Adverse Medical Event Reduction Technologies

Identification of Primary Risk Factors of Adverse Medical Events Using Artificial Neural Networks

submitted by

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Abstract

This thesis presents research into the area of adverse medical events and their resultant medical errors. Key terminology associated with adverse medical events is clarified and five specific categories of adverse medical events are identified. Information technologies that can be very beneficial in the reduction of adverse medical events are discussed and their importance in the healthcare delivery field is emphasised.

Utilising the United States Food and Drug Association's Adverse Event Reporting System database from the first two quarters of 2004 and artificial neural networks, a neural network with optimal performance was determined and the resultant weights were used to calculate the relative importance of the inputs into the ANN. The optimal ANN was a three-layer feed-forward back-propagation structure using the hyperbolic tangent transfer function.

An expanded model was prepared to capture a larger set of input variables that may be more highly linked to the occurrence of adverse medication events. The recommended model contains seventeen additional input parameters. A recommended model was also prepared for similar databases in the other areas of adverse medical events in the healthcare field based on the adverse medical event risk factors identified in this work. The FDA AERS is a mandatory reporting system. Recommendation from this work is to utilise this expanded model to establish a mandatory adverse medication event reporting system in Canada.

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Glossary of Terms and Acronyms

Active Errors:	Errors which occur at the level of the individual and whose effects are felt almost immediately
Adverse Medical Event:	An injury caused by medical management rather than the underlying condition of the patient
Adverse Diagnostic Events:	Adverse medical events attributable to a diagnostic error
Adverse Medication Events:	Adverse medical events attributable to an error in medication management
Adverse Surgical Events:	Adverse medical events attributable to a surgical error
Adverse Systems Events:	Adverse medical events attributable to problems in procedure or process within the healthcare delivery field
AERS:	Adverse Event Reporting System
Artificial Neural Network:	A set of connected artificial neurons where input data is introduced, fed through each layer of the network, and produces a resultant output. (ANN)
Average Squared Error:	The difference between each predicted value and its corresponding actual value squared over all cases (ASE)
Clinical Engineering:	Supporting and advancing patient care by applying engineering and managerial skills to healthcare technology

Correct Classification Rate:	<p>The rate at which the ANN correctly classifies the data as falling into either the primary or secondary outcome categories. (CCR)</p> <p>Functionally defined as</p> $\frac{(TruePositive + TrueNegative)}{(TruePositive + TrueNegative + FalsePositive + FalseNegative)}$
CP:	Constant Predictor
Equipment Failures:	Adverse medical events attributable to a failure in medical equipment management or use
Errors of Execution:	Errors that result from the failure of a human action (errors of omission)
Errors of Planning:	Errors that result from the use of an incorrect plan (errors of commission)
External Events:	Items outside the HAZOP node being reviewed that affect the operation of the HAZOP node to the extent that a preventable adverse medical event is possible.
False Negative:	The artificial neural network predicted a negative outcome when the actual outcome was positive
False Positive:	The artificial neural network predicted a positive outcome when the actual outcome was negative
FDA:	United States Food and Drug Administration
Hazard:	Any operation that could possibly cause a catastrophic release of toxic, flammable or explosive chemicals or any action that could result in injury to personnel.
HAZOP:	Hazard and Operability
Human Error:	Errors of execution or planning that result in the occurrence or potential occurrence of a preventable adverse medical event.
Human Factors Engineering:	The study of the way in which systems interface with users.

IOM:	United States Institute of Medicine
Latent Errors:	Errors which are beyond the control of the individual, typically unrecognised and may not surface for significant periods of time
Logarithmic Sensitivity:	Parameter that maximises both the sensitivity and specificity of the experiment but is more weighted towards the sensitivity.
Medical Error:	The failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim. An underlying problem within the healthcare delivery system that may or may not impact the users of the system
MIRG:	Medical Information technologies Research Group
Operability:	Any operation inside the design envelope that would cause a shutdown that could possibly lead to a violation of environmental, health and safety regulations or negatively impact profitability.
PAE:	Preventable Adverse medical event. Adverse medical events attributable to medical errors (also known as a sentinel event or iatrogenic event)
Potential Adverse Medical Events:	Medical errors that could have resulted in an adverse medical event but did not
ROC Curve:	A receiver operating characteristic curve is a plot of the true positive rate and false positive rate. The area under the curve describes the accuracy of the experiment.
Sensitivity:	<p>The percentage of cases that are the primary outcome and are classified as such by the ANN. Functionally defined as</p> $\frac{TruePositive}{(TrueNegative + TruePositive)}$

Specificity:

The percentage of cases that are not the primary outcome and are correctly classified as such by the ANN. Functionally defined as

$$\frac{TrueNegative}{(TrueNegative + TruePositive)}$$

True Negative:

The artificial neural network predicted a negative outcome when the actual outcome was negative

True Positive:

The artificial neural network predicted a positive outcome when the actual outcome was positive

1. Introduction

Nuclear facilities and the aviation industry are driven by a reliability requirement not equaled in many other industries, including healthcare. Much study has been performed in these industries to determine ways in which to ensure safe operation of the tools and procedures available to individuals at all levels of control. Detailed investigation into the role that human error plays in the eventual occurrence of various erroneous situations has been performed, and the results of these investigations have led to the implementation of multiple changes. The majority of suggested changes have been applied at the systems level, as opposed to the level of the individual, through changes in process or design.

Many techniques have been developed in an attempt to increase the reliability of the healthcare delivery system. Although it is impossible to fully eliminate error from any system, efforts can be made to increase the ability of the healthcare delivery system to produce outcomes, which, in most cases, are free from errors. A vast majority of the suggested techniques require a significant overhaul in the way in which the present healthcare delivery system operates, and as such, resistance from healthcare workers is being encountered when attempting to introduce these techniques into the existing system (California Healthcare Foundation 2000).

1.1. Motivation and Significance of Research

The topic of medical errors has been receiving much attention recently due to the publication of key reports in the United States, Australia and the United Kingdom, which outline the significant impact that adverse medical events are having on society (Kohn

2000; Wilson 1995; Leape 1994). As a result of these publications a call has been made to incorporate more reliability into the healthcare delivery system and, thus reduce the number of adverse medical events that currently occur.

Since 1984, documentation has revealed that the majority of medical errors are caused by human error (Wilson 1999). Chopra and others found human error as the cause of adverse medical events in 70 percent of the cases reviewed (Chopra 1992). The topic of human error has been studied in detail for many years, with one of the leading theorists being James T. Reason. Although human error is inevitable in any situation, there are many tools and techniques that can be employed to first detect and then reduce the number of human errors that occur. Key to this reduction is the incorporation of human factors engineering into the design cycle of the system. Human factors engineering is the study of the way in which systems interface with users (Bogner 1994). This area of research focuses on the design of systems that are intuitive and easy to use by most common users, increasing their successful use of the system through hardware and software design that is compatible with their abilities (Sawyer 1997).

Multiple studies have been performed on the topic of adverse medical events. The most visible was by the Institute of Medicine in the United States titled “To Err is Human: Building a Safer Health System”. This report was released in 1999 and estimated that approximately 44,000 to 98,000 hospital deaths are caused annually in the United States by preventable adverse events (PAEs). The associated costs were estimated to be between \$17 billion and \$29 billion annually (these amounts include consideration for lost income, lost household production, disability, and healthcare costs) (Kohn 2000).

In 1984 a study was commissioned by the Harvard Medical School to review 30,000 patient records in hospitals in the New York State. This study determined that adverse medical events occurred in approximately 3.7 percent of the hospitalised patients, with 58 percent of these events being preventable (Kohn 2000). A subsequent study in 1992 in Colorado and Utah estimated that 1.54 percent of patients hospitalised experienced PAEs (Kohn 2000). The death rate from these adverse medical events was estimated at 13.6 percent in the Harvard study and 6.6 percent in the Colorado and Utah studies (Kohn 2000).

In 1995, the Australian government commissioned a study into PAEs. In this study, medical records of 14,179 patients admitted into 28 hospitals in New South Wales and Southern Australia in 1992 were reviewed. The study recorded an adverse medical event rate of 16.6 percent, with 51 percent of these events being preventable and 4.9 percent leading to patient death (Weingart 2000; Wilson 1995). It was estimated that the adverse medical events encountered resulted in an average of 7.1 additional days in the hospital (Wilson 1995). When extrapolated to all hospitals in Australia in the same year, it was estimated that 470,000 admitted patients experienced adverse medical events, with 3.3 million additional in-hospital bed days required (Wilson 1995).

In 2001, a study was commissioned in Britain to study the impact that PAEs were having on the British healthcare delivery system. As a result of this study, an adverse medical event rate of 11.7 percent was found, with 48 percent of these events being preventable (Vincent 2001).

Extrapolating the results of the Institute of Medicine study in the United States from 1999, it is estimated that approximately 10,000 Canadians die in hospitals annually

as a result of PAEs (Vallis). A study has been commissioned by the Canadian Institute of Health Research in Canada to determine a PAE rate based on data from Canadian hospitals (Campbell 2002).

There are not many databases in existence today that contain information about the occurrence of adverse medical events. This is a difficulty encountered by any researcher attempting to learn additional information about the occurrence of adverse medical events within the healthcare delivery field. For the select databases that do exist, such as the Canadian Health Institute's Discharge Abstract Database, it can be very difficult to obtain access to the data of research potential.

1.2. Adverse Medical Events and Medical Errors

Errors within the healthcare delivery system are typically made evident by the resultant adverse medical event witnessed by the patient or any other individual directly or indirectly involved with the patient. Unfortunately, this adverse medical event may have been the result of many other errors, which have cumulated into a single event. Individually, each error may not have caused visible impact to individuals within the healthcare delivery system, but the need to eliminate these errors is as important, if not more than, the visible adverse medical event.

1.2.1. Definitions and Nomenclature

Studies performed to evaluate errors within the healthcare delivery system have revealed that there is an issue surrounding the use of various key terms (Briggs 2002). Prior to the presentation of the topic of medical errors, and more specifically adverse

medical events, it is useful to establish precise functional definitions that will be used throughout this thesis.

The commonly accepted definition of the term “medical error” is “the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim” (Kohn 2000). This definition is adapted from James T. Reason in his book Human Error. In this book, Reason discusses two main categories of human error, errors of execution and errors of planning. Errors of execution describe those errors that result from the failure of a human action, whereas, errors of planning describe those errors that result from the use of an incorrect plan (1990). Errors of execution are also known as errors of omission and errors of planning are also termed errors of commission (Weingart 2000).

All errors can be classified as either active or latent (Reason 1990). Active errors occur at the level of the individual and their effects are felt almost immediately. These errors are committed by individuals, which appear to be in control of the system at the time of error occurrence (Spath 2000). Latent errors are beyond the control of the individual, typically unrecognised, and may not surface for significant periods of time (Reason 1990). Examples of latent errors include system design flaws, lack of system maintenance and faulty system installation (Reason 1990; Kohn 2000). Active errors are typically the result of one or more latent errors, and as such, it is the study of latent errors that is of most interest when attempting to reduce the occurrence of errors (Reason 1990; Reason 1994).

An adverse medical event is defined as “an injury caused by medical management rather than the underlying condition of the patient” (Kohn 2000). Many adverse medical events are not caused by medical error but are simply the result of unpreventable factors

such as the inability to communicate with a patient or unknown patient allergies. Adverse medical events attributable to medical errors are commonly referred to as preventable adverse medical events (PAEs), since the adverse medical event would have typically been avoided if the medical error or errors had not occurred. These events have also been termed sentinel events or iatrogenic events (Kohn 2000). The primary goal of error reduction within any field is to reduce the occurrence of PAEs within the system. Errors that could have resulted in an adverse medical event but did not are commonly known as potential adverse medical events and typically represent latent errors within the healthcare delivery system. Approaches towards reducing errors within the healthcare delivery system should also attempt to reduce these kinds of errors (Kohn 2000). Unfortunately, difficulty can be found in the identification of specific occurrences of latent errors, as it is the adverse medical event, which is more visible and as such more identifiable. Most research into the topic of medical errors has focused on adverse medical event evaluation and reduction. This approach will be continued with the research performed for this thesis.

1.2.2. Adverse Medical Event Types and Risk Factors

Various studies on the impact that PAEs are having on the healthcare delivery system have chosen different classifications for the types of adverse medical events. The Institute of Medicine classifies PAEs into four categories: diagnostic, treatment, preventative, and other. Diagnostic events include delays in diagnosis or the failure to act on results from a prescribed test. Treatment events include errors in the dose of a medication, failure to administer a test or treatment, and delay in treatment. Preventative events include failure to appropriately monitor or follow-up on a patient's progress. Other

medical events include equipment failures and communications failures (Kohn 2000). This classification scheme is based on the characterisation provided by Brennan and associates in the Harvard Medical Practice Study from 1984.

The Quality of Australian Healthcare Study classifies the sources of PAEs in a somewhat different fashion. Adverse medical events are classified as delay, treatment, and investigation. Delay events include diagnosis delay and failure to request or arrange a required test or consultation. Treatment events include wrong or inappropriate treatment, the use of an unclassified treatment and inadequate treatment. Investigation events include lack of investigation and inappropriate investigation (Wilson 1999).

For the purpose of this thesis, adverse medical events are categorised into five types, including medication, surgical, diagnostic, systems and equipment failure. Occurrence of any of these types of adverse medical events can be greatly increased through the presence of various risk factors. Each risk factor can result in the occurrence of multiple adverse medical events. Human errors are prevalent and the main cause of each type of PAE (Wilson 1999).

1.2.3. Adverse Medication Events

Adverse medication events or drug events include the omission of medication, administration of the wrong medication or medication form, incorrect frequency or time of administration, administration of the improper dose or quantity of medication, missed dose, use of an unauthorised medication, mix-up of multiple medications resulting in the administration of the incorrect medication to a patient, medication-medication interactions, known medication allergy, illegible orders, incorrect medication preparation, or unavailability of a required medication (Australian Council for Safety and Quality in

Health Care 2001; Bates 1999; Spath 2000). The most common type of adverse medication event is dose errors, followed by frequency and route errors (Bates 1999). Adverse medication events are the most common type of PAE (Evans 2002; Kohn 2000). In the United States in 2000, it was estimated that approximately one million adverse medication events occurred in hospitals annually, with more than half resulting in PAEs (Briggs 2002).

Risk factors that can increase the occurrence of a medication event include distractions, staffing shortages and overloaded staff, physicians and nurses being rushed, lack of knowledge of patient or medication (including indications for use, available dose forms, appropriate doses, and administration routes), medications with similar names or packaging, multiple medications administered, deviations from procedures, interruptions of the clinical staff, and the introduction of inexperienced clinicians or new techniques (Cook 2003; Weingart 2000; Evans 2002; California Healthcare Foundation 2000; Coiera 2002; Spath 2000). More prescribing errors occur among first year postgraduate residents than among other clinicians (Weingart 2000). Staffing shortages can lead to various adverse medication events including the wrong medications or doses being administered (Cook 2003). In rushed scenarios, physicians and nurses may fail to obtain essential information regarding the patient's history, including medications currently being used or any allergies the patient may suffer from. In 1998, a study of 134 ambulatory cases found that clinicians asked only 59 percent of the essential history items, which was partially due to the requirement to quickly process patients (Bachman 2003).

There are four main phases to the medication administration process: prescribing, dispensing, administering and monitoring (Kohn 2000). Medication events can occur in

any phase of the medication administration process with the most common adverse medication events occurring during the ordering and administration phases (Weignart 2000). In 2000 it was estimated that 56 percent of adverse medication events occurred during the ordering phase, while 24 percent of the same events occurred during the administration phase (Weignart 2000). Illegible physician handwriting is known to increase the risk of medication events during the ordering phase (Briggs 2002). The failure to place a zero before a decimal point when indicating a fractional dose amount can lead to serious adverse medication events resulting from a ten-fold overdose (Applegate 1994).

1.2.4. Adverse Surgical Events

In the Harvard Medical Practice Study, performed by Leape and associates, it was found that nearly half of the adverse medical events could be attributed to a surgical operation (1994). Adverse surgical events include wrong site surgeries (most commonly found in orthopedic procedures), performance of surgeries on the wrong patient, surgical implements being left in the patient, wound infections, the use of the wrong medical device, burns from electrosurgical equipment, and malfunction of devices within the surgical unit (Evans 2002; Campbell 2002; Australian Council for Safety and Quality in Health Care 2001; Calgary Herald 2003; Kohn 2000; Cook 2003). Surgical risk factors include having more than one surgeon or surgical team involved in the case, multiple procedures being performed on a single patient, unusual time pressures or circumstances, inadequate processes for assessing and checking the patient before operation, and unfamiliarity of members of the surgical team with the surgical technique being performed (Australian Council for Safety and Quality in Health Care 2001; Evans 2002).

1.2.5. Adverse Diagnostic Events

Adverse diagnostic events include missed diagnosis, delays in diagnosis, misdiagnosis, failure to employ indicated tests, or employment of outdated tests or therapies (Australian Council for Safety and Quality in Health Care 2001; Evans 2002; Leape 1994). Delays in diagnosis can lead to an aggravation of the illness, which may result in the inability of the healthcare facility to fully treat the patient. Missed diagnosis is related to a delay in diagnosis, and can result in the patient remaining untreated until such time as the ailment is much worse with a longer recovery time or the inability to treat the patient with any existing methods. In many cases, early detection of an ailment greatly increases the chance of the patient recovering fully (Australian Council for Safety and Quality in Health Care 2001). Misdiagnosis can cause severe emotional trauma and anxiety to the patient and their families and can lead to a significant amount of unnecessary treatment procedures.

Risk factors that can increase the occurrence of diagnostic events include unfamiliarity of the clinician with the recommended diagnostic technique, lack of communication, delays in follow-up testing, or delays in relaying pertinent patient information, such as laboratory results, to the clinician treating the patient (Australian Council for Safety and Quality in Health Care 2001). Adverse diagnostic events can also result from cognitive lapses due to the inability of the clinician to recall pertinent information from memory, caused by interruptions, distractions, or other physical factors including fatigue or stress. The Institute of Medicine has recommended that the healthcare delivery system reduce reliance on human memory as a way to reduce the occurrence of adverse diagnostic events, since the more information to be processed and

remembered by an individual, the higher the likelihood for an adverse medical event to occur (Kohn 2000; Spath 2000).

1.2.6. Equipment Failures

Equipment failures can result due to a variety of reasons. The design of the equipment may not have taken into consideration the end-users, and as such may not be easy to use or operate by the healthcare personnel (Bogner 1994). In addition, there may be many varieties of the same piece of equipment from different manufacturers located in different areas within the healthcare delivery environment (Australian Council for Safety and Quality in Health Care 2001). As healthcare personnel, including physicians, nurses, clinical engineers and biomedical technicians, rotate throughout the healthcare delivery environment, they may not be familiar with the operation of the specific piece of equipment they are attempting to use or maintain.

Equipment failure events can result from inaccurate labeling, instructions or packaging, defective components, poor construction or design, electromagnetic interference, restriction of visual field, incorrect equipment setup or adjustment, cleaning or other maintenance of the equipment, or the unfamiliarity of the healthcare worker with the equipment being used (Australian Council for Safety and Quality in Health Care 2001; Dhillon 2000). The most common cause of medical equipment failures is operator error, including misuse of the correct equipment or use of the incorrect equipment for the current situation (Bogner 1994). Operator error is associated with over 50 percent of equipment failures in the healthcare delivery system (Dhillon 2000). The most error prone healthcare devices include the glucose meter, balloon catheter, and orthodontic bracket aligner (Dhillon 2000).

1.2.7. Adverse Systems Events

Adverse systems events describe errors in procedure or process within the healthcare delivery system that lead to an error and are typically the core cause of most other types of errors (Bogner 1994). According to Leape, “*accidents are generally the outcome of a chain of events set in motion by faulty system design that either induces errors or makes them difficult to detect*” (1994). These types of errors are associated with the organisation of healthcare delivery and how resources are provided in the delivery system (Evans 2002). The Quality of Australian Healthcare study of 2000 found that failures at the systems level were responsible for over three-fourths of adverse medication events (Australian Council for Safety and Quality in Health Care 2001). Systems events can include an undocumented change in the order of surgical patients to enter the surgical theatre, resulting in a specific surgical procedure being performed on the wrong patient (Australian Council for Safety and Quality in Health Care 2001). Systems events can also include the incorrect labeling of patient medication in the hospital pharmacy, causing the wrong patient to be given a specific medication, which might lead to an adverse medication event (Australian Council for Safety and Quality in Health Care 2001). Unsteady patients falling in their rooms is also a result of an error at the systems level as it is usually caused by a shortage of nursing or support staff available to ensure the safety of such patients as well as the absence of appropriate support mechanisms or incorrect medication administration (Cook 2003; Perper 1994). The contraction of an infection while in the healthcare delivery setting is also seen as a systems event as it results from either a lack of appropriate procedures to ensure a sanitary environment or the inappropriate execution of the correct sanitisation procedures on the part of the healthcare

personnel (Australian Council for Safety and Quality in Health Care 2001; Perper 1994). Additional types of systems events include preventive suicides, burns, and mistaken patient identity (Kohn 2000).

The healthcare delivery system is highly complex and tightly coupled. There is not much room within the system for flexibility in times of change, little or no tolerance to process changes, and a lack of ability to employ alternative resources or methods. As a result of this structure, failures within the healthcare delivery system can quickly grow into large accidents. Since this potential does exist within this system, it is important to increase the level of reliability of the healthcare delivery system (Kohn 2000).

Risk factors that increase the likelihood of an adverse systems event include lack of systems support for the members of the healthcare delivery team, rapid change within the clinical organisation, inadequate staff numbers, or lack of reminders, protocols and checklists within the processes utilised by the healthcare team (Rosner 2000; Australian Council for Safety and Quality in Health Care 2001).

1.2.8. Risk Factors

Although various risk factors can be specific to the type of adverse medical event, many risk factors can increase the probability of occurrence of any type or multiple types of PAEs. The majority of these risk factors are the result of errors at the systems level of the healthcare delivery system.

The length of stay of a patient within the healthcare setting has been shown to increase the risk of PAEs. The risk of the occurrence of a PAE increases by six percent for each day spent in a hospital (Weingart 2000). Clinician distraction or interruption can also increase the potential of a PAE. A study by the United States Pharmacopeia in 2000

found that one of the primary risk factors for an adverse medication event was distraction of the pharmacist (Evans 2002). Distractions and interruptions can make it more difficult for clinicians to fully concentrate on the care being given, and can lead to many types of PAEs, dependent on the current task being performed. This risk can be further aggravated by high-pressure situations, which may cause the clinician to perform tasks too quickly or to omit important procedures in order to ensure that the demands of time or workload are met (Evans 2002). In 1999, Coiera and associates conducted a study of clinician interruption and determined a rate of 11.15 interruptions per hour per clinician. A study by Donchin et al. found that interruption within intensive care units accounts for 37 percent of error reports (Donchin 1994).

Multiple procedures being performed on the same patient at the same time or during the same visit can increase the likelihood of the occurrence of a PAE (Evans 2002; Weingart 2000). A common risk factor of PAEs is problems with communication. Communication problems can exist between the clinician and the patient, or within the clinical team (Bachman 2003; Rosner 2000). Research has revealed that the patient and physician disagree on the presenting complaint 50 percent of the time, which could be a result of the failure of the patient to disclose or the failure of the clinician to request pertinent information. Estimates reveal that 54 percent of patient problems are not disclosed by patients or requested by clinicians (Bachman 2003). Bhsale et al. conducted an observational study between 1993 and 1995 of Australian General Practices and found that 23 percent of the time poor communication between the patient and health professional contributed to the occurrence of an adverse medical event. In addition, they found that 19 percent of the time, poor communication between health professionals

contributed to the occurrence of an adverse medical event (1998). Additional risk factors that can increase the likelihood of the occurrence of a PAE include fatigue, alcohol or other medications, illness, emotional state, inadequate supervision and unsafe working conditions (Evans 2002; Felciano 1995).

The impact of PAE occurrence can range in severity. Many PAEs can lead to significant complications such as permanent physical disabilities or death, while many others can cause no physical harm. Although no physical harm may have resulted from the event occurrence, the emotional trauma to the patient and others impacted by the PAE may be significant. An effort must be made to reduce the occurrence of all PAEs.

1.3. Thesis Objective

The main objective of this work is to identify information technologies to aid in the reduction of PAEs. Another objective was to test the predictive capabilities of a new artificial neural network research framework developed by MIRG. This thesis was the first to use this new software tool and, as far as the author knows, this is the first time that adverse medical event data has been processed and analysed with ANNs. Included in this analysis is the identification of key risk factors in the occurrence of preventable adverse medication events in order to develop a direction for future work in the prediction of adverse medical events.

Completion of the above objectives was achieved through extensive research in the area of medical errors and adverse medical events. The ANN research framework developed by the Medical Information technologies Research Group (MIRG) was trained to identify key input variables (risk factors) associated with data related to the occurrence

of adverse medication events provided by the Food and Drug Administration (FDA) in the United States through their Adverse Event Reporting System (AERS).

1.4. Thesis Outline

Chapter 1 presents concepts pertinent to the study of PAEs and their reduction including definitions of commonly used terms and a clear segregation of the types of adverse medical events. An overview of the current information and various studies relating to PAEs is also provided.

Chapter 2 describes many key PAE reduction techniques that currently exist and can be incorporated into the healthcare delivery system. Basic techniques for PAE prediction are briefly discussed to highlight the importance of a proactive approach to PAE reduction.

In Chapter 3, the artificial neural network tool developed by MIRG is described and its applicability to the research associated with this thesis through the use of the FDA AERS database for the January to July, 2004 timeframe is highlighted. The AERS database is described and the methodology that is used in the data pre-processing and analysis of this database is also presented.

Chapter 4 discusses the results obtained through the execution of tests using the MIRG ANN research framework. The identification of key risk factors associated with the occurrence of adverse medication events is provided.

In Chapter 5, a conclusion of the research for this thesis is provided including identification of a recommended model to capture useful information about PAE occurrence. In addition, the contributions to knowledge achieved through the research

associated with this thesis are highlighted. Finally, future work is discussed to allow for the continuation of research in this area of study.

2. Preventable Adverse Medical Event Reduction and Prediction Techniques

The various studies described in the previous chapter highlight the need for the introduction of methods to reduce and predict the occurrence of PAEs within the healthcare delivery field. Much research has been performed on techniques that can be used to reduce each of the different types of PAEs. Various research studies emphasise a reduction in patient or procedural hand-offs between healthcare personnel (such as during shift changes). Increased communication between healthcare workers to encourage redundancy checking and utilisation of the correct policies, procedures and checklists and with the patient using standardised terminology is also an effective way to encourage the reduction of PAEs (Dhillon 2000; Kohn 2000; Australian Council for Safety and Quality in Health Care 2001; Bogner 1994; Tanner 2003; Spath 2000). Standardisation of common procedures within the healthcare delivery system is also encouraged as a method to reduce PAEs. Through procedure standardisation, healthcare personnel will be less likely to cause errors as they have implemented the specific procedures in the same manner each time they are used (Spath 2000).

Significant steps can be made in the reduction of PAEs through the clear documentation and dissemination of information surrounding the various erroneous situations that have occurred. Through knowledge of existing adverse medical event situations, healthcare workers may prevent similar situations from occurring in the future within their localised systems. The development of an adverse medical event tracking system can allow this information to be captured and used to educate healthcare personnel (Briggs 2002; Quality Interagency Coordination Task Force 2000). The

Institute of Medicine has suggested there be two forms of adverse medical event tracking systems, mandatory and voluntary. Mandatory reporting systems track information on serious adverse medical events such as death or serious injuries or deaths associated with the use of a new device, operation or medication (Kohn 2000). Voluntary reporting systems are much broader in scope and focus more on system weaknesses prior to the occurrence of a serious adverse medical event (Kohn 2000). This system should be anonymous and non-punitive to encourage healthcare workers to report all adverse medical event occurrences without fear of reprisal or litigation (Briggs 2002; Kohn 2000). The FDA AERS is an example of a mandatory and voluntary reporting program on the occurrence of adverse medication events. The information obtained from both reporting systems can be used as a training tool and as a simple way to track the trends of adverse medical events. The information obtained as a result of both types of reporting systems will not be of use to the healthcare delivery system without a team to analyse the obtained data in order to identify potential gaps and risks within the system (Kohn 2000).

An additional tool that can generally help in the reduction of PAEs is an online clinical information system (Briggs 2002). This tool can allow healthcare workers to obtain information on a variety of healthcare topics that are current and relevant. The information provided by this tool is readily available, and can help in the reduction of any misinformation that may lead to an eventual PAE. The Mayo Clinic and the United States National Library of Medicine and National Institutes of Health provide detailed medical information for healthcare professionals to refer to on both of their websites. (www.mayoclinic.com; www.nlm.nih.gov/medlineplus/encyclopedia.html) This tool can also be integrated into handheld computers to allow clinicians to access information

directly at the patient's bedside. Information such as a clinical medication reference guide or medical calculator can be stored on the handheld computer for the clinician to refer to in cases of uncertainty. McMaster University's Health Sciences Library lists many existing health and medical applications currently available for handheld computers (www.hsl.mcmaster.ca/resources/pda/pdaresources.htm). The key benefits of this tool are the immediate accessibility, localisation and easy updating of clinical information during synchronisation sessions to ensure that the information is current (Tschopp 2001).

2.1. Adverse Medication Events

Since this type of PAE is the most prevalent within the healthcare delivery system, many methods have been researched to reduce adverse medication events (Evans 2002; Kohn 2000). Suggested approaches to reduce the occurrence of adverse medication events include ensuring the attendance of a pharmacist at patient rounds or the packaging of medications into single unit doses within the pharmacy setting to reduce the number of patient overdoses as well as the number of calculations to be performed by other healthcare personnel (Kohn 2000). The elimination of specific abbreviations such as QID (four times daily), QD (every day), QOD (every other day), and u (units) when writing prescriptions can prevent the occurrence of dosage errors. Avoiding the use of trailing zeroes and always using leading zeroes can also reduce dosage adverse medication events (Spath 2000). A majority of the suggested adverse medical event reduction techniques can be implemented through the use of information technologies (Smith 1999).

The California Healthcare Foundation suggests that the first step in the introduction of technology within the medication dispensing process is to create pharmacy and nursing information systems (California Healthcare Foundation 2000). The

information systems contain medication databases that can be consulted during all of the steps of the dispensing process. These databases can contain all of the pertinent information related to medication dispensing, including appropriate dosing formulation, strength, route of administration, total daily dose, age-appropriate dosing, and any alternative medications that might be better suited (Evans 2002; California Healthcare Foundation 2000). These systems can be enhanced to include an interface with the laboratory to allow critical laboratory information to be immediately brought to the attention of the pharmacist (California Healthcare Foundation 2000). It has been estimated that pharmacy information systems prevent 51 percent of prescribing and transcription adverse medication events. The nursing information systems can incorporate medication administration guidelines to encourage the use of correct administration procedures (California Healthcare Foundation 2000).

A computerised physician order entry system can help in the reduction of adverse medication events during the ordering phase (Briggs 2002). With this system, physicians can enter their medication requests, which can be stored in the patient's electronic file. This information can be sent electronically to the hospital pharmacy or printed out for the patient or other healthcare workers, thus ensuring the legibility of the medication order.

Computerised physician order entry can be enhanced to include a database of medications, including appropriate dose amounts and medication conflicts, to further ensure the accuracy of the medication request. In addition, the order entry tool could include standard pre-written orders or order sets, suggested diagnostic pathways or user defined prescribing or blocking rules and forcing functions to further enhance the safety of medication orders. Computerised physician order entry systems can reduce the

occurrence of adverse medication events by 55 to 83 percent (Bates 2000; California HealthCare Foundation 2000; Spath 2000).

Incorporating dosing range limitations and route restrictions into the order entry system will also aid in the reduction of adverse medication events. By limiting the dosing range of a prescribed medication to within acceptable ranges, it is less likely for a patient to receive an incorrect dose, such as a ten-fold error, due to a mistake when ordering the prescription (Kohn 2000; Ash 1998). Additionally, to ensure the dose is accurate, the order entry tool could also include body surface area calculations based on patient height and weight for those medications where the prescription is based on body surface area. This can further ensure that the dosage amount is appropriate for the patient (California HealthCare Foundation 2000).

Alerts can be incorporated into the order entry tool to inform the physician about potential sources of adverse medication events such as common sound-alike or look-alike medications, potential medication-food interactions, potential medication-laboratory interactions, or possible duplicate therapy conflicts (California Healthcare Foundation 2000; Bates 2000; Bates 1999). This will help ensure that physicians and pharmacists are aware of these potential sources of error.

Computerised physician order entry systems can encourage significant reductions in the number of adverse medication events that occur within a healthcare delivery system, especially during the ordering and transcribing phases. However, this tool is the most expensive to introduce into the healthcare setting and is also the most difficult to implement (California Healthcare Foundation 2000). As well, implementation of this tool within the medical setting requires a significant change to the processes followed by

healthcare practitioners and as such is not necessarily being openly accepted in facilities where it has been implemented. One study performed by Ash and associates estimated that the participation rate within hospitals that have computerised physician order entry available was only 10 percent or lower (1998).

An intermediate step in using information technology to help reduce adverse medication events is the introduction of an order management imaging system. With this tool, the hard-copy orders written by the physician can be scanned into an electronic image that is sent to the pharmacy. This image can be enlarged, rotated and reverse-imaged. Order management imaging systems can reduce the turn-around time for orders to be processed as well as reducing the number of distractions for the pharmacists (California Healthcare Foundation 2000).

Electronic patient records in combination with a computerised physician order entry system or order management imaging system can also reduce the risk of adverse medication events during the ordering phase (Briggs 2002). Once the physician has specified the order, the medication and prescribed dose can be compared against the patient information found within the electronic patient record system. The patient's weight, existing allergies, previous adverse medication events, and existing medications being used can all be stored within the electronic patient record system and used by the computerised physician order entry system or the pharmacist to help eliminate dosage errors and adverse medication events (Briggs 2002). Additional information can also be stored in the electronic patient record such as a coverage list, which identifies the clinician currently covering the patient. This can allow quicker notification of the correct clinician when events are detected or clarification is required (Bates 1999).

Automating various tasks within the medication dispensing process can encourage accuracy and reduce dispensing errors. Robotics can be used to ensure the proper amounts of medication are provided when each prescription is filled (Quality Interagency Coordination Task Force 2000). In addition, the automation processes can ensure the correct medication is being dispensed. A key benefit to the automation of dispensing tasks within the pharmacy is the reduction of adverse medication events due to distraction or interruption of the pharmacists and clinicians.

Reducing errors associated with medication mix-up can be achieved through the use of automatic identification technologies including bar codes, radio frequency identification, smart cards and micro electro mechanical systems. The most prominent of these technologies is the use of individual bar codes for each medication being dispensed (Quality Interagency Coordination Task Force 2000; Longe 1989). Each bar code would be unique and would link to an electronic database that provides information about this specific medication, including identifying the patient the medication is intended for, the dosage amount, and the route of administration. This information could be verified by the healthcare workers responsible for administration of the medication to the patient to further ensure that an adverse medication event does not occur. Additionally, electronic patient records could be used to further ensure that adverse medication reactions do not occur. Estimates have determined that bar code technology for medications can reduce medication administration errors by up to 80 percent (Bates 2002).

The use of automated intravenous medication administration and analysis within the administration phase can encourage a reduction in the number of medication overdoses that may occur (Australian Council for Safety and Quality in Health Care

2000; Briggs 2002). A tool of this type interfaces between the healthcare workers and the patient. The medication information is entered into the tool, which then analyses the information provided against the physical parameters of the patient. Dosages can be validated to ensure that an adequate amount of medication is being administered as well as ensuring that an overdose does not occur. The tool is responsible for administration of the intravenous fluid and also to monitor for problems that may arise during the administration process, such as equipment failure.

Each of the tools mentioned above could also support a computerised alert system. This system would trigger alarms of varying urgency to the healthcare workers associated with the particular patient. These alarms could result in an audible signal at the patient bedside, in the example of the automated intravenous medication administration tool, or an alarm sent directly to the patient's physician via a pager, electronic mail, or alternative electronic device (Shabot 2000). As indicated previously, the specification of the appropriate clinician to be contacted when an event occurs can be identified as part of the coverage list located in the electronic patient record (Bates 1999).

2.2. Adverse Diagnostic Events

One method that can be used to aid in the reduction of adverse diagnostic events is through the use of a clinical decision support system (Australian Council for Safety and Quality in Health Care 2000). A decision support system can provide knowledge (through existing healthcare databases) and guidance to help the healthcare practitioner develop a patient diagnosis more quickly and with more accuracy. This tool can incorporate alarms to notify the healthcare worker on pertinent information such as potential medication-medication interactions or changes in the physical status of the

patient (Bates 2002; California Healthcare Foundation 2000). Additional functionality including electronic access to patient records, reminders of required tests or medicine administration, and suggested guidelines for specific patient conditions can also reduce the potential for an adverse diagnostic event (Bates 2002).

As with adverse medication events, an electronic patient record system can also help in the reduction of adverse diagnostic events (Briggs 2002). Providing quick access to a patient's history can greatly reduce the amount of time required to determine a diagnosis of the patient's ailment. In addition, an electronic patient record system would allow patient test results to become available more quickly than would occur with a manual reporting system. As stated previously, an increase in the speed in which patient information is delivered can greatly reduce the amount of time required to diagnose a patient. The less time required in determining the diagnosis, the quicker treatment can begin, which in some cases is of vital importance to the probability of the patient overcoming the ailment (Australian Council for Safety and Quality in Health Care 2001).

Bar codes or other automatic identification technologies can also be used within pathology labs and other testing environments to ensure that patient samples are not mixed up (Australian Council for Safety and Quality in Health Care 2001). Misdiagnosis of a patient's ailment can occur if the results of a test are provided for the wrong patient. This can lead to treatment that is not required and may have very damaging effects on the patient both physically and emotionally. Through the use of unique bar codes to identify each sample, the chance of mixing up patient test results is less likely. The results provided by the laboratory can also be validated by the healthcare workers through the use of the system of bar codes.

2.3. Adverse Surgical Events

The occurrence of adverse surgical events can be greatly reduced through modifications to processes utilised by the surgical teams at any healthcare facility. Wrong-site surgery events can be reduced if the surgeon marks and signs the surgical site in permanent ink with the involvement of the patient to ensure the correct site is indicated. Once in the surgical theatre, each member of the surgical team could verbally verify the correct surgical site to be operated upon (Evans 2002). Additionally, verbal verification by all members or select members of the surgical team could be required to better ensure that surgical implements are not left inside the patient after the surgery is complete (Evans 2002).

To reduce the likelihood of an operation being performed on the wrong patient, the surgical process could be enhanced to be more robust in situations of change. If there is a modification in the queue of surgical patients, the process should be clear on the specific steps that are required in order to notify the entire surgical team of the change. Again, verbal verification by each member of the surgical team on the identity of the patient who is about to be operated on would reduce the likelihood of operations being performed on the wrong patients (Evans 2002).

Patient identification bracelets that possess a unique electronic identifier, which identifies the patient currently in the surgical theatre, can also reduce the likelihood of a surgical procedure being performed on the wrong patient (Australian Council for Safety and Quality in Health Care 2001). The electronic information associated with the identifier can include the patient name, prescribed surgical procedure, medical history, and any other specific information required by the surgical team. This information can be

obtained through simple automatic identification technology located on the patient's identification bracelet with a bedside interface that is either wire line or wireless. This system would connect to the main electronic patient record information system of the hospital and allow the surgical team to obtain any required information.

2.4. Equipment Failures

Many techniques exist to reduce equipment failures. Standardisation of equipment throughout the healthcare delivery system can reduce the number of operator errors as a result of unfamiliarity with the equipment (Australian Council for Safety and Quality in Health Care 2001). Human factors engineering can be employed during the design of healthcare equipment and the environment in which the equipment will be used. Human factors engineering involves the study of the interrelationships between humans, the tools they use, and the environment in which they work (Kohn 2000). By ensuring the usability of healthcare equipment, the likelihood of medical errors occurring as a result of equipment misuse is reduced.

Selected techniques from the study of human factors engineering that can be incorporated into the design of medical devices include those listed below (Chen-Wing 1998; Dhillon 2000; Sawyer 1997; Kohn 2000). An expanded list can be found in Appendix A.

- Building constraints to limit operations to acceptable ranges;
- Making use of colour and shapes coding to facilitate rapid identification of controls and displays;
- Ensuring prompt and clear feedback is provided following user entries;

- Ensuring alarms effectively satisfy normal hearing and visual limits of the average user and that the alarms identify the source of the problem;
- Using prompts, menus and other cues to guide the user regarding important steps. It is important to ensure that the user is always capable of determining how to execute a specific function, what the next step should be, and that an appropriate recourse is provided for the user in case an error does occur;
- Ensuring that in a device failure scenario, the device resorts back to a safe mode.

The introduction of a clinical engineering department within the healthcare delivery system can further ensure a reduction in the occurrence of equipment failures. Clinical Engineering involves the supporting and advancing of patient care by applying engineering and managerial skills to healthcare technology (American College of Clinical Engineering). Clinical engineers can contribute to PAE reduction through usability analysis of healthcare technology or systems. They are responsible for the support and maintenance of existing healthcare technology within the healthcare delivery system as well as the analysis and recommendation of new technology to enter into the system. They have a responsibility to investigate incidents involving medical devices and deal with alerts effectively. They can also manage reporting systems related to healthcare technology to document the medical equipment design or operation errors. Clinical engineering departments are also responsible for educating the healthcare delivery staff on the proper use and maintenance procedures for all medical devices within the healthcare facility (American College of Clinical Engineering).

2.5. Adverse Systems Events

Multiple latent errors at the systems level manifest themselves as active errors within one of the other four main types of PAEs (Evans 2002; Bogner 1994). Modifications to the systems of healthcare delivery have the potential to significantly reduce the number of adverse systems events presently occurring. Human factors engineering, increased communication with the patient and within the healthcare delivery team, the use of technology such as biometric identification and tracking, and the implementation of simulated environments with feedback training can all encourage a reduction in the number of PAEs resulting from adverse systems events (Kohn 2000; Ferrans 1991). It is necessary to incorporate tools such as those listed above into the procedures and processes of the healthcare delivery system to create a pattern of error reduction. Policies need to be created requiring use of these tools as part of the everyday function of the various healthcare delivery teams (Wilson 1995).

Human factors engineering can again play a primary role in the migration of the healthcare delivery system policies and procedures to encourage a reduction in PAEs at the systems level. As stated previously, human factors engineering involves the study of the interrelationships between humans, the tools they use, and the environment in which they work (Kohn 2000). Techniques from the study of human factors engineering that can be incorporated into the design of healthcare delivery systems to reduce the occurrence of adverse systems events include (Kohn 2000):

- Anticipation of the different devices that will be used within the environment that the specific device is intended for;

- User expectations of how a system, such as the operating theatre and associated teams will operate;
- Standardisation of order forms, processes, policies, and equipment;
- Designing for recovery so that in the event of a failure, recovery from the failure is quick and easy.

Reduction in the occurrence of mistaken or unknown patient identity can be achieved through the use of biometric identification and tracking. This tool involves the utilisation of a digital scanning device that converts the patient's fingerprint into a unique number that is stored within the electronic patient record. Upon future visits, the patient will be easily identifiable, even when unconscious. This tool can also prevent adverse systems events as a result of similar or same patient names and false identity, since the correct patient information will always be accessible electronically for that patient's unique fingerprint (Ferrans 1991). This technology may also be useful to ensure that access to electronic information is only allowed for those individuals within the healthcare delivery system who have permission. This can be achieved by requiring a scan of the clinician's fingerprint prior to accessing any protected electronic information (Ferrans 1991).

Usability testing with feedback training within the healthcare delivery team may encourage a reduction in the occurrence of PAEs. Employing such a technique would require the identification of specific scenarios where training via a simulated environment, such as models or virtual reality, would decrease the likelihood of adverse systems events in the actual environment. Feedback from observers, other team members and video footage could be used to improve the skills of the healthcare personnel in these

simulated situations. For example, in emergency medicine, due to the time pressures associated with emergent cases, training healthcare personnel within a simulated environment may aid these personnel to remain calm and properly follow processes when facing these high-stress situations (Kohn 2000). In addition, simulated situations could include problems or failures within the healthcare delivery system and training on ways in which to safely recover from these failure situations (Kohn 2000).

In summary, automatic identification technology can encourage the reduction of many adverse systems events through the reduction of various errors including key-entry, patient misidentification, medication or pathology mix-ups, and incorrect blood transfusions. This technology provides the ability to quickly and easily identify the required information within many different situations. As previously highlighted, adverse medication events are the most prominent form of PAEs encountered in healthcare delivery. Automatic identification technology can aid in the reduction of these adverse systems events by reducing the occurrence of misinformation associated with data capture within the healthcare delivery system.

2.6. Preventable Adverse Medical Event Prediction

Given the significance of adverse medical events in the healthcare delivery field, adverse event prediction techniques may have a very positive impact in the reduction of adverse medical event occurrence. This allows adverse medical event reduction methodologies to move from a reactive context to a proactive one.

The majority of techniques that would be useful in the prevention of adverse medical events in the healthcare delivery field involve analysis of the healthcare delivery system involved in the occurrence of the event. By analysing all of the factors, it may be

possible to better understand which factors may contribute more significantly. In all systems level studies, it is important to consider the human side of the system failure, as this type of failure is very common. The discussion below highlights some of the systems analysis tools that may be used to find faults within the healthcare delivery system and possibly enhance the ability to predict the occurrence of an adverse medical event.

There are two main categories of systems analysis, deductive and inductive. Deductive systems analysis involves starting with the system level failure and parsing the system into its individual components in order to better identify the underlying factors involved in the occurrence of the event (United States Nuclear Regulatory Commission 1981). Inductive systems analysis involves starting with each failure condition, making general hypotheses about the failure of the system as a whole and then identifying contributors to this failure. (Wikipedia Online) There are many systems analysis techniques that can be utilised to increase reliability and reduce the occurrence of adverse medical events. The following sections provide a brief discussion of some of the most commonly used deductive and inductive techniques.

2.6.1. Deductive Methods

Deductive systems analysis involves analysing the adverse medical event beginning with the event and identifying any contributing factors until the factors have been parsed down to their pure components (United States Nuclear Regulatory Commission 1981). This method uses a “top-down” approach to analysing the system. The most popular deductive adverse event prediction method is Fault Tree Analysis, which is discussed below.

2.6.1.1. Fault Tree Analysis

A potential adverse medical event-causing situation is described and then depicted via a fault tree, which is an inverted tree. Each branch represents a potential causal event. Sub-branches can be used to represent additional events until the branching reaches the basic causal events. The premise of this technique is that it is these basic causal events that are primarily responsible for the occurrence of an erroneous situation (Spath 2000).

In the analysis of the adverse medical event, the fault tree is created to identify the main contributing factors to the event's occurrence. Only the factors that are considered of importance to the investigation are included in the analysis. These factors are modeled into a fault tree, where each factor represents a node of the tree. These nodes are combined together using a series of gates, which create sub conditions or events. A sample fault tree graph is depicted in Figure 1.

Figure 1. Simple Fault Tree Analysis Diagram

From Figure 1 we can see that the adverse medical event could occur as a result of the following: (component 1 and component 2) or (component 2 and component 4 and component 5) or (component 1 and component 3) or (component 3 and component 4 and component 5).

The fault tree graphs can become very complicated. The graphs can include hardware failures, human failures and shaping factors (such as environmental conditions) that all may have contributed to the primary adverse medical event (United States Nuclear Regulatory Commission 1981; Institution of Electrical Engineers 2004). There are five different types of events, including basic, conditioning, undeveloped, external and intermediate. In addition, there are five different gates (AND, OR, EXCLUSIVE OR, PRIORITY AND and INHIBIT) and two different types of transfer symbols

(TRANSFER IN and TRANSFER OUT). The events and gates are described in greater detail in Table 1 and Table 2.

Event	Image	Description
Basic		"A basic initiating fault requiring no future development"
Conditioning		"Specific conditions or restrictions that apply to any logic gate (used primarily with PRIORITY AND and INHIBIT gates)"
Undeveloped		"An event which is not further developed either because it is of insufficient consequence or because information is unavailable"
External		"An event which is normally expected to occur"
Intermediate		"A fault event that occurs because of one or more antecedent causes acting through logic gates"

Table 1. Fault Tree Analysis Event Descriptions¹

¹ (United States Nuclear Regulatory Commission 1981)

Gate	Image	Description
AND		"Output fault occurs if all of the input faults occur"
OR		"Output fault occurs if at least one of the input faults occurs"
EXCLUSIVE OR		"Output fault occurs if exactly one of the input faults occurs"
PRIORITY AND		"Output fault occurs if all of the input faults occur in a specific sequence (the sequence is represented by a conditioning event drawn to the right of the gate)"
INHIBIT		"Output fault occurs if the (single) input fault occurs in the presence of an enabling condition (the enabling condition is represented by a conditioning event drawn to the right of the gate)"

Table 2. Fault Tree Analysis Gate Descriptions²

Probabilities can be added to the graph if they are known. This added information gives the analysis team the ability to identify the probability at which a specific basic event could cause the adverse medical event to occur. This detailed information is typically not available during a systems analysis, but is very beneficial if known.

² (ReliaSoft; United States Nuclear Regulatory Commission 1981)

2.6.2. Inductive Methods

In order to perform systems analysis using inductive methods, the system is analysed using the individual components. The goal is to identify which components may contribute to the adverse medical event by analysing the effect that each component has on the system (United States Nuclear Regulatory Commission 1981). This method type uses a “bottom-up” approach to analysing the system.

A discussion of select inductive adverse event prediction methods is provided below. Additional prediction methods include, Preliminary Hazard Analysis, Double Failure Matrix and the “Parts Count” Approach (United States Nuclear Regulatory Commission 1981).

2.6.2.1. Failure Mode Effect Analysis (FMEA)

This technique primarily focuses on the equipment used within the healthcare community. Each piece of equipment is evaluated to determine the possible ways in which their components might fail (Spath 2000). This technique can also be applied to the healthcare delivery system by evaluating each of the components within this system, from the general hospital system to the sponges used in surgical procedures.

Vorley (1999) provides a thorough description of the Failure Modes and Effects Analysis (FMEA) approach to systems analysis and identification of systems failures. The FMEA process consists of six steps as listed below:

1. Define the system (typically through a graphical approach using a simple flow chart)
2. Identify potential failure modes and their causes (such as user error)

3. Evaluate the effects on the system of each failure mode including the severity of the failure and its probability of occurrence (if known)
4. Identify failure detection methods including identification of the detection rating and calculation of the risk priority number
5. Identify corrective measures for failure modes
6. Document analysis or prepare FMEA report.

Vorley (1999) discusses the FMEA process and the indicators used to help identify key areas of concern within the system. The primary indicators are the severity, rate of occurrence and rate of detection of a system failure mode. The severity classification for a failure mode is one of ten categories as listed in Table 3 as written by Vorley.

Classification	Description
1	Unlikely to be detected
2	20 percent chance of a customer return
3	40 percent chance of a customer return
4	60 percent chance of a customer return
5	80 percent chance of a customer return
6	100 percent chance of a customer return
7	Failure results in customer complaint
8	Failure results in sever customer complaint
9	Failure results in non compliance with statutory safety standard
10	Failure results in death

Table 3. FMEA Severity Classification

The occurrence rating for a failure mode identifies the likelihood that the failure mode will occur while the system is in operation and is one of ten categories as listed in Table 4 as written by Vorley.

Classification	Description
1	10^{-6} chance of occurrence
2 & 3	10^{-5} chance of occurrence
4 & 5	10^{-4} chance of occurrence
6 & 7	10^{-3} chance of occurrence
8	10^{-2} chance of occurrence
9	10^{-1} chance of occurrence
10	100 percent chance of occurrence

Table 4. FMEA Occurrence Classification

The detection rating for a failure mode identifies the likelihood of detecting the failure mode using the currently implemented methods and is one of ten categories as listed in Table 5 as written by Vorley.

Classification	Description
1	Failure will be detected
2	80% chance of detection
3	70% chance of detection
4	60% chance of detection
5	50% chance of detection
6	40% chance of detection
7	30% chance of detection
8	20% chance of detection
9	10% chance of detection
10	no chance of detection

Table 5. FMEA Detection Classification

The Risk Priority Number (RPN) is used to identify the areas of primary focus for system's improvement and is calculated using the following formula (Hammett):

$$RPN = SeverityRating * OccurrenceRating * DetectionRating \quad (2.1)$$

2.6.2.2. Failure Mode Effect and Criticality Analysis

The Failure Mode Effect and Criticality Analysis (FMECA) technique is similar to FMEA with an additional layer of analysis. Namely, the criticality of the failure mode is identified to further indicate which areas of systems failure should be a priority for further investigation (ReliaSoft).

The criticality of the adverse medical event is calculated using the severity rating, occurrence rating and detection rating from the original analysis and the formula below (Wilcox):

$$C_r = \sum_{n=1}^j (\alpha\beta\lambda_p t)_n = \sum_{n=1}^j C_{m_n} \quad (2.2)$$

Where,

C_m = Failure mode criticality number

C_r = Item criticality number

α = probability item will fail in a particular mode

β = Conditional probability of failure effect given a specific failure mode

λ_p = item's failure rate

t = Time

r = Severity classification

n = Failure modes in the items that fall under a particular criticality classification.

A criticality matrix can be used to determine the criticality of the adverse medical event. The criticality is determined by using the results of either the quantitative or qualitative analysis combined with a severity classification. Those adverse medical events deemed to be of highest severity should be the first to be investigated.

2.6.2.3. Hazard and Operability Study

This technique requires a review and analysis of the design and operation of the healthcare delivery system to uncover any hazards that may encourage PAEs. The specific areas of focus of this study are the areas in which the healthcare personnel are operating (Spath 2000). Eighty percent of the time, an issue with process or operations is uncovered, versus a specific system hazard being found (Acusafe).

A system or process is broken down into nodes, which are analysed by the hazard and operability (HAZOP) team. Process parameters, guidewords and deviations are identified within the indicated node and each specific deviation is analysed to identify the causes of the deviation (Acusafe).

Acusafe defines a hazard as *“any operation that could possibly cause a catastrophic release of toxic, flammable or explosive chemicals or any action that could result in injury to personnel.”* Operability is defined as *“any operation inside the design envelope that would cause a shutdown that could possibly lead to a violation of environmental, health and safety regulations or negatively impact profitability.”* From a healthcare perspective, focus could be directed towards injury hazards and any of the operability parameters specified above.

Combining specific guidewords and parameters together gives the HAZOP team the opportunity to identify any potential deviations from standard process within a given node. Suggested guidewords include: no, more, less, as well as, reverse and other than (Acusafe). The parameters can be tailored to the specific system being analysed. From a healthcare perspective, parameters could include: instrumentation, maintenance, safety, reaction, administration, diagnosis, operation or implement.

Once a node, parameter and guideword are identified, the focus turns to identifying potential deviations from the standard process. Typically, the deviation will fall into one of three categories: human error, equipment malfunction or external events (Acusafe). Description of these categories is provided below.

Human error:	Errors of execution or planning that result in the occurrence or potential occurrence of a PAE.
Equipment failure:	PAEs attributable to a failure in medical equipment management or use.
External events:	Items outside the node being reviewed affect the operation of the node to the extent a PAE is possible. External events can include environmental or situational conditions that affect the safe operation of the node being studied (Acusafe).

Once all four components are identified, the HAZOP team can then identify if any new or enhanced safeguards are required to prevent, detect or mitigate the occurrence of the PAE.

2.6.2.4. Hazard Analysis and Critical Control Point

This technique evaluates specific processes within a system to identify any potential hazards. A detailed outline of the process is created with the help of management personnel. The hazards identified through this evaluation process are used to determine critical points within the process that should be modified or further protected to ensure that an adverse medical event does not occur. In addition, a training plan can be developed surrounding these critical points to ensure that human error does not occur (Spath 2000).

The United States Food and Drug Association describes the basic format for Hazard Analysis and Critical Control Point (HACCP) systems analysis. There are seven main steps to the HACCP approach (United States Food and Drug Association 2001):

1. “Analyse hazards associated with the system and existing measures in place to control or avoid these hazards.
2. Identify critical control points. This stage involves identification of critical points in the processes of the system at which the potential hazards can be controlled or eliminated.
3. Establish preventative measures with critical limits for each control point.
4. Establish procedures to monitor the critical control points.
5. Establish corrective actions to be taken when monitoring shows that a critical limit has not been met.
6. Establish procedures to verify that the system is working properly.
7. Establish effective record keeping documenting the HACCP system.”

The systems analysis techniques discussed above all require in-depth knowledge of the system including all of its individual components. In a tightly coupled system such as healthcare delivery, it can be exceptionally difficult to have the extensive knowledge required to effectively use these techniques. In the next chapter an alternative approach to adverse medical event prediction is investigated. Previous work has been performed in training an artificial neural network to predict a specific outcome within the healthcare field. More details will be provided in Chapter 3. The premise of this form of predictive tool is that as the network is trained the predictive effectiveness is increased, making it more capable of predicting the outcome of interest. Training an artificial neural network

to predict the occurrence of an adverse medical event is a novel concept that may prove to be a very useful alternative to the various approaches discussed in this chapter. The previous success of MIRG with ANNs analysing medical data outcomes has led to a logical choice in using this tool for further data analysis in this research.

For the purposes of this research, focus is placed on the identification of specific input parameters that appear to have a more significant impact on the occurrence of an adverse medical event. These parameters can be identified using the results of the training performed on the artificial neural network. Identification of primary risk factors can help healthcare personnel to identify patients at a higher risk of being affected by an adverse medical event. Incorporating this information into a clinical decision making tool would allow care providers to be alerted when there is a risk of an adverse medical event occurring.

3. Methodology

This section discusses the methodology used for the experimental portion of this thesis. The primary focus of this thesis was on the identification of information technologies that can be used in the reduction of medical errors and adverse medical events. Another aspect uses a new artificial neural network research framework developed by MIRG in October 2005 to predict adverse medication events and identify which input parameters into the network are of highest relative importance to the occurrence of the adverse medication event.

3.1. MIRG's Artificial Neural Network Research Framework

In order to identify factors that might have a more significant impact on the occurrence of adverse medication events, an ANN research framework already developed by the MIRG research team was used in conjunction with data from the FDA AERS database.

3.1.1. A Brief History of Artificial Neural Networks

The first neural model was developed in 1943 by Warren S. McCulloch and Walter Pitts. The neurons described in their work were simple processors that were variable in nature. In 1949, Hebb described a process that might be used for learning in biological neural networks, known as Hebbian Learning. The process was described as follows:

When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased (Hebb 1949, 50).

This concept became the basis for the first learning algorithms for artificial neural networks.

It is believed that the first simulation of an artificial neural network was in 1956 by Rochester and associates. The simulated network consisted of 512 neurons similar to those described by McCulloch and Pitts (1943) and was executed using an IBM Type 704 Electronic Calculator. The simulations were targeted towards further understanding how neural network structures grow. The first attempted simulation failed, but further attempts were eventually successful.

The perceptron type of artificial neural network was first developed by Rosenblatt (1958). The basic structure of the perceptron is a layered network of input and output neurons. The output neurons defined are similar to the binary neurons described by McCulloch and Pitts and the input neurons represent any real value. The functioning of the network is such that the input neurons can influence the output neurons via connection weights but the output neurons have no impact on the input neurons.

Marvin Minsky and Seymour Papert exposed many flaws with the perceptron in 1969. They showed that the network could not handle the calculation of parity, exposing the fact that the perceptron could not learn to evaluate the logical function of exclusive or. In addition, they found that the perceptron was very inefficient. As the number of inputs increased, the training time increased exponentially (Minsky and Papert 1969).

Research of artificial neural networks continued in a minimal fashion after the results of Minsky and Papert's research were published. Werbos (1974) developed and used the back propagation learning method, which is one of the most popular learning algorithms used today. Rumelhart et al. (1986) further researched the back propagation learning algorithm and its applicability to the multi-layer perceptron. Hornik et al. (1989) showed that multi-layer perceptron networks were capable of approximating any continuous function to an arbitrary degree of accuracy.

3.1.2. Artificial Neural Network Structure and Technology

MIRG uses a feedforward multi-layer perceptron similar to the one described by Rumelhart, Hornik and others in the 1980's and 1990's. Ennett and Frize (1999) used an artificial neural network to predict mortality for coronary artery bypass grafting patients in American hospitals. The classification performance results were similar to those of comparative models. Erdebil (2005) used artificial neural networks to predict the occurrence of severe ATV injuries as part of the research for her Master of Applied Science in Electrical Engineering thesis. The results of this research provided insight into the primary factors present during the injurious situations studied.

The artificial neurons are connected in parallel, with input data being fed through each layer of the network and producing a single output. Each input into a node is assigned a weight representing the relative importance of the input in the network. The summed input weights are presented to a transfer function, which limits the sum to a specified range that is passed to the connected node (Haykin 1999).

Figure 2 depicts an ANN consisting of three layers; an input layer, hidden layer and output layer. The network is fully connected, meaning that all nodes in each layer receive

connections from all nodes in each preceding layer. It is a feed-forward network, which means that the outputs of one layer are used as inputs into the next layer.

Figure 2. Three-Layer ANN (Rounds 2002)

Weights are applied to each of the inputs at each layer and the outputs are normalised by using a transfer function to cause the output to be limited to a specific range of values. An example of a node with these characteristics can be found in Figure 3.

Figure 3. Typical ANN Node (Pan 2002)

For a network that does not contain any hidden layer, meaning it is linear in nature, a step transfer function is used. For non-linear networks, a non-linear mapping function such as one of two sigmoid functions, logistic or hyperbolic tangent, is used for the transfer function. The logistic function allows for outputs between 0 and 1 with its inflection point located at (0, 0.5). Figure 4 depicts the graphical representation of the logistic function.

Figure 4. Logistic Function (Wikipedia 2006)

Although the logistic function is the most commonly used transfer function, MIRG's ANN research framework uses the hyperbolic tangent transfer function (Equation 3.1 and Figure 5). The hyperbolic tangent function allows for outputs between -1 and 1 with its inflection point located at (0, 0). The location of the inflection point at (0, 0) causes a steep slope around zero, which causes a larger number of non-zero outputs. In addition, Penny (1998) stated that the network learns at a quicker rate if the output is between -1 and 1 and the inputs are limited to values with a mean close to zero.

Figure 5. Hyperbolic Tangent Function (Weisstein)

$$\tanh x = \frac{e^{2x} - 1}{e^{2x} + 1} \quad (3.1)$$

Back propagation is also used with MIRG's ANN research framework in order to readjust the weights associated with each node in the network based on the resultant error calculated from the initial results of the ANN execution. The higher the weight, the more impact that input has on the node.

3.2. Adverse Event Reporting System Database

Since November 1, 1997 the United States Food and Drug Administration (FDA) has been maintaining a database of adverse medication events that have occurred within the healthcare delivery system. Manufacturers of medications and other biological products are required to report any adverse medical events to the FDA, while healthcare practitioners and other members of the healthcare field can report on a voluntary basis.

Access to the most current data contained within the AERS database can be obtained directly from the FDA website at <http://www.fda.gov/cder/aers/extract.htm>. Research for this thesis was performed using data from the first two quarters of 2004

(January to March and April to June). Appendix B outlines the full set of database attributes.

Table 6 outlines the attributes within the AERS database, as described by the US FDA, that were used in the research associated with this thesis. In total, five of the 41 attributes were used as input variables into the ANN. The outcome code (OUTC_COD) was used as the output variable to be measured against as the patient outcome was the adverse medical event of interest in this research. The five input parameters and one output parameter were chosen in consultation with a physician, Dr. Robin Walker, from the Children's Hospital of Eastern Ontario, who is also a co-principal investigator of MIRG. The majority of the parameters listed in the AERS database were administrative in nature and were deemed to not be variables that would have any impact on the occurrence of an adverse medication event.

Attribute	Description
ISR	Unique sequencing number (primary key)
AGE	Numeric value of patient's age at time of event. This attribute was represented in years with any patient ages under one year listed as 0 years.
GNDR_COD	Code representing patient's gender. UNK – Unknown M – Male F – Female NS – Not Specified
WT	Numeric value of patient's weight. This attribute was represented in pounds (1 KG = 2.20462262 LBS)
ROUTE	The route of medication administration
OUTC_COD	Code for patient outcome DE – Death LT – Life-Threatening HO – Hospitalisation (Initial or Prolonged) DS – Disability CA – Congenital Anomaly RI – Required Intervention to Prevent Permanent Impairment or Damage OT – Other
DUR	The duration that the medication was administrated in days

Table 6. FDA AERS Attributes

3.2.1. Data Distribution

Insight into adverse medication events can be obtained by analysing the data from the FDA AERS database. Specifically, the distribution of the data between the various outcomes, the age, gender and weight of the patients affected by the adverse medication event, the specific medication administered, the route the medication was administered and the duration of the medication administration can provide much information into the specific attribute values in which adverse medication events are more prevalent. The following charts describe these specific points of analysis for the portion of the subset

database where the outcome was hospitalisation. Analysis of the full subset database can be found in Appendix C.

Figure 6. AERS Subset Outcome Distribution

Figure 6 outlines the distribution of possible outcomes from an adverse medication event from the AERS subset database. The outcome of hospitalisation is the most prevalent with 48.4 percent of the data population. The next most common is Other with 26 percent of the data population. Death is the least common outcome with 3.1 percent of the data population.

For the subset data associated with an outcome of hospitalisation, the following charts highlight the data distribution.

Figure 7. Data Distribution by Decade

The age distribution for the hospitalised patients shows that with 20.4 percent of the data population, patients aged 30 to 39 years were at most risk of being hospitalised or prolonging their hospitalisation as a result of an adverse medication event. This was followed closely by patients aged 40 to 49 years with 19.3 percent of the data population.

Figure 8. Data Distribution by Gender

Males were more prone to being hospitalised or prolonging their hospitalisation as a result of an adverse medication event with 68.9 percent of the data population. This data

distribution is opposite of the full database data distribution (Figure 29), where females represent 55 percent of the data population and males represent 38.5 percent of the data population. This indicates that males are more prone to be hospitalised or having their hospitalisation stay prolonged as a result of an adverse medication event than women. This result might also be impacted by elimination of missing variables as the full subset database, with all of the outcomes represented, has a data distribution of 50.8 percent males and 49.2 percent females.

Figure 9. Data Distribution of Weight by Decade

Patients aged 40 to 49 years and 50 to 59 years had almost the same average weight at 173.27 pounds and 173.24 pounds. The average weight for the hospitalisation outcome was 143.76 pounds. The averages for the age ranges of 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79 and 80 to 89 all exceeded the overall average.

Figure 10. Data Distribution by Medication

Figure 10 depicts the distribution of the experimental data by medication. The most prevalent medication was Vioxx with 16.2 percent of the data population followed by Decortin with 3.4 percent of the data population. The experimental data distribution differs from that of the full database in that the medication Aspirin is not featured as a key medication within the experimental database (it only represented 0.3 percent of the data population versus 1.2 percent of the full data population). This may be partly a result of the number of data records associated with Aspirin that were missing one or more pieces of data and were removed from the final data set used in this thesis work.

Figure 11. Data Distribution by Route

As with the full AERS database, oral administration of medication is the most common route. For the outcome of hospitalisation, oral administration represented 66.4 percent of the data population.

Duration (days)	Percentage
1	20.9
2	4.9
4	3.5
6	2.8
3	2.8
5	2.3
7	2.2
0	1.9
14	1.6
11	1.3

Table 7. Data Distribution by Duration

The most common duration of medication administration was one day with 20.9 percent of the data population. This result would indicate that for the patients that are hospitalised or have their hospitalisation stay prolonged as a result of an adverse medication event, a significant majority of them were on medication that was administered only a small number of times.

3.3. Artificial Neural Network Research Framework Analysis

3.3.1. Data Pre-Processing

For the purposes of this research, it was decided that the outcome to be identified by the ANN would be hospitalisation. This decision was based on research performed by Ennett and Frize (1998). They found that if the measured outcome represented less than 15 percent of the total data population, the ANN would fail to learn anything and would classify all cases as belonging to the larger outcome class. From Figure 6 the only single outcome that represents more than 15 percent of the data population is hospitalisation with 48.4 percent representation. It is estimated that approximately 80 percent of a researcher's time is spent preparing the training data for input into the neural network (Yale 1997). The ANN developed by MIRG requires that the training data be formatted as a space delimited file. The AERS database files were formatted as a text file delimited by a dollar sign (\$). The text files were imported into Microsoft Excel to be saved into a format acceptable for MIRG's ANN. Pre-processing of the data involved removing all cases with one or more missing values, standardising the input variable values, enumerating all text input variables and normalising the data using the z-score formula (defined on page 60, equation 3.2). The required Excel files were then saved as comma

delimited text files, opened in Microsoft Word where all commas were replaced by spaces and the files were finally saved without any extension.

The input variables AGE, WT and DUR were all standardised to represent values of the same type. AGE and DUR were standardised to be in days, and WT was standardised to be in pounds. There were two input variables in this database that required enumeration as they were represented as text values. The GNDR_COD variable represented the gender of the patient referred to in each case. For this variable, the data was enumerated to be 0 for male patients and 1 for female patients. The ROUTE variable also had to be enumerated. This variable represented the route that the medication associated with each case was administered. Table 8 outlines the 51 different route types for this variable with their associated enumerated value.

Route Type	Enumerated Value
Auricular (OTIC)	1
Buccal	2
Cutaneous	3
Dental	4
Endosinusial	5
Endotracheal	6
Epidural	7
Hemodialysis	8
Intra-Arterial	9
Intra-Articular	10
Intracavernous	11
Intracoronary	12
Intradermal	13
Intradiscal (Intraspinal)	14
Intrahepatic	15
Intralesional	16
Intrameningeal	17
Intramuscular	18
Intraocular	19
Intraperitoneal	20

Route Type	Enumerated Value
Intrapleural	21
Intrasynovial	22
Intrathecal	23
Intrathoracic	24
Intratracheal	25
Intratumor	26
Intra-uterine	27
Intravenous	28
Intravenous Bolus	29
Intravenous Drip	30
Intravesical	31
Nasal	32
Occlusive Dressing Technique	33
Ophthalmic	34
Oral	35
Oropharyngeal	36
Other	37
Parenteral	38
Perineural	39
Rectal	40
Respiratory (Inhalation)	41
Retrobulbar	42
Subconjunctival	43
Subcutaneous	44
Subdermal	45
Sublingual	46
Topical	47
Transdermal	48
Transplacental	49
Urethral	50
Vaginal	51

Table 8. Route Type Enumerations

Once all of the input parameters were represented by numerical values, they were normalised using the z-score formula to obtain input values between -1 and 1. The z-score formula used in this work is described below (Pan 2002).

$$Z_n = \frac{(X_n - \mu)}{3\sigma} \quad (3.2)$$

Where,

Z_n = Standardised value of input variable X

X_n = Input variable X for observation n

μ = Mean for input variable X

σ = Standard deviation for input variable X

Each set or case of input parameters (age, weight, gender, duration and route) was randomly selected to be placed into one of two data sets. The first contained 2/3 of the data for training and testing purposes and the other contained the remaining 1/3 for verification purposes. The verification data set is used for verifying the ANN output for the single best epoch found during the training and testing phase of the experiment and that the ANN has not over trained with the initial data. The training and testing data set was then further subdivided into 2/3 for training and 1/3 for testing and the verification data was subdivided into ten equal data sets.

Table 9 and Table 10 outline the outcome distribution for each of the test, train and ten verification data sets.

Cases	Test	Train	v1	v2	v3	v4	v5	v6	v7	v8	v9	v10
Positive	3392	6815	527	511	526	523	516	511	514	517	522	505
Negative	3275	6518	473	489	474	477	484	489	486	483	478	495
Total	6670	13333	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000

Table 9. Outcome Distribution Values

Cases	Test	Train	v1	v2	v3	v4	v5	v6	v7	v8	v9	v10
Positive	50.9	51.1	52.7	51.1	52.6	52.3	51.6	51.1	51.4	51.7	52.2	50.5
Negative	49.1	48.9	47.3	48.9	47.4	47.7	48.4	48.9	48.6	48.3	47.8	49.5
Total	100	100	100	100	100	100	100	100	100	100	100	100

Table 10. Outcome Distribution Percentages

3.3.2. Experimental Measures

Six measures of performance that were used: sensitivity, specificity, correct classification rate (CCR), average squared error (ASE), logarithmic sensitivity index, and area under the receiver-operating characteristic (ROC) curve.

Relating specifically to this research, the CCR is the rate at which the ANN correctly classifies the data as falling into either the primary (hospitalisation) or secondary outcome categories. Accordingly, the constant predictor (CP), evaluated using a priori statistics, is the number of cases found in the most prevalent category of the outcome (in this problem, it is the outcome where there was no hospitalisation). Sensitivity is defined as the percentage of cases that are hospitalised (primary outcome category) and are correctly classified as such by the ANN. Specificity is defined as the percentage of cases that are not hospitalised (secondary outcome category) and are correctly classified as such by the ANN (Ennett, 2003). The functional definitions for each of these terms are provided below:

$$Sensitivity = \frac{TruePositive}{(TruePositive + FalseNegative)} \quad (3.3)$$

$$Specificity = \frac{TrueNegative}{(TrueNegative + FalsePositive)} \quad (3.4)$$

$$CCR = \frac{(TruePositive + TrueNegative)}{(TruePositive + TrueNegative + FalsePositive + FalseNegative)} \quad (3.5)$$

True negatives, true positives, false negatives and false positives are determined based on the predicted versus actual outcomes of the ANN. Table 11 describes in which scenario each situation occurs.

	<i>Actual Negative</i>	<i>Actual Positive</i>
<i>Predicted Negative</i>	True Negative	False Negative
<i>Predicted Positive</i>	False Positive	True Positive

Table 11. Predicted Versus Actual Outcomes³

The Average Squared Error (ASE) parameter is “the difference between each predicted value and its corresponding actual value squared over all cases” (Rybchynski 2005). This calculation is described by the formula provided below.

$$ASE = \frac{(desired - actual)^2}{\sum_{allCases} (desired - actual)} \quad (3.6)$$

A receiver operating characteristic (ROC) curve is a plot of the true positive rate (sensitivity) and the false positive rate (1 – specificity). The area under the curve describes the accuracy of the experiment. A perfect ROC curve is one where the area under the curve is one. That is, all true positives were found and no false positives were found. A useless ROC curve is one where there is a straight line from 0 to 1, indicating that the experiment is predicting on a completely random basis (Tape). Figure 12 provides examples of an excellent, good and useless ROC curve.

³ (Ennett, Weight-Elimination 4)

Figure 12. Sample Receiver Operator Characteristics Curve (Tape)

The logarithmic sensitivity index is typically the chosen stopping criterion for MIRG's ANN research framework. The key attribute with this performance measure is that it maximises both sensitivity and specificity, but is more weighted towards the sensitivity of the experiment to encourage the ANN to better predict the less frequent outcome (hospitalisation) (Ennett 2002). The functional representation of the logarithmic sensitivity index is found below (equation 3.7):

$$Index = -Sensitivity^n * \log(1 - Sensitivity * Specificity) \quad (3.7)$$

Where,

n = Weighting factor to bias the result in favor of sensitivity

The ANN learns from one epoch to the next via nine different control parameters that modify the weights and biases of each node in the network to encourage optimal performance from the network. Table 12 lists the nine parameters and their function in

the ANN's learning as explained by Ennett (2002) and Table 13 lists their default ranges found to be ideal by previous researchers in MIRG (Ennett 2002, Rybchynski 2005).

Parameter	Description
Learning rate (lr)	The learning rate determines the speed at which the network will converge on the specified minimum for the ANN learning function. Too high a learning rate will prevent the ANN from being able to converge.
Learning rate increment (lr_inc)	"Learning rate's incremental value"
Learning rate decrement (lr_dec)	"Learning rate's decrement value"
Weight-decay constant (λ)	Parameter used to penalise large input weights in order to reduce the amount of variance in the output
Weight-decay constant increment (λ_{inc})	"Weight-decay constant's incremental value"
Weight-decay constant decrement (λ_{dec})	"Weight-decay constant's decremental value"
Weight-elimination scale factor (w_0)	Factor to encourage the elimination of extraneous large weights (weight-elimination) or small weights (weight-decay) from influencing the output variance
Momentum	"Adds a proportion of the previous weight-change value to the new value, thereby giving the algorithm some "momentum" to prevent it from getting caught in the local minima"
Error ratio (err_ratio)	"Controls how the back propagation makes adaptive changes in the learning rate, weight-decay constant and the momentum term"

Table 12. ANN Learning Parameters

Parameter	Start Point	Minimum	Maximum
Learning rate (lr)	0.0005	0.00005	0.01
Learning rate increment (lr_inc)	1.001	0.75	1.25
Learning rate decrement (lr_dec)	0.999	0.75	1.25
Weight-decay constant (λ)	0.0001	0.00001	0.0001
Weight-decay constant increment (λ_{inc})	1.001	0.75	1.25
Weight-decay constant decrement (λ_{dec})	0.999	0.0001	1.25
Weight-elimination scale factor (w_0)	0.01	0.0001	0.999
Momentum	0.5	0.0001	0.999
Error ratio (err_ratio)	1.02	1.0001	1.5

Table 13. ANN Learning Parameters Default Ranges

The research framework runs by holding eight of the nine parameters from Table 12 steady and varying one. The optimal value for each of the parameters is found using the logarithmic sensitivity index by default. The network with the best value combination for the nine parameters is chosen as the optimal network (Ennett et. al. 2004). The research framework is executed multiple times for one experiment depending on the number of input variables into the framework. The experiment begins with a network with no hidden nodes and finishes with a network with one hidden layer and $2n + 1$ hidden nodes, where n is equal to the number of input variables into the network.

Relative weight reduction can be performed on an input dataset to help identify the variables with little impact on estimating the outcome variable. Each input and output node connection is assigned a weight based on the learning of the ANN within an epoch of the training cycle. The assigned weight values are carried into the next epoch and

utilised to remove any input parameters with minimal weight associated with them. As soon as degradation in the performance measures is observed, the training cycle finishes and the final weights of the input parameters are identified (Frize 2001). The resultant weights can be used to evaluate the relative importance of each of the input variables. Rybchynski developed a modified Garson-Goh relative weight algorithm to calculate the relative importance of the input variables. The Garson algorithm is highly complicated to calculate, and the simplified approach by Goh eliminates the weights associated with the hidden nodes to output node connections. Her modified Garson-Goh relative weight algorithm is described below.

Calculation parameters:

i : the number of input nodes

j : the number of hidden nodes

k : the number of output nodes

w_{ij} : the connection weight between input node i and hidden node j

w_{jk} : the connection weight between hidden node j and output node k

rw_{ij} : the relative connection weight between input node i and hidden node j

rw_{jk} : the relative connection weight between hidden node j and output node k

RI_i : the Relative Importance of input node i

Relative Weight Equations:

Step 1: Calculate the relative weighting of the hidden-output connections into the output node. For a single output node set $k = 1$

$$rw_{jk} = \frac{abs(w_{jk})}{\sum_j abs(w_{ij})} \quad (3.8)$$

Step 2: Calculate the relative weighting of the input-hidden connections into each hidden node. For each hidden node j :

$$rw_{ij} = \frac{abs(w_{ij})}{\sum_i abs(w_{ij})} \quad (3.9)$$

Step 3: Multiply each relative weighting input-hidden connection value by the relative weighting value of its connected hidden-output weight. For each input i :

$$P_{ij} = rw_{ij} * rw_{jk} \quad (3.10)$$

Step 4: Sum the final relative weighting products (P_{ij}). For each input i :

$$S_i = \sum_j P_{ij} \quad (3.11)$$

Step 5 Divide the sum of the final relative weightings for each input node by the total of all relative weightings. For each input i :

$$RI_i = \frac{S_i}{\sum_i S_i} \quad (3.12)$$

4. Results

The FDA AERS database provided input information associated with adverse medication events that occurred in hospitals and other medical facilities in the United States. The ANN research framework was run against the data from the first and second quarters of 2004. The input variables considered were: patient age, patient gender, patient weight, the administration route of the medication and the duration the medication was administered.

The results of the execution of the ANN research framework showed that the ideal neural network structure (number of hidden layers and number of nodes) contained one hidden layer with four nodes as shown in Figure 13. This structure was found to have the best convergence. Figure 14, Figure 15, Figure 16, Figure 17, Figure 18 and Figure 19 outline the logarithmic sensitivity, ROC area, ASE, sensitivity, specificity and CR for the test and train set over all eleven structures. Table 14, Table 15 and Table 16 contain the numerical results for the test, train and averaged verification set over all eleven structures.

Figure 13. One Hidden Layer, Four Node ANN

Figure 14. ANN Research Framework Log Sensitivity

Figure 15. ANN Research Framework ROC Area

Figure 16. ANN Research Framework ASE

Figure 17. ANN Research Framework Sensitivity

Figure 18. ANN Research Framework Specificity

Figure 19. ANN Research Framework Classification Rate

Structure	Logarithmic Sensitivity	ROC Area	ASE	Specificity	Sensitivity	Classification Rate	Constant Predictor
0	0.0013	0.6541	0.2528	0.0031	0.9996	51.2413	51.1138
1	0.0011	0.6606	0.2324	0.0026	0.9997	51.2263	51.1138
2	0.1481	0.6570	0.4325	0.5976	0.6685	63.3841	51.1138
3	0.1438	0.6430	0.4058	0.5493	0.6922	62.2291	51.1138
4	0.1470	0.6528	0.4257	0.5832	0.6754	63.0541	51.1138
5	0.1444	0.6130	0.9938	0.4632	0.7629	61.6365	51.1138
6	0.0019	0.4380	0.4219	0.0044	0.9982	51.2413	51.1138
7	0.1437	0.6514	0.4447	0.5635	0.6822	62.4166	51.1138
8	0.0011	0.5011	0.4898	0.0026	0.9996	51.2188	51.1138
9	0.1381	0.6546	0.3812	0.5005	0.7162	61.0740	51.1138
10	0.1066	0.6133	0.4345	0.3401	0.7875	56.8814	51.1138
11	0.0012	0.5011	0.4898	0.0026	0.9996	51.2188	51.1138

Table 14. Train Data Set Parameter Values

Structure	Logarithmic Sensitivity	ROC Area	ASE	Specificity	Sensitivity	Classification Rate	Constant Predictor
0	0.0020	0.6489	0.2547	0.0046	0.9996	51.0724	50.8775
1	0.0013	0.6529	0.2348	0.0031	0.9994	50.9975	50.8775
2	0.1429	0.6458	0.4325	0.5966	0.6589	62.8319	50.8775
3	0.1393	0.6387	0.4066	0.5432	0.6869	61.6319	50.8775
4	0.1435	0.6469	0.4310	0.5832	0.6686	62.6669	50.8775
5	0.1360	0.6027	1.0036	0.4571	0.7482	60.5220	50.8775
6	0.0023	0.4480	0.4195	0.0052	0.9994	51.1024	50.8775
7	0.1402	0.6441	0.4477	0.5634	0.6760	62.0669	50.8775
8	0.0013	0.5015	0.4912	0.0031	1.0000	51.0274	50.8775
9	0.1342	0.6477	0.3849	0.4974	0.7170	60.9120	50.8775
10	0.1068	0.6083	0.4423	0.3463	0.7807	56.7272	50.8775
11	0.0012	0.5014	0.4912	0.0027	1.0000	51.0124	50.8775

Table 15. Test Data Set Parameter Values

Structure	Logarithmic Sensitivity	ROC Area	ASE	Specificity	Sensitivity	Classification Rate	Constant Predictor
0	0.1466	0.6575	0.9292	0.5720	0.6815	62.8495	51.72
1	0.1488	0.6650	0.9293	0.5355	0.7114	62.6265	51.72
2	0.1539	0.6636	1.0634	0.5848	0.6871	63.758	51.72
3	0.1508	0.6704	0.9209	0.6252	0.6556	64.0872	51.72
4	0.1328	0.6522	0.9584	0.5768	0.6497	61.4486	51.72
5	0.1463	0.6588	0.9288	0.5697	0.6820	62.768	51.72
6	0.1490	0.6691	0.9315	0.5569	0.6964	62.888	51.72
7	0.1463	0.6690	0.9253	0.5433	0.7003	62.4324	51.72
8	0.1388	0.6528	0.9477	0.6509	0.6190	63.4442	51.72
9	0.1479	0.6349	0.9855	0.5762	0.6813	63.0405	51.72
10	0.1476	0.6721	0.9270	0.6170	0.6544	63.6286	51.72
11	0.1543	0.6815	0.9241	0.5317	0.7259	63.1922	51.72

Table 16. Averaged Verification Set Parameter Values

For completeness, Table 17 provides the constant predictor values for each of the verification sets. These values were averaged and used as the constant predictor value in Table 16.

v1	v2	v3	v4	v5	v6	v7	v8	v9	v10
52.7	51.1	52.6	52.3	51.6	51.1	51.4	51.7	52.2	50.5

Table 17. Verification Constant Predictors

Although the results are not as high as one would hope, for a very first attempt at this approach with this data, they are promising. For the training data set, the classification rate exceeds the constant predictor by 11.9403 ($63.0541 - 51.1138$) percent for the four-node structure. For the test data set, the classification rate exceeds the constant predictor by 11.7894 ($62.6669 - 50.8775$) percent for the four-node structure. For the averaged verification data set, the classification rate exceeds the constant predictor by 9.7286 ($61.4486 - 51.72$). Further analysis of the results is discussed below.

The ANN research framework uses an automated parameter update function to choose the best parameter to be carried forward in each epoch of the training cycle. For the experiment performed with the FDA AERS subset database, the logarithmic sensitivity index was used as the stopping criterion for the ANN research framework at the 57th epoch of training. Based on the data at the 57th epoch, an ANN network with one hidden layer with four nodes was chosen to be the best. Figure 20 provides the graphical description of the logarithmic sensitivity for the four-node structure over the 57 epochs. Sensitivity and specificity curves for the four-node structure for the 57 epochs can be found in Figure 34 in Appendix D. ASE and CR curves for the four-node structure for the 57 epochs can be found in Figure 35 in Appendix D.

Figure 20. Logarithmic Sensitivity Curve for Four Node Structure

Figure 21 depict the ROC curve for both a one-node structure and a four-node structure.

Figure 21. ROC Curve for Four Node Structure

The results for all nine parameters used by the ANN for the optimal four-node structure can be found in Table 18.

Parameter	Results
Learn Rate	0.000283
Learn Rate Increment	1.1177
Learn Rate Decrement	0.999
Weight Decay (λ)	0.94218
Weight Decay Increment	1.001
Weight Decay Decrement	1.25
Weight Scale Parameter (w_o)	0.4606
Momentum	0.25
Error Ratio	1.375

Table 18. ANN Research Framework Resultant Parameter Values

Using the modified Garson Goh computations to determine the relative importance for each of the input variables using the input weights for a four-node structure determined by the execution of the ANN research framework, the following relative importance values were determined.

Input Variable	Relative Importance (percentage)
Route	28.8
Weight	25.0
Age	16.5
Gender	15.5
Duration	14.2

Table 19. Relative Importance of Input Variables

Although the area under the ROC curve indicates that an artificial neural network with one hidden layer with one node is optimal, the other parameters are not in agreement. From Table 14 and Table 15 we see that the network was unsuccessful at classifying almost any of the cases where the patients were not hospitalised (specificity) with a train specificity value of 0.0026 and a test specificity value of 0.0031. As such, performing analysis on which input parameters have the highest relative importance for a one-node structure would not provide useful results.

5. Conclusions, Contributions and Future Work

5.1. Conclusions

Much confusion still exists in the terminology surrounding medical errors and adverse medical events within the healthcare field. This thesis clarified the main terminology in order to ensure that a common understanding was maintained throughout the text. Classification of the various types of adverse medical events in the healthcare field is vital to further investigation in this area. Identification of the five main types of adverse medical events: medication, surgical, diagnostic, equipment failure and systems, creates a clear foundation for research in this area to progress from.

There are a significant number of information technologies available to aid in the reduction of adverse medical events. This work highlighted many of the key technologies including physician order entry systems, pharmacy and nursing information systems, automatic and biometric identification technologies and clinical decision support systems. Much research is still needed to enhance the capabilities of these technologies to reduce the occurrence of adverse medical events and medical errors.

With adverse medication events being the most commonly occurring adverse medical events within the healthcare field (Evans 2002; Kohn 2000) it was logical to begin investigation into the primary risk factors for the occurrence of adverse medical events with this specific type of adverse medical event.

Investigation was performed using MIRG's artificial neural network framework to identify the input parameters with the highest relative importance. Utilising the

logarithmic sensitivity index with a one layer, four-node structure, the route of administration was identified as being the primary risk factor with the highest percentage of relative importance in comparison to the other four input variables obtained from the Adverse Event Reporting System developed by the United States Food and Drug Administration. The primary route of medication administration was orally with 66.8 percent of the data population for the subset database used in the experiments. This indicates that a primary contributing factor to the hospitalisation of a patient due to an adverse medication event is oral administration of the medication.

The patient weight may also be a core factor into the hospitalisation of a patient (initial or prolonged) as a result of an adverse medication event. More investigation will need to be made into the way in which weight impacts the outcome of adverse medication events. From the input database we can see that 43.2 percent of the patient weights are greater than the average 163.6 pounds, but there is no conclusive evidence from the experiments performed in this thesis as to whether the weight is the contributing factor to the relative importance of patient weight in the hospitalisation outcome.

This study has led to the identification of a primary contributing factor to patient hospitalisation as a result of an adverse medication event. However, the FDA AERS database has very few potential risk factors associated with the occurrence of adverse medical events. This thesis has highlighted risk factors that have been found to be attributable to an adverse medication event. A recommendation from this research is to create a new adverse medication event reporting model with a larger set of input parameters. The suggested additional input parameters can be found in Table 20.

Input Variable	Description
Distraction/Interruption	Was the healthcare practitioner or consumer distracted or interrupted during the administration of the medication
Clinician experience	Level of experience of the clinician administering the medication
Communication issue	Were there problems with communication within the healthcare team or between the clinician and patient
Number of hours working	The number of hours the clinician administering the medication has been on duty
Stress	Any physical or emotional stress on the party administering the medication (clinician or consumer)
Administration setting	The location where the medication was administered - Consumer's home, healthcare facility
Setting situation	Were there any exceptional situational issues during the time of medication administration - Rushed clinicians, overloaded clinicians, multiple clinicians working on the same case
Length of stay	The amount of time that the patient was in the healthcare facility if admitted
Similar medication name	Did the administered medication have a name similar to another medication - Note: it may be possible to provide this information as an internal function of the database based on an on-line database from the FDA, which is updated daily to include approved and tentatively approved prescription, over-the-counter and discontinued medications (Drugs@FDA, www.accessdata.fda.gov/scripts/cder/drugsatfda)
Similar medication packaging	Did the administered medication have packaging similar to another medication
Multiple medications	Were there multiple medications being administered at the same time
Procedural deviation	Did the healthcare provider or consumer deviate from the recommended procedural path - For example, did the consumer not take their medication as directed
Diagnostic delay	The amount of time between first patient contact and diagnosis of ailment

Input Variable	Description
Administration delay	The difference in hours between actual medication administration versus the ideal time to be given
Equipment failure	Were there any failures associated with the equipment required for administration of the medication
Operator error	Was there any misuse of the equipment required for administration of the medication - For example, an infuser being incorrectly setup (dosage values or incorrect medication used)
Length of stay	The amount of time that the patient was in the healthcare facility if admitted

Table 20. Additional Database Input Parameters

The FDA AERS database focuses solely on capturing adverse medication events. Although this form of adverse medical event is the most prevalent in the healthcare setting, the opportunity exists to enhance research in the areas of adverse surgical events, adverse diagnostic events, equipment failures and systems events. Creation of reporting models similar to the adverse medication event reporting system used by the FDA could greatly enhance understanding into the causes for the occurrence of these events and possibly allow predicting several of these events prior to their occurrence.

Risk factors associated with each of these additional areas of adverse medical events have been highlighted within this work. Identifying these risk factors would allow development of effective prevention mechanisms, at least for those that could be accurately predicted. Adverse systems events risk factors found in this analysis are defined in Table 21. Table 22, Table 23 and Table 24 provides a list of specific parameters that should be considered in creating a new reporting model in the three additional areas of adverse medical events previously discussed.

Parameter	Description
Patient length of stay	What was the duration in days the patient was admitted to the hospital
Situational characteristics	Were there any time pressures, understaffing, other exigent circumstances
Stress or fatigue	Was the clinician under any stress or fatigue
Distraction or interruption	Was the clinician distracted or interrupted in the middle of a procedure, diagnosis or medication administration
Communication issues	Were there any communication issues - Between team members - Between clinician and patient
Number of procedures	Number of procedures being performed on the patient at the same time
Number of clinical teams	Number of clinical teams working on the patient at the same time

Table 21. Adverse Systems Event Parameters

Parameter	Description
Number of surgeons or surgical teams	Was there more than one surgeon or surgical team working on the patient
Number of parallel procedures	Were multiple procedures being performed on the patient at the same time
Procedural deviations	Were there any deviations from standard recommended procedures
Unfamiliar surgical technique	Was the surgical technique unfamiliar to the surgeon or surgical team (new procedure, uncommon procedure, younger surgeon or surgical team)

Table 22. Adverse Surgical Event Parameters

Parameter	Description
Unfamiliar diagnostic technique	Was the diagnostic technique unfamiliar to the clinician or clinical team (new technique, uncommon technique, younger clinician or clinical team)
Delays in follow-up testing	Were there any abnormal delays in the required follow-up testing in order to diagnose the patient (how much time in hours or minutes)
Delays in obtaining patient information	Were there any abnormal delays in obtaining information on the patient (may fall under situational characteristics; how much time in hours or minutes)

Table 23. Adverse Diagnostic Event Parameters

Parameter	Description
Inaccurate labeling or instructions	The labels or instructions provided with the equipment did not provide sufficient information to ensure proper use of the equipment
Defective components	Components in the equipment were defective
Poor construction, design	The equipment was poorly constructed or designed, lessening the usability of the equipment
Electrical Interference	Electrical interference caused a malfunction in the operation of the equipment
Restriction of visual field	The visual field of the equipment in use was restricted as a result of the situational characteristics
Incorrect equipment setup or adjustment	The equipment was not setup or adjusted correctly, resulting in the incorrect operation of the equipment
Cleaning or other maintenance	The maintenance of the equipment was not adequate or resulted in damage to the equipment
Unfamiliarity of use	The equipment was new or not commonly used

Table 24. Equipment Failure Parameters

The research performed as part of this thesis has laid a strong foundation to allow much more investigation into the area of adverse medical events within the healthcare field. A multitude of systems engineering technologies exist that can be utilised to aid in the reduction of adverse medical events. Included in this list are those technologies that can predict the occurrence of an adverse medical event. Artificial neural networks have successfully been used in other research to effectively predict outcomes such as patient mortality. Using this powerful technology in the area of adverse medical event reduction

and prediction is promising and exciting. With patient safety being very important within the healthcare field, the utilisation of such a tool would potentially be of great benefit to the clinician.

The intent of the research performed by MIRG is to ensure that the data collected and results obtained from the experiments performed by the researchers in this group get into the hands of the physicians and policy makers in the healthcare delivery field. Dr. Robin Walker, as co-principal investigator of MIRG, and being a physician with the Children's Hospital of Eastern Ontario provides the opportunity to broadcast our results within the healthcare community.

5.2. Contributions

The following contributions were made as a result of the research performed in this thesis:

1. Organised and clarified medical error and adverse medical event information and terminology to ensure a common conceptual understanding. Classified five specific categories for adverse medical events: diagnostic, surgical, medication, equipment failures and systems.
2. Identified and described several systems engineering technologies that can be utilised in the healthcare delivery field to reduce the occurrence of adverse medical events.
3. Highlighted the significance of adverse medical events within the healthcare delivery field and the need for research in order to help reduce their occurrence.

4. In spite of the lack of databases of adverse medical events, identified one that was appropriate for analysis, containing recorded cases of adverse medication events to be used for research. This the first known analysis of such data with ANNs.
5. Identified a primary contributing factor to patient hospitalisation as a result of an adverse medication event based on the limited number of input variables from the United States Food and Drug Administration's Adverse Event Reporting System.
6. Created an enhanced set of database input variables for use in databases to capture more of the potential contributors to adverse medication events.
7. Developed a new data collection model for medical errors and other types of adverse medical events using the risk factors identified during the literature survey.

5.3. Future Work

This work is a first step in the investigation of medical errors and adverse medical events within the healthcare field. The required information has been extracted and compiled in order to obtain a solid foundation to work from. An extensive set of information technologies was presented to highlight the many areas of research that are available in the effort to reduce adverse medical events with one area being the prediction of the occurrence of adverse medical events. Through the utilisation of a database with limited input variables, MIRG's ANN research framework was used to predict the outcome of hospitalisation as a result of an adverse medication event. The research framework identified one key variable contributing to the occurrence of adverse

medication events requiring patient hospitalisation. The following sections describe areas where additional research can be performed in the areas of medical errors and adverse medical events.

5.3.1. ANN Analysis Using the Outcome “Death”

MIRG’s ANN research framework was used in conjunction with the FDA AERS database to predict the outcome of hospitalisation. This outcome was used as it was the only single outcome that represented more than 15 percent of the data population, a value that Ennett and Frize (1998) determined to be the lowest representational percentage in order to ensure adequate performance of the artificial neural network.

Ennett (2001) and Rybchinsky (2005) have performed research on the topics of imputing missing values into the input data as well as randomly re-sampling the positive outcomes into the original dataset to increase the positive outcome representation. Using these techniques to increase the representation of other outcomes within the FDA AERS database will allow research to be performed on more significant outcomes, specifically patient death. In addition, imputing missing values into the original FDA AERS database will provide access to many more cases as the original dataset used in this work contained over 200 000 records.

5.3.2. Adverse Medication Event Database Enhancement

Using the existing FDA AERS database and the recommended additional input variables identified in Table 20, enhance the adverse medication event reporting model to include more detailed information. Presently there is no mandatory adverse medication event reporting system in Canada. This work will hopefully influence the implementation

of such a system, which would include the recommended set of variables as described in this thesis.

As research continues in this area, additional risk factors may be identified that could have an impact on the occurrence of an adverse medication event. In such case, the new adverse medical event reporting system would have to be able to evolve to include these new variables as they are identified.

5.3.3. Analysis of Extended Databases

The opportunity will exist to extract much additional information from the extended databases once a satisfactory number of cases have been recorded. Ideally, this new data, when run through MIRG's ANN research framework, will lead to new insight into the primary risk factors in the occurrence of adverse medical events. These new results may also point out input variables that have negligible impact versus others, which may have significant impact.

5.3.4. Further Analysis of Predictive Abilities of the Research Framework

The research performed for this thesis focused on the identification of primary risk factors in the occurrence of adverse medication events. Utilising the same AERS database from the FDA, further analysis could be performed to identify other input variables, not directly linked to the occurrence of the adverse medication event, but that could potentially enhance the predictive ability of this research framework.

Additional parameters are available in the existing AERS database that may be of interest. Suggested additional parameters of interest are:

- Occupation of the initial reporter (OCCP_COD)

- Did the voluntary reporter also notify the manufacturer (TO_MFR)
- Was confidentiality requested from the voluntary reporter (CONFID)
- Initial source of the report (RPSR_COD)
- Did the negative reaction lessen or stop when the therapy was stopped (DECHAL)
- Did the negative reaction reoccur when the therapy was restarted (RECHAL)

Research questions that may be of interest include:

- Is there any significance in the occupation of the initial reporter and the outcome being reported?
- Is there any significant correlation between the occupation of the initial reporter and the confidentiality request?
- Is there any significance in the initial source of the report and the outcome being reported?

5.3.5. Creation of an Adverse Medical Event Notification System

Analysis of the extended databases could yield new insight into the occurrence of adverse medical events. The identification of key factors with a higher relative importance could be used as input into the development of an adverse medical event notification system, where notification is provided when a combination of key factors are recognised, thus putting the indicated patient at higher risk for an adverse medical event.

As more healthcare facilities move toward the use of intelligent systems to aid them in their daily tasks, adding an adverse medical event notification tool to their tools will hopefully allow clinicians to become more efficient and effective.

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Appendix A: Additional Human Factors Engineering Concepts

The list below outlines additional human factors engineering concepts that can be incorporated into the design of a healthcare delivery system to aid in the reduction of adverse medical events due to equipment failure (Chen-Wing 1998; Dhillon 2000; Sawyer 1997; Kohn 2000).

- Designing control knobs and switches that correspond to user conventions and arranging them in a way that reduces the likelihood of inadvertent activation;
- Ideally making the intensity and pitch of auditory signals easily heard by device users with the consideration of ambient noise that might be present in the intended use environment;
- Ensuring tactile feedback is provided by controls;
- Ensuring controls, workstations and displays are designed around the basic capabilities of users (including strength, vision, hearing, memory, age, gender, equipment familiarity and reach);
- Designing brightness of visual signals that is adequate for users performing their tasks under varying conditions of ambient illumination;
- Avoiding overloading users with unformatted, densely packed, or insufficient information;
- Ensuring all alarms used are distinguishable from one another, wherever possible;
- Considering operator reach and their ability to set controls, read displays accurately and associate controls with their related displays;

Appendix B: Food and Drug Administration Adverse Event Reporting System Attributes

Table 25 provides a complete listing of the attributes in the FDA AERS database.

In total, there are 41 attributes separated into seven different files.

Attribute	Description
ISR	Unique number for identifying an AERS report (primary key)
CASE	Number for identifying an AERS case.
I_F_CODE	Code for initial or followup status of report as reported by manufacturer: I – Initial F – Followup
FOLL_SEQ	The sequence number of a followup report, as reported by manufacturer
IMAGE	Identifier for an AERS report image. Character field consisting of the ISR number, a dash, and a check digit or letter
EVENT_DT	Date adverse medical event occurred or began
MFR_DT	Date manufacturer first received initial (or follow-up) information.
FDA_DT	Date FDA received report
REPT_COD	Code for the type of report submitted: EXP – Expedited (15-day) PER – Periodic DIR – Direct
MFR_NUM	Manufacturer's unique report identifier
MFR_SNDR	Verbatim name of manufacturer sending report
AGE	Numeric value of patient's age at event
AGE_COD	Unit abbreviation for patient's age: DEC – Decade YR – Year MON – Month WK – Week DY – Day HR – Hour

Attribute	Description
GNDR_COD	Code for patient's gender: UNK – Unknown M – Male F – Female NS – Not Specified
E_SUB	Whether this report was submitted under the electronic submissions procedure for manufacturers
WT	Numeric value of patient's weight
WT_COD	Unit abbreviation for patient's weight: KG – Kilograms LBS – Pounds GMS – Grams
REPT_DT	Date report was sent
OCCP_COD	Abbreviation for initial reporter's type of occupation: MD – Physician PH – Pharmacist OT – Other health-professional LW – Lawyer CN – Consumer
DEATH_DT	Date patient died
TO_MFR	Whether or not voluntary reported also notified manufacturer
CONFID	Whether or not voluntary reported stated that his identity should not be disclosed to the product manufacturer
DRUG_SEQ	Unique number for identifying a medication for an ISR (secondary key)
ROLE_COD	Code for medication's reported role in event: PS – Primary Suspect Medication SS – Secondary Suspect Medication C – Concomitant I – Interacting
DRUGNAME	Name of medicinal product
VAL_VBM	Code for source of DRUGNAME: 1 – Validated trade name used 2 – Verbatim name used
ROUTE	The route of medication administration
DOSE_VBM	Verbatim text for dose, frequency and route, exactly as entered on report

Attribute	Description
DECHAL	Dechallenge code, indicating if reaction abated when medication therapy was stopped: Y – Positive dechallenge N – Negative dechallenge U – Unknown D – Does not apply
RECHAL	Rechallenge code, indicating if reaction recurred when medication therapy was restarted: Y – Positive rechallenge N – Negative rechallenge U – Unknown D – Does not apply
LOT_NUM	Lot number of the medication
EXP_DT	Expiration date of the medication
NDA_NUM	Verbatim NDA number
PT	Preferred term level medical terminology describing the event using the Medical Dictionary for Regulatory Activities (MedRA)
OUT_COD	Code for a patient outcome: DE – Death LT – Life-Threatening HO – Hospitalisation (Initial or Prolonged) DS – Disability CA – Congenital Anomaly RI – Required Intervention to Prevent Permanent Impairment/Damage OT – Other
RPSR_COD	Code for an initial source of the report: FGN – Foreign SDY – Study LIT – Literature CSM – Consumer HP – Health Professional UF – User Facility CR – Company Representative DT – Distributor OTH – Other
START_DT	A date therapy was started (or re-started)
END_DT	A date therapy was stopped
DUR	Numeric value of the duration (length) of therapy

Attribute	Description
DUR_COD	Unit abbreviation for duration of therapy: YR – Years MON – Months WK – Weeks DAY – Days HR – Hours MIN – Minutes SEC – Seconds
INDI_PT	Preferred term level medical terminology describing the Indication for use using the Medical Dictionary for Regulatory Activities (MedDRA)

Table 25. FDA AERS Attributes⁴

⁴ Note that the descriptions for these attributes are found in the Asc_nts.doc document found with the database package. (United States Food and Drug Administration, AERS)

Appendix C: Adverse Event Reporting System Data Distribution

The figures and table below outline the data distribution for the subset database used for this research.

Figure 22. AERS Subset Age Distribution

Figure 22 provides the distribution of patient age in decades within the AERS subset database. The patient ages that were most affected by an adverse medication event were between 50 and 59 years (19.5 percent) and 60 and 69 years (19.4 percent). Within this data subset, only 4.2 percent of the cases were of patients under the age of nine years.

Figure 23. AERS Subset Gender Distribution

Figure 23 describes the distribution of patient gender within the AERS subset database. The patient gender was almost evenly distributed with 50.8 percent of the patients being male and 49.2 percent of the patients being female.

Figure 24. AERS Subset Weight Distribution by Age

Figure 24 describes the data distribution for patient weight by age for the subset dataset that was used for analysis in this thesis. The average weight for all cases in the

subset database was 163.7 pounds. The average weight for age ranges of 30 to 39, 40 to 49, 50 to 59 and 60 to 69 years all exceeded the overall average weight for the subset database. In total, 43.2 percent of the patients in the subset database had a weight higher than the average. Of that 43.2 percent, the age range with the most patients over the average weight was ages 50 to 59 with 24.4 percent of the data population. This was closely followed by ages 60 to 69 with 23.2 of the data population.

Figure 25. AERS Subset Medication Distribution

Figure 25 provides insight into which medications were most prevalent in the occurrence of adverse medication events during the first half of 2004 for the data subset. The medication Vioxx had the most significant impact with 17.4 percent of the data population. The next closest medication was Decortin at 2.9 percent.

Figure 26. AERS Subset Route Distribution

In Figure 26 we see the distribution for the top ten routes of medication administration within the subset AERS database. The primary route of administration was orally with 66.8 percent of the data population. The next closest route of medication administration was intravenously with 20 percent of the data population.

Duration (days)	Percentage
1	19.9
2	4.7
4	3.5
3	2.8
6	2.7
5	2.2
7	2.2
0	2.0
14	1.6
11	1.3

Table 26. AERS Subset Duration Percentages

Finally, the duration of the medication administration may be an important factor into the occurrence of adverse medication events. Table 26 outlines the most frequent durations of medication administration in days. The most frequent was one day with 19.9 percent of the data population. The next most frequent was two days at 4.7 percent of the population. The figures below describe the data distribution for the overall FDA AERS database without the removal of the missing values.

Figure 27. AERS Outcome Distribution

From Figure 27, it is shown that for the first half of 2004, the most common outcome for patients affected by an adverse medication event was hospitalisation at 36.8 percent. This was followed closely by the general other group of adverse medication event outcomes at 32.9 percent.

Figure 28. AERS Age Distribution

Figure 28 describes the distribution of the adverse medication events dependent on the age of the patient affected by the event. The age ranges most impacted by adverse medication events include ages 50 to 59 years at 12.8 percent, ages 60 to 69 years at 12.8 percent and ages 70 to 79 years at 11.9 percent. In this data set, only 3.2 percent of the individuals affected by the adverse medication events fell into the ages 0 to 9 years. 25.2 percent of the dataset did not have a patient age associated with the individual case record.

Figure 29. AERS Gender Distribution

Figure 29 shows that females appear to be impacted more significantly by adverse medication events with respect to the data analysed for this thesis. The data revealed that 55 percent of the population was female, 38.5 percent of the population was male and the remaining 6.5 percent of the population being listed as either not specified, unknown or missing the gender data entirely. The larger percentage of females in the study could be a result of many factors including the fact that the second most common drug within the AERS database was Vioxx (Figure 32) with 1.2 percent of the data population. In 2003, Rossignol and associates performed a study on osteoarthritis in France and found that 66.2 percent of the data population were females.

Figure 30. AERS Average Weight by Age

Within the dataset, 65.9 percent of the records did not have a weight value entered. Of the remaining records, the average weight was 155.7 pounds. Figure 30 outlines the weight distribution per age range based on the records with an associated weight and age. Note that out of the remaining 34.1 percent of the data records, 8.0 percent did not have an associated age, resulting in 31.4 percent of the total dataset depicted in Figure 30 above.

Figure 31. AERS Initial Reporter Occupation Distribution

Figure 31 describes the distribution of the initial report occupation for the AERS dataset. The most common reporters to the AERS system were physicians (MD) at 32.2 percent of the data population, followed by consumers (CN) at 18.3 percent of the data population. The least common initial reporter occupation was lawyers (LW) at 1.1 percent. It is important to note that 25.4 percent of the data population did not contain a value for the initial reporter occupation.

Figure 32. AERS Top Ten Medications

Figure 32 lists the top ten medication names associated with adverse medication events according to the AERS database. Each individual adverse medication event could have been the result of multiple medications and as such there were 469,254 individual medication cases listed within the database. The most common medication associated with an adverse medication event was Aspirin with 5793 of the 469,254 cases or 1.2

percent. This was followed closely by Vioxx at 5543 or 1.2 percent and Ortho Evra at 5227 or 1.1 percent.

Figure 33. AERS Top Ten Routes of Medication Administration

Finally, Figure 33 lists the top ten routes of administration for the medications associated with adverse medication events. The most common route of medication administration was orally with 63.1 percent of the data population. This was significantly larger than the next closest route, intravenously, with only 14.9 percent of the data population.

Appendix D: Artificial Neural Network Research Framework Full Results

Figure 34. Sensitivity and Specificity Curves for Four Node Structure

Figure 35. ASE and CR Curves for Four Node Structure