | 982 |
| 0.6719 | 1 | 4 | 1 | 10 | 983 |
| 0.6730 | 1 | 1 | 1 | 1000020 | 984 |
| 0.6731 | 1 | 3 | 1 | 500 | 985 |
| 0.6737 | 1 | 2 | 1 | 1500 | 986 |
| 0.6752 | 1 | 1 | 2 | 900 | 987 |
| 0.6759 | 2 | 1 | 2 | 99.97211378 | 988 |
| 0.6777 | 2 | 1 | 1 | 900 | 989 |
| 0.6792 | 1 | 2 | 2 | 200 | 990 |
| 0.6805 | 1 | 1 | 1 | 1000010 | 991 |
| 0.6809 | 3 | 1 | 1 | 100 | 992 |
| 0.6817 | 2 | 2 | 1 | 200 | 993 |
| 0.6827 | 1 | 3 | 1 | 400 | 994 |
| 0.6850 | 1 | 1 | 2 | 800 | 995 |
| 0.6875 | 2 | 1 | 1 | 800 | 996 |
| 0.6880 | 1 | 2 | 1 | 1000 | 997 |
| 0.6882 | 1 | 1 | 1 | 1000001 | 998 |
| 0.6883 | 1 | 1 | 3 | 12 | 999 |
| 0.6892 | 2 | 1 | 2 | 1.01010101 | 1000 |
| 0.6901 | 1 | 2 | 2 | 100 | 1001 |
| 0.6926 | 2 | 2 | 1 | 100 | 1002 |
| 0.6933 | 3 | 1 | 1 | 10 | 1003 |
| 0.6938 | 1 | 3 | 1 | 300 | 1004 |

| | | | | | |
|---|---|---|---|---|---|
| 0.6949 | 1 | 1 | 2 | 700 | 1005 |
| 0.6965 | 1 | 2 | 1 | 900 | 1006 |
| 0.6974 | 2 | 1 | 1 | 700 | 1007 |
| 0.7025 | 1 | 2 | 2 | 10 | 1008 |
| 0.7035 | 1 | 1 | 1 | 5000 | 1009 |
| 0.7050 | 2 | 2 | 1 | 10 | 1010 |
| 0.7051 | 1 | 3 | 1 | 200 | 1011 |
| 0.7057 | 1 | 1 | 2 | 600 | 1012 |
| 0.7063 | 1 | 2 | 1 | 800 | 1013 |
| 0.7081 | 2 | 1 | 1 | 600 | 1014 |
| 0.7157 | 1 | 1 | 2 | 500 | 1015 |
| 0.7162 | 1 | 2 | 1 | 700 | 1016 |
| 0.7167 | 1 | 1 | 1 | 3000 | 1017 |
| 0.7182 | 2 | 1 | 1 | 500 | 1018 |
| 0.7210 | 1 | 3 | 1 | 99.84152139 | 1019 |
| 0.7270 | 1 | 2 | 1 | 600 | 1020 |
| 0.7278 | 2 | 1 | 1 | 400 | 1021 |
| 0.7304 | 1 | 1 | 1 | 2000 | 1022 |
| 0.7306 | 1 | 1 | 2 | 399.4219653 | 1023 |
| 0.7330 | 1 | 3 | 1 | 8.695652174 | 1024 |
| 0.7370 | 1 | 2 | 1 | 500 | 1025 |
| 0.7389 | 2 | 1 | 1 | 300 | 1026 |
| 0.7415 | 1 | 1 | 2 | 299.9442276 | 1027 |
| 0.7422 | 1 | 1 | 1 | 1500 | 1028 |
| 0.7467 | 1 | 2 | 1 | 400 | 1029 |
| 0.7477 | 1 | 1 | 2 | 200 | 1030 |
| 0.7502 | 2 | 1 | 1 | 200 | 1031 |
| 0.7565 | 1 | 1 | 1 | 1000 | 1032 |
| 0.7577 | 1 | 2 | 1 | 300 | 1033 |
| 0.7586 | 1 | 1 | 2 | 100 | 1034 |
| 0.7611 | 2 | 1 | 1 | 100 | 1035 |
| 0.7650 | 1 | 1 | 1 | 900 | 1036 |
| 0.7664 | 1 | 1 | 2 | 11.09375 | 1037 |
| 0.7690 | 1 | 2 | 1 | 200 | 1038 |
| 0.7735 | 2 | 1 | 1 | 10 | 1039 |
| 0.7748 | 1 | 1 | 1 | 800 | 1040 |
| 0.7799 | 1 | 2 | 1 | 100 | 1041 |
| 0.7847 | 1 | 1 | 1 | 700 | 1042 |
| 0.7923 | 1 | 2 | 1 | 10 | 1043 |
| 0.7955 | 1 | 1 | 1 | 600 | 1044 |
| 0.8055 | 1 | 1 | 1 | 500 | 1045 |
| 0.8152 | 1 | 1 | 1 | 400 | 1046 |
| 0.8262 | 1 | 1 | 1 | 300 | 1047 |
| 0.8375 | 1 | 1 | 1 | 200 | 1048 |
| 0.8484 | 1 | 1 | 1 | 100 | 1049 |
| 0.8608 | 1 | 1 | 1 | 10 | 1050 |

# APPENDIX D. PAIRWISE COMPARISON SURVEYS

**QUESTION 2:**
**How much impact does each risk factor have on the overall risk of IV harm for the scenario type?**
Please compare each pair of risk factors and select the relative impact using the following linguistic variables.

*Example 1 - If you think risk factor A has* ***strong impact*** *than risk factor B on overall risk of IV harm:*
***Please Press Ctrl + B*** ***to select your answer***

| | ***Relative Impact*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **factor A** | Very Strong | **Strong** | Moderate | Equal | Moderate | Strong | Very Strong | **factor B** |

*Example 2 - If you think risk factor B has* ***moderate impact*** *than risk factor A on overall risk of IV harm:*
***Please Press Ctrl + B*** ***to select your answer***

| | ***Relative Impact*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **factor A** | Very Strong | Strong | Moderate | Equal | **Moderate** | Strong | Very Strong | **factor B** |

**ASSESSMENT TABLE:**

| ***Care Area*** | ***Relative Impact*** | | | | | | | ***Medication*** |
|---|---|---|---|---|---|---|---|---|
| **Adult Intensive Care Unit** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **Propofol** |

| ***Care Area*** | | | | | | | | ***Field Limit Type &Soft Max Limits*** |
|---|---|---|---|---|---|---|---|---|
| **Adult Intensive Care Unit** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **Continuous Dose (51 mcg/kg.min)** |

| ***Care Area*** | | | | | | | | ***Hard Max Drug Limits Provided?*** |
|---|---|---|---|---|---|---|---|---|
| **Adult Intensive Care Unit** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **Yes (80 mcg/kg.min)** |

| ***Care Area*** | | | | | | | | ***Infusion Rate and Ratio*** |
|---|---|---|---|---|---|---|---|---|
| **Adult Intensive Care Unit** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **56, 68, 80 mcg/kg.min (Ratio: 1.1, 1.3, 1.6)** |

| ***Care Area*** | | | | | | | | ***Drug Amount*** |
|---|---|---|---|---|---|---|---|---|
| **Adult Intensive Care Unit** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **50, 530, 1000 mg (5, 53, 100 mL)** |

| ***Medication*** | | | | | | | | ***Field Limit Type &Soft Max Limits*** |
|---|---|---|---|---|---|---|---|---|
| **Propofol** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **Continuous Dose (51 mcg/kg.min)** |

| ***Medication*** | | | | | | | | ***Hard Max Drug Limits Provided?*** |
|---|---|---|---|---|---|---|---|---|
| **Propofol** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **Yes (80 mcg/kg.min)** |

| ***Medication*** | | | | | | | | ***Infusion Rate and Ratio*** |
|---|---|---|---|---|---|---|---|---|
| **Propofol** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **56, 68, 80 mcg/kg.min (Ratio: 1.1, 1.3, 1.6)** |

| ***Medication*** | | | | | | | | ***Drug Amount*** |
|---|---|---|---|---|---|---|---|---|
| **Propofol** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **50, 530, 1000 mg (5, 53, 100 mL)** |

| ***Field Limit Type &Soft Max Limits*** | | | | | | | | ***Hard Max Drug Limits Provided?*** |
|---|---|---|---|---|---|---|---|---|
| **Continuous Dose (51 mcg/kg.min)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **Yes (80 mcg/kg.min)** |

| ***Field Limit Type &Soft Max Limits*** | | | | | | | | ***Infusion Rate and Ratio*** |
|---|---|---|---|---|---|---|---|---|
| **Continuous Dose (51 mcg/kg.min)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **56, 68, 80 mcg/kg.min (Ratio: 1.1, 1.3, 1.6)** |

| ***Field Limit Type &Soft Max Limits*** | | | | | | | | ***Drug Amount*** |
|---|---|---|---|---|---|---|---|---|
| **Continuous Dose (51 mcg/kg.min)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **50, 530, 1000 mg (5, 53, 100 mL)** |

| ***Hard Max Drug Limits Provided?*** | | | | | | | | ***Infusion Rate and Ratio*** |
|---|---|---|---|---|---|---|---|---|
| **Yes (80 mcg/kg.min)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **56, 68, 80 mcg/kg.min (Ratio: 1.1, 1.3, 1.6)** |

| ***Hard Max Drug Limits Provided?*** | | | | | | | | ***Drug Amount*** |
|---|---|---|---|---|---|---|---|---|
| **Yes (80 mcg/kg.min)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **50, 530, 1000 mg (5, 53, 100 mL)** |

| ***Infusion Rate and Ratio*** | | | | | | | | ***Drug Amount*** |
|---|---|---|---|---|---|---|---|---|
| **56, 68, 80 mcg/kg.min (Ratio: 1.1, 1.3, 1.6)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **50, 530, 1000 mg (5, 53, 100 mL)** |

## QUESTION 3:

**Which level of the risk factor "infusion rate (ratio)" is more risky?**

Please compare each pair of the infusion rate (ratio) under the senario setting using the following linguistic variables.

***Please Press Ctrl + B to select your answer***

| *Scenario* | *Relative Risky Level* | | | | | | | *Scenario* |
|---|---|---|---|---|---|---|---|---|
| **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 56 mcg/kg.min**<br>**Ratio: 1.1**<br>**Drug Amount: (e.g. 530 mg)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 68 mcg/kg.min**<br>**Ratio: 1.3**<br>**Drug Amount: (e.g. 530 mg)** |

| *Scenario* | *Relative Risky Level* | | | | | | | *Scenario* |
|---|---|---|---|---|---|---|---|---|
| **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 56 mcg/kg.min**<br>**Ratio: 1.1**<br>**Drug Amount: (e.g. 530 mg)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 80 mcg/kg.min**<br>**Ratio: 1.6**<br>**Drug Amount: (e.g. 530 mg)** |

| *Scenario* | *Relative Risky Level* | | | | | | | *Scenario* |
|---|---|---|---|---|---|---|---|---|
| **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 68 mcg/kg.min**<br>**Ratio: 1.3**<br>**Drug Amount: (e.g. 530 mg)** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 80 mcg/kg.min**<br>**Ratio: 1.6**<br>**Drug Amount: (e.g. 530 mg)** |

## QUESTION 4:

**Which level of the risk factor "total dose patient receive" is more risky?**

Please compare each pair of the totoal dose patient receive under the senario setting using the following linguistic variables.

***Please Press Ctrl + B to select your answer***

| *Scenario* | *Relative Risky Level* | | | | | | | *Scenario* |
|---|---|---|---|---|---|---|---|---|
| **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 68 mcg/kg.min**<br>**Ratio: 1.3**<br>**Drug Amount: 50 mg** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 68 mcg/kg.min**<br>**Ratio: 1.3**<br>**Drug Amount: 530 mg** |

| *Scenario* | *Relative Risky Level* | | | | | | | *Scenario* |
|---|---|---|---|---|---|---|---|---|
| **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 68 mcg/kg.min**<br>**Ratio: 1.3**<br>**Drug Amount: 50 mg** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 68 mcg/kg.min**<br>**Ratio: 1.3**<br>**Drug Amount: 1000 mg** |

| *Scenario* | *Relative Risky Level* | | | | | | | *Scenario* |
|---|---|---|---|---|---|---|---|---|
| **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 68 mcg/kg.min**<br>**Ratio: 1.3**<br>**Drug Amount: 530 mg** | Very Strong | Strong | Moderate | Equal | Moderate | Strong | Very Strong | **AICU**<br>**Propofol**<br>**Continuous Dose**<br>**Soft Max: 51 mcg/kg.min**<br>**Hard Max: 80 mcg/kg.min**<br>**Dose Rate: 68 mcg/kg.min**<br>**Ratio: 1.3**<br>**Drug Amount: 1000 mg** |

# APPENDIX E. THE TYPE I AND TYPE II NORMALIZED EIGEN VECTORS FOR CALCULATING OVERALL COMPOSITE WEIGHTS (AHP RISK PRIORITIES)

***Scenario Type 1***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0602 | 0.1193 | 0.1161 | 0.1148 | 0.2083 | 0.3812 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0349 | 0.0260 | **0.0628** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0349 | 0.0773 | **0.0823** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0349 | 0.2301 | **0.1406** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0861 | 0.0260 | **0.0734** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0861 | 0.0773 | **0.0930** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0861 | 0.2301 | **0.1513** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2123 | 0.0260 | **0.0997** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2123 | 0.0773 | **0.1193** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2123 | 0.2301 | **0.1776** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 2***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0438 | 0.1655 | 0.0906 | 0.2525 | 0.2153 | 0.2322 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0542 | 0.0231 | **0.0784** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0542 | 0.0815 | **0.0920** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0542 | 0.2288 | **0.1262** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0733 | 0.0231 | **0.0825** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0733 | 0.0815 | **0.0961** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0733 | 0.2288 | **0.1303** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2059 | 0.0231 | **0.1111** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2059 | 0.0815 | **0.1246** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2059 | 0.2288 | **0.1588** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 3***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0419 | 0.0831 | 0.0847 | 0.3068 | 0.2265 | 0.2570 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.0289 | **0.0716** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.0843 | **0.0859** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.2201 | **0.1208** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.0289 | **0.0833** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.0843 | **0.0976** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.2201 | **0.1325** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.0289 | **0.1150** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.0843 | **0.1292** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.2201 | **0.1641** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 4***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0880 | 0.0961 | 0.0589 | 0.4407 | 0.2160 | 0.1003 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0304 | 0.0249 | **0.0850** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0304 | 0.0879 | **0.0913** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0304 | 0.2206 | **0.1047** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0709 | 0.0249 | **0.0938** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0709 | 0.0879 | **0.1001** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0709 | 0.2206 | **0.1134** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2321 | 0.0249 | **0.1286** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2321 | 0.0879 | **0.1349** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2321 | 0.2206 | **0.1482** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 5***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.1296 | 0.2853 | 0.0462 | 0.3656 | 0.0993 | 0.0740 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0687 | 0.0756 | **0.1043** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0687 | 0.1002 | **0.1061** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0687 | 0.1575 | **0.1103** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1163 | 0.0756 | **0.1090** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1163 | 0.1002 | **0.1108** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1163 | 0.1575 | **0.1151** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1484 | 0.0756 | **0.1122** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1484 | 0.1002 | **0.1140** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1484 | 0.1575 | **0.1182** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 6***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0580 | 0.2604 | 0.0884 | 0.1504 | 0.2400 | 0.2028 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.0817 | **0.0857** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.0817 | **0.0857** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.1699 | **0.1036** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.0817 | **0.0981** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.0817 | **0.0981** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.1699 | **0.1160** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.0817 | **0.1316** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.0817 | **0.1316** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.1699 | **0.1495** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 7***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0561 | 0.1097 | 0.0605 | 0.2322 | 0.2384 | 0.3032 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0206 | 0.0190 | **0.0616** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0206 | 0.0736 | **0.0781** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0206 | 0.2407 | **0.1288** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0623 | 0.0190 | **0.0716** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0623 | 0.0736 | **0.0881** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0623 | 0.2407 | **0.1388** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2505 | 0.0190 | **0.1164** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2505 | 0.0736 | **0.1330** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2505 | 0.2407 | **0.1836** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 8***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0438 | 0.1769 | 0.0578 | 0.0668 | 0.2317 | 0.4230 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0395 | 0.0209 | **0.0564** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0395 | 0.0711 | **0.0776** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0395 | 0.2413 | **0.1496** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0771 | 0.0209 | **0.0651** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0771 | 0.0711 | **0.0863** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0771 | 0.2413 | **0.1583** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2168 | 0.0209 | **0.0974** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2168 | 0.0711 | **0.1187** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2168 | 0.2413 | **0.1907** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 9***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.1952 | 0.1060 | 0.0949 | 0.1532 | 0.0575 | 0.3933 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0223 | 0.0249 | **0.0721** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0223 | 0.0879 | **0.0969** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0223 | 0.2206 | **0.1491** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0728 | 0.0249 | **0.0750** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0728 | 0.0879 | **0.0998** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0728 | 0.2206 | **0.1520** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2382 | 0.0249 | **0.0845** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2382 | 0.0879 | **0.1093** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2382 | 0.2206 | **0.1615** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 10***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0312 | 0.0752 | 0.0693 | 0.5492 | 0.2048 | 0.0703 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0217 | 0.0371 | **0.0876** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0217 | 0.0439 | **0.0881** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0217 | 0.2524 | **0.1027** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1226 | 0.0371 | **0.1083** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1226 | 0.0439 | **0.1087** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1226 | 0.2524 | **0.1234** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1890 | 0.0371 | **0.1218** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1890 | 0.0439 | **0.1223** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1890 | 0.2524 | **0.1370** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 11***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0323 | 0.2956 | 0.0794 | 0.2401 | 0.2761 | 0.0766 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0268 | 0.0238 | **0.0811** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0268 | 0.0823 | **0.0856** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0268 | 0.2273 | **0.0967** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0782 | 0.0238 | **0.0953** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0782 | 0.0823 | **0.0998** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0782 | 0.2273 | **0.1109** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2284 | 0.0238 | **0.1368** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2284 | 0.0823 | **0.1413** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2284 | 0.2273 | **0.1524** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 12***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0420 | 0.0515 | 0.1145 | 0.1911 | 0.2788 | 0.3221 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0410 | 0.0241 | **0.0636** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0410 | 0.1217 | **0.0950** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0410 | 0.1875 | **0.1162** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1379 | 0.0241 | **0.0906** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1379 | 0.1217 | **0.1220** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1379 | 0.1875 | **0.1432** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1544 | 0.0241 | **0.0952** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1544 | 0.1217 | **0.1266** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1544 | 0.1875 | **0.1478** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 13***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0497 | 0.0717 | 0.0984 | 0.2126 | 0.2484 | 0.3192 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0456 | 0.0218 | **0.0663** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0456 | 0.0739 | **0.0830** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0456 | 0.2376 | **0.1352** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0940 | 0.0218 | **0.0783** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0940 | 0.0739 | **0.0950** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0940 | 0.2376 | **0.1472** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1938 | 0.0218 | **0.1031** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1938 | 0.0739 | **0.1198** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1938 | 0.2376 | **0.1720** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 14***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0286 | 0.0774 | 0.1262 | 0.1207 | 0.3170 | 0.3300 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0588 | 0.0213 | **0.0649** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0588 | 0.0752 | **0.0827** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0588 | 0.2368 | **0.1360** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0751 | 0.0213 | **0.0701** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0751 | 0.0752 | **0.0878** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0751 | 0.2368 | **0.1412** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1994 | 0.0213 | **0.1095** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1994 | 0.0752 | **0.1272** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1994 | 0.2368 | **0.1806** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 15***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0426 | 0.0795 | 0.1684 | 0.1240 | 0.1511 | 0.4344 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.0239 | **0.0610** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.1163 | **0.1011** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0302 | 0.1931 | **0.1345** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.0239 | **0.0688** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.1163 | **0.1089** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0817 | 0.1931 | **0.1423** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.0239 | **0.0899** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.1163 | **0.1300** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2214 | 0.1931 | **0.1634** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 16***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0446 | 0.2874 | 0.1323 | 0.1676 | 0.2798 | 0.0883 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0296 | 0.0794 | **0.0855** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0296 | 0.1077 | **0.0880** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0296 | 0.1462 | **0.0914** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0973 | 0.0794 | **0.1045** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0973 | 0.1077 | **0.1070** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0973 | 0.1462 | **0.1104** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2064 | 0.0794 | **0.1350** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2064 | 0.1077 | **0.1375** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2064 | 0.1462 | **0.1409** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 17***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0681 | 0.1557 | 0.1161 | 0.1054 | 0.1748 | 0.3799 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0328 | 0.0260 | **0.0651** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0328 | 0.0719 | **0.0825** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0328 | 0.2354 | **0.1446** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0703 | 0.0260 | **0.0717** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0703 | 0.0719 | **0.0891** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0703 | 0.2354 | **0.1512** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2302 | 0.0260 | **0.0996** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2302 | 0.0719 | **0.1170** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2302 | 0.2354 | **0.1791** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 18***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0545 | 0.1519 | 0.0428 | 0.2520 | 0.1453 | 0.3535 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0392 | 0.0223 | **0.0693** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0392 | 0.0958 | **0.0953** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0392 | 0.2152 | **0.1375** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1003 | 0.0223 | **0.0782** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1003 | 0.0958 | **0.1041** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1003 | 0.2152 | **0.1463** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1938 | 0.0223 | **0.0917** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1938 | 0.0958 | **0.1177** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1938 | 0.2152 | **0.1599** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 19***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0681 | 0.1502 | 0.1050 | 0.0520 | 0.2104 | 0.4142 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0273 | 0.0218 | **0.0565** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0273 | 0.0740 | **0.0781** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0273 | 0.2376 | **0.1458** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0732 | 0.0218 | **0.0661** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0732 | 0.0740 | **0.0878** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0732 | 0.2376 | **0.1555** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2329 | 0.0218 | **0.0997** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2329 | 0.0740 | **0.1214** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2329 | 0.2376 | **0.1891** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 20***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0461 | 0.1096 | 0.0890 | 0.2342 | 0.2313 | 0.2899 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0475 | 0.0217 | **0.0705** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0475 | 0.0864 | **0.0892** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0475 | 0.2253 | **0.1295** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0884 | 0.0217 | **0.0799** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0884 | 0.0864 | **0.0987** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0884 | 0.2253 | **0.1390** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1974 | 0.0217 | **0.1051** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1974 | 0.0864 | **0.1239** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1974 | 0.2253 | **0.1642** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 21***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.1348 | 0.2516 | 0.0375 | 0.1981 | 0.1221 | 0.2559 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0327 | 0.0263 | **0.0798** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0327 | 0.0886 | **0.0958** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0327 | 0.2185 | **0.1290** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0908 | 0.0263 | **0.0869** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0908 | 0.0886 | **0.1029** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0908 | 0.2185 | **0.1361** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2098 | 0.0263 | **0.1015** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2098 | 0.0886 | **0.1174** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2098 | 0.2185 | **0.1506** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 22***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.1264 | 0.1314 | 0.0870 | 0.2360 | 0.1937 | 0.2255 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0384 | 0.0219 | **0.0769** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0384 | 0.0817 | **0.0904** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0384 | 0.2298 | **0.1238** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1031 | 0.0219 | **0.0894** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1031 | 0.0817 | **0.1029** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1031 | 0.2298 | **0.1363** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1918 | 0.0219 | **0.1066** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1918 | 0.0817 | **0.1201** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1918 | 0.2298 | **0.1535** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 23***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0895 | 0.1628 | 0.1592 | 0.0915 | 0.4028 | 0.0942 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0423 | 0.0853 | **0.0810** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0423 | 0.1089 | **0.0832** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0423 | 0.1391 | **0.0860** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0730 | 0.0853 | **0.0933** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0730 | 0.1089 | **0.0955** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0730 | 0.1391 | **0.0984** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2181 | 0.0853 | **0.1518** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2181 | 0.1089 | **0.1540** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2181 | 0.1391 | **0.1568** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 24***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0770 | 0.2075 | 0.0601 | 0.2634 | 0.2824 | 0.1096 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0293 | 0.0387 | **0.0801** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0293 | 0.0923 | **0.0860** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0293 | 0.2024 | **0.0980** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1197 | 0.0387 | **0.1056** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1197 | 0.0923 | **0.1115** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1197 | 0.2024 | **0.1235** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1843 | 0.0387 | **0.1238** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1843 | 0.0923 | **0.1297** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.1843 | 0.2024 | **0.1418** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 25***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0865 | 0.2642 | 0.1054 | 0.1794 | 0.1476 | 0.2170 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0309 | 0.0305 | **0.0818** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0309 | 0.0659 | **0.0895** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0309 | 0.2370 | **0.1266** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0687 | 0.0305 | **0.0874** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0687 | 0.0659 | **0.0950** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0687 | 0.2370 | **0.1322** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2337 | 0.0305 | **0.1117** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2337 | 0.0659 | **0.1194** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2337 | 0.2370 | **0.1565** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 26***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.1910 | 0.1893 | 0.0769 | 0.2108 | 0.1215 | 0.2105 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0327 | 0.0245 | **0.0834** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0327 | 0.1009 | **0.0994** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0327 | 0.2080 | **0.1220** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0787 | 0.0245 | **0.0889** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0787 | 0.1009 | **0.1050** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0787 | 0.2080 | **0.1276** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2219 | 0.0245 | **0.1063** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2219 | 0.1009 | **0.1224** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2219 | 0.2080 | **0.1450** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 27***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0552 | 0.1475 | 0.0855 | 0.0680 | 0.2139 | 0.4299 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0253 | 0.0209 | **0.0540** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0253 | 0.0763 | **0.0778** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0253 | 0.2361 | **0.1465** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0685 | 0.0209 | **0.0632** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0685 | 0.0763 | **0.0871** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0685 | 0.2361 | **0.1557** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2395 | 0.0209 | **0.0998** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2395 | 0.0763 | **0.1236** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2395 | 0.2361 | **0.1923** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 28***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0791 | 0.0975 | 0.1008 | 0.2055 | 0.2730 | 0.2441 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0454 | 0.0658 | **0.0821** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0454 | 0.0840 | **0.0866** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0454 | 0.1835 | **0.1108** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0748 | 0.0658 | **0.0901** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0748 | 0.0840 | **0.0946** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0748 | 0.1835 | **0.1188** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2132 | 0.0658 | **0.1279** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2132 | 0.0840 | **0.1324** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2132 | 0.1835 | **0.1566** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 29***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.0453 | 0.1593 | 0.0746 | 0.3269 | 0.2659 | 0.1280 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0335 | 0.0200 | **0.0788** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0335 | 0.0788 | **0.0863** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0335 | 0.2346 | **0.1063** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0819 | 0.0200 | **0.0917** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0819 | 0.0788 | **0.0992** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0819 | 0.2346 | **0.1192** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2179 | 0.0200 | **0.1278** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2179 | 0.0788 | **0.1354** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2179 | 0.2346 | **0.1553** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

***Scenario Type 30***

| Level 1 | Crit-1 | Crit-2 | Crit-3 | Crit-4 | Crit-5 | Crit-6 | **Glb. Pr.** |
|---|---|---|---|---|---|---|---|
| p (L1) | 0.1420 | 0.1998 | 0.0684 | 0.2483 | 0.1713 | 0.1703 | |
| Level 2 (alternatives) | p (L2) | | | | | | |
| **SS1** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0288 | 0.0239 | **0.0822** |
| **SS2** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0288 | 0.0835 | **0.0923** |
| **SS3** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0288 | 0.2260 | **0.1166** |
| **SS4** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0804 | 0.0239 | **0.0910** |
| **SS5** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0804 | 0.0835 | **0.1011** |
| **SS6** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.0804 | 0.2260 | **0.1254** |
| **SS7** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2241 | 0.0239 | **0.1156** |
| **SS8** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2241 | 0.0835 | **0.1258** |
| **SS9** | 0.1111 | 0.1111 | 0.1111 | 0.1111 | 0.2241 | 0.2260 | **0.1500** |
| **sum** | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

# APPENDIX F. QUANTIFIED SCORES VS. BENCHMARKS (SUB-SCENARIOS)

Table F-1: Correlation Coefficient for the SS147 Sub-scenarios

| Pearson's Correlation Coefficient | Predicted Risk – Linear Predictive Model | IV Harm Scores – IV Medication Harm Index | Risk Ranking Scores – Matrixed-based Method |
|---|---|---|---|
| ρ | 0.9055*** | 0.1984 (p-value: 0.06) | -0.3427*** |

Note. *Correlation is significant at the 0.05 level (two-tailed); number of data (n): 90; Significant codes: '***' $p \leq 0.001$; '**' $0.001 < p \leq 0.01$; '*' $0.01 < p \leq 0.05$

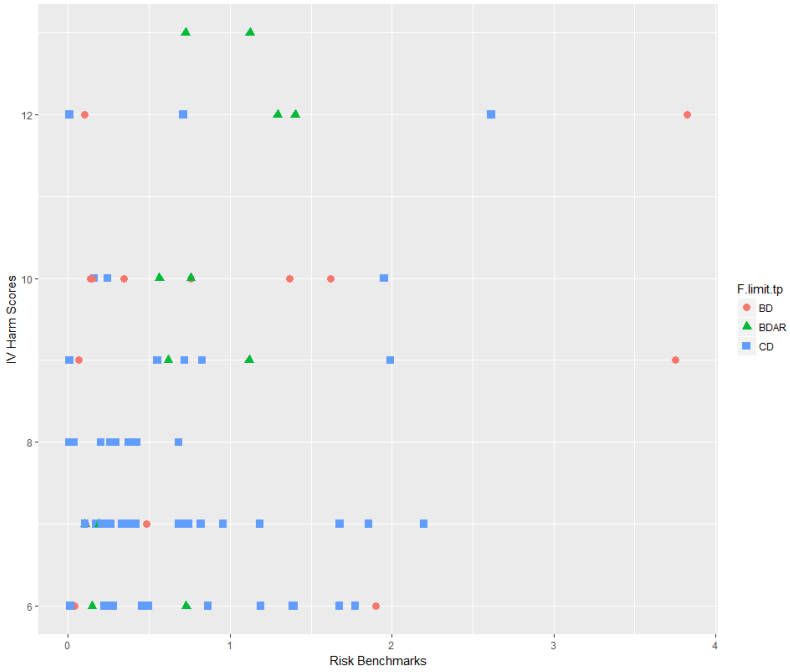


Figure F-1: The Relationship between Benchmarks and IV Harm Scores (Sub-scenarios)

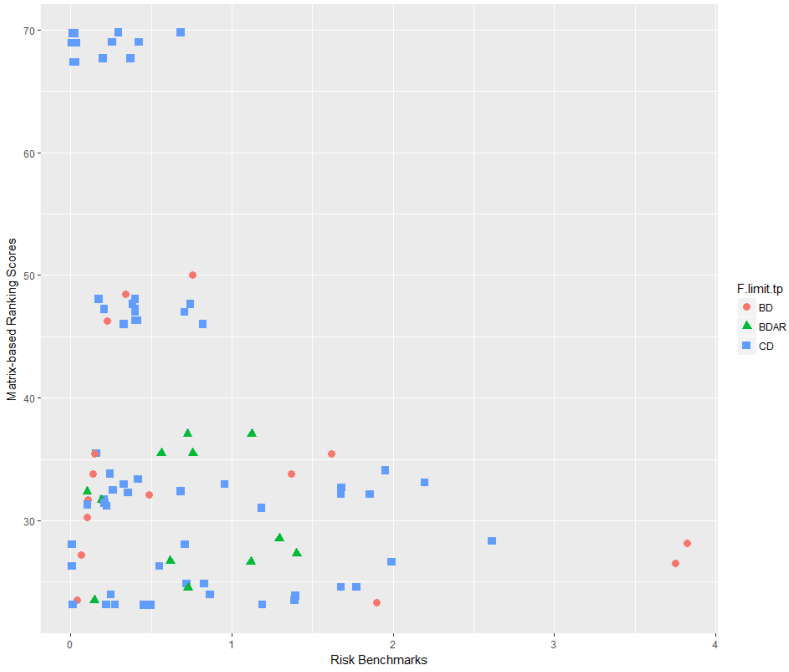


Figure F-2: The Relationship between Benchmarks and Ranking Scores (Sub-scenarios)

Table F-2: Correlation Coefficient for the SS147-sub-scenarios Classified by Factor $X_3$

| Pearson's Correlation Coefficient | CD (n=63) | BD (n=15) | BDAR (n=12) |
|---|---|---|---|
| Benchmarks vs. IV harm scores | 0.0222 | 0.2465 | 0.7269* |
| Benchmarks vs. Matrix-based Ranking Scores | -0.4128*** | -0.3089 | -0.0081 |

Note. *Correlation is significant at the 0.05 level (two-tailed); Significant codes: '***' $p \leq 0.001$; '**' $0.001 < p \leq 0.01$; '*' $0.01 < p \leq 0.05$

Table F-3: Correlation Coefficient for the SS147-CD-sub-scenarios Classified by Factors $X_4$ and $X_5$

| | | Linear predicted risk | | IV harm scores | | Matrix-based ranking scores | |
|---|---|---|---|---|---|---|---|
| | $X_4$*$X_5$ | $X_5$ - Y | $X_5$ - N | $X_5$ - Y | $X_5$ - N | $X_5$ - Y | $X_5$ - N |
| *n* | $X_4$-Small | 21 | 12 | 21 | 12 | 21 | 12 |
| ρ | $X_4$-Small | 0.4203 | 0.8313*** | 0.1951 | -0.4128 | -0.2753 | 0.2258 |
| *n* | $X_4$-Large | 18 | 12 | 18 | 12 | 18 | 12 |
| ρ | $X_4$-Large | 0.9349*** | 0.9352*** | -0.0876 | 0.4051 | -0.6723** | -0.7480** |

Note. *Correlation is significant at the 0.05 level (two-tailed); Significant codes: '***' $p \leq 0.001$; '**' $0.001 < p \leq 0.01$; '*' $0.01 < p \leq 0.05$; $X_5$ – Y: Hard Limit Provided; $X_5$ – N: Hard Limit Not Provided

Table F-4: Correlation Coefficient for the SS147-BD-sub-scenarios Classified by Factors $X_4$ and $X_5$

| | Linear predicted risk | | IV harm scores | | Matrix-based ranking scores | |
|---|---|---|---|---|---|---|
| | $X_5$ - Y | $X_5$ - N | $X_5$ - Y | $X_5$ - N | $X_5$ - Y | $X_5$ - N |
| *n* | 9 | 6 | 9 | 6 | 9 | 6 |
| ρ | 0.8968** | 0.9744*** | 0.4060 | 0.2433 | -0.0820 | 0.0326 |

Note. *Correlation is significant at the 0.05 level (two-tailed); Significant codes: '***' $p \leq 0.001$; '**' $0.001 < p \leq 0.01$; '*' $0.01 < p \leq 0.05$; $X_5$ – Y: Hard Limit Provided; $X_5$ – N: Hard Limit Not Provided

Table F-5: Correlation Coefficient for the SS147-BDAR-sub-scenarios Classified by Factors $X_4$ and $X_5$

| | | Linear predicted risk | | IV harm scores | | Matrix-based ranking scores | |
|---|---|---|---|---|---|---|---|
| | $X_4$*$X_5$ | $X_5$ - Y | $X_5$ - N | $X_5$ - Y | $X_5$ - N | $X_5$ - Y | $X_5$ - N |
| *n* | $X_4$-Small | 3 | 0 | 3 | 0 | 3 | 0 |
| ρ | $X_4$-Small | 0.9859 | NA | 0.9749 | NA | 0.9999** | NA |
| *n* | $X_4$-Large | 3 | 0 | 3 | 0 | 3 | 0 |
| ρ | $X_4$-Large | 0.9981* | NA | 0.9868 | NA | 0.9995* | NA |
| *n* | $X_4$-D | 3 | 3 | 3 | 3 | 3 | 3 |
| ρ | $X_4$-D | 0.9961 | 0.9955 | 0.9960 | 0.9947 | 0.9799 | 0.9664 |

Note. *Correlation is significant at the 0.05 level (two-tailed); Significant codes: '***' $p \leq 0.001$; '**' $0.001 < p \leq 0.01$; '*' $0.01 < p \leq 0.05$; $X_5$ – Y: Hard Limit Provided; $X_5$ – N: Hard Limit Not Provided

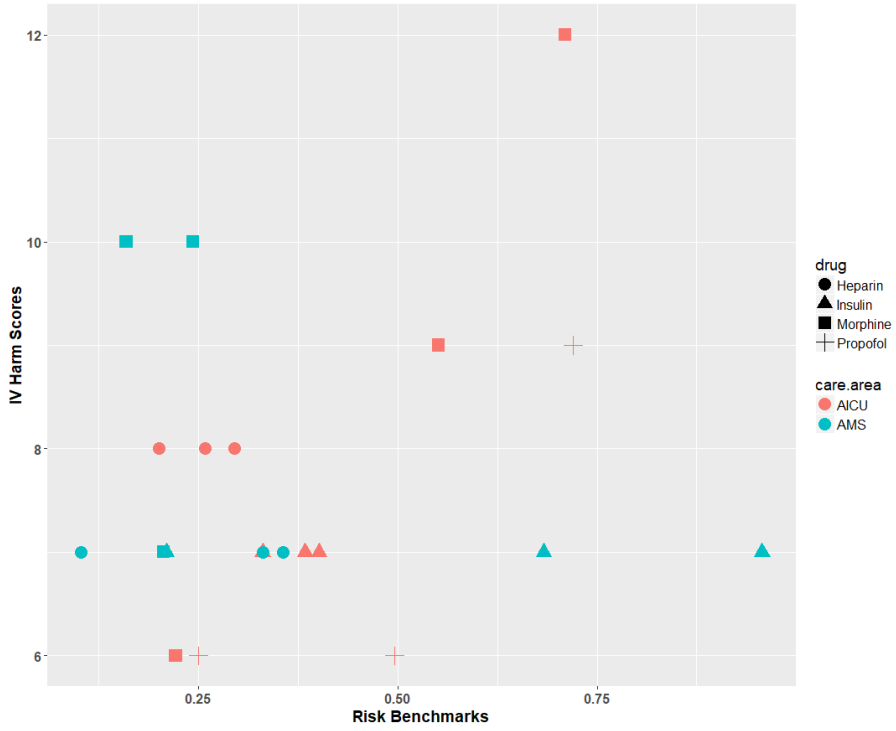


Figure F-3: An Example of the Relationship between Benchmarks and IV harm Scores (SS147-CD-sub-scenarios Classified by Factors $X_4$ and $X_5$)

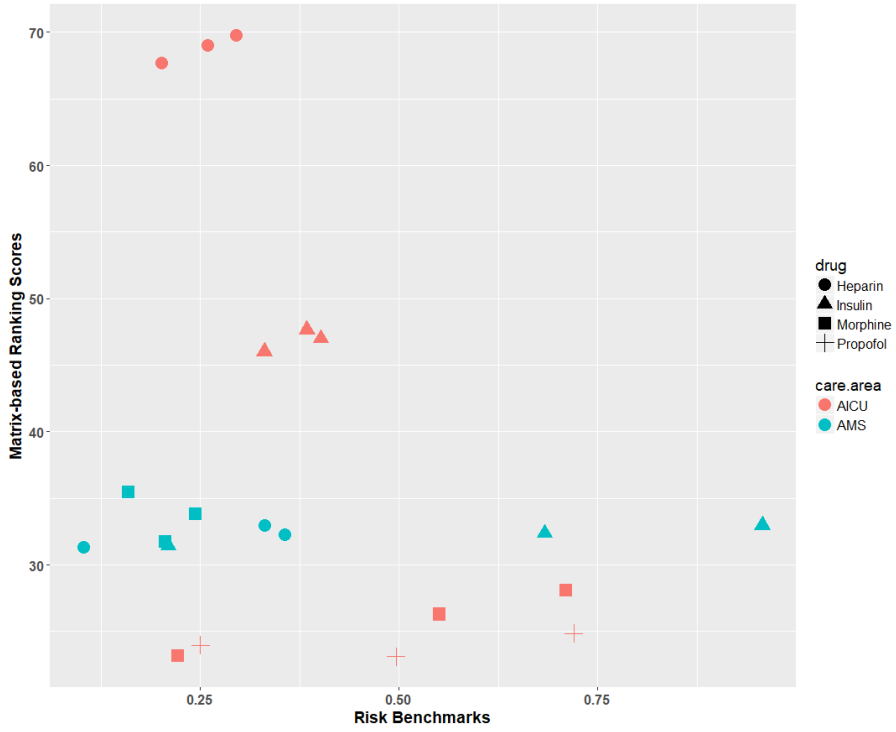


Figure F-4: An Example of the Relationship between Benchmarks and Ranking Scores (SS147-CD-sub-scenarios Classified by Factors $X_4$ and $X_5$)

# APPENDIX G. PAPER 1

## Healthcare Professionals Risk Assessments for Alert Overrides in High-Risk IV Infusions using Simulated Scenarios

Wan-Ting Su, Mark R. Lehto, Daniel D. Degnan, Yuehwern Yih, Vincent Duffy, Poching DeLaurentis

**ABSTRACT (limits: 250 words)**

**Objectives:** This study aimed to use healthcare professionals' risk assessments to calculate expected risk of intravenous infusion harm for simulated high-risk medications that exceed soft limits and to investigate the impact of relevant risk factors.

**Methods:** 30 scenarios of alert-overridden infusions were designed for four high-risk medications, propofol, morphine, insulin, and heparin, infused in adult intensive care unit and adult medical and surgical care unit. A total of 20 pharmacists and 5 nurses provided their assessed expected risk of patient harm in each scenario. Descriptive statistics, ANOVA with least square mean, and post hoc test were conducted to test the risk factor effects of field limit type, soft and hard limit type, and care area-medication combination on risk of harm.

**Results:** Overdosing scenarios with continuous and bolus dose types were assessed with significantly higher risks than those of bolus does rate type. The expected risk in the group with a large soft maximum limit was significantly higher than the group with a small maximum limit. Care area and medication did not have significant impacts on expected

risk; however, for AICU and AMSU, the effect of soft limit type and that of drug amount levels on the expected risk were different.

**Conclusions:** This study obtained expected risk for simulated high-risk IV Infusions and found that different field limit and soft maximum limit types can affect expected risk based on healthcare professionals' perspectives. The findings will be regarded as benchmarks for validating risk quantification models in future research.

**Key Words:**

IV infusions, Risk assessment, Medication safety, High-risk medications, Patient safety

## INTRODUCTION

Intravenous (IV) medication errors may cause severe patient harm. Smart pumps with a built-in dose error reduction system (DERS) can help ensure safe IV administration in clinical settings. A clinician may choose to override a drug limit alert triggered by DERS when the infusion programming values are outside of the pre-set drug limits, and doing so could potentially cause patient harm of various degrees, especially for high-risk medications. One large dataset with 5-year smart pump alerts showed that propofol and heparin infused in the adult intensive care unit (AICU*)* were top two with higher frequency of alert overrides, which were 17,669 (propofol) and 8,469 (heparin) within these 5 years. There is a need to study and estimate the risk for the representative alert overrides with high alert frequency.

As a way to quantify IV medication harm, the IV Medication Harm Index Study Group, a patient safety expert organization, developed an IV medication harm index for overdosing infusions[1,2] using three sub-scales: drug risk and overdose ratio (ratio means programming values (overdose) divided by the soft maximum drug limit), level of care/acuity, and detectability of adverse drug events (ADEs)[1,2]. The higher overall harm scores, the higher risk of patient harm. However, there are some limitations to using this IV medication harm index. One is that the created discrete scale can be easily changed by small changes of the continuous overdose ratio. Another issue is that the quantified harm sub-scores for all high-risk drugs with specific overdoing ranges are the same even though there may cause various degrees of harm. Yet another limitation is that some other risk factors, such as drug limit types and total drug amounts patients receive, are not considered. Therefore, a better quantification method is needed to improve the existing IV medication

harm index and adequately estimate *risk of harm* (defined as incorporating likelihood of potential degrees of harm[3]) for individual overridden alerts. Risk is a two-dimensional measure and can be quantified by calculating the summation of the product of the probability and the severity of harm[4,5]. Previous studies indicated that a non-linear relationship exists between the subjective probability and true probability when humans make decision under uncertainty[6,7]. And a non-linear severity impact on patients was proposed[8]. In this study, we adjusted probability and severity based on the literature to calculate expected risk for each simulated scenario.

Due to the fact that in most healthcare systems, alert-overridden infusions are not directly linked to clinical patient outcomes, we invited healthcare professionals to assess *risk of harm* for simulated scenarios of alert-overridden infusions associated with four high-risk drugs, propofol, morphine, insulin, and heparin, based on the Institute for Safe Medication Practices (ISMP) categories of high-alert medication list[9]. The goal of this study was to (1) use experts' risk assessment surveys to obtain expected risk for the simulated infusion scenarios, and (2) understand the association between the potential risk factors and the risk. Four research questions were addressed in this study:

*Research Question 1*: *Will the risk differ in regard to field limit type?*

*Research Question 2*: *Will the risk differ in regard to care area and medication?*

*Research Question 3*: *Will the risk differ in regard to soft maximum drug limit type?*

*Research Question 4*: *Will the risk differ in regard to hard maximum drug limit type?*

The contribution of this research is to examine whether different levels of the potential risk factors affect the expected risk based on healthcare professionals' perspectives. The

expected risk obtained from the experts' risk assessment surveys would be regarded as risk benchmarks for validating the risk quantification models to be developed in future research.

## METHODS

### Participants

The voluntary participants of IV harm risk assessment in this study included 20 pharmacists and 5 nurses who had experience working with intravenous (IV) infusions. Most of them were members of their hospitals' medication safety committees.

### Scenario Design

Infusion scenarios with specific programming values and drug limits were designed to associate with infusion dose rate, drug amount, infusion duration, etc. They were based off a dataset of 5-year worth of infusion alerts (from January 2010 to May 2015) from one representative member of the Regenstrief National Center for Medical Device Informatics (REMEDI) collabrative[f], since drug limit settings (the drugs in each care unit for the specific field limit type[g]) vary across hospital systems. Table 1 shows the definition of the field limit type associated with continuous and bolus infusion types[10]. In this study, we focused on overridden alerts associated with four high-risk medications defined by ISMP, namely, propofol, morphine, insulin, and heparin, used in the settings of adult intensive

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[f] Regenstrief National Center for Medical Device Informatics (REMEDI) system is a web-based analytics tool, contributed by members of the community and supported by the Regenstrief Center for Healthcare Engineering (RCHE) of Purdue University.

[g] The field limit types in Becton Dickinson Alaris™ System include continuous does rate (CD), bolus dose (BD), and bolus dose rate (BDAR), which have different units. The continuous infusion by entering infusion rate and total volume could trigger CD field limit type, and the bolus infusion by entering infusion drug amount and duration (min) could trigger either BD or BDAR type.

care unit (AICU) and adult medical and surgical care unit (AMSU). The targeted alerts were then classified into 30 scenario types (with *higher frequency of alert overrides*) based on the programming and alert information (Appendix A). Figure 1 show scenario design structure and information. Within each scenario type, four numerical variables identified as the 3rd layer scenario factors were provided: (1) total dose (drug amount) patient received, (2) infusion duration, (3) infusion rate ((1) divided by (2)), and (4) ratio of programming rate/dose to the SoftMax (Table 1). Furthermore, each scenario type was composed of nine different sub-scenarios (Figure 1) according to each of the three level of the 3rd layer scenario factors (Appendix B).

---

(Insert Table 1 here)

(Insert Figure1 here)

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**Experimental Design**

Our 30 infusion scenario types were designed as unbalanced scenario combinations based on the principle of incomplete factorial design[11], incoporating the typical and most frequent scenarios observed in pump alerts. Because of the unbalanced combinations, the number of scenario types and the sample size that we used to test the factor effects were different as shown in Appendix C. Since it was inpractical to have any study participant to review and assess all 270 survey questions (30 types x 9 sub-scenarios), we applied an Incomplete Block Design (IBD) in which the individual difference was treated as a blocking factor that controlled the sources of variation and eliminated the effect on the statistical comparisons among treatments[12,13]. Statistical software packages, R and

JMP® (SAS institute), were used to create model matrices and generate D-optimal criteria for evaluating and comparing various designs[14]. We followed the selected IBD to assign the specific three scenario types, including nine sub-scenarios per type, for each of the 25 participants. Each scenario type was repeated two or three times based on the IBD. A total of 675 (25 x 3 x 9) assessments were collected.

The experimental design with the scenario effects can be illustrated using the following statistical model[12]:

$$y_{ijk} = \mu + \tau_i + \beta_j + \cdots + (\tau\beta)_{ij} + \cdots + \delta_k + \varepsilon_{ijk} \quad (1)$$

where $\tau_i$ represents the first effect from factor A, $\beta_j$ represents the second effect from factor B, $(\tau\beta)_{ij}$ is the interaction effect from factors A and B, $\delta_k$ is the block effect, and $\varepsilon_{ijk}$ is the NID $(0, \sigma^2)$ error component.

**Survey and Procedures**

This research was given an exempt status from the Purdue University Institutional Review Board (IRB Protocol #: 1703018925). In the surveys, we described the scenarios and questions, also presented the risk rating tables for the participants (Appendix D). This risk rating table was designed using a two-dimensional rating scale, probability (likelihood) and its severity impact (ordinal linguistic scale: No harm, Minor, Moderate, Major, and Extreme harm to the NCC MERP index[15]).

The survey progressed over a face-to-face interview or a conference call with about two hours for each participant. All responses were kept anonymous and secured.

**Measures**

We used subjective assessments, which are vectors in the form of five probabilities associated with a severity of harm, to calculate the *risk of harm*. Specifically, we applied

the Absolute Probability Judgment (APJ) method[16] for the participants to answer the survey questions and provided an estimated absolute probability value.

In this study, we calculated the risk measure using the summation of the product of the probability and the severity of harm with the non-linear transformation suggested by previous studies[6–8]. Therefore, the subjective probabilities ($p$) in this study were adjusted as $p'$ using a non-linear transformation:

$$Lo(p') = \frac{1}{\gamma} \times Lo(p) - \frac{1-\gamma}{\gamma} \times Lo(p_0) \quad (2)$$

where $p'$ indicates true probability, $p$ indicates the subjective probability, $\gamma$ and $p_0$ were respectively selected as 0.6 and 0.4[6], and

$$Lo(probability) = log \frac{probability}{1-probability} \quad (3)$$

is the log odds[17] or logit function[18].

And the severity of harm was quantified using exponential growth using the order of magnitudes for five degrees of harm ($10^0$, $10^1$, $10^2$, $10^3$, $10^4$) due to the non-linear severity impact proposed by the literature[8].

**Analytical Approach**

Descriptive statistics, including sample size (n), sample mean (M), and standard deviation of the samples (SD) within each group, were reviewed. It was noted that the sample means could be affected by individual differences among the assessors and the potential risk factors. Participants who tended to assess with higher ratings could lead to greater sample means. Thus, for each hypothesis associated with the factor effect testing, the least squared means (LS mean)[h] were estimated using analysis of variance (ANOVA)

[h] Least square means are means for groups that are adjusted for means of other factors in the model. In this study, we adjusted the difference among the individuals in each group.

with a random block[i] in the lmerTest Package of R software, to control for the assessment impact by individual difference[19]. The post hoc tests with Tukey adjustment were further conducted to test the risk difference among the levels of risk factors.

## RESULTS

In this section, we tested the potential risk factor effects of field limit type, soft and hard maximum drug limit type, and care area-medication combination on expected risk of IV harm.

### Field Limit Type

The data selected from the simulated scenario types associated with morphine and propofol was used to test the effect of field limit type, continuous dose (CD), bolus dose (BD), and bolus dose rate (BDAR). Table 2 shows the sample mean and LS mean estimated by a mixed model, in which the expected risk of field limit type is the lowest in BDAR, followed by BD and CD. There was a significant difference across these three levels of field limit type ($F(2, 219) = 42.58$, $p < 0.001$). The post hoc test showed that overdosed infusions of continuous and bolus dose types were percieved by clinicians to possess a significantly higher risk to the patient than the bolus dose rate ($p < 0.001$, see Table 3), while the continuous dose and bolus dose did not differ on risk ($p = 0.73$).

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(Insert Table 2 here)

(Insert Table 3 here)

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[i] The ANOVA analysis with a random block (type III sums of squares with Satterthwaite approximation for degrees of freedom) was conducted with a mixed-effects model using R software, with the treatments treated as a fixed effect and the blocks, the individuals blocked in the experimental design, treated as a random effect.

**Soft Maximum Drug Limit Type**

The data selected from the simulated scenario types associated with continuous dose for all four medications was used to test the effect of soft maximum drug limit (soft max) type. Table 4 shows that the means of expected risk in the group with large soft max were significantly larger than those of the small soft max ($F(1, 464) = 15.45$, $p < 0.001$).

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(Insert Table 4 here)

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**Hard Maximum Drug Limit Type**

The simulated scenarios of drug infusions in AICU using continuous dose were selected to test the effect of hard maximum drug limit (hard max) type. The descriptive analysis for the hard max type showed that the means of expected risk for the scenarios with (*M*ean = 1.58, *SD* = 1.22) and without (*M*ean = 1.62, *SD* = 1.11) hard limit were similar, and no significant main effect of hard max type was found ($F(1, 288) = 3.08$, $p = 0.080$). The interaction effect between hard max and soft max types was not significant ($F(1, 147) = 3.16$, $p = 0.078$). Also, the interaction between hard max type and medication was found to have no significant effect ($F(3, 118) = 1.37$, $p = 0.256$).

**Care Area and Medication**

The data selected from the simulated scenario types associated with continuous dose for heparin, insulin, and morphine was used to test the main effects of care area and medication. Table 5 shows the descriptive analysis for each combination of care area and medication. In addition, the results by the two-way ANOVA indicated that there was no significant difference on risk between the Adult Intensive Care Unit (AICU) and the Adult

Medical/Surgical Care Unit (AMSU) ($F(1, 89) = 0.45$, $p = 0.121$), neither was among the three medications ($F(2, 224) = 2.54$, $p = 0.08$). There was no significant interaction between the impact of care area and medication ($F(2, 80) = 1.20$, $p = 0.306$). Therefore, we further tested the effects of care area and medication with each of the following variables, soft limit type, hard limit type, drug amount level, and dose rate level, using a three-way ANOVA. The results showed that soft limit type and the drug amount levels had interactions with the care area as explained below.

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(Insert Table 5 here)

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The first three-way ANOVA (care area, medication, and soft limit type) showed that there was no significant care area effect ($F(1, 58) = 1.41$, $p = 0.24$) and medication effect ($F(2, 144) = 2.73$, $p = 0.07$) on risk, but there was a significant difference between the groups of small and large soft limit types ($F(1, 183) = 6.59$, $p = 0.01$). Furthermore, the descriptive analysis and the estimated LS mean for the four scenario combinations (care area-soft limit type combination) were shown in Table 6. There was a significant interaction between care area and soft limit type ($F(1, 173) = 5.46$, $p = 0.02$). The post hoc analysis showed that only the contrast between AICU-large soft max and AICU-small soft max was significant ($t\ ratio = 4.31$, $p < 0.001$). The expected risk for the group of AICU-Soft small is the lowest, followed by the groups of AMSU-Soft small and AMSU-Soft large, and the highest expected risk is the group of AICU-Soft large (see Table 6 and Figure 2).

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(Insert Table 6 here)

(Insert Figure 2 here)

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The second three-way ANOVA (care area, medication, and drug amount levels) showed that there was no significant care area effect ($F(1, 143) = 3.21$, $p = 0.08$). However, the expected risk was significantly different among the three medication groups ($F(2, 264) = 4.16$, $p = 0.017$) and among three drug amount levels ($F(2, 354) = 148.61$, $p < 0.001$). Table 7 shows the descriptive analysis and the estimated LS means for the six scenario combinations (care area-drug amount level combination). There was a significant interaction between care area and drug amount level ($F(2, 354) = 5.16$, $p = 0.006$). The post hoc analysis indicated that expected risk for the six combinations can be classified into four different groups as shown in Table 7 and Figure 3.

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(Insert Table 7 here)

(Insert Figure 3 here)

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# DISCUSSION

## Field Limit Type

The factor of field limit type (CD, BD, and BDAR) had significant effect on the expected risk. Specifically, the effects of CD and BD led to significantly higher risk than that of BDAR, while there was no difference between CD and BD. A possible reason that leads to different expected risk between CD and BDAR is the infusion duration. Note that a nurse needs to enter infusion dose rate and total volume when selecting the continuous infusion, so the infusion duration will be generated (see Table 1). The range of infusion duration for CD scenarios could be short (a few minutes) or long (a few hours), and that for BDAR scenarios was within minutes. Obviously, the longer overdose situations without clinicians' check-in (CD) could cause patients a higher risk of harm.

To compare BD and BDAR, although the units of field limit setup for BD and BDAR differed (i.e. drug amount and infusion rate, respectively), the total dose infused to patients for BDAR could be calculated given the infusion duration. In this study, the design of drug amounts of morphine for BD scenarios were 29, 49 and 68 mg, and the infusion rates for BDAR scenarios were 6, 10 and 14 mg per minute with the infusion duration of 1, 2 and 3 miniutes. Therefore, for BDAR, the drug amount could be low at 6 mg or high at 42 mg, , most of which had drug amount less than that in BD scenarios. Thus it was reasonable that BD scenarios had higher expected risk than BDAR. Furthremore, the participating pharmacists and nurses indicated that, the higher overdosing drug amounts, such as morhpine, could lead to greater risk of harm for general populations who cannot tolerant hight dose. Their opinions can also explain why the overall risk of BD scenarios were higher than BDAR. This is consistent with previous research findings that showed,

compared to other infusion types, bolus dose (BD) infusions have higher risk of incurring mediation errors[20] and severe patient harm[21,22] due to programming errors. Therefore, we suggest that for infusions , the start key on smart pumps should be disabled in Dose Error Reduction System if a BD overdosing alert has been triggered. The nurse cannot override this alert type from a patient sfaty standpoint, except in special circumstances.

**Soft and Hard Maximum Drug Limit Type**

The factor of soft maximum drug limit type (small/large) had significant effect on the expected risk, where the higher risk of potential patient harm was found for those alert-overridden scenarios with large soft maximum limits. In general, for any care area-medication combination case, the large soft maximum limit usually is intended for patients who have special health conditions or those who need specific therapies. Therefore, infusions of overridden alerts of large soft max limit correspond to the higher dose rate or total dose, which present higher risk for adverse events, especially to critically ill patients[23,24]. This could be the main reason why the experts rated the scenarios with large soft maximum limits with higher risk than those with small soft maximum limits.

For the hard maximum limit, the expected risk had no difference between the scenarios with and without hard limit. Most of the pharmacists and nurses who participated in this study review infusion alert resports frequently. According to our observation during the interviews, many of them could easily estimate the thresholds of drug amount and the infusion rate for the specific care area-medication combination, which could affect the risk of harm they perceived on patients whether the hard limits were provided. In other words, these pharmacists and nurses used forward reasoning approach to validate assumptions

based on the scenarios they interpreted[25]. It explains that providing hard limit did not have an impact on the experts' ratings, since most experts did not refer to the limit.

**Care Area and Medication**

The significant interaction between care area and soft maximum limit indicated that, in AICU, there was higher risk of harm to the patient if a nurse overdoses with the infusion over a large soft maximum limit than versus a small soft maximum limit. However, such difference in risk does not exist in AMSU. One possible reason could be that AICU patients are sicker than those in AMSU. A larger overdose of drug infusions understandably may cause more serious patient harm in AICU.

Our analysis also showed the significant interaction between care area and drug amount, and risk was different among the infusion cases with three levels of drug amount in AICU: higher total drug amount causes higher risk, followed by moderate and lower drug amount. In AMSU, higher and moderate drug amount led to significantly higher risk than lower drug amount, and there was no difference between higher and moderate drug amount. The finding in AMSU was not consistent with what was proposed in the IV mediation harm index[1,2], where the increase of the drug amount levels cause higher risk of harm. These results encourage clinicians to carefully check the infusions parameters, especially for infusing high-risk drugs in AICU.

**Limitation**

There are some limitations to this study. First, the patient in each scenario was assumed to be a 35-year-old male weighing 70 kg. By doing so, we did not consider the impacts of the patients' age, gender, and body weight[26]. Secondly, the patient's conditions and physician's orders were not provided in the scenario design. The expert participants

were asked to consider all possible patient conditions and provide the likelihoods of each degree of harm given the limited information. Lastly, the effect of pharmacist's and nurse's roles was not considered and the number of each was not balanced (5 nurses, 20 pharmacists). A hospital medication safety team typically includes these two healthcare professional roles, so their perspectives are both important in this study. Future research may focus on studying the effect of pharmacist's and nurse's roles and experience on their assessed risk of IV harm.

## CONCLUSIONS

The goal of this research was to calculate the expected risk of harm for the simulated scenarios by utilizing the adjusted experts' risk assessments and also investigate whether the identified risk factors had associations with risk of IV harm. Our findings supported that the field limit type (CD, BD, and BDAR) and the small or large soft maximum drug limit have significant impact on risk. The overdose infusion in AICU over a large soft maximum limit resulted in higher risk of harm than over a small one, but not in AMSU. The effect of drug amount was the other inconsistency between AICU and AMSU that greater drug amount led to higher risk, except the insignificant difference between moderate and higher drug amount in AMSU. The expected risk calculated from this study for the simulated high-risk alert-overridden scenarios can be regarded as risk benchmarks to validate some risk quantification models of overdosed infusions in the future.

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**Tables**

Table 1. Continuous and bolus infusion type and field limit type

| | **Continuous Infusion** | **Bolus Infusion** |
|---|---|---|
| **Infusion Parameters** | Enter infusion rate and total volume<br>*Infusion duration will be automatically calculated by given infusion rate and total continuous drug amount (total volume and concentration) | Enter infusion drug amount and infusion duration (min)<br>*Infusion rate will be automatically calculated by given drug amount and infusion duration (min) |
| **Field Limit Type** | Continuous Dose (CD) | Bolus Dose (BD), Bolus Dose Administration Rate (BDAR) |
| **An Example of Field Limit in AMSU for Morphine** | CD: 50 mg/h | BD: 10 mg<br>BDAR: 5 mg/min |
| **Field Limit Alert** | An alert can be triggered when a programming continuous dose rate is outside the CD filed limit type | An alert can be triggered when a programming bolus dose/dose rate is outside the BD or BDAR filed limit type |

Table 2. Descriptive analysis and LS mean for expected risk of the field limit type

| Field limit type | *n* | *M* | *SD* | *LSmean* | *SE* | *df* | *group* |
|---|---|---|---|---|---|---|---|
| BDAR | 90 | 1.080 | 0.675 | 0.036 | 0.283 | 34.67 | a |
| BD | 63 | 1.785 | 1.346 | 2.134 | 0.251 | 30.51 | b |
| CD | 180 | 1.879 | 1.119 | 2.281 | 0.237 | 22.31 | b |

Note. LS mean = least squared mean; df = Satterthwaite approximation for degrees of freedom; group = expected risk was significantly different in a and b groups identified using post hoc test

Table 3. Post hoc test for field limit type

| Contrast | *estimate* | *SE* | *df* | *t.ratio* | *p.value* |
|---|---|---|---|---|---|
| BD - BDAR | 2.098 | 0.233 | 267.61 | 8.987 | <0.001*** |
| BD - CD | -0.147 | 0.195 | 298.79 | -0.757 | 0.730 |
| BDAR - CD | -2.246 | 0.281 | 156.25 | -7.985 | <0.001*** |

Table 4. The descriptive analysis and LS mean for expected risk of the softmax limit type

| Soft limit type | *n* | *M* | *SD* | *LSmean* | *SE* | *df* | *group* |
|---|---|---|---|---|---|---|---|
| Small | 243 | 1.555 | 1.090 | 1.437 | 0.144 | 27.48 | a |
| Large | 225 | 1.865 | 1.168 | 1.857 | 0.147 | 29.20 | b |

Table 5. Descriptive analysis of the combinations of care area and mediation

| Care Area | Medication | *n* | *M* | *SD* |
|---|---|---|---|---|
| AICU | Heparin | 108 | 1.365 | 1.257 |
| AMSU | Heparin | 54 | 1.846 | 0.857 |
| AICU | Insulin | 72 | 1.789 | 1.058 |
| AMSU | Insulin | 54 | 1.544 | 1.166 |
| AICU | Morphine | 54 | 1.836 | 1.353 |
| AMSU | Morphine | 54 | 2.311 | 1.011 |

Note. AICU = Adult Intensive Care Unit; AMSU = Adult Medical/Surgical

Table 6. Descriptive analysis and LS mean for the combinations of care area and soft limit type

| Care Area | Soft limit type | *n* | *M* | *SD* | *LSmean* | *SE* | *df* | *group* |
|---|---|---|---|---|---|---|---|---|
| AICU | Small | 126 | 1.438 | 1.101 | 1.297 | 0.173 | 37.52 | a |
| AMSU | Small | 81 | 1.876 | 1.135 | 1.699 | 0.206 | 60.15 | ab |
| AMSU | Large | 81 | 1.925 | 0.989 | 1.756 | 0.208 | 60.08 | ab |
| AICU | Large | 108 | 1.798 | 1.361 | 2.002 | 0.177 | 40.27 | b |

Table 7. Descriptive analysis and LS mean for the combinations of care area and drug amount level

| Care Area | Drug amount level | *n* | *M* | *SD* | *LSmean* | *SE* | *df* | *group* |
|---|---|---|---|---|---|---|---|---|
| AICU | 1 | 78 | 0.559 | 0.706 | 0.591 | 0.156 | 38.05 | a |
| AMSU | 1 | 54 | 1.161 | 0.979 | 1.002 | 0.172 | 52.74 | a |
| AICU | 2 | 78 | 1.806 | 1.057 | 1.838 | 0.156 | 38.05 | b |
| AMSU | 2 | 54 | 2.108 | 0.906 | 1.950 | 0.172 | 52.74 | bc |
| AMSU | 3 | 54 | 2.431 | 0.868 | 2.273 | 0.172 | 52.74 | cd |
| AICU | 3 | 78 | 2.449 | 1.074 | 2.481 | 0.156 | 38.05 | d |

## Figures

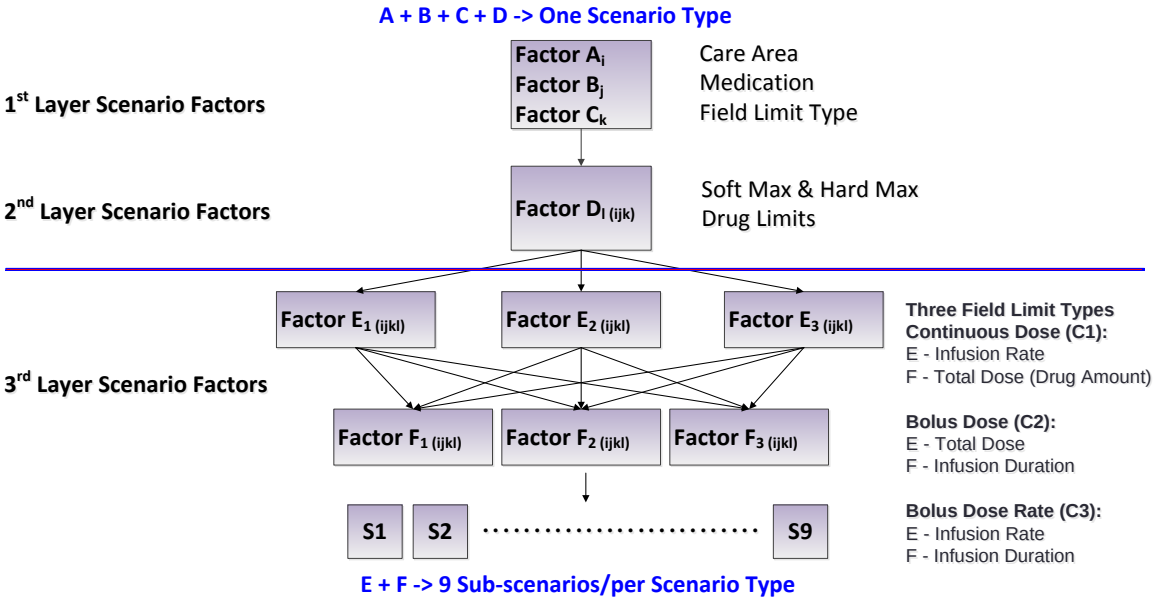



Figure 1. Scenario design structure

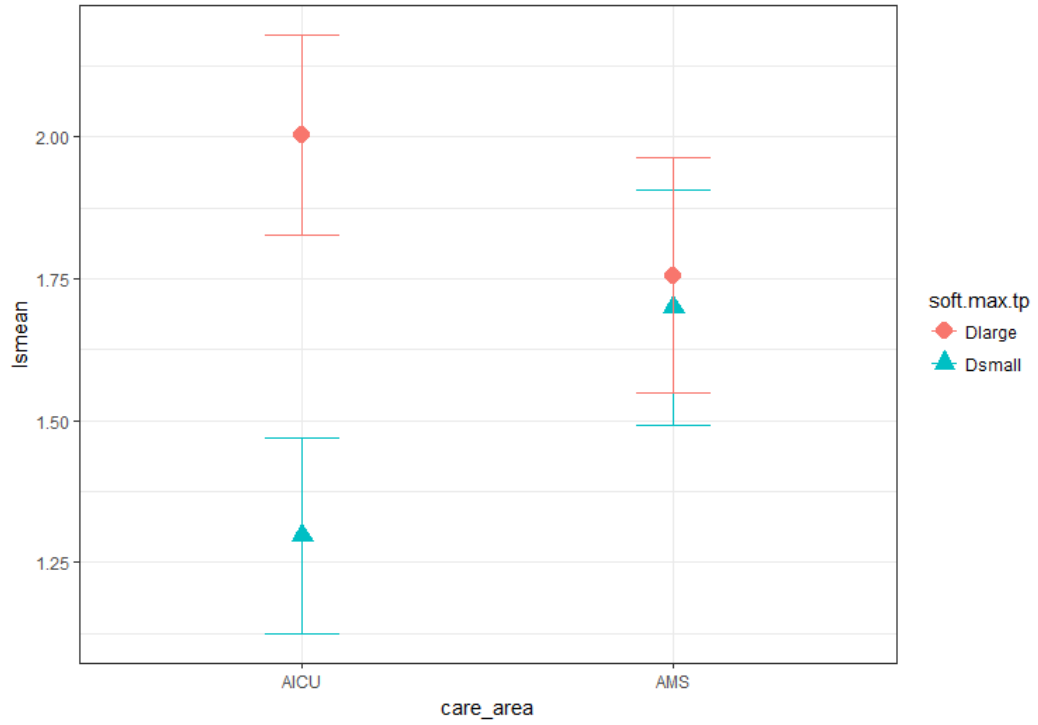



Figure 2. The expected risk for the interaction between care area and soft limit type

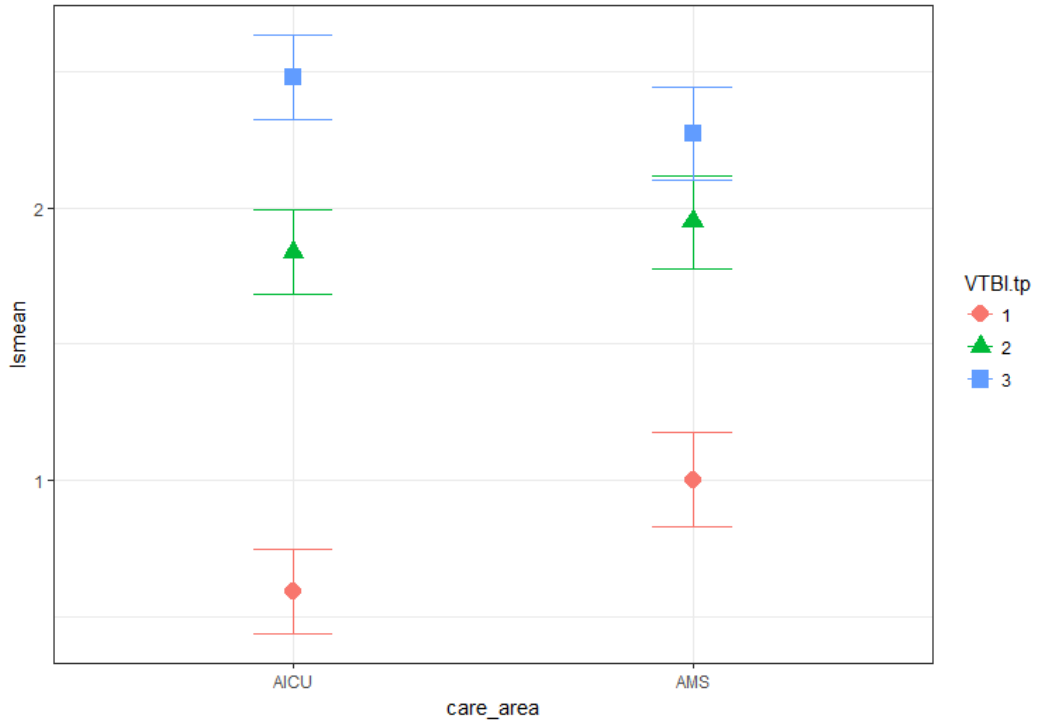



Figure 3. The expected risk for the interaction between care area and drug amount level

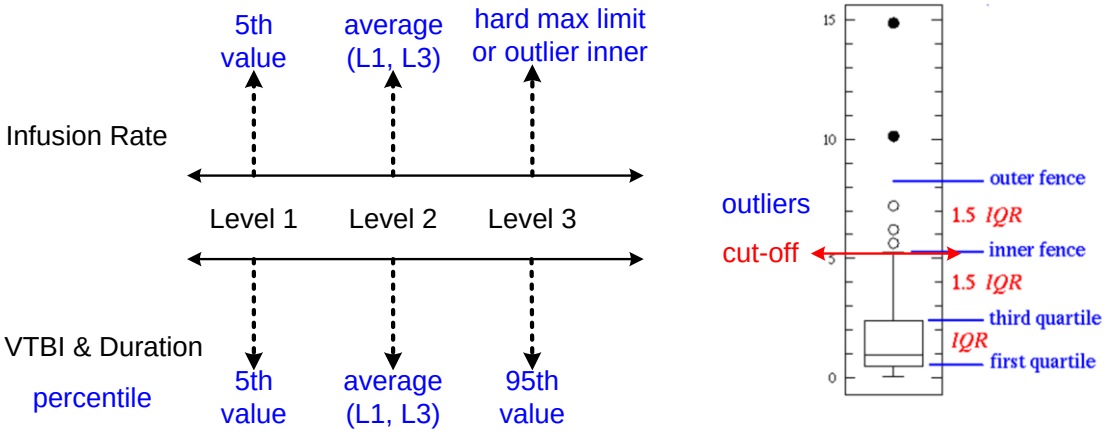
Appendix A. 30 scenario types and information

| | 1st Layer Scenario Factor | | | 2nd Layer Scenario Factor | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Scenario Type | Care Area | Medication | Field Limit Type | Soft Max Drug Limit | Hard Max Drug Limit | Drug Limit Unit | Conc* | Conc* Unit | Alert Frequency |
| 1 | AICU | propofol | CD | 51 | 80 | mcg/kg.min | 10 | mg/mL | 2236 |
| 2 | AICU | propofol | CD | 51 | - | mcg/kg.min | 10 | mg/mL | - |
| 3 | AICU | propofol | CD | 100 | 150 | mcg/kg.min | 10 | mg/mL | 1208 |
| 4 | AICU | propofol | CD | 100 | - | mcg/kg.min | 10 | mg/mL | - |
| 5 | AICU | propofol | BD | 20 | - | mg | 10 | mg/mL | 12119 |
| 6 | AICU | propofol | BDAR | 10.1 | 25 | mg/min | 10 | mg/mL | 2106 |
| 7 | AICU | morphine | CD | 20 | - | mg/h | 1 | mg/mL | 642 |
| 8 | AICU | morphine | CD | 20 | 54 | mg/h | 1 | mg/mL | - |
| 9 | AICU | morphine | CD | 50 | - | mg/h | 5 | mg/mL | 41 |
| 10 | AICU | morphine | BD | 25 | - | mg | 1 | mg/mL | 15 |
| 11 | AICU | morphine | BDAR | 5 | - | mg/min | 1 | unit/mL | 65 |
| 12 | AICU | insulin | CD | 35 | 49 | unit/h | 1 | unit/mL | 1206 |
| 13 | AICU | insulin | CD | 35 | - | unit/h | 1 | unit/mL | - |
| 14 | AICU | insulin | CD | 81 | 121 | unit/h | 1 | unit/mL | 361 |
| 15 | AICU | insulin | CD | 81 | - | unit/h | 1 | unit/mL | - |
| 16 | AICU | insulin | BD | 10 | 20 | unit | 1 | unit/mL | 336 |
| 17 | AICU | heparin | CD | 2601 | 3500 | unit/h | 100 | unit/mL | 7974 |
| 18 | AICU | heparin | CD | 2601 | - | unit/h | 100 | unit/mL | - |
| 19 | AICU | heparin | CD | 4501 | 6001 | unit/h | 100 | unit/mL | 495 |
| 20 | AICU | heparin | CD | 4501 | - | unit/h | 100 | unit/mL | - |
| 21 | AMSU | morphine | CD | 10 | 20 | mg/h | 1 | mg/mL | 1022 |
| 22 | AMSU | morphine | CD | 30 | 50 | mg/h | 5 | mg/mL | 76 |
| 23 | AMSU | morphine | BD | 5 | 10 | mg | 1 | mg/mL | 137 |
| 24 | AMSU | morphine | BDAR | 2 | 5 | mg/min | 1 | mg/mL | 255 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 25 | AMSU | morphine | BDAR | 4 | 10 | mg/min | 5 | mg/mL | 10 |
| 26 | AMSU | insulin | CD | 35 | 49 | unit/h | 1 | unit/mL | 28 |
| 27 | AMSU | insulin | CD | 81 | 121 | unit/h | 1 | unit/mL | 22 |
| 28 | AMSU | insulin | BD | 10 | 20 | unit | 1 | unit/mL | 90 |
| 29 | AMSU | heparin | CD | 2500 | 3500 | unit/h | 100 | unit/mL | 3179 |
| 30 | AMSU | heparin | CD | 4501 | 6001 | unit/h | 100 | unit/mL | 46 |

*Conc: Concentration; “-“: NA

Appendix B. Three levels design for the numerical variables



Appendix C. Scenario combinations and the sample size for testing factor effects

| Factor Effect | Scenario Type (Appendix A) | Number of Scenario Types | Sample Size |
|---|---|---|---|
| Field limit type | S1-S11, S21-S25 | 16 | 333 |
| Soft limit type | S1-S4, S7-S9, S12-S15, S17-S22, S26-S27, S29-S30 | 21 | 468 |
| Hard limit type | S1-S4, S7-S9, S12-S15, S17-S20 | 15 | 306 |
| Care area and medication | S7-S9, S12-S15, S17-S22, S26-S27, S29-S30 | 17 | 396 |

Appendix D. An example of survey design

## Alert and Pump Information

**AICU - Propofol** **Soft Max:** 100 mcg/kg.min

**Field Limit Type: Continuous Dose** **Hard Max:** NA

| *Scenario I - Infusion Information* | *Total Amount Patient Received* |
|---|---|
| **Dose (Dose Rate):** 130 mcg/kg.min | **Drug Amount:** 590 mg (59 mL) |
| **Ratio =** $\frac{\textit{Dose (Dose Rate)}}{\textit{Soft Max (100 mcg/ kg.min)}}$ **= 1.3** | |
| **Volume Rate:** 0.9 mL/min (54 mL/h) (Concentration: 10 mg/mL) | |

## Alert-overridden Scenario

In **ACIU**, a 35-year-old male patient (70 kg) was prescribed **propofol** via **continuous** IV infusion at **130 mcg/kg.min**. A soft alert was triggered by the Soft Max drug limit at a dose of **100 mcg/kg.min**. The patient received **590 mg (59 mL) after 1.1 hours.** The nurse chose to **OVERRIDE** this alert. Any harm to the patient?

**QUESTION 1:**

**What is your expected severity of IV infusion harm in this scenario?**

Please consider **ALL conditions of non-anesthesia patients** and select the potential severity of IV harm, which maps on to the NCC MERP category index as shown in the rating table. **Mark** the estimated probability (in percentage) of **EACH** possible severity of IV harm. The sum of the probabilities does not need to be equal to 100%.

**[NOTE]:**

**"In many cases, you may not have all the clinical information you may want to make a sound care decision or assessment. It is important to use your best judgement to identify the expected level of harm given the limited information presented in the scenario."**

**NCC Category - Harm Definition**

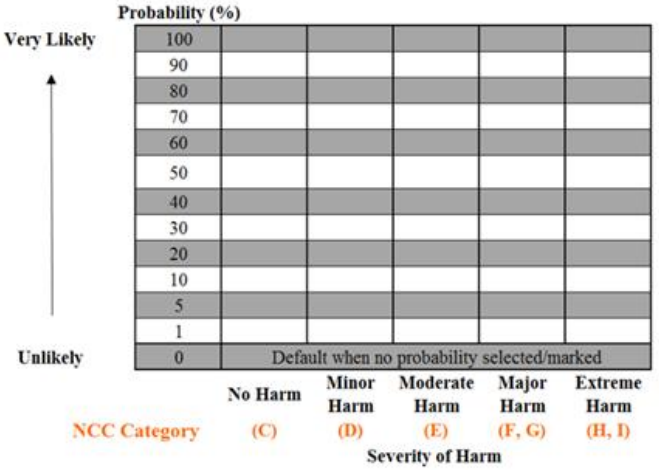
C - No detectable harm

D - No detectable harm; Minimum temporary harm

E - Moderate/Serious temporary harm

F, G - Serious temporary harm; Minimum/Moderate/Serious permanent harm

H, I - Serious temporary/permanent harm; Death



# APPENDIX H. PAPER 2

## A Risk Prediction Model for Alert Overrides in High-Risk Intravenous (IV) Medication Infusions

Wan-Ting Su, Mark R. Lehto, Poching DeLaurentis

**ABSTRACT**

Overriding alerts triggered by the infusion pump when programming intravenous (IV) medication infusions can potentially lead to patient harm, especially with high-risk medications. We developed a statistical regression model to quantify risk of IV harm for individual alert overrides of four high-risk medications, propofol, morphine, insulin, and heparin, in the settings of adult intensive and adult medical and surgical care units. We used the expected risk of the simulated infusion scenarios collected from our prior risk assessment study as risk benchmarks for creating and validating the risk quantification models in this study. We selected final predictive models with main and interaction effects as risk predictors for each infusion field limit alert type, continuous dose, bolus dose, and bolus dose rate. The selected final models were cross-validated as best prediction models with the minimum mean squared prediction error (*MSPR*). In addition, these models were evaluated as the best overall fitting performance with the majority of all four individual performance values, the minimum Akaike information criterion (*AIC*), Bayesian information criterion (*BIC*), mean squared errors (*MSE*), and the maximum adjusted r-square ($R^2_{adj}$). Compared to the previous frequency-based analysis tools, such as Key Performance Indicators and Infusion Pump Safety Score, these predictive models provide a risk-based analytical method to support evaluating alert-overridden infusions. Healthcare systems can apply these three field limit types of risk-based models to efficiently identify the riskiest medication-care unit combinations (e.g. propofol in adult intensive care unit) using infusion alert data for early intervention.

**Key Words:** IV infusions, Risk assessment, Medication safety, High-risk medications, Predictive Models

## INTRODUCTION

Intravenous (IV) infusion administration has been identified as having the greatest potential for severe patient harm during the medication-use process (Eskew, Jacob, Buss, Warhurst, & Debord, 2002; Fields & Peterman, 2005; Hatcher, Sullivan, Hutchinson, Thurman, & Gaffney, 2004; Westbrook, Rob, Woods, & Parry, 2011; Williams & Maddox, 2005; Wilson & Sullivan, 2004). The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) defined patient harm as "death or temporary or permanent impairment of body function/structure requiring intervention," where intervention includes "monitoring the patient's condition, change in therapy, or active medical or surgical treatment" (NCC MERP, 2014). NCC MERP classified medication error and harm into nine categories from categories A to I (NCC MERP index) based on the severity of patient outcomes (NCC MERP, 2001). To ensure the safety of IV medication administration in clinical settings and to avoid potentially serious harm associated with IV medication errors, smart infusion pumps (SIPs) with a built-in dose-error reduction system (DERS) have been adopted by more than 70% of the healthcare systems in the United States as of 2012 (AAMI, 2016). A healthcare system can customize its drug limit settings defined in the drug limit library in DERS. Such a drug limit library includes minimum and maximum drug limits for each of the selected drugs (Hertzel & Sousa, 2009). While increasing the usage of the pumps with the DERS safety feature can reduce the risk associated with IV drug infusions (Harding, 2012), a clinician can either choose to override or reprogram the infusion parameters in response to an alert triggered by DERS. In particular, overriding an alert is not always preferred because it can potentially lead to patient harm, especially when infusing high-risk medications or in case of user error.

Currently, frequency-based analysis tools, such as Key Performance Indicators (CareFusion Corporation, 2015) and Infusion Pump Safety Score (Carlson, Johnson, & Ensign, 2015), are available for evaluating infusion alert overrides. However, these frequency-based analysis tools consider every alert override to cause the same degree of harm on patients, and the total counts of alert overrides during a period of time are regarded as an overall risk measure. Compared to those frequency-based analysis tools, the IV Harm Index, developed by the IV Medication Harm Index Study Group, composed of

professionals in patient safety (Sullivan, 2004; Williams et al., 2006), is the only published method to quantify risk of harm for individual alert overrides, in which risk of harm incorporates the likelihood of potential degree of harm (Cure, Zayas-Castro, & Fabri, 2014). The IV harm index used drug risk and overdose ratio (ratio means programming values (overdose) divided by the soft maximum drug limit), level of care/acuity, and detectability of ADEs to generate overall IV medication harm scores (range from 3.5 to 14). However, this IV Harm Index did not consider that differences exist in field limit alert type (e.g., continuous or bolus dose infusions), drug limit types (e.g., small/large maximum soft limits), and some interaction effects between care area and drug limit type as well as between care area and drug amount level, all should be considered potential risk factors for patient harm. In contrast, we have indicated these potential factors in our previous risk assessment study, obtaining experts' assessments on the expected risk of the simulated alert overriding scenarios (Su et al., 2018).

The goal of this research is to utilize the expected risk of the simulated scenarios with alert overrides obtained from domain experts in our prior study to develop a statistical regression model for individual alert overrides of four high-risk medications, propofol, morphine, insulin, and heparin in the settings of AICU and AMSU. These four high-risk medications are on the Institute for Safe Medication Practices (ISMP) categories of high-alert medication list (ISMP, 2018), and are representative set of those with alert overrides and high alert frequency (Su et al., 2018). The contribution of this research is to provide a risk-based analytical method in support of evaluating alert-overridden infusions, such that healthcare systems can use infusion alert data to efficiently identify the riskiest medication-care unit combinations (e.g. propofol in adult intensive care unit) as first step to improve infusion practice including nursing practices, workflow, or drug limit settings (Miller, 2016).

## METHODS

### Study Design

We applied stepwise *AIC* regression for feature selection (key important predictors) of the study data, which reduced the potential predictor variables and selected the most

important ones using *AIC* criteria. A few selected variables were used to build the candidate models. We finally conducted the proper K-fold cross validation to validate the candidate models and selected the final models using model selection criteria. Also, we conducted ANOVA and Post Hoc Tests to investigate the important risk factors and the least-square means difference among the levels of the factors from the perspective of the selected final models, which are multi-variate linear regression models.

**Outcome Variable**

The outcome variable is expected risk of IV harm obtained from the previous risk assessment study (Su et al., 2018), also called risk benchmarks to create and validate the risk predictive models in this research. The expected risk is defined as a sum of each likelihood from 5 degrees of harm multiplied by the corresponding quantified scales of severity impacts. In the previous study, we assumed an exponential growth for five degree of harm $(10^0, 10^1, 10^2, 10^3, 10^4)$ due to nonlinear severity impacts (Chang, Lawless, Newcomb, & Uhl, 2003). In addition, we adjusted the probabilities subjectively estimated by the healthcare professionals $(p)$, to true probability $(p')$ using the following non-linear function suggested by Tversky and Kahneman (1992) when human make decision under uncertainty:

$$Lo(p') = \frac{1}{\gamma} \times Lo(p) - \frac{1-\gamma}{\gamma} \times Lo(p_0) \quad (1)$$

where $p'$ indicates true probability, $p$ indicates subjective probability, $\gamma$ and $p_0$ were respectively selected as 0.6 and 0.4 (Tversky & Kahneman, 1992), and $Lo(probability)$ is the log odds (Barnard, 1949).

**Predictor Variables**

According to the study design (Su et al., 2018), there are three-layer scenario factors and one blocking factor, which are assigned as 10 variables ($X_1$ - $X_{10}$), in addition to the patient information (Table 1). When building linear regression models, the variables $X_4$ and $X_5$, soft and hard maximum drug limits, were transferred as the categorical variables (drug limit types), since we were interested in the effect of small or large soft limits and were also interested in the effect of that whether providing hard limits could have an impact on the outcome variables. The levels for the categorical variables are indicated in Table 1. In addition, the variables $X_8$ and $X_9$ were selected only on the 3rd layer because there is a

linear relationship between the variables $X_6$, $X_7$, and $X_8$, ($X_6 = X_7/X_8$), so only two variables are needed to create the models. However, the ranges and units of infusion rate ($X_6$) and dose ($X_7$) for different medications varied. Therefore, the ratio of the soft maximum drug limit ($X_9$), which can be the ratio of infusion rate or dose depending on the variable field limit type ($X_3$), was selected to represent $X_6$ and $X_7$.

Table 1: Scenario Information and Selected Main Independent Variables

| Scenario Information | Variable Code | Main Independent Variable | Levels of Categorical Variable | Categorical or Numerical Variable |
|---|---|---|---|---|
| Patient<br>(35-year-old male patient, 70 kg) | | | | |
| **Layer I** | | | | |
| Care Area | $X_1$ | V | AICU, AMSU | Categorical |
| Medication | $X_2$ | V | P, M, I, H | Categorical |
| Field Limit Alert Type | $X_3$ | | CD, BD, BDAR | Categorical |
| **Layer II (nested by Layer I)** | | | | |
| Soft Maximum Limit | $X_4$ | V | Small/Large, Soft Drug Limit Type | Categorical |
| Hard Maximum Limit | $X_5$ | V | Hard Drug Limit Type: Hard Limit Provided Y/N | Categorical |
| Concentration | | | | Numerical |
| **Layer III (nested by Layer I & II)** | | | | |
| Infusion Rate (Rate) | $X_6$ | | | Numerical |
| Total Dose Patient Receive (Dose) | $X_7$ | | | Numerical |
| Infusion Duration (Duration) | $X_8$ | V | | Numerical |
| Ratio of (Rate or Dose)/Soft Max | $X_9$ | V | | Numerical |
| **Blocking Factor** | | | | |
| Participant | $X_{10}$ | V | Participant ID | |

Note. P: propofol; M: morphine; I: insulin; H: heparin

**Development of Risk Predictive Models Using Linear Regression Model**

We applied a generalized linear mixed model (GLMM), an extension of the generalized linear model (GLM), to predict the expected risk since the predictors consist of the usual fixed effects and the random effect (Breslow & Clayton, 1993; Jiang, 2007). In this research, the participant factor was treated as a random effect that had an expected value of zero in the population. There were three phases to build a linear mixed model, which were data preparation in phase 1, reduction of predictor variables in phase 2, and model validation and model selection in phase 3.

*Phase 1: Data Collection and Preparation*

After defining the outcome and predictor variables, we classified data into three sub-groups based on three field limit types, continuous dose (CD), bolus dose (BD), and bolus dose administration rate (BDAR) groups for building three types of linear regress models. Three reasons led to the grouping: (1) the range of $X_8$ for CD group is larger than BD and BDAR groups; (2) there is no different level of $X_4$ being designed for the data in the BD group, so this variable is not relevant for creating models for the BD group; (3) the drug limit settings for BD and BDAR are different, which $X_9$ for BD means infusion dose, but meaning infusion rate for BDAR. In other words, the larger $X_8$ means smaller infusion rate with fixed dose for BD, but meaning larger infusion dose with fixed rate for BDAR, so the data in these two groups should be separated.

*Phase 2: Reduction of Predictor Variables*

Due to a large number of potential independent variables in the pool, including main X variables and their interaction effects, the number of possible models is large. Evaluating all the possible alternatives is not a simple task (Neter, Kutner, Nachtsheim, & Wasserman, 1996). Therefore, we applied a stepwise *AIC* regression for selecting predictor variables, which is an automatic procedure to fit and compare the regression models sequentially using the Akaike information criterion (*AIC*) (Neter et al., 1996). Further, we selected the backward stepwise regression (Draper & Smith, 2014) to sequentially subset the predictor variables, also called a backward elimination search procedure, for the CD, BD, and BDAR groups. In the beginning of the stepwise procedure, all potential X variables, was involved. At each step, one variable would be subtracted, which made the regression model with a minimum *AIC* value in comparison to others at this step. Note that

a lower *AIC* indicates a better fitting performance, and the procedure was repeated until no further X variables can be dropped. We selected three candidate regression models with three minimum *AIC* values for each group, including the subset of the predictor X variables.

*Phase 3: Model Validation and Model Selection*

We conducted the K-fold cross validation to validate the candidate models and select the final model. In the beginning, we need to choose a proper number of folds of data splits for each field limit type since the datasets of each field limit type, CD, BD, and BDAR, for building linear regression models are small (less than 500 samples). Then, we used the selected K-fold cross validation results to evaluate and compare the performance of the candidate models. Referring to K-fold cross validation, also called repeated K times cross validation, the data is first split into K number of roughly equal folds (Neter et al., 1996). The K-1 folds were used as the training dataset to build a model and the other Kth fold was used as the testing dataset to examine the predictive capability, which uses the model fitted from the training dataset to predict the outcomes of the testing dataset. The sample size of the training dataset is equal to or larger than the testing dataset. The measure for the actual predictive capability is denoted by the mean squared prediction error, *MSPR*. The smaller *MSPR* means the higher predictive capability (Neter et al., 1996).

$$MSPR = \sum_{i=1}^{n^*}(Y_i - \widehat{Y_{\iota(\iota)}})^2/n^* \quad (2)$$

Where: $Y_i$ is the observed response and $\widehat{Y_{\iota(\iota)}}$ is the predicted value obtained for the i-th validation case; $n^*$ is the sample size of validation dataset

In addition, for each candidate model, both training and testing ith case datasets can fit two types of regression models, which are defined as a training type model and a testing type model in this research. Within each K-fold split, the variation of goodness of fit measures, $R^2_{adj}$ values, obtained from the two types of fitting models for all candidate models were initially examined. The smaller variation of $R^2_{adj}$ values within the repeated K-times cross validation means that the fitting performance within the repeated times of the K-folds data split for both types of models are more consistent. The processes of choosing proper K-folds to split training and testing datasets for reviewing the cross-validation results and selecting final models are as follows: (1) We assigned the number of total folds as 2, 3, 4, etc. until the number, N, where the sample size of the testing datasets

for the N-folds is larger than the number of parameters, (2) initially targeted the number of folds with smaller variation of $R^2_{adj}$ values (i.e. 3- or 4-folds), and (3) chose the specific number of total folds, K, with the minimum *MSPR* value and regarded it as proper K-folds.

After the specific number of folds, K, were selected for each field limit type, the measure of actual prediction capability, the *MSPR* values, from a validation method were reviewed to assess the validity of the candidate regression models built by the training datasets. We selected the models with the minimum *MSPR* as the final models. We further used the fitting performance criteria, which included Akaike information criterion (*AIC*), Bayesian information criterion (*BIC*), mean squared errors (*MSE*), and adjusted R-square ($R^2_{adj}$), to confirm the selected final models built by the entire datasets. Compared to the other candidate models, the overall performance of using model-selection criteria, *MSPR, AIC, BIC, MSE,* and $R^2_{adj}$, for the final selected model should be the best. We also conducted Analysis of Variance (ANOVA) and the post hoc tests using the final models to investigate which risk factors (X variables) have significant impacts on expected risk, which were regarded as strong predictors for the multi-variate linear mixed regression models.

## RESULTS

### Phase 1: Data Collection and Preparation

We classified data into three sub-groups and built models based on each field limit type. The total number of data points in the continuous dose (CD) group are 468, 117 in the bolus dose (BD), and 90 in the bolus dose administration rate (BDAR). These main variables and the interactions among these variables were initially to create three types of full models. We reviewed the fitting performance using $R^2$ values for the full models of CD, BDAR (Eq. 3). $X_4$ was not involved in the full model of BD (Eq. 4) due to its one level design for this field limit type. There was a maximum $R^2$ for BD full model ($R^2$ = 0.91), following for BDAR ($R^2$ = 0.84), then for CD ($R^2$ = 0.76). The full models are indicated as follows:

$$Y \sim \underbrace{X_1 \times X_2 \times X_4 \times X_5 \times X_8 \times X_9}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \quad (3)$$

$$Y \sim \underbrace{X_1 \times X_2 \times X_5 \times X_8 \times X_9}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \quad (4)$$

### Phase 2: Reduction of Potential Predictor Variables

We run stepwise *AIC* regressions and selected predictor variables to build the candidate models. According to the stepwise *AIC* results, we built three candidate models (Appendix A) for each group using the subset of the predictors with three minimum *AIC* values.

### Phase 3: Model Validation and Model Selection

In phase 3, we chose proper K-folds to split the dataset and conduct K-folds cross-validation for the candidate models, then selected the final models using the model prediction capability and fitting performance criteria. The number of folds to split data for the CD field limit type is 2 to 8, for BD is 2 to 7, and for BDAR is 2 to 5, which are the initial input number of folds. The total sample size of the training and testing datasets for the CD group is 468, and Figure 1 shows the sample size of the two datasets across the K-folds split. For example, when using 3 folds to split data, it means that 312 datasets (468 x 2/3) were used as the training dataset and 156 (468 x 1/3) as the testing dataset. According to the boxplot of $R^2_{adj}$ values for two model types shown in Figure 2, the variation of $R^2_{adj}$

for the 2- to 4-folds are smaller in comparison to the 5- to 8- folds. Since the average *MSPR* of the 4-folds, including all candidate models, is minimum among 2- to 4-folds data splits (Table 2), we selected 4-folds split to conduct cross-validation across the three CD candidate models. We regarded model 2 as the final model since it has the minimum average *MSPR* value. It also has the best overall model fitting performance, with the minimum *AIC*, *MSE*, and the maximum $R^2_{adj}$ across all three candidate models (Table 3). The selected final model for the continuous dose infusion is expressed in Eq. 5.

$$Y \sim \underbrace{X_1 + X_2 + X_4 + X_5 + X_8 + X_9 + X_1 * X_2 + X_1 * X_4 + X_4 * X_5 + X_4 * X_8}_{fixed\ effect} + \underbrace{X_1 * X_2 * X_4 + X_1 * X_2 * X_8 + X_1 * X_4 * X_8 + X_4 * X_8 * X_9 + X_1 * X_2 * X_4 * X_9}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \quad (5)$$

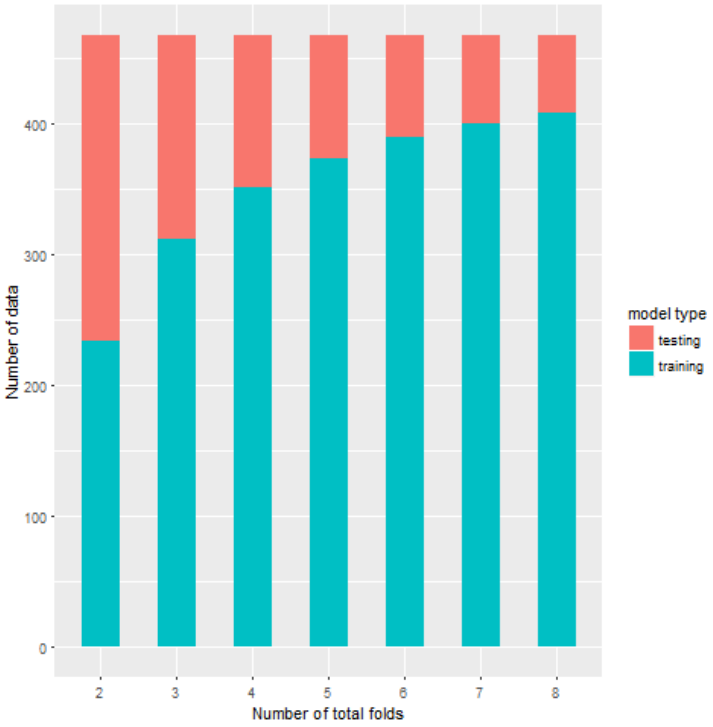



Figure 1: The Stacked Bar Plot of Number of Training (Green) and Testing (Red) Datasets for Different Folds – CD Group

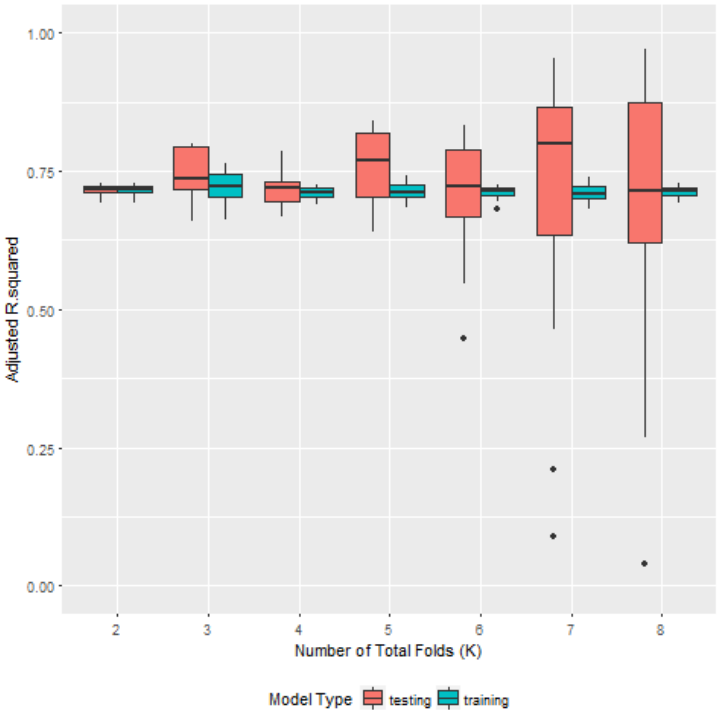



Figure 2: The Boxplot of $R^2_{adj}$ Values for Different Folds – CD Group
The Training Model is Green and Testing Model is Red

Table 2: The average MSPR for CD, BD, and BDAR Groups

| Field Limit Alert Type | Total N | Ave. *MSPR* for Different K-Folds split | | | Selected K-folds |
|---|---|---|---|---|---|
| | | 2-folds | 3-folds | 4-folds | |
| CD | 468 | 0.523 | 0.528 | **0.453** | 4-folds |
| BD | 117 | 0.251 | **0.191** | 0.203 | 3-folds |
| BDAR | 90 | 0.140 | 0.147 | **0.136** | 4-folds |

Note. The minimum average *MSPR* was marked in bold within each field limit alert type.

Table 3: The Performance Criteria for the Candidate Models – CD Group
The Values with Best Individual Performance are Marked in Bold

| Candidate model | 4-folds ave. *MSPR* | Number of parameters | *AIC* | *BIC* | *MSE* | $R^2_{adj}$ |
|---|---|---|---|---|---|---|
| Model 1 | 0.455 | 30 | 1185.244 | **1309.698** | 0.395 | 0.695 |
| **Model 2*** | **0.441** | 43 | **1154.427** | 1332.811 | **0.369** | **0.715** |
| Model 3 | 0.463 | 48 | 1159.719 | 1358.845 | 0.372 | 0.713 |

Note. The minimum average *MSPR*, the minimum *AIC*, *BIC*, *MSER*, and the maximum $R^2_{adj}$ among the candidate models were marked in bold. *Final selected model.

We followed the same procedures for analyzing the BD and BDAR datasets. For the BD group, the variation of $R^2_{adj}$ for the 2- to 4-folds are smaller in comparison to the 5- to 7- folds (Figure 3). Also, the average *MSPR* for the 3-folds, including all candidate models, is minimum among 2- to 4-folds (Table 2). Therefore, a 3-folds cross-validation was conducted to evaluate the three BD candidate models. Table 4 shows that the average *MSPR* across the 3 models are the same, so the overall fitting performance criteria for comparing the regression models was further examined to help select the final model. The overall fitting performance for model 1 was the best, which was regarded as the final model. The selected final model for the bolus dose infusion is expressed in Eq. 6.

$$Y \sim \underbrace{X_1 + X_2 + X_5 + X_8 + X_9 + X_2 * X_9 + X_5 * X_9}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \quad (6)$$

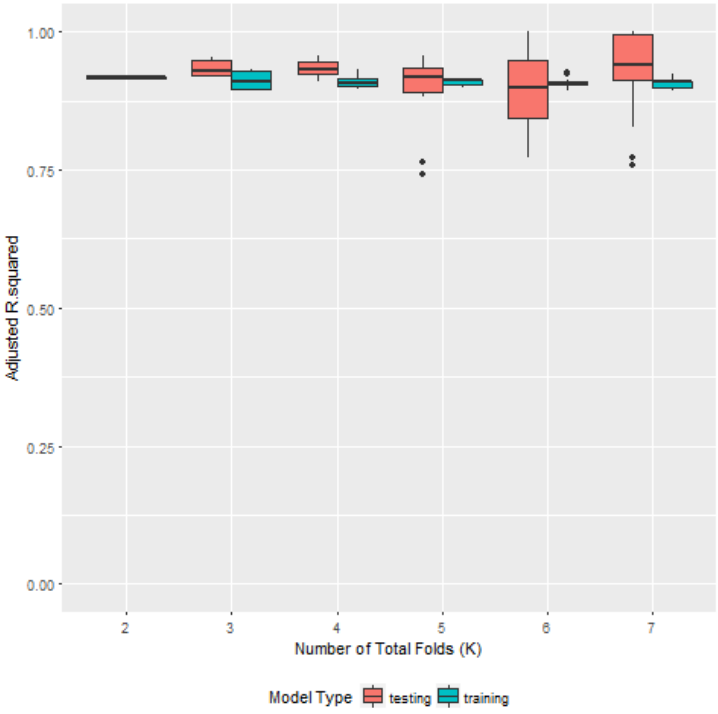



Figure 3: The Boxplot of $R^2_{adj}$ Values for Different Folds – BD Group
The Training Model is Green and Testing Model is Red

Table 4: The Performance Criteria for the Candidate models – BD Group
The Values with Best Individual Performance are Marked in Bold

| Candidate model | 3-folds ave. *MSPR* | Number of parameters | *AIC* | *BIC* | *MSE* | $R^2_{adj}$ |
|---|---|---|---|---|---|---|
| **Model 1*** | **0.193** | 12 | **170.034** | **203.181** | **0.130** | **0.907** |
| Model 2 | **0.190** | 13 | 175.007 | 210.915 | **0.129** | **0.907** |
| Model 3 | **0.192** | 14 | 179.894 | 218.564 | **0.131** | **0.906** |

Note. The minimum average *MSPR*, the minimum *AIC*, *BIC*, *MSER*, and the maximum $R^2_{adj}$ among the candidate models were marked in bold. *Final selected model.

For the BDAR group, the variation of $R^2_{adj}$ for the 2- and 4-folds is smaller in comparison to the 3- and 5- folds since there are some outliers presented in the 3- and 5-folds (Figure 4). In addition, the average *MSPR* of the 4-folds split, including all candidate models, is smaller than the average *MSPR* of the 2-folds split (Table 2). Therefore, we conducted 4-folds cross-validation to evaluate the three BDAR candidate models. We regarded model 1 as the final model with the minimum average *MSPR* value. Also, the overall model fitting performance for model 1 is the best, including the minimum *AIC*, *BIC*, *MSE*, and the maximum $R^2_{adj}$ across the three candidate models (Table 5). The selected final model for the bolus dose rate of infusion is expressed in Eq. 7.

$$Y \sim \underbrace{X_2 + X_4 + X_8 + X_9 + X_4 * X_8 + X_4 * X_9 + X_8 * X_5 + X_9 * X_5}_{fixed\ effect} + \underbrace{X_{10}}_{random\ effect} \quad (7)$$

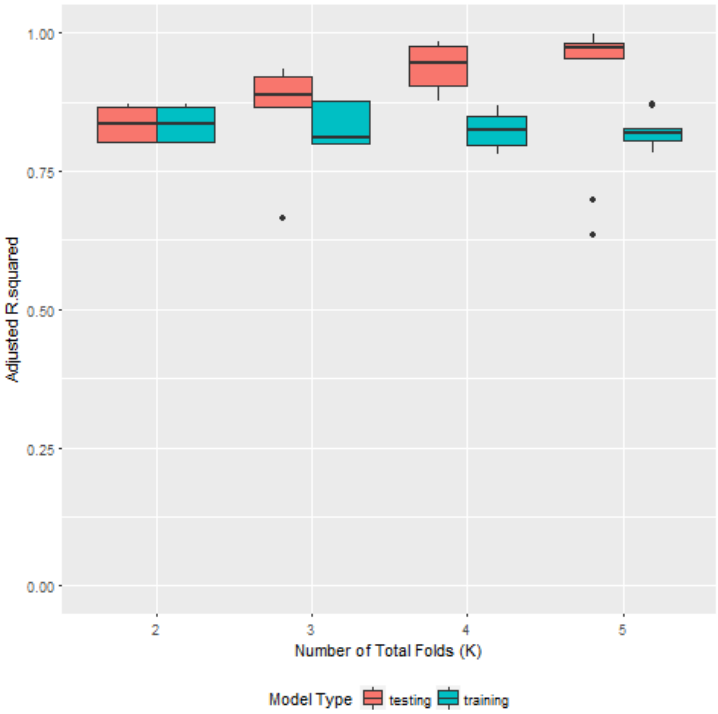



Figure 4: The Boxplot of $R^2_{adj}$ Values for Different Folds – BDAR Group
The Training Model is Green and Testing Model is Red

Table 5: The Performance Criteria for the Candidate models – BDAR Group
The Values with Best Individual Performance are Marked in Bold

| Candidate model | 4-folds ave. *MSPR* | Number of parameters | *AIC* | *BIC* | *MSE* | $R^2_{adj}$ |
|---|---|---|---|---|---|---|
| **Model 1*** | **0.129** | 14 | **102.335** | **137.332** | **0.083** | **0.817** |
| Model 2 | 0.139 | 15 | 107.193 | 144.690 | **0.084** | **0.816** |
| Model 3 | 0.139 | 15 | 107.193 | 144.690 | **0.084** | **0.816** |

Note. The minimum average *MSPR*, the minimum *AIC*, *BIC*, *MSER*, and the maximum $R^2_{adj}$ among the candidate models were marked in bold. *Final selected model.

**ANOVA and Post Hoc Tests for the Final Regression Models**

*Continuous Dose*

Table 6 shows the ANOVA table using the final CD regression model, and the significant effects were considered as the strong risk predictors for this continuous dose filed limit alerts. The positive estimate of the model (0.436) and the significant effect of $X_9$, on the expected risk for the CD group indicated that the increase of ratio of soft max

drug limit, meaning the increase of infusion dose for CD field limits (Su et al., 2018), can increase the expected risk of IV harm.

In addition, the effects of $X_2$, $X_1*X_2$, and $X_1*X_2*X_4$ were significant on the expected risk showing that the effects of medication ($X_2$) under each care area group ($X_1$) or under each combination of care area ($X_1$) and soft max limit type ($X_4$) were different. We conducted post hoc test for $X_1*X_2$ and the $X_1*X_2*X_4$ effect to estimate the least-square means of expected risk (Table 7), an estimated marginal means of the groups, and the difference of the least-square means (LS means). The results of the $X_1*X_2$ showed that in AICU, the expected risk of insulin overdose was significantly higher than that of propofol and heparin ($p < 0.001$), and the expected risks of propofol and heparin were significantly higher than that of morphine ($p < 0.001$). On the other hand, in AMSU, the expected overdose risks of insulin, heparin, and morphine were similar. Furthermore, we observed the LS means difference of the expected risk between small and large soft maximum limit types under each combination of care area and medication using the post hoc test of $X_1*X_2*X_4$ interaction effect. The results showed that the expected risk of the large soft limit group is significantly higher than the small soft limit group for heparin ($p = 0.006$) and propofol ($p = 0.009$) in AICU, and for insulin in both AICU ($p < 0.001$) and AMS ($p = 0.05$) (Figure 5). In this study, we used the high-order interaction variables to increase the model fitting performance.

Table 6: ANOVA Table – CD Group

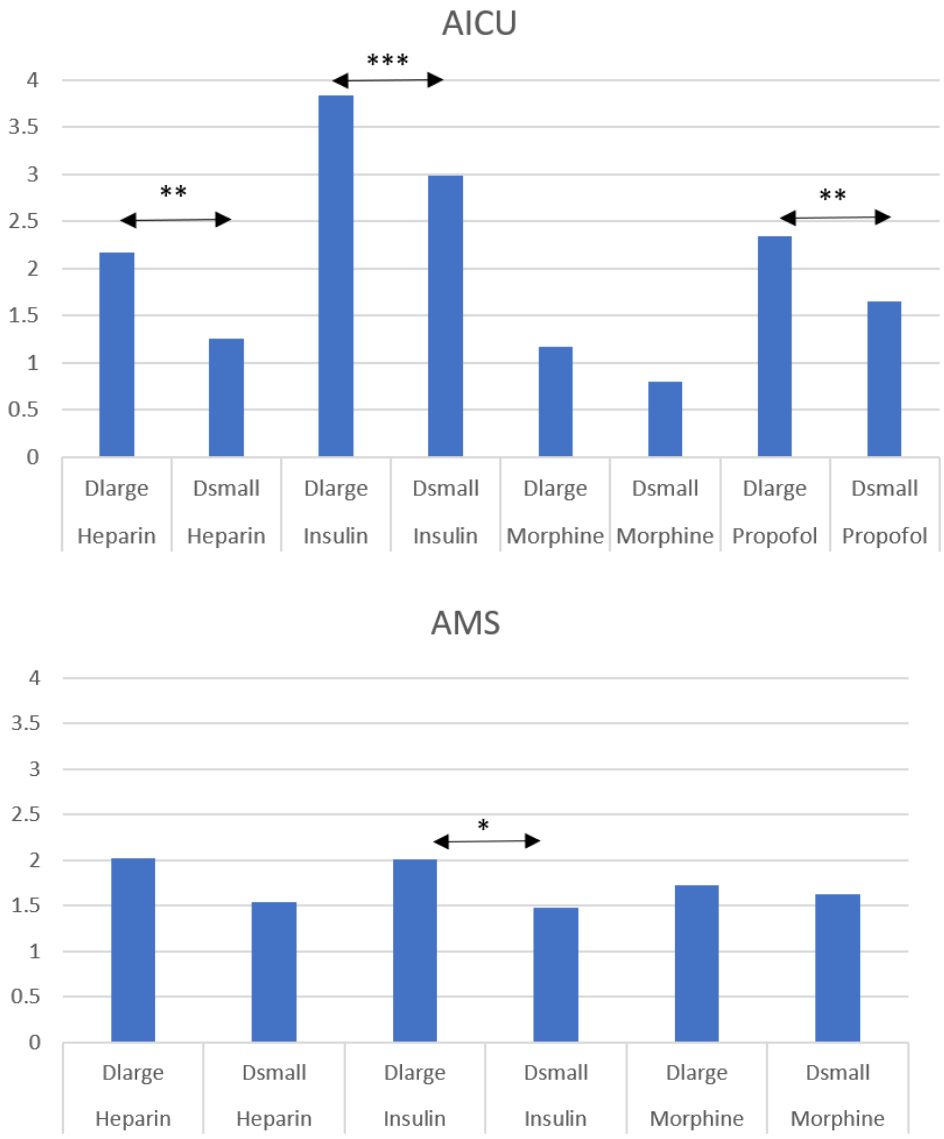
| Effect | Sum Sq | Mean Sq | DF | DenDF | F.value | Pr(>F) |
|---|---|---|---|---|---|---|
| $X_1$ | 0.07 | 0.07 | 1 | 419 | 0.18 | 0.672 |
| $X_2$ | 5.58 | 1.86 | 3 | 411 | 4.83 | **0.003** |
| $X_4$ | 0.52 | 0.52 | 1 | 403 | 1.34 | 0.248 |
| $X_5$ | 0.72 | 0.72 | 1 | 314 | 1.87 | 0.172 |
| $X_8$ | 0.59 | 0.59 | 1 | 402 | 1.53 | 0.217 |
| $X_9$ | 8.16 | 8.16 | 1 | 402 | 21.20 | **<0.001** |
| $X_1$*$X_2$ | 4.91 | 2.45 | 2 | 420 | 6.38 | **0.002** |
| $X_1$*$X_4$ | 1.48 | 1.48 | 1 | 404 | 3.84 | 0.051 |
| $X_4$*$X_5$ | 2.73 | 2.73 | 1 | 202 | 7.11 | **0.008** |
| $X_4$*$X_8$ | 4.88 | 4.88 | 1 | 402 | 12.68 | **<0.001** |
| $X_1$*$X_2$*$X_4$ | 5.22 | 1.04 | 5 | 408 | 2.71 | **0.020** |
| $X_1$*$X_2$*$X_8$ | 31.12 | 6.22 | 6 | 402 | 16.18 | **<0.001** |
| $X_1$*$X_4$*$X_8$ | 8.57 | 8.57 | 1 | 402 | 22.27 | **<0.001** |
| $X_4$*$X_8$*$X_9$ | 10.09 | 5.05 | 2 | 402 | 13.11 | **<0.001** |
| $X_1$*$X_2$*$X_4$*$X_9$ | 16.00 | 1.23 | 13 | 402 | 3.20 | **<0.001** |

Note. $X_1$: AICU, AMSU; $X_2$: heparin, insulin, morphine, propofol; $X_4$: soft maximum limit is large or small; $X_5$: hard maximum limit provided Y/N

Table 7: Least Squares Means (LS mean) of $X_1$* $X_2$ Interaction Effect – CD Group

| $X_1$ | $X_2$ | Estimated LS mean | Std. Error | DF | t-value | Lower CI | Upper CI |
|---|---|---|---|---|---|---|---|
| AICU | Heparin | 1.71 | 0.22 | 52 | 7.71 | 1.27 | 2.16 |
| AMSU | Heparin | 1.78 | 0.28 | 78 | 6.4 | 1.23 | 2.34 |
| AICU | Insulin | 3.40 | 0.27 | 73 | 12.87 | 2.88 | 3.93 |
| AMSU | Insulin | 1.74 | 0.22 | 48 | 8.06 | 1.31 | 2.18 |
| AICU | Morphine | 0.99 | 0.25 | 62 | 3.92 | 0.48 | 1.49 |
| AMSU | Morphine | 1.67 | 0.25 | 54 | 6.68 | 1.17 | 2.18 |
| AICU | Propofol | 2.00 | 0.22 | 45 | 9.28 | 1.56 | 2.43 |
| AMSU | Propofol | NA | NA | NA | NA | NA | NA |

Note. LS mean: means for groups that are adjusted the individual difference




Note. Significant codes: '***' $p \leq 0.001$; '**' $0.001 < p \leq 0.01$; '*' $0.01 < p \leq 0.05$
Figure 5: LS mean of Soft Limit Type in Different Combination of Care Area and Medication

*Bolus Dose*

The significant effects of the ANOVA table were regarded as the strong risk predictors for the final BD regression model (Table 8). The negative estimate of $X_8$ (-0.079) indicated the decrease of infusion rate with fixed dose for the BD field limits can decrease the expected risk. Also, the post hoc test of $X_5$ effect showed that the expected risk for the BD alert overrides without hard maximum drug limits was higher than the cases with hard drug limits ($p$ = 0.017). The significant $X_2$*$X_9$ interaction effect indicated that when

increasing ratio of soft max drug limit, $X_9$, (infusion dose for BD field limits setting), the increase trend of the expected risk was different for the four medications (heparin, insulin, morphine, and propofol). The further post hoc test showed that the expected risk for the alert overrides associated with morphine was significantly higher than propofol ($p = 0.002$), and that insulin overrides have higher risk than propofol overrides ($p = 0.026$).

Table 8: ANOVA Table – BD Group

| Effect | Sum Sq | Mean Sq | DF | DenDF | F.value | Pr(>F) |
|---|---|---|---|---|---|---|
| $X_1$ | 0.13 | 0.13 | 1 | 8 | 0.95 | 0.358 |
| $X_2$ | 0.87 | 0.43 | 2 | 17 | 3.16 | 0.069 |
| $X_5$ | 1.29 | 1.29 | 1 | 14 | 9.39 | **0.008** |
| $X_8$ | 1.27 | 1.27 | 1 | 99 | 9.27 | **0.003** |
| $X_9$ | 12.67 | 12.67 | 1 | 99 | 92.50 | **<0.001** |
| $X_2$*$X_9$ | 2.39 | 1.19 | 2 | 99 | 8.70 | **<0.001** |
| $X_5$*$X_9$ | 0.13 | 0.13 | 1 | 99 | 0.93 | 0.338 |

Note. $X_1$: AICU, AMSU; $X_2$: insulin, morphine, propofol; $X_5$: hard maximum limit provided Y/N

*Bolus Dose Administration Rate*

The significant predictor variables of the BDAR model are shown in Table 9. The significant $X_4$*$X_8$ and $X_4$*$X_9$ interaction effects indicated that when increasing infusion duration, $X_8$, or ratio of soft max drug limit, $X_9$, (infusion rate for BDAR field limits), the increase trend of the expected risk for the different levels of soft limit type were different. The increase of infusion duration or infusion rate increased the expected risk due to the positive estimates of the regression models ($X_8$ is 0.286, $X_9$ is 0.856).

Table 9: ANOVA Table – BDAR Group

| Effect | Sum Sq | Mean Sq | DF | DenDF | F.value | Pr(>F) |
|---|---|---|---|---|---|---|
| $X_2$ | 0.02 | 0.02 | 1 | 49 | 0.29 | 0.596 |
| $X_4$ | 0.21 | 0.11 | 2 | 75 | 1.21 | 0.303 |
| $X_8$ | 1.07 | 1.07 | 1 | 72 | 12.28 | **0.001** |
| $X_9$ | 7.42 | 7.42 | 1 | 72 | 85.06 | **<0.001** |
| $X_4$*$X_8$ | 0.56 | 0.28 | 2 | 72 | 3.19 | **0.047** |
| $X_4$*$X_9$ | 0.69 | 0.35 | 2 | 72 | 3.96 | **0.023** |
| $X_8$*$X_5$ | 0.27 | 0.27 | 1 | 72 | 3.09 | 0.083 |
| $X_9$*$X_5$ | 0.25 | 0.25 | 1 | 72 | 2.91 | 0.093 |

Note. $X_1$: AICU, AMSU; $X_2$: morphine, propofol; $X_4$: soft maximum limit is regular, large or small; $X_5$: hard maximum limit provided Y/N

## DISCUSSION

The combinations of the main and interaction effects of expected risk, which were regarded as predictors to create the final models, were different for three field limit types (CD, BD, and BDAR). High-order interactions were included as predictors for the CD final risk predictive model but not the BD and BDAR models. The adjusted R-square value was 0.7 for the CD model, while that was higher for BDAR (0.8) and BD (0.9). A possible reason is that much was unknown in the simulated infusion scenarios, such as patient conditions and prescriptions from physicians (Su et al., 2018). In addition, patients may be on continuous dose infusions (CD) for a few hours. Since patient conditions could change during the infusion, predicting risk for hours (CD type model) can be more difficult and less accurate than that for just minutes behind (BD and BDAR types models). For better fitting performance and predictive capability of the CD models, the variables with high-order interactions were considered as predictors after stepwise *AIC* procedures. On the other hand, if more patient clinical information associate with drug infusions, such as physician's orders, DRG codes (Diagnosis Related Group), or Current Procedural Terminology (CPT[10]) code, is available, we can include more potential model predictors, replacing the high-order predictors, to improve the current model in future research.

According to the ANOVA results, the effect of $X_9$, the ratio of soft maximum drug limit, was regarded as a strong predictor for the final models of three field limit types. Based on different field limit settings (Su et al., 2018), where higher ratio of soft maximum drug limit, for the CD and BDAR types being corresponding with larger infusion rate and for the BD type being corresponding with larger infusion drug amount, could lead to higher risk of harm on patients. The finding was consistent with that of the IV harm index (Sullivan, 2004; Williams et al., 2006). On the other hand, we found that the effect of $X_5$, infusions with/without hard maximum hard limits, was a strong predictor only for the BD model. When BD field limit alerts were triggered and being overridden, the clinician

[10] CPT® codes are a medical code set maintained by the American Medical Association. These codes are for medical professionals report medical, surgical, radiology, laboratory, diagnostic procedures, and services. https://www.ama-assn.org/practice-management/cpt-current-procedural-terminology?-process-how-code-becomes-code=

intended to overdose the soft maximum drug limits within a few minutes, which created a very high-risk condition for the patient, especially if it's a high-risk drug. Therefore, we suggested that the hospital system should set up hard maximum drug limits for the BD field limits of high-risk medications to reduce risk of harm when conducting a bolus dose infusion.

The risk-based models we developed in this study for three different field limit types were more complex than the IV harm index since our models consider not only the main key risk factors, but also the expected risk that could vary across different combinations of the risk factors using interaction effects. There are some limitations to our risk-based models. First, the outcome variable, risk benchmark, was defined using the adjusted likelihoods assessed from the experts multiplied by the quantified severity, since pump alert reports currently do not link to the clinical patient outcomes in most hospital systems. If some small datasets in which the overridden alerts link to the patient outcomes can be obtained, we could map the clinical outcomes to the NCC MERP index (Rozich et al., 2003) and use these new data and outcomes to validate and improve our current models, which we could address in future research. Second, the proposed models can only quantify risk for the alert overrides associated with the four high-risk medications (propofol, morphine, insulin, and heparin) in AICU or AMSU settings. Third, the risk-based models were created based on the drug limit settings and alert datasets in a large teaching hospital. Some validations and revision for the models might be needed when applying to other alert datasets. Applying the proposed linear mixed models to quantify risk for real alert datasets is not included in this study and can be addressed in future research. The framework of the application concept was indicated in Appendix B.

## CONCLUSION

We presented three types of risk-based predictive models for different field limit alerts (continuous dose, bolus dose, bolus dose administration rate), which can be used to demonstrate the important risk factors, including main and interaction effects, for predicting expected risk of IV harm considering multivariate analysis (multiple independent variables). The models can be used to quantify risk for real infusion programming alerts associated with four high-risk medications from hospitals of similar

characteristics, likely with customized adjustments. For future research direction, we could quantify risk for individual alerts (risk-based approach) and sum of the individual scores (frequency-based approach) during a specific time period for each medication-care unit. The sum of risk quantified scores from the proposed models can be regarded as an indicator of drug infusion performance, which can be composited with the current indicators (i.e. DERS compliance rate) for evaluating performance using an aggregated view (Mansfield & Jarrett, 2013). The medication-care units with the higher sum of risk scores (or the higher frequency of major and extreme harm) and other lower performance indicators will be highlighted as the high-priority areas for proper improvements on nursing practices, workflow, or drug limit settings in the healthcare systems.

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## Appendix A. Candidate Models for the CD, B, and BDAR Groups

A.1: Three Candidate Models for the CD Group

| | |
|---|---|
| Model 1 | $Y \sim X_1 + X_2 + X_4 + X_5 + X_8 + X_9 + X_1 \times X_2 + X_1 \times X_4 + X_4 \times X_5 + X_4 \times X_8 + X_1 \times X_2 \times X_4 + X_1 \times X_2 \times X_8 + X_1 \times X_4 \times X_8 + X_4 \times X_8 \times X_9 + X_{10}$ |
| Model 2 | $Y \sim X_1 + X_2 + X_4 + X_5 + X_8 + X_9 + X_1 \times X_2 + X_1 \times X_4 + X_4 \times X_5 + X_4 \times X_8 + X_1 \times X_2 \times X_4 + X_1 \times X_2 \times X_8 + X_1 \times X_4 \times X_8 + X_4 \times X_8 \times X_9 + \boldsymbol{X_1 \times X_2 \times X_4 \times X_9} + X_{10}$ |
| Model 3 | $Y \sim X_1 + X_2 + X_4 + X_5 + X_8 + X_9 + X_1 \times X_2 + X_1 \times X_4 + X_4 \times X_5 + X_4 \times X_8 + X_1 \times X_2 \times X_4 + X_1 \times X_2 \times X_8 + X_1 \times X_4 \times X_8 + \boldsymbol{X_2 \times X_4 \times X_5} + X_4 \times X_8 \times X_9 + \boldsymbol{X_1 \times X_2 \times X_4 \times X_9} + X_{10}$ |

A.2: Three Candidate Models for the BD Group

| | |
|---|---|
| Model 1 | $Y \sim X_1 + X_2 + X_5 + X_8 + X_9 + X_2 \times X_9 + X_5 \times X_9 + X_{10}$ |
| Model 2 | $Y \sim X_1 + X_2 + X_5 + X_8 + X_9 + X_2 \times X_9 + \boldsymbol{X_5 \times X_8} + X_5 \times X_9 + X_{10}$ |
| Model 3 | $Y \sim X_1 + X_2 + X_5 + X_8 + X_9 + \boldsymbol{X_1 \times X_8} + X_2 \times X_9 + \boldsymbol{X_5 \times X_8} + X_5 \times X_9 + X_{10}$ |

A.3: Three Candidate Models for the BDAR Group

| | |
|---|---|
| Model 1 | $Y \sim X_2 + X_4 + X_8 + X_9 + X_4 \times X_8 + X_4 \times X_9 + X_5 \times X_8 + X_5 \times X_9 + X_{10}$ |
| Model 2 | $Y \sim X_2 + X_4 + X_8 + X_9 + X_4 \times X_8 + X_4 \times X_9 + X_5 \times X_8 + X_5 \times X_9 + \boldsymbol{X_8 \times X_9} + X_{10}$ |
| Model 3 | $Y \sim X_2 + X_4 + X_8 + X_9 + \boldsymbol{X_2 \times X_9} + X_4 \times X_8 + X_4 \times X_9 + X_5 \times X_8 + X_5 \times X_9 + X_{10}$ |

**Appendix B. A Framework of Application for Risk-based Quantification Models using Linear Mixed Regression**