Harm during Hospitalizations for Heart Failure:

Adverse Events as a Reliability Measure of Hospital Policies and Procedures

by

Jeanne Huddleston

A Thesis Presented in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Approved April 2012 by the
Graduate Supervisory Committee:

John Fowler, Co-Chair
Douglas Montgomery, Co-Chair
Esma Gel
Dan Shunk

ARIZONA STATE UNIVERSITY

May 2012

ABSTRACT

For more than twenty years, clinical researchers have been publishing data regarding incidence and risk of adverse events (AEs) incurred during hospitalizations. Hospitals have standard operating policies and procedures (SOPP) to protect patients from AE. The AE specifics (rates, SOPP failures, timing and risk factors) during heart failure (HF) hospitalizations are unknown.

There were 1,722 patients discharged with a primary diagnosis of HF from an academic hospital between January 2005 and December 2007. Three hundred eighty-one patients experienced 566 AEs, classified into four categories: medication (43.9%), infection (18.9%), patient care (26.3%), or procedural (10.9%). Three distinct analyses were performed: 1) patient's perspective of SOPP reliability including cumulative distribution and hazard functions of time to AEs; 2) Cox proportional hazards model to determine independent patient-specific risk factors for AEs; and 3) hospital administration's perspective of SOPP reliability through three years of the study including cumulative distribution and hazard functions of time between AEs and moving range statistical process control (SPC) charts for days between failures of each type.

This is the first study, to our knowledge, to consider reliability of SOPP from both the patient's and hospital administration's perspective. AE rates in hospitalized patients are similar to other recently published reports and did not improve during the study period. Operations research methodologies will be necessary to improve reliability of care delivered to hospitalized patients.

DEDICATION

I dedicate this scholarly work to Paul, Jessica and Martin. Thank you for your love, patience and support throughout the pursuit of this academic milestone. And in the loving memory of Will, my loyal companion during the early days of writing this thesis.

ACKNOWLEDGMENTS

I would like to express my gratitude to my Graduate Supervisory Committee for their guidance, support and patience.

John Fowler, PhD – Committee Co-Chair

Douglas Montgomery, PhD – Committee Co-Chair

Esma Gel, PhD – Committee Member

Daniel Shunk, PhD – Committee Member

I would specifically like to express my heartfelt gratitude to Sherine Gabriel, MD, MSc. Dr. Gabriel took a chance on a mid-career clinician and supported my application to pursue education and scientific expertise outside of the traditions of clinical research. I have found my passion and will be forever grateful to Dr. Gabriel for opening these doors of opportunity.

I would also like to thank Dr. James Naessens and Rachel Gullerud for their time and crucial guidance during the analysis phase; Donna Lawson for her coordination of, and participation in, data collection; Kathleen Wolfert and Cherie Dolliver for their assistance with data collection.

Funding Sources

This research was supported in part by NIH/NCRR Center for Translational Science Activities Grant Number KL2 RR024151. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Resources from the Center for Translational Science Activities grant support (UL1 RR024150) were used during the course of study completion.

TABLE OF CONTENTS

APPENDIX Page

LIST OF TABLES

TABLE Page

LIST OF FIGURES

FIGURE Page

FIGURE Page

PREFACE

Modern health research has traditionally used the patient as the denominator for all quality metrics. Whether counting and recording cases of measles, broken bones or depression, researchers has devised both simple and complex methods of “counting heads” to aid in their search for understanding. Regardless of the specific disease studied, the disciplines of basic science, epidemiologic research and clinical trials all focus on the patient as the unit of measurement. While appropriate on a patient or personal level, this analytic framework may have some serious limitations when attempting to define reliability of the four major groupings of adverse medical events; infection, medication errors, patient care, and procedural. Never the less, “patient centric” traditional clinical research has strongly influenced the approach to the concepts of quality and safety as they were rapidly infused and diffused into a variety of health care settings during the last decade.

The resultant cottage-industry approach to health care combined with no globally competitive market allowed it to ignore the basics of systems and industrial engineering for the preceding three or four decades. Health care was sheltered from many of the pressures facing other industry sectors such as manufacturing that embraced these areas of expertise out of the necessity to survive in a new internationally competitive market. The last two decades in health care witnessed defining changes in the management of hospitals as the concepts of quality and patient safety, combined with technologic advancements, have changed the landscape of hospital operations management forever. Now health care must do the same in order to improve the health of populations at an affordable cost without inducing more harm.

My own conclusions about health care safety and systems are colored by not only by experiences from my profession but also from personal experience. Although it was enlightening and validating to see the improved clinical results of a clinical trial integrating hospitalist-orthopedist care on outcomes after hip fracture, I was surprised and perplexed when confronted with the situation of my Grandmother in a small critical access hospital in northern Michigan. Although she had a challenging hospital stay after her femur fracture, I marveled at how the small town hospital "system" still managed to outperform my larger tertiary care organization in many ways. What concepts did my hometown hospital appreciate, either consciously or unconsciously, that allowed for quality care without the aid of electronic medical records, digital imaging or teams of specialists? And if these interventions could be quantified, would they be scalable to a larger multi-physician group, hospital, clinic, or system?

Competitive market forces and increasing regulatory burden are forcing health care entities to consolidate into larger multidisciplinary clinics. These consolidations add new dimensions to competition as hospitals attempt to secure large enough patient bases to provide some financial security for the future and compete on perceived value of care, not just production. With these strong influences, health care providers and managers are actively changing their interpretation of the concept of reliability. They will be shifting from a consideration of reliability in terms of the technology and products they use to deliver care (computers, laboratory machines, X-ray machines, medication dispensers, treatment devices such as pacemakers, etc), to thinking about the services they deliver from the lens of reliability.

Chapter 1

INTRODUCTION

Substantial risk is posed to hospitalized patients (Ornstein 2007, Kohn, Corrigan and Donaldson 2000, Leape and Berwick 2005, Landrigan et al. 2010, OIG 2010b). This is not because of lack of national and local hospital investment in medical quality and patient safety initiatives. Health care institutions have invested millions in improving the care of their respective patients. Public stakeholders have responded to this risk in hospitals with state mandates for public reporting of "never events" (Minnesota), payment penalties for preventable harm (Center of Medicaid and Medicare Services), public reporting of hospital-level performance by the Center of Medicaid and Medicare Services, Leapfrog, Agency of Healthcare Research and Quality (AHRQ), etc. Another recent federal initiative is the Partnership for Patients, a portion of the Affordable Care Act legislation of 2011, which seeks to build a framework for national learning to increase the rate of identification and elimination of harm (McCannon and Berwick 2011). In spite of all of the attention given to patient safety efforts, AEs remain common with rates underestimated in most studies (Landrigan et al. 2010, OIG 2010b).

In addition to being relatively common, AEs are costly and have significant associated resource utilization issues. Potentially preventable adverse drug events (ADEs) double the LOS and cost attributable to the ADE, compared to non-preventable ADEs (Bates et al. 1997). Length of stay, cost and mortality attributable to hospital-acquired AEs range from 0 to more than 10 days, $50,000 and 20%, respectively (Zhan 2003). In another study, AEs

occurring in the ICU added an average of 31 days in the hospital (Forster et al. 2008).

We will focus our research on patients hospitalized with a primary diagnosis of heart failure (HF), the most common inpatient diagnosis in the U.S.A. (Kozak, DeFrances and Hall 2006). Limiting patient selection to a single primary inpatient diagnosis will address some issues of patient heterogeneity and resultant unknown collinearity found in current patient safety literature. HF is also a prime target for investigation as one of the largest public health concerns in the U.S.A. (Kozak, DeFrances and Hall 2006, Lloyd-Jones et al. 2010). HF was the most common cause of hospitalization for patients over 65 years of age in 2009, accounting for more than 762,000 hospitalizations and $10.7 billion where HF was the principal Medicare diagnosis (Wier et al. 2011). The sheer volume of HF patients implies that they are exposed to the workings of the systems and processes of inpatient healthcare delivery on a scale larger than any other patient diagnostic group. Through the 1980's and 1990's there was an increase in the severity of heart failure with increase in number of invasive procedures and a decrease in hospital mortality (Polanczyk et al. 2000). As the American population ages, we can only expect this group to become an even larger proportion of our inpatients as patients survive to later ages with larger burdens of comorbidity.

With HF and AE being two of the largest public health concerns and the topics of many academic and lay publication, it is surprising that there is a void of literature at the interface. This research builds upon traditional epidemiologic clinical research and adds three new pieces of analysis to the existing body of patient safety research 1) epidemiology of AEs in HF patients with patient-

specific risk factors; 2) hazard of experiencing an AE from the patient's perspective; and 3) reliability of this institution's standard operating procedures and policies that serve as AE prevention measures.

Chapter 2

LITERATURE SURVEY

To Err is Human: In the years that have passed since the publication of the Institute of Medicine's To Err is Human report (Kohn, Corrigan and Donaldson 2000), health care organizations across the country have expended enormous energy and resources to improve the safety of health care delivery. However, there remains an ever-growing national concern regarding perceived less than ideal improvements in safety and quality of health care delivery since the release of this report (Longo et al. 2005, Wachter 2004, Berwick, Nolan and Whittington 2008). This report was based on data that already existed in the medical literature but had received little attention. For example, the Harvard Medical Practice Study reported an incidence of adverse events to be 3.7% of New York hospitalizations in 1984 (Brennan et al. 1991). The Colorado and Utah, Canadian, Greater London, and the Australian studies reported rates between 2.9 – 16.6% (Thomas et al. 2000, Wilson, Harrison and Gibberd 1999, Gawande, Thomas and Zinner 1999, Neale, Graham and Woloshynowych 2001, Baker et al. 2004). More recently, studies have reported AE rates as high as 27.7% (OIG 2010b, Landrigan et al. 2010). These studies were most often descriptive and reported basic frequencies of events, with only a few designed to determine risk factors of AEs. None of these studies evaluated the interactions of patient and health care delivery system factors as they contributed to not only the occurrence of the AEs, but also to the severity of iatrogenic illness that results.

Adverse event definition: The range of AEs occurring during hospitalizations varies widely as reported above. Explanations for the variable estimates include differences in methodology of AE detection and lack of consensus on definitions

and taxonomy. Yu and Nation (2005) found eight different definitions of AEs with three different functional meanings. From here forward, an AE is defined as an unanticipated illness or injury caused by medical evaluation and/or management rather than by the underlying disease or condition of the patient (Kohn, Corrigan and Donaldson 2000). Presence, or absence, of an error or distinction of preventability was not considered in this study.

Risk factors for adverse events: Both the patient and the health care delivery system can manifest risk for the occurrence of AEs. The elucidation of patient- and/or system-specific risk factors for an AE was the focus of several clinical studies. Some of these independently predictive risk factors (identified with regression or Cox proportional hazards analyses) for the occurrence of an AE during a hospitalization are listed in *Table 1.*

The majority of risk factors for AEs appear to be based on the patient's health or personal characteristics such as age. System-specific factors are infrequently studied. An example of the importance of understanding both aspects of this risk relates to unplanned hospital readmission for HF patients. Unplanned readmission to the hospital is considered a marker of diminished quality of care. If the readmission is a consequence of care delivered by the hospital, then it is also considered an AE. For HF patients, there are many patient-specific risks or causes of readmission. Some include compliance with medication and diet or multiple other comorbidities and lack of social support at home. However, from a system of care delivery perspective, failure of providers to document the delivery of the discharge education mandated by the Joint Commission on Accreditation and Healthcare Organizations is, in-and-of itself, associated with unplanned hospital readmission [68% of the patients studied

received all of the discharge instructions and had a significant decrease in number of hospital readmissions (p=0.003)] (VanSuch et al. 2006).

Heart failure and adverse events: The vast majority of inpatient AE research focuses on medication-related events and is performed in general medical and surgical populations. The wide range of disease, in these primarily tertiary care referral centers, makes it difficult, if not impossible, to account statistically for all of the possible confounding factors that may influence measurement and analysis of rates and outcomes of adverse events. There is a paucity of data in the literature regarding adverse events and their outcomes in more homogeneous populations, such as those admitted with the same diagnosis, which would eliminate a few of the concerns regarding confounding in the analysis.

Heart failure, accounting for the largest number of hospitalizations in a year for any single diagnosis (Kozak, DeFrances and Hall 2006), combined with its ranking as one of the most significant public health concerns, makes an excellent inpatient model on which to study AEs and their untoward effects with iatrogenic illness. In an Olmsted County epidemiology study 83.1% of patients were hospitalized during a mean (SD) period of 4.7 (3.9) years following their initial HF diagnosis (Dunlay et al. 2009). Medicare HF patients have a forty percent 90-day readmission rate following a discharge of a HF hospitalization (Krumholz et al. 1997). The incidence of HF is rising and these patients are surviving longer (Lloyd-Jones et al. 2010). The chronicity of this disease with need for recurrent hospitalizations exposes this aging and growing population to the problems of inpatient health care delivery at a larger scale than any other clinical subgroup of patients.

Table 1: Predictors of Adverse Events

Author (yr)	Type of Hospital Patient Population	Patient Demographic or Medical Morbidity Characteristics	Environment or Process of Care Characteristics
Hanlon et al. (2006)	Elderly medical patients	# medications warfarin benzodiazepines	
Pasarelli, Jacob-Filho and Figueras (2005)	Elderly medical patients	# diagnoses # medications	
Geraci et al. (1999)	Patients with COPD		Adherence to evidence based care on evaluation and treatment
Baker et al. (2004)	Medical and surgical patients	Age	
Petersen, Brennan and O'Neil (1994)	General medical	High APACHE II score Concomitant GI bleed	Resident cross coverage
Stelfox, Bates and Redelmeier (2003)	General medical		Illness requiring isolation for infection control
Brennan et al. (1991)	Medical and surgical patients	Age	
Thomas and Brennan (2000)	Medical patients	Age	

There is abundant HF clinical outcomes research; yet curiously, there is a marked paucity of information regarding AEs and iatrogenic illness during a hospitalization for HF. There were only three studies that specifically discussed AEs in this population.(Fanikos et al. 2007, VanSuch et al. 2006, Sztramko, Chau and Wong 2011).

Adverse event detection: In order to for a health care organization to learn about hazards in care delivery unintentionally endangering patients and employees, it is essential to identify health care delivery failures, or AEs. It is necessary to investigate inciting causes in order to mitigate future harm. However, identifying failures in SOPP in the care system that lead to adverse events is challenging and often not obvious. Very rarely is a SOPP failure a hard failure, e.g. resulting in a patient death, which would be easier to detect. As a result, there is a fair amount of research investigating and comparing methodologies for AE identification and classification (Murff et al. 2003, Yu and Nation 2005, Melton 2005).

All Joint Commission certified hospitals have AE or safety, reporting policies and processes for health care providers. The most common method utilized by hospitals is a voluntary reporting process (incident and prompted). Others utilize an involuntary (chart review, observers, patient interviews) or electronic data sources (single, multiple, rule-based alert logic, some using natural language processing); often in combination with the voluntary reporting systems.

Table 1: Predictors of Adverse Events

Author (yr)	Type of Hospital Patient Population	Patient Demographic or Medical Morbidity Characteristics	Environment or Process of Care Characteristics
Hanlon et al. (2006)	Elderly medical patients	# medications warfarin benzodiazepines	
Pasarelli, Jacob-Filho and Figueras (2005)	Elderly medical patients	# diagnoses # medications	
Geraci et al. (1999)	Patients with COPD		Adherence to evidence based care on evaluation and treatment
Baker et al. (2004)	Medical and surgical patients	Age	
Petersen, Brennan and O'Neil (1994)	General medical	High APACHE II score Concomitant GI bleed	Resident cross coverage
Stelfox, Bates and Redelmeier (2003)	General medical		Illness requiring isolation for infection control
Brennan et al. (1991)	Medical and surgical patients	Age	
Thomas and Brennan (2000)	Medical patients	Age	

Naessens et al. (2009) reported a comparison of three widely used detection methods (GTT, AHRQ's patient safety indicators (PSI), and voluntary reporting). The AHRQ's PSI are a set of adverse events defined by a computer algorithm run on administrative data sources using secondary diagnosis codes. They found that each of the different methods identified different types of events. The investigators determined that less than 10.5% of events identified through one method were detected with other methods (Naessens et al. 2009). So while chart review is considered the gold standard; it is labor intensive, introduces bias issues inherent in all retrospective studies, and potentially misses a significant amount of harm occurring during hospitalizations. Combination methods are likely to yield increased opportunities for organizational learning by increasing the yield of detection.

Active surveillance (concurrent to patients hospitalizations) using electronic triggers (laboratory findings or detection of use of certain predefined medications often associated with an adverse event) are increasing in use as technology and increased use of electronic medical records have advanced. Electronic surveillance for triggers without incorporation of logic-based rules limits the personnel needed for screening, but still requires clinical interpretation to determine if an adverse event occurred or if the clinical condition was an expected progression or course of illness (Szekendi, Sullivan and Bobb 2006). The addition of natural language processing to allow for incorporation of cues from clinical documentation increase the positive predictive value of the triggers reported (Melton 2005).

To be consistent with recently published research (OIG 2010a, OIG 2010b, Landrigan et al. 2010), the GTT was used to identify AE. This involved a

two-phased approach to chart review as previously used for the majority of the major AE studies (Leape et al. 1991, Thomas et al. 2000, Wilson, Harrison and Gibberd 1999, OIG 2010a, Landrigan et al. 2010, Naessens et al. 2010, Baker et al. 2004). One of the problems with relying on chart review for identification of the primary outcome is the variable clinical documentation in the record and varying rates of physician agreement regarding assessment of AE presence. The agreement reported in the literature has kappa statistics varying between 0.40 to 0.61 (Localio 1996, Thomas Lipsitz and Studdert 2002, Sharek et al. 2011). The GTT uses a two-phase approach, but since it requires two nurses for identification of triggers and does not require MD agreement, the inter-rater (nurses) reliability is higher (Naessens et al. 2010).

Reliability in Health Care Delivery: The discipline of reliability is not well defined in the process or service aspects of health care delivery, as compared to medical diagnostic equipment and durable goods. As an example, if dismissing a HF patient from the hospital were considered a process that should be reliably executed, than a 40% readmission rate for Medicare HF patients (Fonarow et al.1997) would be considered a highly unreliable process. Furthermore, if the goal is to improve the reliability of this process for HF patients, then documentation of an 80% improvement in this process by one hospital (Fonarow et al.1997) more than a decade ago, should have been adopted readily by all hospitals by now.

One key indicator of the lack of reliability of health care delivery is manifested in the tremendous variability in expenditures and outcomes for common diseases across the United States and world. The Commonwealth Fund Commission on the High Performance Health System and the Dartmouth

Atlas both published evidence painting U.S. health care delivery in less than a favorable light. The U.S. received a score of 64 out of 100 overall score from the Commonwealth Fund Commission in comparison to the best performing industrialized nations (McCarthy et al. 2011) In fact, the U.S. ranked last compared to the 16 other countries in regards to possibly preventable death. This is defined as mortality that could be avoided if chronic medical conditions (e.g. diabetes mellitus) were treated most effectively to yield outcomes similar to the best performing countries. This 2011 report estimates that up to 91,000 American lives could be saved if the American health system performed at the level of the leading country (McCarthy et al. 2011). In addition to international variation, the Dartmouth Atlas of Health Care reported that the hospitalization rate for HF varied significantly by state from 8.7 to 29.3 per 1,000 Medicare enrollees in 2007 (Dartmouth Atlas of Health Care 2012).

One interpretation for this wide variability in health care performance is a lack of reliability in the delivery of health care. In 2004, the Institute of Healthcare Improvement (IHI) released a whitepaper entitled “Improving the Reliability of Healthcare”. This report defined reliability principles in health care as the “methods of evaluating, calculating, and improving the overall reliability of a complex system” that will be required “to improve both safety and the rate at which a system consistently produces appropriate outcomes” (Nolan, Haraden and Griffin 2004). Their report was technically superficial and did not include the detailed quantitative and scientific aspects required for appropriate engineering study of the reliability of a product or service.

There is a paucity of information in the published literature regarding the translation of scientific reliability principles into health care environments. Yet,

there is some evidence of its application. Many health care systems view concepts of reliability through the lens of compliance with external rules and regulations. Although not defined by most health care systems as reliability of their processes, participants of IHI's 5 Million Lives Campaign were encouraged to adopt the concept of bundles for some higher risk areas of care provision (IHI 2012b). A bundle is a group of three to five evidence-based interventions or processes of care that are derived from the literature and all necessary to ensure the best possible outcomes for patients (IHI 2012a, Levy et al. 2004). These bundles, when implemented according to IHI's definitions, are considered to be in a binary state (success or failure) with a hard failure measurement – the bundle ceases to function as a synergistic set of interventions when even one aspect is not carried out. As a portion of this work, compliance measurements with the bundle implementation report time [days] between episodes of central line-associated blood stream infection or events per 1000 ventilator days – thus moving away from the patient as the unit of analysis and promoting a reliability metric of performance through time.

Pogorzelska et al. (2011) reported a key research finding regarding use of a ventilator bundle on rates of the hospital-acquired infection, ventilator associated pneumonia (VAP). Of 415 intensive care units in 250 hospitals, two-thirds reported adoption of a VAP-prevention bundle. Sixty-six percent of the ICU's had monitored the implementation of the bundle and only 39% reported high compliance. The primary outcome of this study (VAP) was reported in events per 1000 ventilator days and not by patient, which is the unit of analysis in most clinical research studies. They found that compliance with the bundle process was associated with a significant reduction in VAP ($\beta = -1.81$, $P < 0.01$).

While IHI defines evidence-based bundles as having a binary state function for the purposes of compliance measurement, the groups of standard operating policies and procedures have a more multi-state function in bedside application. For example, providers can be completely, partially compliant with infection control policies and procedures. The outcome of the policy then can be a soft failure – a partial loss of function. In this case, a patient may *not* become victim to the colitis that is spreading on the floor, but may obtain a urinary tract infection from an indwelling catheter that remained in too long.

Adverse events and reliability: Like the bundles promoted by IHI to improve outcomes, there are a number of standard operating policies and procedures (SOPP) that are ubiquitous across hospitals accredited by the Joint Commission. These SOPP standards are required to maintain hospital accreditation. The Joint Commission also has a set of published National Patient Safety Goals, which are measured, monitored and reported publically. The SOPPs set forth by the Joint Commission standards and goals include infection prevention, safe medication delivery, universal precautions for safe peri-procedural care, and injury and illness prevention (e.g. falls, skin tears, readmissions). Standard of care also dictates the following of safe medication indication and dosing guidelines published by the Food and Drug Administration. These SOPP are necessary to prevent injury to patients during their hospitalizations. The reliability of these SOPP for the prevention of AE during HF hospitalizations, or through time, is unknown.

Chapter 3

METHODOLOGY

Study design and setting: A retrospective cohort evaluation based on review of the clinical record and institutional administrative data sources was conducted at an academic, tertiary care medical center with two hospitals and 1,500 beds in Rochester, Minnesota. Prior to proceeding with any patient cohort identification or data collection, a study protocol was reviewed by the Mayo Clinic Institutional Review Board. This study was considered to be of minimal risk to participants and granted approval to proceed without direct patient contact. Only those patients who authorized the use of their medical records for research were considered eligible (Melton 1997).

Study participants: Patients discharged from the hospital with a primary diagnosis of HF from January 1, 2005 through December 31, 2007 were eligible for the study. Study participants were identified by searching the administrative data for the following Medicare diagnosis-related group (DRG) 127 (ICD-9) codes: acute HF (428.9); combined systolic and diastolic failure (428.40-428.43); non-specified heart failure (428.0); hypertensive heart disease with HF (402.91); systolic HF (428.20-428.23); diastolic HF (428.30-428.33); and rheumatic heart failure (396.30). Only those who met the Framingham Criteria for HF (McKee 1971) were included in the final patient cohort. When multiple hospitalizations occurred within the study period, only the first hospitalization was included in order to maintain statistical assumptions of independent observations in the analysis. Potential subjects were excluded from the study cohort if they had any one of the following: congenital heart disease, severe leukopenia (absolute neutrophil count less than 500 WBC/mm^3), active chemotherapy or radiation

therapy, an admission for palliative care, or a hospitalization less than 24 hours. In an effort to maintain, as much as possible, a homogeneous study population, we limited the study to medical portions of HF admissions. Those who later required major surgery as a portion of their hospitalization were censored on the day of surgery.

Study adverse event definitions: This study focused on AEs as opposed to errors. The Institute of Medicine (IOM) defines a medical error as "the failure to complete a planned action as intended or the use of a wrong plan to achieve an aim," whereas an AE is defined as "an injury caused by medical management rather than by the underlying disease or condition of the patient" (Kohn, Corrigan and Donaldson 2000). Adverse outcomes caused solely by the underlying disease or intended consequences of treatment were not considered AEs. AEs were categorized into one of 4 areas: infection, medication, patient care, or procedural. Medication events were screened using the Naranjo algorithm detailed in *Appendix B* (Naranjo, Busto and Sellers 1981). Severity of the events ranges from those with transient harm requiring incremental testing or treatment, to significant permanent harm, or death. Definitions and examples of these adverse event categories are detailed in *Table 2*.

Detection of Adverse Events: AEs were identified using a two-stage review, as reported in our prior work (Naessens et al. 2006). The Global Trigger Tool (GTT) (Resar et al. 2003; Rozich et al. 2003) was used to detect potential AEs during each patient's indexed HF hospitalization. The triggers are patient symptoms, laboratory findings, medications, or infections often associated with AEs. This trigger approach allowed the reviewer to focus only on those portions of the medical record where these data are found, thus decreasing the amount of time

reviewers spend evaluating a particular record. All nurse and physician GTT reviewers underwent formal training, and each reviewed medical records in a random order. A specifically designed, web-based, data-capture tool was used to facilitate uniform data collection and to streamline the independent reviewers' workflow, reconciliation process, and capture of all evaluations into a single source (Naessens et al. 2010). Two nurses, blinded to other reviews, independently reviewed each hospital record to identify triggers and record details of clinical care occurring near the time of the trigger.

The physician reviewers carefully reconciled nurses' findings with the medical record and made the final determinations regarding the presence and severity of an AE versus an expected course of care. The inter-rater reliability for nurses and between physician and nurse reviewers was previously reported as adequate within our institution (Naessens et al. 2009), and recently recounted by Landrigan et al. (2010) and Sharek et al. (2011). The process for determining presence or absence of an AE from the GTT is delineated in *Figure 1.*

The severity of AEs was classified according to the National Coordinating Council for Medication Error Reporting and Prevention (2001, NCC MERP) as outlined in *Table 3*. Events were included if they were classified as NCC MERP level E (temporary harm with documented patient symptoms or intervention) or higher.

Table 2: Definitions and examples of adverse event categories

Adverse Event	Definition
Infection	Presence of one or more positive cultures obtained at least 48 hours following admission in a clinically ill patient. If there is a possibility that the culture result is a contaminant, then the following criteria must be met in order for a nosocomial infection to be diagnosed: 1) presence of an intravascular catheter (for blood stream infections) or endotrachial tube (ventilator associated pneumonia) or presence of a urinary catheter (for urinary tract infections) or characteristic infiltrate on chest xray (for pneumonia); 2) initiation of antibiotics; and 3) any one or more of the following: chills, fever > 38.0 or < 36.0, or systolic BP < 90 mmHg. Example: Catheter associated urinary tract infection
Medication	Illness as an unintended consequence of medication prescription and/or administration of a medication. Causation will be assessed with the Naranjo algorithm (Appendix B) Example: Narcotic-induced respiratory failure
Patient care	Illness as a consequence of evaluation or treatment, including failure to recognize a serious illness that leads to temporary or permanent harm. Example: Fall
Procedural	Injury as an unintended consequence of a diagnostic or therapeutic procedure Example: Hematoma at intravenous catheter site

For instance, documentation of a fall with “no injury” recorded in the record did not meet the NCC MERP criteria for an E level harm and therefore was not included as an AE. Possible AEs with symptoms present at the time of admission were not included in this study. Detailed descriptions for each AE were collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic (Harris et al. 2009).

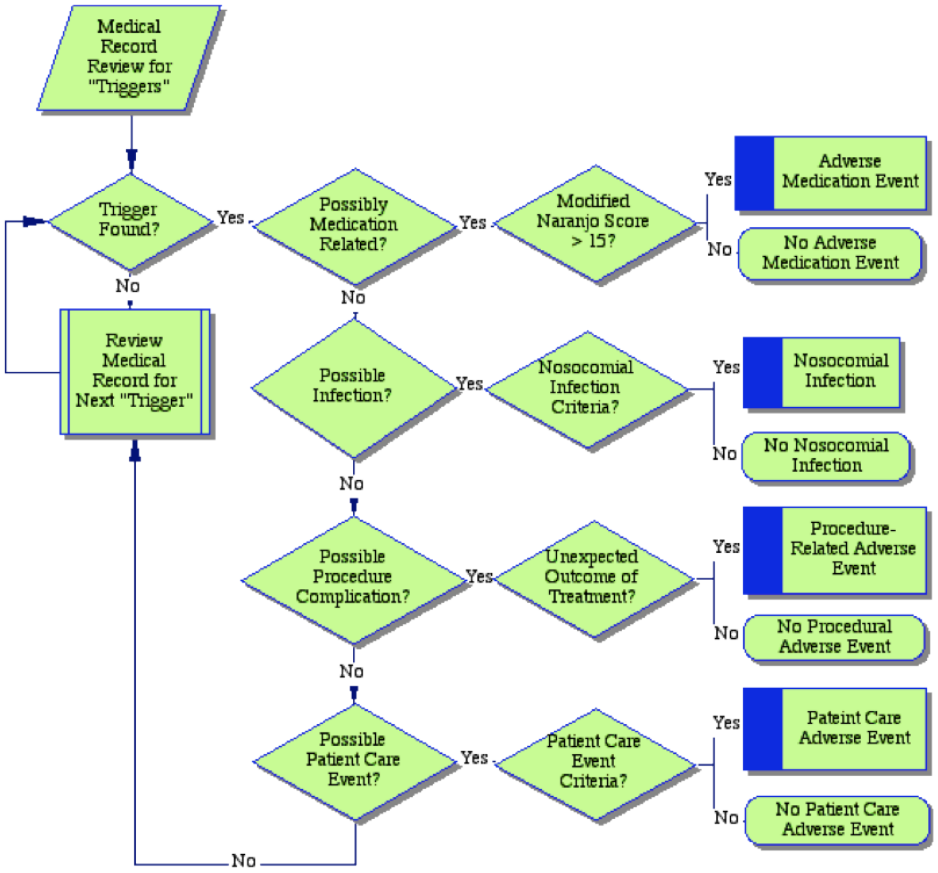


Figure 1: Process for determining presence of adverse event from clinical record

Table 3: **NCC MERP severity of adverse event definitions and examples**

Severity	Definition	Examples
D	Event/error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm	Fall with no documented injury
E	Event/error occurred that may have contributed to or resulted in temporary harm to the patient an required intervention	Catheter associated urinary tract infection
F	Event/error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization	Retroperitoneal hematoma in a patient with supratherapeutic anti-coagulation treatment
G	Event/error occurred that may have contributed to or resulted in permanent patient harm	Renal toxicity requiring ongoing hemodialysis
H	Event/error occurred that required intervention necessary to sustain life	Narcotic-induced respiratory failure requiring transfer to ICU
I	Event/error occurred that may have contributed to or resulted in the patient's death	Fatal pulmonary embolus in patient not receiving DVT prophylaxis

Reliability: Reliability is technically defined as "the probability that a product [or service] performs its intended function without failure under specific conditions for a specified period of time" (Yang 2007). There are several operational components to this definition that warrant clarification for this study: product or service, intended function, specific conditions, and specified period of time. The service and intended function in this study is the group of standard operating policies and procedures (SOPP) designed for the prevention of patient harm occurring as an unintended consequence of evaluation and treatment. The specific condition is a hospitalization for an episode of HF. The specified period of time is segmented by two differing perspectives: Model A) from the patient's perspective, the duration of a hospitalization for HF; Model B) from the hospital administration's perspective, all HF hospitalizations during the calendar years 2005 - 2007. Reliability will be assessed and analyzed from each of these perspectives. *Figure 2* depicts the 4 major categories of SOPP in hospitals. Each of the SOPP is considered independent shaped by relative evidence-based guidelines published by national trade organizations and governmental agencies. The AE resulting from failures of the individual SOPP are therefore independent as well. However, failure of a SOPP more than once during a single hospitalization for a single patient may not be an independent occurrence. Therefore, only the first failure of each individual SOPP is considered in the analyses where the patient is the unit of analysis.

For the purposes of this study, reliability will be considered to be a multi-state function. Complete or partial success of SOPP are both measurable outcomes. It is possible for some portions of a SOPP to fail while others continue functioning through time. For example, the standard of care for medication

selection may be met, but the initial dose selected may be too high for a patient's clinical condition and they suffer an adverse drug event. The reliability of each of the four main SOPP represented in this study (infection control, safe medication delivery, injury and illness prevention and universal precautions and safe practices for procedures) will be assessed as both mean time to failure as well as mean time between failures. The cumulative density function (cdf), F(*t*), and the hazard function, denoted h(*t*), will both be determined. The cumulative density function is defined as the probability that a component of the SOPP will fail, resulting in an AE, by time *t*. In the case of this study, time *t* has been selected to be both end of day one of hospitalization and day 4 (median duration of hospitalization for HF). The hazard function delineates the instantaneous failure rate for HF patients who have survived to a point in the hospital without already having an AE.

Definition of outcome (dependent) variables: The primary outcome variable for all of the analyses is time to failure. In this study, an AE is considered a failure of the SOPP to prevent harm during the HF hospitalization. Time to AE is evaluated from the two distinct perspectives illustrated in *Figure 3*. The first (Model A: patient perspective) uses the individual patient as the primary unit of analysis. Within Model A, there are two different types of analyses performed. The first evaluates possible patient-specific characteristics as risk factors for developing an AE during their HF hospitalization. The second group of analyses in Model A (patient perspective) evaluates to *first* AE, regardless of cause, and time to the *first* AE of each of the four types.

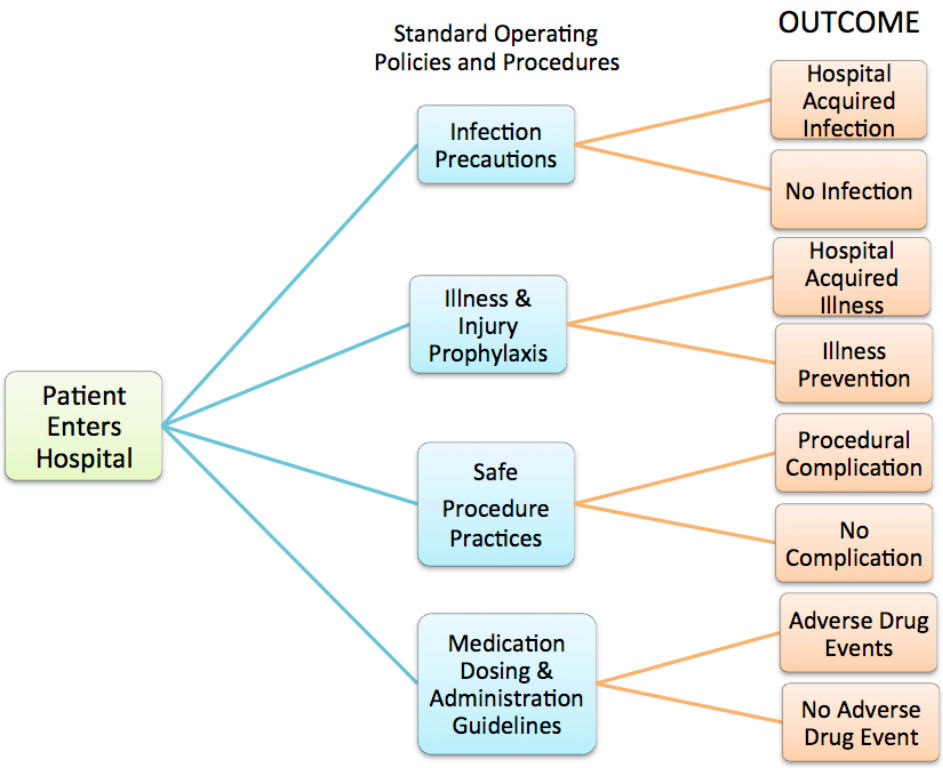
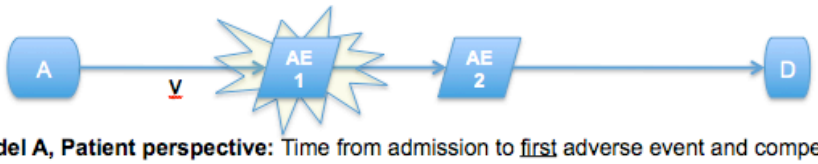


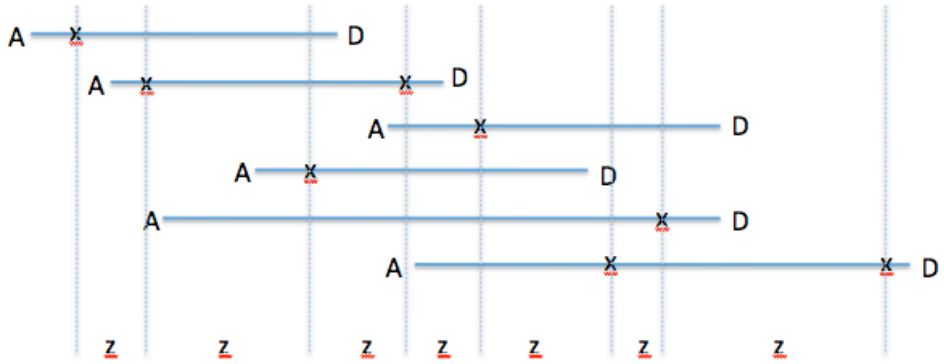
Figure 2: **Standard operating policies and procedures utilized in hospital health care delivery to prevent risk of adverse events secondary to failures of any of these processes**

These patient-level analyses view the risk of experiencing an AE from a patient's perspective as mean time to failure. Types of questions that could be answered from the patient-level analyses include the following: 1) Do I have any personal characteristics or comorbidities that increase my risk of having an AE? 2) What is the chance that I will have an AE given that I have been in the hospital for 4 days? 3) What is the cause of that AE likely to be? Knowing when the failure rate is highest for patients and what they are most likely to experience may help mitigate harm at the bedside for a particular patient by educating both care providers and the patients themselves of these vulnerabilities.

In the second approach (Model B: administration perspective) the reliability of each SOPP through time is the primary consideration. In this case, the time between failures of SOPP is investigated. The time between these failures is important for hospitals' administrations to understand if the work they are doing to improve safety is yielding expected results; thereby, increasing the failures. Examples of questions that could be answered from this system-level perspective include the following: 1) What is the hazard of failure of any, or all, of the SOPPs through time (2005-2007) for hospitalized population of HF patients? 2) What type of hazard were the hospitalized population of HF patients exposed to between 2005 and 2007? 3) What is the mean time between failures? Is the hospital performance improving or degrading through time?



Model A, Patient perspective: Time from admission to first adverse event and competing causes



Model B, Administration perspective, multiple patients through time: Time between all adverse events and competing causes
A: admission; D: discharge; x: AE; v: time to first AE; z: time between AE

Figure 3: Pictorial representation of time to event and competing cause analysis

Definition of patient-specific variables (independent covariates): Baseline characteristics were abstracted from the medical record and administrative data sources. Age, gender, social habits (tobacco or alcohol use), number of

admission medications, and documentation of comorbid medical conditions were taken from physician documentation in the clinical medical record. A patient's baseline status, or pre-hospitalization health is an important aspect of their inpatient health care experience. The severity of their illness, complexity of multiple chronic illnesses and abilities to independently care for themselves or move around in their room, dictates the intensity of treatments and hands-on care provided by hospital staff. Several categories of patient-specific variables (covariates) were included in the analysis. *Table 4* provides study definitions for each of the demographic and social covariates used in the statistical analyses. Functional status, a person's ability to independently perform their activities of daily living and ambulatory status are key components of overall health. Those who are dependent upon others for completion of their activities of daily living (bathing, dressing, eating, toileting or housekeeping) have a different hospital experience than those who are completely independent for their own cares. The covariates used to measure functional and ambulatory status are defined in *Table 5.* Another important measure of health is burden of chronic disease. The patient-specific chronic medical conditions utilized as covariates are listed in *Table 6* and defined in detail in the glossary. Medical treatments for these chronic conditions contain their own risks of side effects or AEs. The classes of medications patients were taking at the time of admission are listed in *Table 7* and were included as covariates in the model. Finally, some covariates required calculations to be performed from clinical data abstracted from the medical record. The definitions of these calculated covariates are detailed in *Table 8*. All of the covariates listed are time independent; therefore, are time-fixed and do not change through the hospitalization.

Table 4: Definitions of patient demographic and social covariates

Covariate	Definition
Age	Continuous variable of length of time in years from date of patient's birth to the date of admission to the hospital
Gender	Categorical variable of gender (male or female)
Residence	Categorical variable referring to the geographical location of patient's primary residence. Patients were considered local if they resided within 120-mile radius of Rochester, MN. Patients who lived beyond this distance were categorized as 'national'.
Marital status	Categorical variable indicating patient's marital status (married or not married)
Type of home	Categorical variable for type of living situation (home, assisted living or skilled nursing facility)
Tobacco use	Categorical variable of current tobacco use in any form: current, former or never
Alcohol use	Categorical variable of any amount of alcohol use
Transfer from another hospital	Categorical variable indicating if patient was hospitalized in a different hospital and transferred to one of the study's hospitals

Table 5: Definitions of functional and ambulatory status covariates

Covariate	Definition
Functional status	Five categorical variables indicating independence or dependence with each of the following activities of daily living: eating, bathing, dressing, toileting and housekeeping.
Ambulatory status	Five categorical variables indicating the degree of assistance required for basic movement or ambulation: walk completely independently, walk with assistance of a device (cane or walker), use of a wheelchair or motorized vehicle required in the home, assistance needed for any changes in position (standing to sitting, bed to chair, etc.), or completely bedridden.

Table 6: List of chronic diseases included as covariates

Atrial arrhythmia	Heart failure/Cardiomyopathy	Pacemaker/defibrillator
Autoimmune disease	Home CPAP	PUD/GI bleed
Cancer	Home oxygen	PVD
Cerebrovascular disease	Hyperlipidemia	Pulmonary embolus
Chronic kidney disease	Hypertension	Renal transplant
Coronary artery disease	Myocardial infarction	Severe aortic stenosis
Dementia	Obstructive sleep apnea	Ventricular arrhythmia
Depression	Osteoarthritis	Systolic/diastolic dysfunction

COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; PUD: peptic ulcer disease; GI: gastrointestinal; PVD: peripheral vascular disease. Comorbidity definitions are found in the glossary.

Table 7: List of medication classes Patients were taking at the time of admission

Allopurinol	Coumadin	Insulin
Amiodarone	Digoxin	Nitrates
ACE-I or ARB	Diuretic	NSAID
Aspirin	GI protection	Oral diabetes medication
Other antiplatelet	HMG-CoA reductase inhibitor	Potassium supplementation
Beta blocker	Hydralazine	Prednisone
Calcium channel blocker		

ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; NSAID: Nonsteroidal anti-inflammatory drug; Other antiplatelet: ticlopidine, clopidigrel, prasugrel, dipyridamole; Oral diabetes medications: sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, dipeptidyl peptidase IV inhibitors; GI protection: Histamine 2 receptor blocker or proton pump inhibitor. Definitions are found in the glossary.

Table 8: Definitions of patient-specific calculated covariates

Covariate	Definition and/or calculation
BMI	Body mass index = mass (kg) / (height(m))^2
Charlson (1987) Index	Weighted index of comorbidity. The score reflects the additive burden of chronic diseases and has been used in longitudinal and in-patient mortality prediction studies. (Binary data points summed to yield the score include history of the following: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease mild, diabetes, hemiplegia, renal disease moderate to severe, diabetes with end organ damage, any malignancy, leukemia, malignant lymphoma, liver disease moderate or severe, AIDS)
Inpatient Physiology Failure Score: IPFS (Gray 2002)	Weighted index of acute illness derived and validated as a mortality prediction tool in elderly medical patients, including patients with HF. Each of the 12 physiological measurements included were given a point value of 6, 4, 3, or 2 based upon the adjusted odds ratio of the variable's association with inpatient mortality. All measurements are taken within the first 48 hours of admission. These variables (point values assigned for abnormal results) include: level of consciousness* (6), highest bilirubin (4), O2 saturation* (4), highest blood urea nitrogen (4), lowest glucose (3), lowest albumin (3), lowest sodium (3), diastolic blood pressure* (3), highest white blood cell count (3), highest glucose (2), systolic blood pressure* (2), highest creatinine (2). Maximum raw score is 39 points. Higher values indicate elevated severity of acute illness at time of presentation to the hospital. [* only the first value recorded within 48 hours of admission]

Chapter 4

DATA ANALYSIS AND RESULTS

All data analyses were performed using JMP version 9.0.3 (SAS Institute Inc., Cary, North Carolina).

Adverse event descriptive analyses: Two different ratios were utilized to estimate rates of overall AEs: number of events per 100 patient discharges and number of events per 1000 patient days. AEs were categorized and reported in two ways: 1) by severity according to the NCC MERP; and 2) by type of AE (infection, medication, patient care or procedural). Pareto diagrams were created to visualize the distributions of categories and types of AE.

Patient perspective analyses: Four distinct analyses were performed to achieve a full patient perspective in this study. First was the descriptive analysis of the patients' general characteristics. Second, Cox proportional hazard analyses were performed between each patient-specific covariate and time to first adverse event. Third, the statistically significant patient-specific covariates from the bivariate Cox proportional hazard analyses were subjected to multivariable models. Finally, the timing of AEs was assessed in detail for all types. Hazard functions, including competing causes, were plotted for time to first AEs.

Study cohort characteristics: Baseline characteristics were presented as frequencies for categorical variables and means with standard deviations for continuous variables. These were also calculated for separately for those who had one or more AEs and those who did not have an AE.

Timing of adverse events and competing causes (patient's perspective): To determine timing of AEs from a patient's perspective, two histograms were plotted to show the count of AEs occurring on each day of the hospitalization

(day 1 equivalent to the first 24 hours following admission). Histograms were plotted by day of first AE and day of all AEs. Competing causes of first AEs were assessed through analysis of time to event distributions. These distributions for time from hospital admission to first AE were assessed by fitting 2 and 3 parameter (threshold) Weibull distributions along with lognormal and exponential distributions to the data. AICc, BIC, -2Loglikelihood values were used to determine the best fitting distribution by selecting the distribution with the lowest values for these parameters.

Information gleaned from the best fitting distributions were utilized to plot hazard functions (h(*t*)). The following were identified from the cumulative density function, F(*t*), and hazard function: fraction failing by the end of the first and fourth hospital day, and identification of peak periods of first-event risk. Since patients could have more than one type of AE during the course of their hospitalization, the mean cumulative function for AE recurrence was plotted (average number of events per patient versus time from hospital admission).

In the assessment of competing causes, an assumption is made that all events and the possible causes are independent of each other. However, to account for correlations within subject and within hospital, the standard variance estimate is replaced by a robust Wald test. In the case of ties in time between events or time to an AE, the Breslow likelihood approximation was used.

Patient-specific bivariate Cox proportional hazards analyses: Cox proportional hazards regression analyses were performed with each individual patient-specific covariate. The covariates tested in the bivariate comparisons are listed in *Tables 4, 5, 6, 7 and 8*. Time to first AE (of any cause) was the primary outcome variable. If no AE occurred, patients were censored at time of

discharge, death or transfer to the operating room for major surgery (changing the course of a typical HF hospitalization). Hazard ratios were calculated with their 90% and 95% confidence intervals (CI). Highly correlated covariates were identified and collapsed into single binary categorical variables to minimize potential collinearity. For example, three of the activities of daily living (ADL) with very similar bivariate outcomes (bathing, dressing and toileting) were collapsed into a single dichotomous variable "personal hygiene." Requiring assistance with any one or more of these ADL resulted in a value of requiring assistance with personal hygiene.

Patient-specific multivariable Cox proportional hazards analyses: Cox proportional hazard regression analyses were performed to determine the combination of patient characteristics that most completely explained variance in the relationship between patient-specific covariates and the occurrence of at least one AE during the hospitalization. Time to first AE (of any cause) was the primary outcome variable. If no AE occurred, patients were censored at time of discharge, death or transfer to the operating room for major surgery (changing the course of a typical HF hospitalization). Hazard ratios were calculated with their 95% CI. Six distinct models were built sequentially to reflect the clinician's typical initial history and physical exam approach to information acquisition at the time of patient admission. Only those covariates that were statistically significant within the 90% CI in the bivariate analyses were introduced into these multivariable models. Patient-specific covariates were introduced in the following order: Model 1) patient pre-hospital characteristics; Model 2) past medical history; Model 3) admission medications; Model 4) functional status; Model 5) social habits; and Model 6) severity of presenting illness. For each of the six

models, backward elimination was used to determine the best selection of covariates for a particular model. Age and gender were force fit throughout every model. Other covariates whose multivariate odds ratio 95% CI did not contain 1.0, either bivariately or as a portion of an interaction term, were removed from further model building. Statistically significant factors carried forward as fixed covariates for the subsequent model.

Administration perspective analysis: For the purposes of this analysis, the patient safety system at this hospital is the aggregate of all four SOPs – infection control, safe medication delivery, illness and injury prophylaxis and safe procedure practices. Development of an AE was considered a failure in the SOPPs in place to prevent harm to hospitalized patients. From a system perspective it is important for hospital leadership to understand failure rates through time given the amount of capital, time and monetary investment put into safety and quality performance.

SOPP failure modes were assumed to be independent. Time to all AEs and time between all AEs (as an aggregate and by type of SOPP) were assessed and fit to distributions for the time period of 2005 through 2007. Competing causes were assessed for time between specific SOPP failure modes. To account for correlations within subject and within hospital, the standard variance estimate is replaced by a robust Wald test. Patients were censored from the analysis at time of discharge, death or surgery. In the competing cause analysis, failures associated with one SOPP failure mode were also censoring times for the alternative SOPP failure modes. Information gathered from determination of best fit distributions was used to construct graphs of the hazard function (h(t)) and cumulative density function. Peak instantaneous

failure rates were assessed and fraction failing at 24 hours was determined. From prior analyses, it was anticipated that the Weibull distribution would best fit the time between SOPP failures (aggregate system and individual types). Given that the Weibull analysis ignores the actual order of failure times, a cumulative function of number of events and date of failure was also plotted.

Moving range statistical process control charts and analysis of variance tests were used to test the null hypothesis that there was no change in time between AEs of any SOPP failure mode through time.

Descriptive adverse event results: The final study cohort contained 1,722 patients. According to the definitions in Methods, harm occurred during 381 hospitalizations (22.1%; 95% CI, 20.2 to 24.1) among the 1722 HF patients. There were a total of 566 events over 8979 patient-days (63.0 per 1000 patient-days). Two hundred fifty-two (14.6%) patients experienced one event, while 89 (5.2%) experienced two events and 40 (2.3%) had 3 events or more during their hospitalization. The majority of AEs (59.5%) were NCC MERP severity level E (transient, temporary harm with patient symptoms related to the event specifically documented in the medical record). *Appendix D* outlines the types and frequencies of events identified during the two-phase medical record review. The majority of AEs were medication related (43.9%). The others were distributed amongst the event categories of hospital acquired infection (18.9%), patient care (26.3%), and procedurally related (10.9%). Pareto diagrams demonstrating the types of AE within each of these categories are illustrated in *Figures 4-7.*

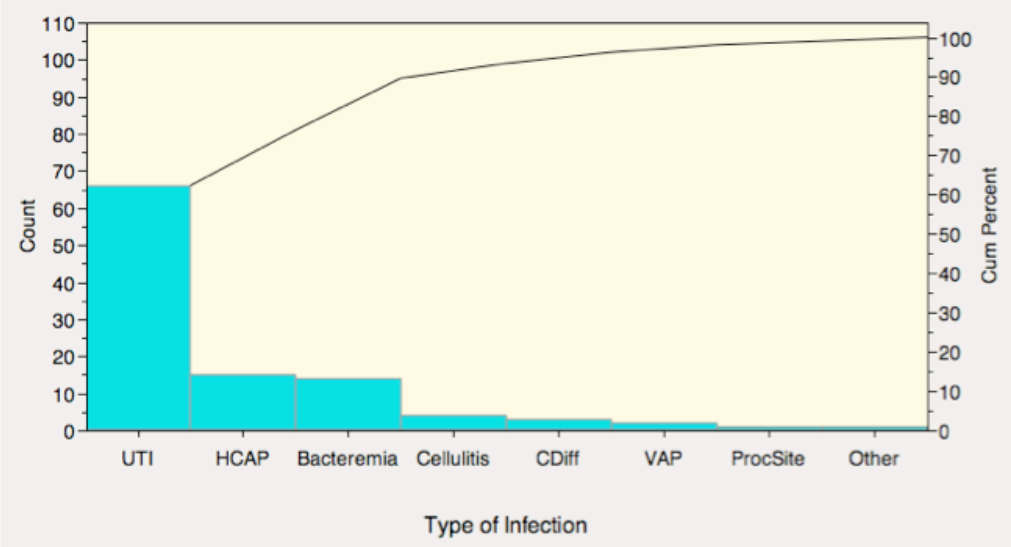


Figure 4: Pareto diagram: sub-types of hospital acquired infections

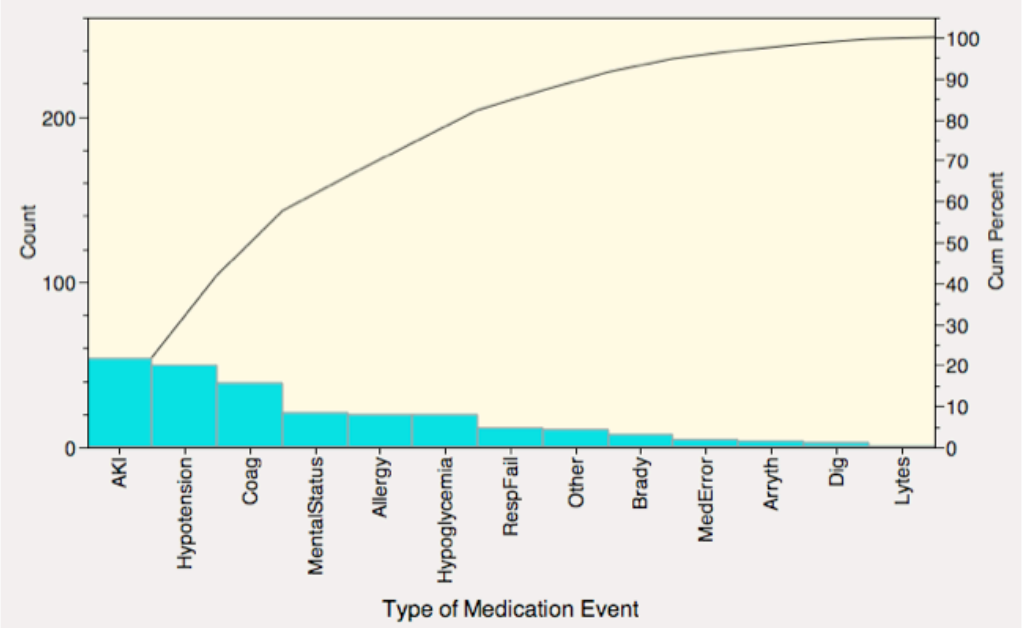


Figure 5: Pareto diagram: sub-types of medication adverse events

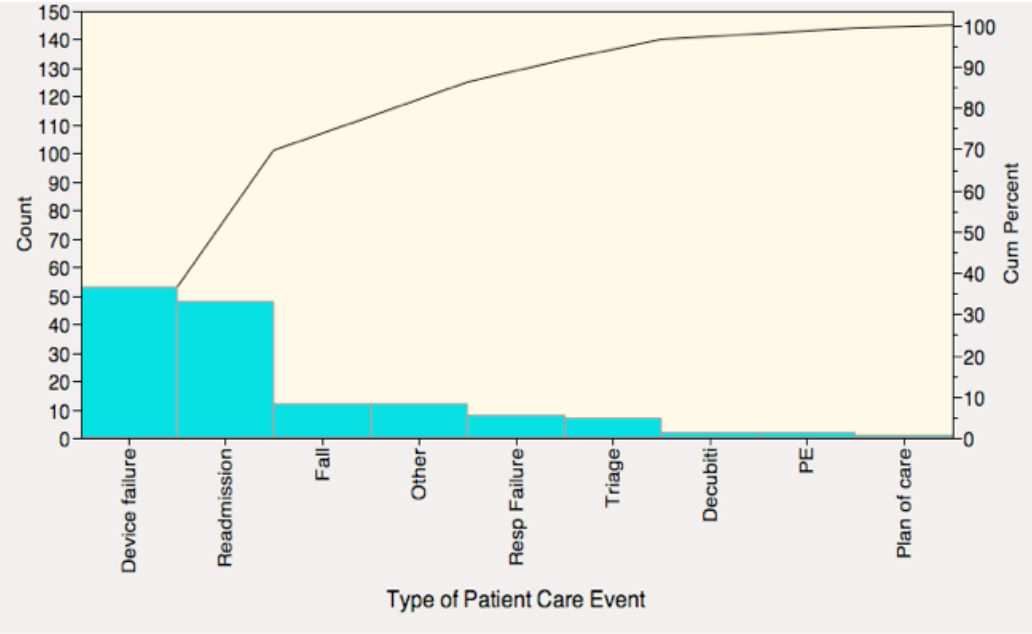


Figure 6: Pareto diagram: sub-types of patient care adverse events

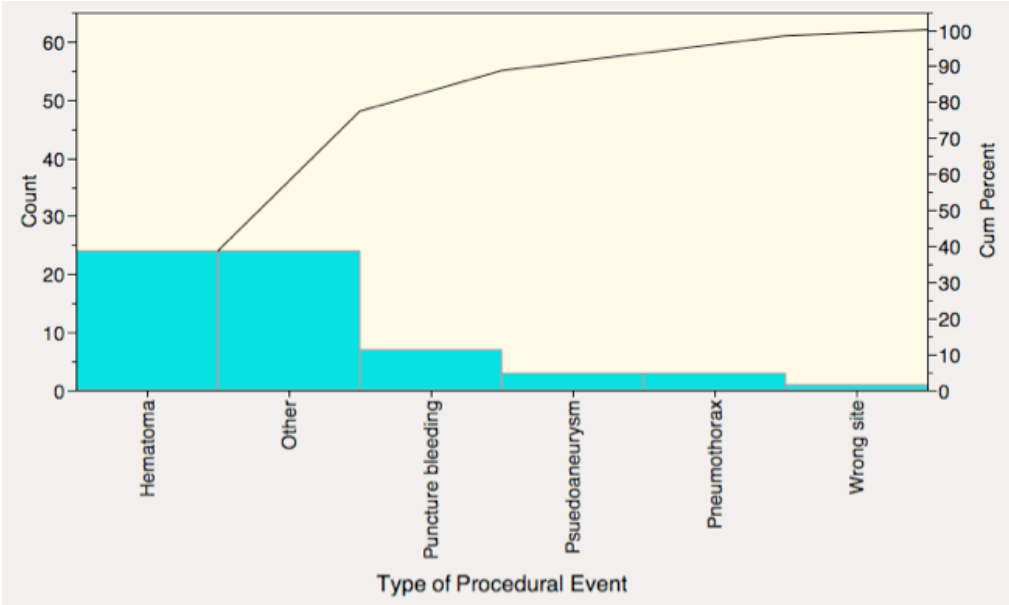


Figure 7: Pareto diagram: sub-types of hospital acquired infections

Patient perspective analysis results

Study cohort characteristics: Mean length of hospital stay was 5.2 ± 4.8 days with a median of 4.0 days. The mean age of patients was 75.7 ± 12.5 years; 96.3% were Caucasian; and 54.9% were male. Altogether, 26.4% were from the local community, while 29.9% lived within a 120-mile radius immediately outside of the local community and 43.7% were distant referrals. More than half of the patients were married (59.2%), and 84.7% lived at home. Patients were taking an average of 6.2 ± 3.2 prescribed medications at the time of admission. Their mean Charlson Index was 3.9, with an IPFS of 4.1 ± 3.7. No patients were admitted with a palliative care designation and 80% were self-designated as "full code." The ejection fraction distribution was bimodal, with a mean ejection fraction of 42.7± 18.6%. All of the univariate parameters assessed are delineated in *Tables 4 - 8*.

Timing of adverse events and competing causes (patient's perspective): Of those 381 patients who experienced one or more AEs during their HF hospitalization, 89 (23.4%) of them experienced their first AE during the first 24 hours of their hospitalization. *Figure* 8 is the histogram depicting the count of first AE by day of hospitalization. In contrast, *Figure 9* is the histogram illustrating the count of all 566 AE identified by day of hospitalization.

Competing causes were assessed with two sets of distribution curves for time from admission to AE by fitting 2 and 3 (threshold) parameter Weibull distributions along with lognormal, threshold lognormal and exponential distributions to the data: time to first AE only and time to all AEs.

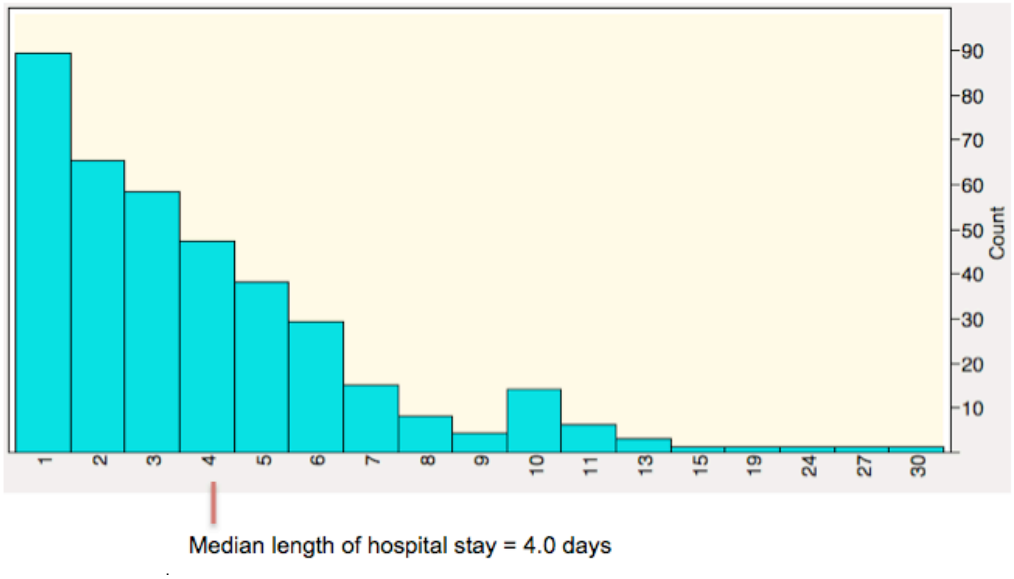


Figure 8: Count of first adverse event experienced by day of hospitalization (n=381)

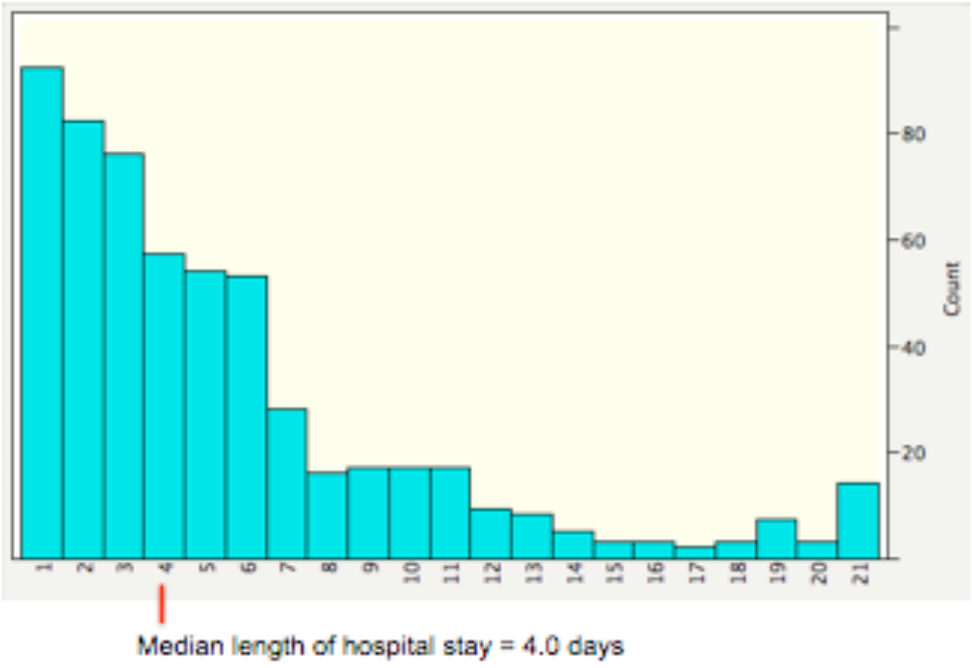


Figure 9: Count of all adverse events experienced by day of hospitalization (n=566)

The results for distribution of time from admission to first AE (Model A – patient perspective) for aggregate any-cause first AE with competing causes, including distribution paramenters, AICc, BIC, -2Loglikelihood values are displayed in aggregate in *Figure 10, Table 9* and detailed in *Appendix J.* The distribution results, when all AEs were treated as independent events, for time from admission to any and all AEs (for aggregate all cause AEs and competing causes), including distribution paramenters, AICc, BIC, -2Loglikelihood values are displayed in aggregate in *Figure 11, Table 10 and* detailed in *Appendix K.*

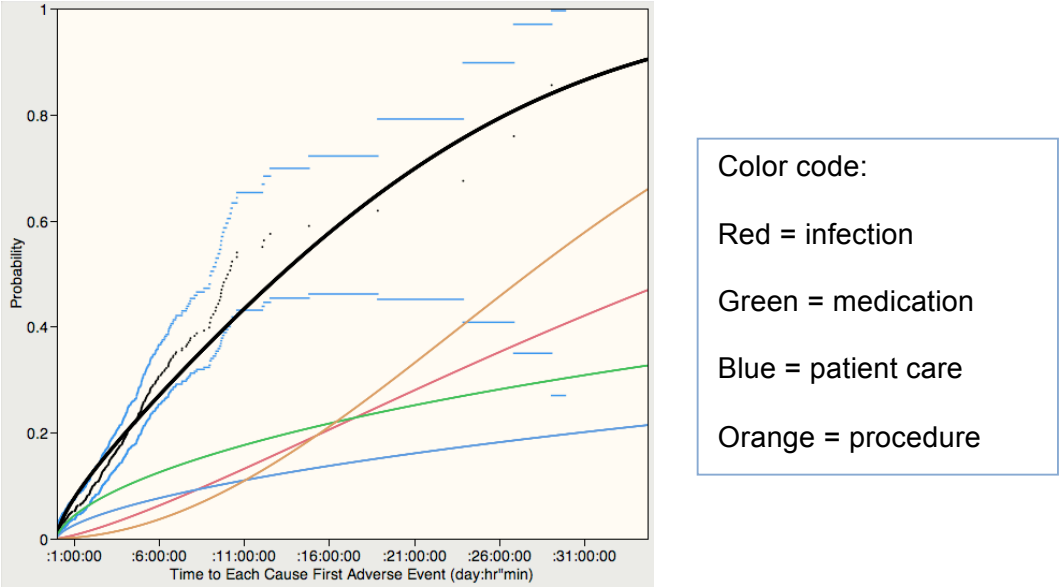


Figure 10: Distribution of time from admission to the absolute first SOPP failure per patient with competing causes

The results above, evaluated only the very first AE experienced by HF patients. However, as mentioned in the introduction, there are four key standard operating procedures or processes (SOPPs) intended to keep patients safe during their hospitalizations. Each of these SOPPs function independently of the others and

an adverse event is considered a failure of the respective SOPP. The following analysis evaluated the reliability of these SOPPs. If a patient had more than one AE within a single type of SOPP, only the first event was considered a failure (subsequent ones were removed from the analysis). As with the first AE, the evaluation of competing causes found a larger proportion of early failures in the medication and patient care SOPPs compared to patient care and procedural safe practice SOPPs. By 1.35 days, the instantaneous failure rate of a patient care event drops precipitously and becomes relatively constant ranging from 0.0000001 to 0.00000008 at 10 days for those remaining in the hospital.

Table 9: Patient's@ perspective of failures and hazard – absolute first SOPP failure experienced during HF hospitalization (only one SOPP failure counted per patient, n=381)

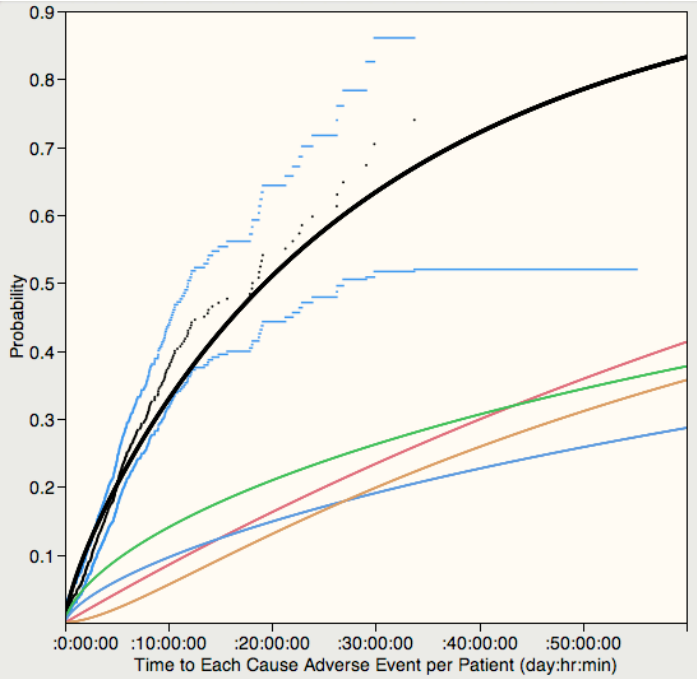
			Fraction Failing by end of hospital day:		Peak Hazard Rate	
Safe care process failures	Number of process failures	Best fitting distribution	1	4*	Instantaneous Hazard Rate	Time (days)
Aggregate	381	threshold Weibull^	0.06	0.17	0.02	0.02
Infection	71	threshold Weibull^	0.007	0.04	0.0000001	4.0*@
Medication	167	threshold Weibull^	0.04	0.10	0.03	0.02
Patient Care	99	threshold Weibull^	0.03	0.06	0.01	0.02
Procedural	44	threshold Weibull^	0.002	0.02	0.00000009	4.0*@

^ Threshold Weibull = 3 parameter Weibull

* Median length of hospital stay = 4 days

@ Arbitrary selection of time, instantaneous hazard rate increases steadily throughout hospitalization

For medication events, the instantaneous failure rate drops abruptly until approximately 1.9 days into the hospitalization. At this point, it too becomes relatively constant at a rate of 0.000002 to 0.0000001 at 10 days for those still hospitalized. Failures in infection precautions leading to hospital-acquired infections occur at a constant rate through a HF patient's hospitalization.



Color code:

Red = infection

Green = medication

Blue = patient care

Orange = procedure

Black = aggregate

Figure 11: Distribution of time from admission to the first SOPP failure of each type with competing causes

In *Figure 11*, HF patients can be represented in more than one line or specific type of process failure, but only once within each specific type. Likewise, in *Table 10*, patients can have more than one type of AE or SOPP failure, but only one of each type. They are therefore, represented in more than one row in the data table for a total of 485 events in this analysis.

Table 10: Patient's® perspective of failures and hazard in standard safe care processes – first SOPP failure of each type (n=485)

Safe care process failures	Number of process failures	Best fitting distribution	Fraction Failing by end of hospital day: 1	Fraction Failing by end of hospital day: 4*	Peak Hazard Rate: Instantaneous Hazard Rate	Peak Hazard Rate: Time (days)
Aggregate	485	threshold Weibull^	0.06	0.17	0.02	0.02
Infection	99	exponential	0.009	0.03	0.0000001	constant rate
Medication	200	threshold Weibull^	0.03	0.08	0.01	0.02
Patient Care	131	threshold Weibull^	0.02	0.05	0.003	0.02
Procedural	55	threshold Lognormal	0.002	0.02	0.0000001	18.0

^ Threshold Weibull = 3 parameter Weibull

* Median length of hospital stay = 4 days

Results of patient-specific risk factor analyses: Bivariate analysis identified several patient characteristics that differed between the patients who experienced at least one AE during the hospitalization and those who had no events (*Appendices C-H*). The patients who resided within the local county (HR 1.60, 95%CI 1.23-2.07) or within a 120-mile radius (HR 1.84, 95%CI 1.42-2.32) had a higher hazard of AEs. Some patient characteristics that seemed to have a protective effect were those who lived in their own home (HR 0.52, 95%CI 0.40-0.70), or walked independently (HR 0.24, 95%CI 0.12-0.57). However, the hazard of AE was higher for those who required help with ADL's, had a renal transplant (HR 2.72, 95%CI 1.23-5.11), or osteoarthritis (HR 1.48, 95%CI 1.18-1.85). Increased acuity of illness at time of presentation to the hospital as measured by the IPFS was also associated with an increased hazard of AEs (HR 2.66, 95%CI 1.66-4.22 over entire range of regressor).

The six successive models tested in the multivariable analysis are delineated in detail in *Appendix I*. Model 1 (pre-hospital characteristics) revealed increased hazard of AEs for residents of skilled nursing facilities (HR 1.75, 95%CI 1.26-2.37), unmarried women (HR 1.15, 95%CI 1.03-1.30) and those residing in southeastern Minnesota (HR 1.50, 95%CI 1.19-1.48). The hazards of AEs for these covariates decreased slightly, but maintained statistical significance, in Model 2 (past medical history). Histories of kidney transplant (HR 3.00, 95% CI 1.34-5.79) or osteoarthritis (HR 1.32, 95% CI 1.05-1.67) were the only chronic medical conditions that statistically added to the model. The Charlson Index was not associated with increased hazard of AEs. All tested covariates not reaching the 95% CI level were removed from the model. The next step was to add classes of medications to the remaining covariates (Model

3, admission medications). The hazard ratios and 95% CIs for home use of beta-blockers and calcium channel blockers were less than one, representing a protective effect. Whereas the hazard ratios and 95% CIs for home use of diuretics and allopurinol exceeded 1.0, indicating an increased hazard of AE. Only these four statistically significant medication classes were retained in the subsequent model functional status covariates were added (Model 4, functional status). Dependence upon others for activities of personal hygiene (bathing, toileting, dressing) demonstrated an increase in hazard for AEs; however, dependence on either a device or another person for ambulation did not statistically impact the model. However, the addition of personal hygiene associated ADLs (HR 1.63, 95%CI 1.25-2.11), caused pre-hospital residence in a nursing home to no longer be independently associated with increased hazard of an AEs (HR 1.15, 95%CI 0.79-1.67). Skilled nursing facility residence was therefore excluded as a covariate from further analysis. Introduction of use of tobacco or alcohol (Model 5, Social Habits) had no impact on the model and were not carried forward to subsequent models. Finally, in Model 6 (severity of illness) addition of severity of illness did not statistically modify the effect size for existing covariates carried forward from prior models; however, a higher degree of organ failure and physiological instability measured by the IPFS were associated with increased hazard of AE (HR 1.86, 95%CI 1.14-3.02). Systolic dysfunction was not associated with increased hazard of an AE in this multivariable analysis and was not carried forward to the final model.

Administration perspective reliability results:

The threshold (3 parameter) Weibull distribution was the best fit for the time between failures analysis through the period of the study (2005-2007). The parameters and criterion of this fit are shown in *Table 10.* The cumulative density function (CDF) is plotted in *Figure 12* with its associated hazard function (h(t)) plotted in *Figure 13*.

Table 11: Threshold Weibull distribution of time between failures of the aggregate standard operating policies and procedures for safe inpatient care

Parameters			Criterion		
Location	Scale	Other	AICc	-2Log-Likelihood	BIC
0.57	1.17	α : 1.78 β : 0.86 threshold: $-4.44x10^{-16}$	1839.57	1833.52	1852.54

The hazard function depicted in *Figure 13* shows an early peak followed by a very steep decent of the instantaneous failure rate in the first several hours. This was also the case for the competing SOP causes of failure, particularly for medication events. These hazard functions can be reviewed in *Appendices L-O*.

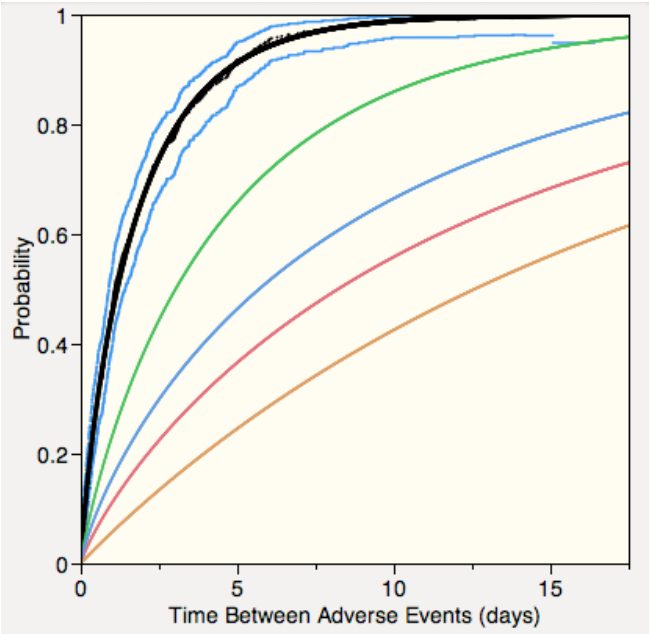


Figure 12: Threshold Weibull distribution of time between failures within the aggregate of standard operating procedures and policies with competing causes

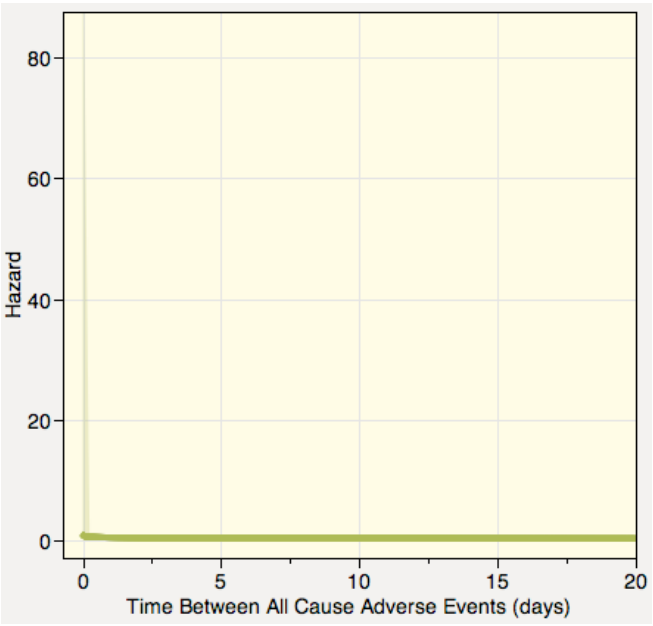


Figure 13: Hazard function (h(*t*)) for aggregate of standard operating policy and procedure failures

Since this analysis was performed using the Weibull distribution, the actual order of events was not taken into consideration – making it a nonrepairable system analysis by default. In order to ensure this was a proper assumption, the graph in *Figure 14* was plotted to assess the rate of the accumulation of adverse events through the period of the study. The approximate straight line indicates that the system is stable with a consistent rate of failure.

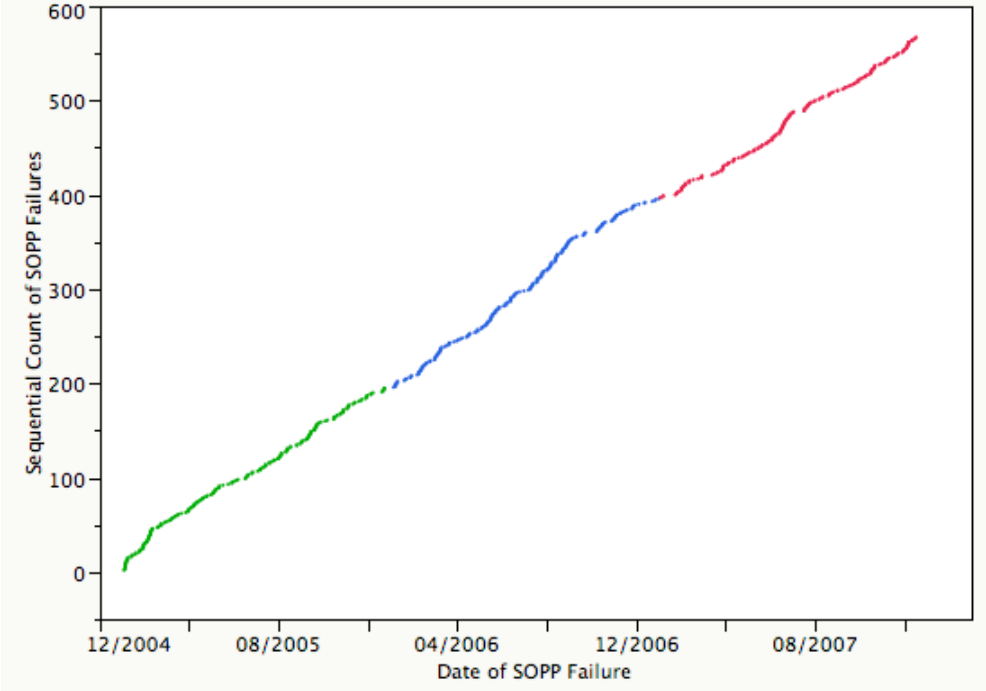


Figure 14: Cumulative failures of the aggregate of standard operating procedures and policies during the period of study (2005-2007)

[2005 green; 2006 blue; 2007 red]

This analytic approach to assess reliability of standard practices was repeated for each of the four types of SOPP being evaluated for safe care delivery to hospitalized HF patients. The details, including tables and figures, are delineated

in the appendices as follows: Appendix L – Infection control failures; Appendix M: Safe medication delivery failures; Appendix N: Prophylaxis against illness or injury failures; Appendix O: Safe procedural practice failures.

In all cases, the instantaneous failure rate was highest very early in the distribution with a fairly abrupt change in slope to nearly flat. From that point forward, the failure rate decreased gradually thereafter.

Table 12: Hazard of recurrent failure of the standard operating procedures and policies for safe inpatient care of HF patients during period of study (2005-2007)

SOP	Number process failures	Best fitting distribution	Fraction failing within one day of last failure	Peak Failure rate	
				Instantaneous Failure rate	Time (days)
Aggregate safe practices	566	Threshold Weibull	0.46	0.74	0.01
Infection	107	Weibull	0.48	0.009	0.01
Medication	248	Threshold Weibull	0.45	124.8	0.001
Patient Care	149	Weibull	0.13	0.24	0.01
Procedural	62	Weibull	0.07	0.08	0.1

SOP: standard operating procedures and processes

The respective time points (x-axis) that marked the significant change in hazard function slope were as follows: infection events, 0.23 days; medication events, 0.45 days; patient care events, 1.2 days; and procedural events, 3.1 days.

Analysis of variance was performed to test the hypothesis that there was no change in time between SOP failures (aggregate or any of the competing causes) when comparing the three study years (2005, 2006 and 2007). The results from this analysis, and those of each of the competing SOPP failure causes, are delineated in *Table 13.* The p-values for the probability of getting a higher F-value than the one calculated indicate that the null hypothesis that there was no difference between the years cannot be rejected.

Table 13: Power calculations and ANOVA results from test to determine if there was a change in time between SOP failures amongst the study years (2005, 2006 and 2007)

Event type	N	F ratio	prob > F	Current power (%) with alpha = 0.05	Least significant number needed for 80% power with alpha = 0.05
Aggregate	566	0.3779	0.6855	11.1	4490
Infection	107	1.7719	0.1751	36.4	184
Medication	248	1.6066	0.2027	33.8	466
Patient care	148	0.1781	0.8370	7.7	2493
Procedural	61	0.0002	0.9998	5.0	1108604

However, the results of the power calculation, also listed in *Table 13*, reveal that the analysis was tremendously underpowered to detect a difference. Therefore, nothing can be concluded from this analysis.

Given the power limitations of this ANOVA analysis, a moving range statistical process chart was used to assess presence, or absence, of changes in the time between SOPP failures through time (*Figure 15)*. This demonstrated no statistical change in mean time between SOPP failures when grouped by year of AE occurrence. There are several points above the upper control limit suggesting possible special cause variation at these points.

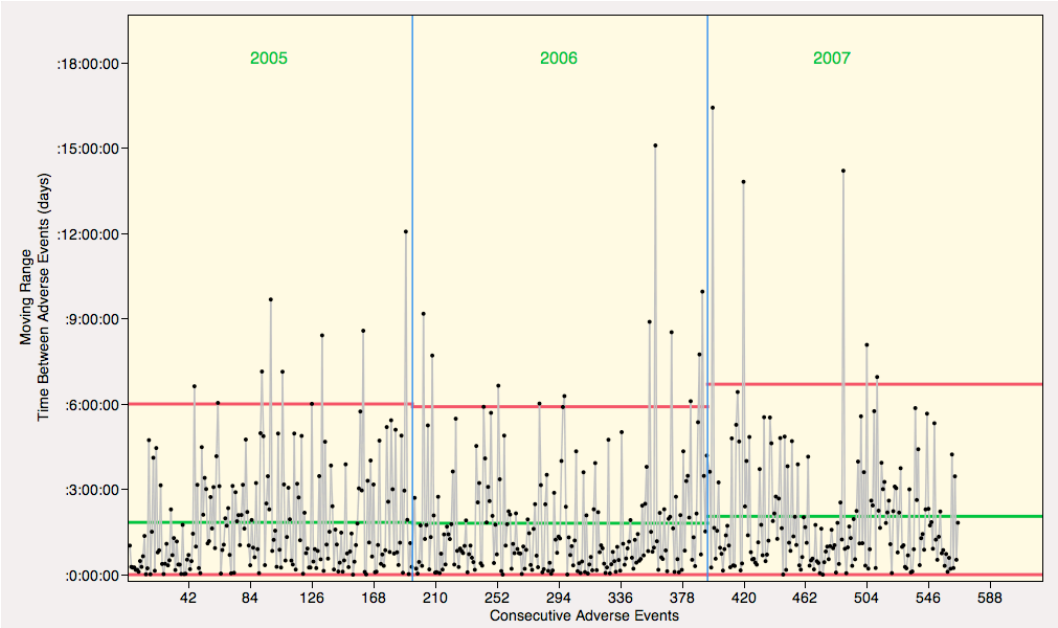


Figure 15: Moving range statistical process control of consecutive failures (aggregate of all types) in the standard operating procedures and policies for safe hospital care during the period of study by year (2005-2007)

Chapter 5

DISCUSSION

Patient-specific risk factors for adverse events: In this study of hospitalized HF patients, overall AEs were similar to aggregated hospital populations in ten North Carolina hospitals (Landrigan et al. 2010), three hospitals of a single academic institution in three different states (Naessens et al. 2009) and a national sample of Medicare beneficiaries (OIG 2010). Although these studies all utilized the IHI Global Trigger Tool to identify AEs, there are some distinct differences among them, as shown in *Table 14*.

Distributions of event types differ among the studies secondary both to study populations and to definitions or categorization of AEs. Specifically, our study was limited to adult medical HF hospitalizations (no major surgeries included), leading to a lower procedure-related AE rate. In addition, Landrigan's data included events that were present on admission (Landrigan et al. 2010) while ours and the other studies specifically excluded events that were present on admission.

To our knowledge, this is the first AE study to evaluate the interaction of gender and marital status in relationship to AE hazard. Unmarried women in this group of HF patients demonstrated increased odds of an AE, even after controlling for duration of risk exposure. We hypothesize that this increased risk could be due to less bedside patient advocacy given known differences in social support for these elderly women. Unmarried women have been reported to have higher mortality rates than unmarried men for some noncardiovascular diagnoses; however, whenever employment is taken into account, these differences are distinguished (Johnson et al. 2000). Marital status and gender

correlations as they relate to issues of patient safety have not been explored. Employment status was not included as a covariate in this study. Further research (including the disciplines and expertise of the social science and operations management fields) is needed to understand the implications of increased hazard amongst unmarried women.

Compared to other studies, we did not find the association of advanced age with hazard of AE (Thomas and Brennan 2000, Baker et al. 2004, Brennan et al. 1991). These other studies did not include residence in a nursing home as a covariate. This was a significant hazard for the patients in our study (pre-hospital residence in a nursing home). From our data, regardless of age, residing in a nursing home prior to admission carried a higher hazard than age alone. Nursing home residence remained a significant hazard until daily functional status was added.

This study indicates that personal hygiene-related ADLs independently increase the hazard of an AE, but dependence for mobility or eating does not. A combination of patients' abilities to participate in their care and the impact of ADL dependence on workload may explain some of this association since studies have shown that patients who have high participation in their care were half as likely to have an AE during a hospitalization (Brennan et al. 1991). Thus, the dependent patients in this study may have been less able to participate in their care, resulting in increased hazard of AE.

Table 14: Adverse event rate comparisons within recent GTT studies

	Naessens et al. (2009)	Current Study	Landrigan et al. (2010)	OIG (2010)
E or higher events per 100 admissions	27.0	22.1	20.7 without POA 25.1 with POA	27.0
(95% CI)	(24.4 – 29.7)	(20.2 – 24.1)	(23.1 – 27.2 with POA)	
E or higher events per 1000 patient days		63.0	56.5	69.3
F or higher events per 100 admissions	13.3	10.8		13.1
(95% CI)	(11.4 – 15.4)	(9.4 – 12.4)		(10.9 – 15.6)
F or higher events per 1000 patient days		25.5	32.9	28.0
Event Severity*:				
E	50.8%	59.6%	41.7%	50%
F or higher	49.2%	40.4%	58.3%	50%
Event Categories				
Infection		18.9%	14.8%	8.3%
Medication		43.9%	27.6%	37.4%
Patient Care		26.3%	11.6%	32.8%
Procedural		10.9%	31.6%	21.5%

For the providers, a patient care unit is a dynamic environment of evolving illnesses in patients with varying degrees of ADL dependence. Even among patients with similar degrees of acute illness severity, the day-to-day changes in patients' personal needs create significant differences in providers' work activities (Upenieks, Kotlerman and Akhavan 2007). It is unknown if the dynamic changes in work activities observed, while caring for patients with ADL dependencies, increase the number of interruptions or further divides care providers' attention, both factors known to increase the likelihood of errors for pharmacists and nurses (Holden et al. 2010, Flynn et al. 1999, Grasha and Schell 2001, Holden et al. 2011). Hurst reported that lower quality of care was associated with fluctuating workloads (Hurst 2005). Nurses bear the brunt of the daily needs required by our hospitalized patients; however, further research is required to understand the impact of patients' dependencies on a hospital's ability to deliver safe care.

Of all the past medical history comorbidities evaluated in the analyses, it is interesting that only presence of osteoarthritis and kidney transplant remained independently related to hazard of AE. The osteoarthritis is consistent with the need for assistance with personal hygiene ADL's because arthritis limits mobility and function by definition. However, history of kidney transplant is a unique finding. There were only 18 patients in this study who had received a kidney transplant. Eight of them (44.4%) experienced an AE. This remained an increased hazard for these patients even after introducing all medications, other comorbidities, social factors, code status and severity of illness into the model.

The most common adverse medication events experienced by this cohort of hospitalized HF patients were bradycardia and hypotension. These are the most prevalent side effects of medications commonly used in treatment of patients with HF. However, there was a protective effect (decreased hazard of AE) for those patients who were taking calcium channel and beta-blockers prior to admission to the hospital. This suggests that patients who were not used to the effects of these medications were vulnerable to treatment doses of these medications typically given for acute episodes of HF. This distinguishing feature of no prior use could be helpful to providers when determining the most appropriate dose to prescribe in the acute hospital setting. It suggests that a titration approach (starting with smaller doses and gradually increasing as physiologic tolerance allows) would be safer for acutely hospitalized HF patients. Of typical HF medication regimens, only prior use of diuretics carried an increased hazard of AE. One unexpected home medication that was related to an increased hazard of AE was allopurinol, even after accounting for comorbidities and functional status. This medication is used to decrease frequency of gout recurrence.

Patient's perspective of adverse event hazard: To our knowledge, this is the first study to demonstrate instantaneous failure rates (h(t)) and the cumulative distribution function (F(t)) of AEs from a hospitalized HF patient's perspective. In the competing cause analysis, the distributions of time from admission to the first SOPP failure of any cause and the first SOPP failure of each type were plotted and assessed. In both cases patients were more likely to experience medication, then patient care-related AE during the first 4 days of hospitalization (median length of hospital stay was 4.0 days). In assessing the competing cause

distributions of mean time from admission to the absolute first SOPP failure, the three-parameter Weibull distribution was the best fitting distribution for infections, medication events and patient care events. However, if the first SOPP failure was a procedural event, then the threshold lognormal distribution was the best fit. Both medication and patient care AEs revealed very early failure periods with rapid descents to a constant random failure rate. For medications SOPP failures, the transition to a constant rate occurs prior to the end of the first day of hospitalization. This indicates that the highest hazard for a medication event to be the cause of the first SOPP failure occurs during presentation to the hospital when providers are the most aggressive regarding the treatment of acute symptoms. On the other hand, the hazard of infections as the cause of the first AE (three-parameter Weibull distribution $\beta=1.3$) increases with time and the failure rate of procedural events being the cause of the first AE (three-parameter Weibull distribution $\beta=1.99$) increases linearly with time. The latter, with a β parameter approximately equal to 2 could be referred to as a Rayleigh distribution. (Elsayed 1996) This distribution is most commonly seen with traditional mechanical components in non-healthcare related industry (Yang 2007).

The instantaneous failure rates for two relevant periods of time in the hospital for patients (end of first day and day of median length of stay) were summarized in *Tables 9 and 10*. There was only one other study in the medical literature that discussed harm as a function of hospital day (Hauck 2011). The investigative team used an econometric approach and identified a risk of 5.5% for a medication event, 3.5% for decubitus ulcers and 17.6% for hospital acquired infections over the course of the hospitalization. These numbers are significantly

different from this study likely secondary to both analytic methodology and definitions of AE. They utilized ICD10 administrative codes to identify their AE and did not perform any degree of clinical record review. Their methodology also did not allow them to perform a time-dependent analysis as they did not have dates and times of the AE. So their report of an additional risk of 0.5% per additional night in the hospital for a medication AE does not take into account the time to event statistical distributions reported in our research. For example, our analysis shows that the instantaneous hazard of medication AE drops precipitously in the first 24 hours and becomes constant and very low at this point. The rate is not the same the first night compared to all of the others.

Limitations: Referral bias is a concern when interpreting clinical study results from academic medical centers. Studies have demonstrated that clinical outcomes can differ depending on patients' distance from the health care institution and therefore need for primary or tertiary level care (Seferian et al. 2008, Kokmen et al. 1996, Ballard et al. 1994). Covariates were introduced to assess for geographical distance from our institution's hospital out of concern that AE rates may be inflated by referral or selection bias. The results were counter to this traditional view of referral bias. Indeed, the hazard of an AE occurrence was higher for those who resided within the 120-mile radius of the hospital, compared to those who lived beyond that distance. This is counter intuitive and was present even with severity of illness, comorbidities and functional status in the Cox model. The numerical values of the hazard ratios were compared before and after the addition of the geographic covariate. The presence of this possible reverse-referral bias did not meaningfully alter the

performance of any other patient-specific covariate in the Cox regression model, as the hazard ratios remained largely unchanged.

This study has many weaknesses and limitations. AEs related to a hospitalization may only become evident after the patient is dismissed from this hospital. AE can be accurately identified with post-hospitalization surveys (Weissman and Schneider 2008); but we did not employ this methodology and may therefore have underestimated the number of events occurring during the hospitalization. The only post-discharge discoveries of AEs possibly detectable in this study were those necessitating an emergency department visit or rehospitalization. These unplanned readmissions and visits to the emergency department within 30 days of discharge from the index hospitalization are triggers in the GTT.

Another limitation of this study is the questionable reliability of AE identification through the use of a retrospective medical record review. The use of the GTT methodology requires interpretation by providers not involved in the care. It also requires judgments to be made about care not fully documented in the medical record. We attempted to adjust for this inherent measurement bias by using objective definitions for dependent variables, minimizing interpretation required for identification of an event. The nurses and physician reviewers were consistent throughout the study. The triggers were used to stimulate a focal in-depth review for documented events and we utilized multiple blinded reviewers with a software tool that guided reconciliation of differences of reviewers' opinions. Both a local study (Naessens et al. 2010) and Landrigan et al. (2010) found the GTT to have adequate inter-rater reliability.

There are two other challenges leading to possible under-identification of AEs. Naessens et al. (2009) published evidence that the GTT does not identify all AE. There were events voluntarily reported by staff and others identified with the AHRQ's PSI algorithm that were not discovered by the GTT. One possible cause is that the GTT triggers identify AEs that occur as a result of acts of commission (e.g. hypotension developing after a medication is delivered or infection from a urinary catheter inserted). Events related to acts of omission (e.g. inadequate antimicrobial coverage for a health care acquired infection or delayed recognition of acute physiological deterioration and delayed intervention) may not be readily identified through the GTT methodology. One other factor that may have caused us to underestimate the number of events was the strict adherence to the study definition of AEs. In order for an event to be considered an AE, there had to be written documentation of patient symptoms. For example, if there were two patients with the same level of hypoglycemia following insulin dosing, but only one had documented symptoms, then only this one would be considered an AE.

The use of the GTT poses another significant definition of AE challenge for study interpretation. The study defined presence or absence of AE by patient symptoms; hence, the time of the AE in this study is the time of the clinical manifestation of the SOPP failure, not the actual inciting event itself. This has little bearing on the time-fixed, patient-specific characteristics used in this research. However, future investigations evaluating the timing of clinical care interventions with the AE will require adjustment of the time of event so as to not confuse statistical relationships. As an example, suppose an infectious AE, identified by patient symptoms, is timed to have occurred in the data set 2 hours

after transfer to an ICU. Assignment of the responsibility of this infectious AE to the ICU would be clinically suspect. It takes hours, or maybe even days, for symptoms to develop after infectious agent is introduced. Therefore, for this scenario, it is likely that the infection was acquired prior to transfer to the ICU. The interpretation for the clinical practice is significantly different: the patient was transferred to the ICU because of a hospital-acquired infection versus the patient obtained a hospital-acquired infection in the ICU.

Another serious limitation of this study is lack of generalizability of results given the primarily Caucasian population. African Americans have been shown to have both a higher incidence of HF (Bahrami et al. 2008, Lloyd-Jones et al. 2010) and AEs. (Brennan 1991a, Brennan 1991b, Chang et al. 2005) It is unclear if racial disparity is an issue in these HF patients, as this study did not have the power to detect differences in this covariate.

Summary: Hospitalized HF patients in this study cohort were more likely to experience failures in the SOPP for safe medication delivery and illness or injury prevention (patient care events) in the first week of hospitalization (median length of stay is 4.0 days). The hazard functions (h(*t*)) for AEs in both of these SOPP followed three-parameter Weibull distributions and had early failure periods with precipitous drops in instantaneous failure rate within the first 24 hours of hospitalization. AEs resulting from failures in the infection control and universal precautions for safe procedural SOPP occur relatively later with a failure rate that increases with time.

From the hospital administration's perspective, time between aggregate all-SOPP failures, or of the individual SOPP types, did not change through the three-year period of this study. The study was not powered to assess

performance differences between years using analysis of variance. Utilizing a moving range statistical process control chart, there were some possible points of special cause variation with an elevated number of days between failures. Investigation into these time periods may yield some insight into possible circumstances or factors that increase reliability of SOPP performance. However, retrospective evaluation of the hospital environment between 2005-2007 would likely prove difficult and effort may be better expended with more real-time monitoring.

Within the HF study cohort, several patient-specific characteristics were found to be associated with increased hazard of an inpatient AEs: history of osteoarthritis or kidney transplant, use of allopurinol, the need for assistance with personal hygiene-related ADL's, and higher severity of acute illness measured by the IPFS. These particular comorbidity and functional status findings are new findings for the medical literature. Marital status modulated the risk of AEs for women; with a significant increase in hazard for unmarried women. This, too, is a new finding. In an exploratory analysis, we created a logistic regression model for risks of one or more AEs using the statistically independent covariates from this analysis. Prior to controlling for length of hospital stay, less than 8% of the model variance is explained with patient-specific factors. After length of stay was introduced into the model, the R-squared was still only approximately 22% with an area under the curve (AUC) of 0.809. Important determinants of risk remain to be identified. There is a significant amount of research that must occur to identify our health care system's vulnerabilities and define interventions to meaningfully mitigate future AEs.

Conclusion: Health care standard operating policies and procedures for prevention on inpatient harm do not function at the high levels of reliability expected in other industries. Operations research is needed to elucidate constellations of health care delivery system factors increasing the risks of AEs. Only then, will we be able to define specific interventions to mitigate harm and meaningfully improve the reliability of hospital care delivery in the United States.

REFERENCES

Bahrami, Hossein, David A. Bluemke, Richard Kronmal, Alain G. Bertoni, Donald M. Lloyd-Jones, Eyal Shahar, Moyses Szklo, and Joao A. Lima. 2008. "Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study." *Journal of the American College of Cardiology* 51(18):1775-83. doi:10.1016/j.jacc.2007.12.048.

Baker, G. Ross, Peter G. Norton, Virginia Flintoft, Régis Blais, Adalsteinn Brown, Jafna Cox, Ed Etchells, William A. Ghali, Philip Hébert, Sumit R. Majumdar, Maeve O'Beirne, Luz Palacios-Derflingher, Robert J. Reid, Sam Sheps, and Robyn Tamblyn. 2004. "The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada." *Canadian Medical Association Journal* 170(11):1678-1686. doi: 10.1053/cmaj.1040498.

Ballard, David J., Sandra C. Bryant, Peter C. O'Brien, David W. Smith, Michael B. Pine, and Denis A. Cortese. 1994. "Referral selection bias in the Medicare hospital mortality prediction model: are centers of referral for Medicare beneficiaries necessarily centers of excellence?" *Health Services Research* 28(6):771-84.

Bates, David W, Nathan Spell, David J Cullen, and Elisabeth Burdick. 1997. "The costs of adverse drug events in hospitalized patients." *Journal of the American Medical Association* 277(4):307-311. doi: 10.1001/jama.1997.03540280045032

Berwick, Donald M., Thomas W. Nolan and John Whittington. 2008. "The Triple Aim: Care, Health, And Cost." *Health Affairs,* 3(27):759-769 doi: 10.1377/hlthaff.27.3.759

Brennan, Troyen. A., Liesi E. Hebert, Nan M. Laird, Ann Lawthers, K. E. Thorpe, Lucian L. Leape, A. Russell Localio, S. R. Lipsitz, Joseph P. Newhouse, and Paul C. Weiler. 1991a. "Hospital characteristics associated with adverse events and substandard care." *Journal of the American Medical Association* 265(24):3265-9.

Brennan, Troyen A., Lucian L. Leape, Nan M. Laird, Liesi Hebert, A. Russell Localio, Ann G. Lawthers, Joseph P. Newhouse, Paul C. Weiler, and Howard H. Hiatt. 1991b. "Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I." *New England Journal of Medicine* 324(6):370-6. doi: 10.1056/NEJM199102073240604.

Chang, Andrew, Paul M. Schyve, R. J. Croteau, D. S. O'Leary, and J. M. Loeb. 2005. "The JCAHO patient safety event taxonomy: a standardized

terminology and classification schema for near misses and adverse events." *International Journal for Quality in Health Care* 17 (2):95-105. doi: mzi021 [pii] 10.1093/intqhc/mzi021.

Charlson, Mary E., Peter Pompei, Kathy L. Ales, and C. Ronald MacKenzie. 1987. "A new method of classifying prognostic comorbidity in longitudinal studies: development and validation." *Journal of Chronic Diseases* 40(5):373-83.

Dartmouth Atlas of Health Care. 2012. "Discharges for Ambulatory Care-Sensitive Conditions per 1,000 Medicare Enrollees, by Gender and Condition." Accessed March 27, 2012. http://www.dartmouthatlas.org/data/table.aspx?ind=61&tf=10&ch=32,117&loc=2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52&loct=2&fmt=86

Dunlay, Shannon M, Margaret M Redfield, Susan A Weston, Terry M Therneau, Kirsten Hall Long, Nilay D Shah, and Véronique L Roger. 2009. "Hospitalizations after heart failure diagnosis a community perspective." *Journal of the American College of Cardiology* 54(18):1695-1702. doi: 10.1016/j.jacc.2009.08.019.

Fanikos, John, Jennifer Cina, Steven Baroletti, Karen Fiumara, Lina Matta, and Samuel Goldhaber. 2007. "Adverse Drug Events in Hospitalized Cardiac Patients." *The American Journal of Cardiology* 100(9):1465-1469. doi:10.1016/j.amjcard.2007.06.041.

Flynn, Elizabeth A., Kenneth N. Barker, J. Tyrone Gibson, Robert E. Pearson, Bruce A. Berger, and Leo A. Smith. 1999. "Impact of interruptions and distractions on dispensing errors in an ambulatory care pharmacy." *American Journal of Health-System Pharmacy* 56(13):1319-25.

Fonarow, Gregg, Lynne Stevenson, Julie Walden, Nancy Livingston, Anthony Steimle, Michele Hamilton, Jaime Moriguchi, Jan Tillisch, Mary Woo. 1997. "Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure." *Journal of the American College of Cardilogy* 3(30):725-732.

Forster, Alan J, Kwadwo Kyeremanteng, Jon Hooper, Kaveh G Shojania, and Carl van Walraven. 2008. "The impact of adverse events in the intensive care unit on hospital mortality and length of stay." *BMC Health Services Research* 8(1):259-266. doi: 10.1186/1472-6963-8-259.

Gawande, Atul A., Eric J. Thomas, and Michael J. Zinner. 1999. "The incidence and nature of surgical adverse events in Colorado and Utah in 1992." *Surgery*.

Geraci, Jane, CarolAshton, David Keykendall, Michael Johnson, Julianne Souchek, Deborah del Junco, and Nelda Wray. 1999. "The association of quality of care and occurrence of in-hospital, teatment-related complications." *Medical Care* 37 (2):140-48.

Grasha, Anthony F., and Kraig Schell. 2001. "Psychosocial factors, workload, and human error in a simulated pharmacy dispensing task." *Perceptual and motor skills* 92(1):53-71.

Gray, Lawrence K., Kathleen A. Smyth, Robert M. Palmer, Xiaofeng Zhu, and Jane M. Callahan. 2002. "Heterogeneity in older people: examining physiologic failure, age, and comorbidity." *Journal of the American Geriatrics Society* 50 (12):1955-61. doi: jgs50606 [pii].

Hanlon, Joseph T, Carl F Pieper, Emily Hajjar, Richard Sloane, Catherine Lindblad, Christine Ruby and Kenneth Schmader. 2006. "Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay." *Journals of Gerontology Series A:Biological Sciences and Medical Sciences* 61(5):511-515.

Harris, Paul A., Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, and Jose G. Conde. 2009. "Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support." *Journal of Biomedical Informatics* 42 (2):377-381. doi: DOI 10.1016/j.jbi.2008.08.010.

Holden, Richard J., Neal R. Patel, Matthew C. Scanlon, Theresa M. Shalaby, Judi M. Arnold, and Ben-Tzion Karsh. 2010. "Effects of mental demands during dispensing on perceived medication safety and employee well-being: a study of workload in pediatric hospital pharmacies." *Research in Social & Administrative Pharmacy* 6 (4):293-306. doi: 10.1016/j.sapharm.2009.10.001.

Holden, Richard J., Matthew C. Scanlon, Neal R. Patel, Rainu Kaushal, Kamisha H. Escoto, Roger L. Brown, Samuel J. Alper, Judi M. Arnold, Theresa M. Shalaby, Kathleen Murkowski, and Ben-Tzion Karsh. 2011. "A human factors framework and study of the effect of nursing workload on patient safety and employee quality of working life." *Quality & Safety in Health Care* 20(1):15-24. doi:10.1136/bmjqs.2008.028381.

Hurst, Keith 2005. "Relationships between patient dependency, nursing workload and quality." *International journal of nursing studies* 42(1):75-84. doi:10.1016/j.ijnurstu.2004.05.011.

IHI (Institute of Healthcare Improvement). 2012. "Evidence-based care bundles". Last modified April 1. Accessed March 27. http://www.ihi.org/explore/Bundles/ Pages/default.aspx

IHI (Institute of Healthcare Improvement). 2012. "5 Million lives campaign." Last modified April 1. Accessed April 6. http://www.ihi.org/offerings/Initiatives/PastStrategic Initiatives/5MillionLivesCampaign/Pages/default.aspx

Johnson, Norman J., Eric Backlund, Paul D. Sorlie, and Catherine A. Loveless. 2000. "Marital status and mortality: The National Longitudinal Mortality study". *Annals of Epidemiology* 4(10): 224-238.

Kohn, Linda T., Janet M. Corrigan, and Molla S. Donaldson. 2000. *To Err is Human: Building a Safer Health System*. Washington, D.C.: National Academies Press.

Kokmen, Emre, Yasef Özsarfati, C. Mary Beard, Peter C. O'Brien, and Walter A. Rocca. 1996. "Impact of referral bias on clinical and epidemiological studies of Alzheimer's disease." *Journal of Clinical Epidemiology* 49(1):79-83. doi: 10.1016/0895-4356(95)00031-3.

Kozak, Lola, Carol DeFrances, and Margaret Hall. 2006. "National Hospital Discharge Survey: 2004 annual summary with detailed diagnosis and procedure data." *Vital Health Statistics* no. 13.

Krumholz, H. M., E. M. Parent, N. Tu, V. Vaccarino, Y. Wang, M. J. Radford, J. Hennen. 1997. "Readmission after hospitalization for congestive heart failure among Medicare beneficiaries." *Archives of Internal Medicine* 157(1):99-104.

Landrigan, Christopher P., Gareth J. Parry, Catherine B. Bones, Andrew D. Hackbarth, Donald A. Goldmann, and Paul J. Sharek. 2010. "Temporal Trends in Rates of Patient Harm Resulting from Medical Care." *New England Journal of Medicine* 363(22):2124-2134. doi:10.1056/NEJMsa1004404.

Leape, Lucian L., Troyen A. Brennan, Nan Laird, Ann G. Lawthers, A. Russell Localio, Benjamin A. Barnes, Liesi Hebert, Joseph Newhouse, Paul Weiler, and Howard Hiatt. 1991. "The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II." *New England Journal of Medicine* 324:377-384.

Levy, M., Peter J. Pronovost, R. Dellinger, S. Townsend, Roger K. Resar, T. P. Clemmer, G. Ramsay. 2004. "Sepsis change bundles: converting guidelines into meaningful change in behavior and clinical outcome." *Critical Care Medicine.* 32(11 Suppl):S595-7.

Lloyd-Jones, Donald, Robert J. Adams, Todd M. Brown, Mercedes Carnethon, Shifan Dai, Giovanni De Simone, T. Bruce Ferguson, Earl Ford, Karen Furie, Cathleen Gillespie, Alan Go, Kurt Greenlund, Nancy Haase, Susan Hailpern, P. Michael Ho, Virginia Howard, Brett Kissela, Steven Kittner, Daniel Lackland, Lynda Lisabeth, Ariane Marelli, Mary M. McDermott,

James Meigs, Dariush Mozaffarian, Michael Mussolino, Graham Nichol, Veronique L. Roger, Wayne Rosamond, Ralph Sacco, Paul Sorlie, Thomas Thom, Sylvia Wasserthiel-Smoller, Nathan D. Wong, and Judith Wylie-Rosett. 2010. "Heart disease and stroke statistics--2010 update: a report from the American Heart Association." *Circulation* 121(7):e46-e215. doi: CIRCULATIONAHA.109.192667 [pii] 10.1161/CIRCULATIONAHA.109.192667.

Localio, A. Russell, Susan. L. Weaver, J. Richard Landis, Ann G. Lawthers, Troyen A. Brennan, Liesi Hebert, and Tonya Sharp 1996. *Annals of Internal Medicine* 125(6):457-464.

Longo, Daniel R., John E. Hewett, Bin Ge, and Shari Schubert. 2005. "The Long Road to Patient Safety: A Status Report on Patient Safety Systems." *Journal of American Medical Association* 294(22):2858-2865.

McCannon, Joseph, Donald M. Berwick. 2011. "A new fronteir in patient safety." *Journal of American Medical Association* 305(21):2221-2. doi: 10.1001/jama.2011.742

McCarthy, Douglas, Sabrine How, Ashley-Kay Fryer, David C. Radley, and Cathy Schoen. 2011. "Why not the best? Results from the national scorecard on U. S. health system performance, 2011." *New York: Commonwealth Fund Commission on a High Performance Health System,* October 2011.

McKee, Patrick A., William P. Castelli, Patricia M. McNamara, and William B. Kannel. 1971. "The natural history of congestive heart failure: the Framingham study." *New England Journal of Medicine* 285(26):1441-6. doi:10.1056/nejm197112232852601.

Melton, Genevieve B. 2005. "Automated Detection of Adverse Events Using Natural Language Processing of Discharge Summaries." *Journal of the American Medical Informatics Association* 12(4):448-457. doi: 10.1197/jamia.M1794.

Melton, L. Joseph, 3rd. 1997. "The threat to medical-records research." *New Engand Journal of Medicine* 337(20):1466-70. doi: 10.1056/nejm199711133372012.

Murff, Harvey, Vimla Patel, George Hripcsak, and David Bates. 2003. "Detecting adverse events for patient safety research: a review of current methodologies." *Journal of Biomedical Informatics* 1-2(36)131-143. doi: 10.1016/j.jbi.2003.08.003

Naessens, James M., Claudia R. Campbell, Jeanne M. Huddleston, Bjorn P. Berg, John J. Lefante, Arthur R. Williams, and Richard A. Culbertson. 2009a. "A comparison of hospital adverse events identified by three widely used detection methods." *International Journal for Quality in Health Care* 21(4):301-7. doi:10.1093/intqhc/mzp027.

Naessens, J. M., T. J. O'Byrne, M. G. Johnson, M. B. Vansuch, C. M. McGlone, and J. M. Huddleston. 2010. "Measuring hospital adverse events: assessing inter-rater reliability and trigger performance of the Global Trigger Tool." *International Journal for Quality in Health Care* 22(4):266-74. doi:10.1093/intqhc/mzq026.

Naessens, James M, Claudia R Campbell, Jeanne M Huddleston, Bjorn P Berg, John J Lefante, Arthur R Williams, and Richard A Culbertson. 2009. "A comparison of hospital adverse events identified by three widely used detection methods." *International Journal for Quality in Health Care* 21(4):301-307. doi:10.1093/intqhc/mzp027.

Naranjo, Claudio A, Usoa Busto, and Edward M Sellers. 1981. "A method for estimating the probability of adverse drug reactions." *Clinical Pharmacology and Therapeutics* 30(2): 230-45.

National Coordinating Council for Medication Error Reporting and Prevention. 2001. "NCC MERP Index for Categorizing Medicaiton Errors" [accessed on January 5, 2007]. Available at http://www.nccmerp.org

Neale, Graham, and Maria Woloshynowych. 2001. "Exploring the causes of adverse events in NHS hospital practice." *Journal of the Royal Society of Medicine* 94(7):322-330.

Nolan T, Resar R, Haraden C, Griffin FA. *Improving the Reliability of Health Care.* IHI Innovation Series white paper. Boston: Institute for Healthcare Improvement; 2004. (Available on www.IHI.org)

OIG (Office of Inspector General). 2010a. Adverse Events in Hospitals: Methods for Identifying Events. Washington, D.C.: Department of Health and Human Services.

OIG (Office of Inspector General). 2010b. Adverse Events in Hospitals: National Incidence Among Medicare Beneficiaries. Washington, D.C.: Department of Health and Human Services.

Ornstein, C. 2007. "Dennis Quaid Files Suit over Drug Mishap." *LA Times*. December 5 [accessed on March 23, 2012]. Available at http://katunes.com/features/health/la-me-quaid5dec05,1,1883436.story

Pasarelli, Maria, Wilson Jacob-Filho, and Albert Figueras. 2005. "Adverse Drug Reactions in an Elderly Hospitalised Population: Inappropriate Prescription is a Leading Cause." *Drugs & Aging* 22:767-777.

Petersen, Laura A, Troyen A Brennan, and Anne C O'Neil. 1994. "Does housestaff discontinuity of care increase the risk for preventable adverse events?" *Annals of Internal Medicine* 11(121):866-872.

Pogorzelska M., P. W. Stone, E. Y. Furuya, E. N. Perencevich, E. L. Larson, D. Goldmann, A. Dick. "Impact of the ventilator bundle on ventilator-associated pneumonia in intensive care unit." International Journal for Quality in Health Care. 23(5):538-44.

Polanczyk, *Carısi A., Luis E. P. Rohde, G. William Dec, Thomas DiSalvo.* 2000. "Ten-year trends in hospital care for congestive heart failure: Improved outcomes and increased use of resources." *Archives of Internal Medicine* 160:325-332.

Resar, Roger K. 2003. "Methodology and rationale for the measurement of harm with trigger tools." *Quality and Safety in Health Care* 12 (90002):39ii-45. doi: 10.1136/qhc.12.suppl_2.ii39.

Resar, Roger, Peter Pronovost, Carol Haraden, Terri Simmonds. 2003. “Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia.” Joint Commission Journal on Quality and Patient Safety. 31(5):243-248.

Rozich, John D., Carol R. Haraden, and Roger K. Resar. 2003. "Adverse drug event trigger tool: a practical methodology for measuring medication related harm." *Quality and Safety and Health Care* 12(3):194-200.

Seferian, Edward G., Bekele Afessa, Ognjen Gajic, Mark T. Keegan, and Rolf D. Hubmayr. 2008. "Comparison of community and referral intensive care unit patients in a tertiary medical center: Evidence for referral bias in the critically ill." *Critical Care Medicine*. doi: 10.1097/CCM.0b013e318186ab1b.

Sharek, Paul J, Gareth Parry, Donald Goldmann, Kate Bones, Andrew Hackbarth, Roger Resar, Frances A Griffin, Dale Rhoda, Cathy Murphy, and Christopher P Landrigan. 2011. "Performance Characteristics of a Methodology to Quantify Adverse Events over Time in Hospitalized Patients." *Health Services Research* 46(2):654-678. doi:10.1111/j.1475-6773.2010.01156.x.

Stelfox, Henry T., David W. Bates, Donald A. Redelmeier. 2003. "Safety of patients isolated for infection control." *Journal of the American Medical Association* 14(290):1899-1905.

Szekendi, Marilyn K, C Sullivan, and A Bobb. 2006. "Active surveillance using electronic triggers to detect adverse events in hospitalized patients." *British Medical Journal of Quality & Safety* 3(15):184-190. doi:10.1136/qshc.2005.014589

Sztramko, Richard, Vicky Chau, and Roger Wong. 2011. "Adverse Drug Events and Associated Factors in Heart Failure Therapy Among the Very Elderly." *Canadian Geriatrics Journal* 14(4). doi: 10.5770/cgj.v14i4.19.

Thomas, Eric J., and Troyen A. Brennan. 2000. "Incidence and types of preventable adverse events in elderly patients: population based review of medical records." *British Medical Journal* 320(7237):741-4.

Thomas, Eric J, Stuart R Lipsitz, and David M Studdert. 2002. "The reliability of medical record review for estimating adverse event rates." *Annals of Internal Medicine* 11(136): 812-816.

Thomas, Eric J, and E John Orav. 2000. "Hospital ownership and preventable adverse events." *Journal of General Internal Medicine* 4(15): 211-219.

Thomas, Eric J., David M. Studdert, Helen R. Burstin, E. John Orav, Timothy Zeena, Elliott J. Williams, K. Mason Howard, Paul C. Weiler, and Troyen A. Brennan. 2000. "Incidence and Types of Adverse Events and Negligent Care in Utah and Colorado." *Medical Care* 38(3):261.

Upenieks, Valda V, Jenny Kotlerman, and Jaleh Akhavan. 2007. "Assessing Nursing Staffing Ratios." *Policy, Politics, & Nursing Practice.* February 2007 1(8):7-19.

VanSuch, Monica, James M. Naessens, Robert J. Stroebel, Jeanne M. Huddleston, Arthur R. Williams. 2006. "Effect of discharge instructions on readmission of hospitalised patients with heart failure: do all of the Joint Commission on Accreditation of Healthcare Organizations heart failure core measures reflect better care?" *Quality and Safety in Health Care* 15(6):414-417. doi:10.1136/qshc.2005.017640

Wachter, Robert M. 2004. "The end of the beginning: patient safety five years after “To Err Is Human"." *Health Affairs* 23(11):534-545.

Weissman, Joel S, and Eric C Schneider. 2008. "Comparing patient-reported hospital adverse events with medical record review: Do patients know something that hospitals do not?" *Annals of Internal Medicine* 149(2):100-108.

Wier LM (Thomson Reuters), A. Pfuntner (Thomson Reuters), J. Maeda(Thomson Reuters), E. Stranges (Thomson Reuters), K. Ryan (Thomson Reuters), P. Jagadish (AHRQ), B. Collins Sharp (AHRQ), A. Elixhauser (AHRQ). 2011. "HCUP Facts and Figures: Statistics on Hospital-based Care in the United States, 2009: exhibits 2.5 Most frequent diagnosis by payer and 4.1 Cost by diagnosis." Rockville, MD: Agency for Healthcare Research and Quality. [accessed April 5, 2012] Available at http://www.hcup-us.ahrq.gov/reports.jsp

Wilson, R. M., B. T. Harrison, R. W. Gibberd. 1999. "The analysis of the causes of adverse events from the Quality in Australian Health Care Study." *Medical Journal of Australia* 170:411-415.

Yang, Guangbin. 2007. *Life Cycle Reliability Engineering.* Hoboken, New Jersey: John Wiley & Sons, Inc.

Yu, KH, and Roger L Nation. 2005. "Multiplicity of medication safety terms, definitions and functional meanings: when is enough enough?" *Quality and Safety in Health Care* (14):358-363.

Zhan, Chunliu 2003. "Excess length of stay, charges, and mortality attributable to medical injuries during hospitalization." *Journal of the American Medical Association* 290(14):1868-1874.

APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL

Principal Investigator Notification:

From: IRB

To: Jeanne Huddleston

CC: Study Team Members that are marked as wishing to receive correspondence regarding the protocol/grant application

Re: Application # 07-003607
07-003607

Please note that all correspondence (modifications, progress reports, reportable events) related to this study/grant application must be submitted electronically in the IRBe system.

The following is an excerpt from the minutes of the Expedited Review A of the Mayo Clinic Institutional Review Boards meeting dated 5/22/2007:
The Committee reviewed and approved for human studies the protocol entitled "Health Care Delivery and Harm to Hospitalized Congestive Heart Failure Patients" from Dr. Jeanne Huddleston. The Committee noted that the human studies aspects involve a retrospective chart review of Mayo Clinic Rochester patients having been hospitalized from January 1, 2005 to May 22, 2007 with a primary diagnosis of congestive heart failure (CHF). The Committee reminds the proponents to submit a modification to include participants hospitalized from May 23, 2007 to December 31, 2007, as the request in this application is to retrospective collect data and therefore the Committee cannot approve prospective collection of data. The Committee noted Dr. John Fowler from Arizona State University will serve as an external collaborator receiving de-identified data. Dr. Huddleston is reminded that no Mayo patient identifying information may be released to the external collaborator. It should also be noted that this approval is valid only for Mayo investigator activities. The IRB approves waiver of specific informed consent in accordance with 45 CFR 46.116 (d) as justified by the investigator, and waiver of HIPAA authorization in accordance with applicable HIPAA regulations. The Committee determined that this constitutes a minimal risk collection of data or specimens that have already been collected for non-research purposes, and therefore was eligible for expedited review in accordance with 45 C. F. R. 46.110 (b) (1) and 63 FR 60364, item 5. This approval is valid for exactly one year unless during the year the IRB determines that it is appropriate to halt or suspend the study earlier. 07-003607

Rubin, Joseph M.D. , Chair
Gina Dahlgren , Specialist
Mayo Clinic Institutional Review Boards
Expedited Review A

APPENDIX B
NARANJO ALGORITHM

Question	Yes	No	Don't Know
1.Are there previous *conclusive* reports on this reaction?	+1	0	0
2.Did the adverse event appear the suspected drug was administered?	+2	-1	0
3.Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0
4.Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5.Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6.Did the reaction reappear when a placebo was given?	-1	+1	0
7.Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8.Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9.Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0
10.Was the adverse event confirmed by any objective evidence?	+1	0	0
Total Score			

The total score calculated from this table defines the category an adverse reaction belongs to. The categories are defined as follows:

Definite(Certain)	(total score>8)
Probable	(total score 5-8)
Possible	(total score1-4)
Doubtful(Unlikely)	(total score <1)

Note: Categories of probable and definite were included as adverse medication events in this study.

APPENDIX C

GLOBAL TRIGGER TOOL WORKSHEET

Cares Module Triggers	+	Event Category and Severity E-I	Medication Module Triggers	+	Event Category and Severity E-I
Transfusion or use of blood products			C. difficile positive		
Any Code or arrest			PTT >100 seconds		
Dialysis			INR >6		
Positive blood culture			Glucose < 50 mg/dl		
X-Ray or Doppler studies for emboli			Rising BUN/S.Creat >2X base		
Abrupt drop in Hct>4% or Hg >gms			Benadryl (**Diphenhydramine**)use		
Patient fall			Vitamin K administration		
Decubiti			Romazicon (Flumazenil) use		
Readmission within 30 days			Narcan (Naloxone) use		
Restraint use			Antiemetic use		
Infection of any kind			Over sedation/hypotension		
In hospital Stroke			Abrupt medication stop		
Transfer to higher level of care			Other		
Any procedure complication					
Other			**ICU Module Triggers**		
			Pneumonia onset		
Surgical Module Triggers*			Readmission to ICU		
Return to surgery			In unit procedure		
Change in procedure			Intubation/reintubation		
Admission to ICU post op					
Intubation/Reintub/BiPap in PACU			**OB Module***		
X-ray intra-op or in PACU			Apgar < 7 at five minutes		
Intra or post-op death			Maternal/neonatal transport/transfer		
Mech Vent >24 hours post op		*Not utilized for this study	Mg Sulfate or terbutaline use		
Intra-op epi or nor epi use			Infant serum glucose <50		
Post-op Troponein level > 5			3rd or degree lacerations		
Change anesthetic during surgery			Induction of delivery		
Consult requested in PACU					
Path report normal or unrelated to dx			**ER Module**		
Insertion of art or CVP during surgery			Readmission to ED within 48 hours		
Operative time > 6 hours			Time in ED > 6 hours		
Removal/Injury or repair					

APPENDIX D

CATEGORIES AND TYPES OF ADVERSE EVENTS

Adverse Event Category	% of all adverse events
Infection	**18.9%**
	types of infections
Bacteremia (line or catheter associated)	13.2%
Catheter associated UTI	62.3%
Cellulitis or local catheter site infection	3.8%
Clostridium Difficile	2.8%
Health care associated pneumonia	14.2%
Ventilator associated pneumonia	1.9%
Procedure site infection	0.9%
Other	0.9%
Medication	**43.9%**
	types of medication events
Acute kidney injury	22.1%
Arrhythmia	1.6%
Allergy	8.0%
Sub-types of allergies	
Rash (95%)	
Anaphylaxis (5%)	
Bradycardia	3.2%

Coagulopathy	15.7%
Sub-types of coagulopathy	
Epistaxis (7.7%)	
GI bleed (33.3%)	
Hematoma (18%)	
(nonprocedural)	
Hematuria (18%)	
Hemoptysis (10.3%)	
Intracranial hemorrhage (12.8%)	
Digoxin toxicity	1.2%
Hypoglycemia	8.0%
Hypotension	20.1%
Medication Error	2.0%
Sub-types of medication errors	
Wrong dose (60%)	
Wrong patient (20%)	
Wrong medication (20%)	
Mental status changes	8.4%
Sub-types of mental status changes	
Delirium/hallucinations (68.2%)	
Lethargy or somnolence (31.8%)	
Respiratory failure	4.8%
Electrolyte abnormalities	0.4%
Other	4.4%

Patient Care		**26.3%**
	types of patient care events	
Fall	8.3%	
Decubiti	1.4%	
Device failure or malfunction	36.6%	
Pulmonary embolus	1.4%	
Plan of care	0.7%	
Readmission	33.1%	
Sub-types of readmission events		
Premature discharge (25.5%)		
Medication change (48.4%)		
Monitoring (0.1%)		
Other (0.5%)		
Respiratory failure	5.5%	
Triage	4.8%	
Other	8.3%	
Procedure		**10.9%**
	types of procedure events (%)	
Bleeding at puncture site	11.3	
Hematoma	38.7	
Pseudoaneurysm	4.8	
Wrong site	1.6	
Pneumothorax	4.8	
Other	38.7	

APPENDIX E

SUMMARY OF PATIENT PRE-HOSPITAL CHARACTERISTICS

INCLUDING RESULTS OF UNIVARIATE AND BIVARIATE ANALYSES

Patient Characteristics	Missing values	Overall (n=1722)	*Of those with and without adverse events, comparison of patient factors between these two subgroups (column %)*		Cox Proportional Hazards Bivariate Analysis Results
			No adverse event (n=1341)	With adverse event (n=381)	Hazard Ratio (95% CI)
Age - mean(sd)		75.8 (12.4)	75.7 (12.6)	75.8 (12.1)	*Per unit change:* 1.01 (1.00-1.02) *Per change over entire range:* 2.28 (1.19-4.41)
Race – Caucasian		1649 (96.3%)	1286 (96.3%)	369 (96.9%)	1.25 (0.74-2.35)
BMI – mean(sd)	1	30.2 (8.0)	30.2 (7.7)	31.6 (9.1)	*Per unit change:* 1.01 (1.00-1.02) *Per change over entire range:* 2.11 (0.82-5.18)
Residence					
Olmsted		454 (26.4%)	357 (26.6%)	97 (25.5%)	1.60 (1.23-2.07)
County		515 (29.9%)	378 (28.2%)	137 (36.0%)	1.84 (1.45-2.32)
SEMN		753 (43.7%)	606 (45.2%)	147 (38.6%)	*
National*					
Married		1019 (59.2%)	810 (60.4%)	209 (54.9%)	0.78 (0.63-0.95)
Male		945 (54.9%)	749 (55.9%)	196 (51.4%)	1.00 (0.82-1.22)
Code status - Full	8	1371 (80.0%)	1072 (80.3%)	299 (78.9%)	0.77 (0.61-1.00)

Prehospital mobility	10				
Walk independently		916 (53.5%)	754 (56.5%)	162 (42.9%)	0.24 (0.12-0.57)
Walk with device		594 (34.7%)	444 (33.3%)	150 (39.7%)	0.35 (0.18-0.84)
Wheelchair independently		22 (1.3%)	17 (1.3%)	5 (1.3%)	0.28 (0.08-0.86)
Dependent for any movement		163 (9.5%)	109 (8.2%)	54 (14.3%)	0.46 (0.23-1.12)
Bedridden		17 (1.0%)	10 (0.7%)	7 (1.9%)	*
Prehospitalization ADL's (dependent)	1				
Eating		52 (3.0%)	37 (2.8%)	15 (3.9%)	1.49 (0.85-2.41)
Bathing		440 (25.6%)	294 (21.9%)	146 (38.4%)	1.90 (1.54-2.33)
Dressing		314 (18.2%)	203 (15.1%)	111 (29.2%)	1.88 (1.50-2.34)
Toileting		274 (15.9%)	177 (13.2%)	97 (25.5%)	1.86 (1.47-2.33)
Housekeeping		766 (44.5%)	543 (40.5%)	223 (58.7%)	1.64 (1.34-2.02)
Living arrangements:					
Home		1459 (84.7%)	1160 (86.5%)	299 (78.5%)	0.52 (0.40-0.70)
AL		98 (5.7%)	72 (5.4%)	26 (6.8%)	0.75 (0.47-1.18)
SNF		165 (9.6%)	109 (8.1%)	56 (14.7%)	*
Direct admission or Transfer from another facility	1	880 (51.1%)	687 (51.7%)	193 (50.7%)	0.70 (0.56-0.85)
Current Tobacco		162 (9.4%)	127 (9.5%)	35 (9.2%)	0.97 (0.68-1.36)
Current ETOH use		452 (26.3%)	367 (22.4%)	85 (22.5%)	0.81 (0.63-1.03)

*, Reference variable; sd: standard deviation; AE: adverse event; AL: assisted living; SNF: skilled nursing facility; ADL: activity of daily living; IPFS: Inpatient Physiology Failure Score; EF: ejection

APPENDIX F

SUMMARY OF PATIENT PAST MEDICAL HISTORY INCLUDG RESULTS OF UNIVARIATE AND BIVARIATE ANALYSES

		Of those with and without AEs, comparison of patient factors between these two subgroups (column %)		Cox Proportional Hazards Bivariate Analysis Results
Past Medical History	Overall (n=1722)	No AE (n=1341)	With AE (n=381)	Hazard Ratio (95% CI)
Hypertension	1211 (70.3%)	939 (70.0%)	272 (71.4%)	1.24 (0.99-1.55)
Dementia	90 (5.2%)	72 (5.4%)	18 (4.7%)	1.04 (0.62-1.61)
CVA	332 (19.3%)	246 (18.3%)	86 (22.6%)	1.33 (1.04-1.68)
PVD	318 (18.5%)	235 (17.5%)	83 (21.8%)	1.27 (0.99-1.61)
MI	476 (27.8%)	363 (27.1%)	115 (30.5%)	1.09 (0.87-1.35)
OSA	294 (17.1%)	221 (16.5%)	73 (19.2%)	1.06 (0.82-1.36)
Home CPAP	196 (11.4%)	149 (11.1%)	47 (12.3%)	0.95 (0.69-1.27)
Home oxygen	237 (13.8%)	175 (13.1%)	62 (16.3%)	1.18 (0.89-1.53)
COPD/Asthma	482 (28.1%)	370 (27.6%)	114 (29.9%)	1.05 (0.84-1.31)
PUD/GI bleed	232 (13.5%)	175 (13.1%)	57 (15.0%)	1.21 (0.91-1.60)
Diabetes mellitus	634 (36.8%)	471 (35.3%)	160 (42.0%)	1.18 (0.96-1.44)

CKD*	674 (39.1%)	509 (38.0%)	165 (43.3%)	1.01 (0.83-1.24)
Renal transplant	18 (1.0%)	10 (0.7%)	8 (2.1%)	2.72 (1.23-5.11)
Autoimmune**	97 (5.6%)	77 (5.7%)	20 (5.2%)	1.00 (0.62-1.53)
Osteoarthritis	413 (24.0%)	308 (23.0%)	105 (27.6%)	1.48 (1.18-1.85)
Osteoporosis	168 (9.8%)	130 (9.7%)	38 (9.9%)	1.02 (0.72-1.41)
CAD	958 (55.6%)	745 (55.6%)	213 (55.9%)	1.08 (0.88-1.33)
Severe AS	166 (9.6%)	128 (9.5%)	37 (10.0%)	0.85 (0.60-1.18)
CHF or CMP	1226 (71.2%)	959 (71.5%)	267 (70.1%)	0.85 (0.69-1.07)
Hyperlipidemia	958 (55.6%)	751 (56.0%)	207 (54.3%)	1.03 (0.84-1.26)
Pulmonary embolus	110 (6.4%)	80 (6.0%)	30 (7.9%)	1.16 (0.78-1.66)
Atrial arrhythmia^	896 (52.0%)	694 (51.8%)	202 (53.0%)	0.97 (0.79-1.19)
Ventricular arrhythmia#	128 (7.4%)	97 (7.2%)	31 (8.1%)	0.92 (0.62-1.30)
Depression	318 (18.5%)	243 (18.1%)	75 (19.7%)	1.18 (0.91-1.51)
Cancer@	416 (24.2%)	325 (24.2%)	91 (23.9%)	1.06 (0.84-1.34)

CVA: cerebrovascular accident; PVD: peripheral vascular disease; CAD: coronary artery disease; CHF: congestive heart failure; CMP: cardiomyopathy; OSA: obstructive sleep apnea; CPAP: continuous positive airway pressure; MI: myocardial infarction; PUD: peptic ulcer disease; GI: gastrointestinal; CKD: chronic kidney disease; AS: aortic stenosis; AE: adverse event.

* Chronic kidney disease is an aggregate of patients with creatinine higher than 2.0 mg/dl or requiring chronic hemodialysis.

**Autoimmune disease is an aggregate of patients with a history of at least one of the following: rheumatoid arthritis, systemic lupus erythematous, mixed connective tissue disease, Sjogren's syndrome, scleroderma and vasculitis.

* Atrial arrhythmia is an aggregate of patients with history of at least one of the following: atrial fibrillation, atrial flutter, multifocal atrial tachycardia, paroxysmal atrial tachycardia or supraventricular tachycardia.

Ventricular arrhythmia is an aggregate of patients with history of either ventricular fibrillation or ventricular tachycardia.

Cancer: any solid tumor (with or without metastases) or any hematologic malignancy

APPENDIX G

SUMMARY OF PATIENT ADMISSION MEDICATIONS

INCLUDING RESULTS OF UNIVARIATE AND BIVARIATE ANALYSE

		Of those with and without adverse events, comparison of patient factors between these two subgroups (column %)		Cox Proportional Hazards Bivariate Analysis Results
	Overall (n=1722)	No adverse event (n=1341)	With adverse event (n=381)	Hazard Ratio (95% CI)
Diuretic	1148 (67.1%)	875 (65.6%)	273 (72.4%)	1.17 (0.93-1.47)
Potassium supplementation	220 (12.8%)	165 (12.4%)	55 (14.6%)	0.91 (0.68-1.20)
ACE-I or ARB	928 (54.2%)	739 (55.4%)	189 (50.1%)	0.96 (0.81-1.21)
Hydralazine	42 (2.5%)	29 (2.2%)	13 (3.4%)	1.30 (0.71-2.17)
Beta blocker	1096 (64.1%)	868 (65.1%)	228 (60.5%)	0.86 (0.70-1.05)
Calcium channel blocker	354 (20.7%)	285 (21.2%)	69 (18.3%)	0.87 (0.67-1.13)
Digoxin	403 (23.6%)	299 (22.4%)	104 (27.6%)	0.86 (0.68-1.08)
Nitrates	284 (16.6%)	227 (17.0%)	57 (15.1%)	1.01 (0.76-1.33)
Amiodarone	111 (6.5%)	81 (6.1%)	30 (8.0%)	1.03 (0.70-1.46)
Allopurinol	192 (11.2%)	134 (10.0%)	58 (15.4%)	1.37 (1.03-1.80)
Coumadin	620 (36.2%)	473 (35.5%)	147 (39.0%)	1.86 (0.68-1.30)
Aspirin	913 (53.4%)	721 (54.0%)	192 (50.9%)	1.04 (0.85-1.27)
Other antiplatelet	191 (11.2%)	150 (11.2%)	41 (10.9%)	1.12 (0.80-1.53)
NSAID	51 (3.0%)	39 (2.9%)	12 (3.2%)	1.47 (0.78-2.49)

Prednisone	132 (7.7%)	95 (7.1%)	37 (9.8%)	1.33 (0.93-1.84)
HMG-CoA reductase inhibitors	741 (43.3%)	580 (43.5%)	161 (42.7%)	1.09 (0.89-1.34)
Insulin	318 (18.6%)	230 (17.2%)	88 (23.3%)	1.25 (0.98-1.58)
Oral diabetes medication	214 (12.5%)	170 (12.7%)	44 (11.7%)	0.87 (0.63-1.18)
GI protection	614 (35.9%)	473 (34.5%)	141 (37.4%)	1.07 (0.87-1.32)
Antidepressant	402 (23.5%)	310 (23.2%)	92 (24.4%)	1.11 (0.87-1.39)

ACE-I: Angiotensin converting enzyme inhibitor

ARB: Angiotensin II receptor blocker

NSAID: Nonsteroidal anti-inflammatory drug

Other antiplatelet: ticlopidine, clopidigrel, prasugrel, dipyridamole

Oral diabetes medications: sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, dipeptidyl peptidase IV inhibitors

GI protection: Histamine 2 receptor blocker or proton pump inhibitor

APPENDIX H

SUMMARY OF PATIENT SEVERITY OF ILLNESS AT ADMISSION

INCLUDING RESULTS OF UNIVARIATE AND BIVARIATE ANALYSES

			Of those with and without AEs, comparison of patient factors between these two subgroups (column %)		Cox Proportional Hazards Bivariate Analysis Results
	Missing	Overall (n=1722)	No AE (n=1341)	With AE (n=381)	Hazard Ratio (95% CI)
Charlson Index – mean(sd)		3.9 (2.7)	3.9 (2.6)	4.2 (2.8)	*Per unit change:* 1.02 (0.98-1.06) *Per change over entire range:* 1.38 (0.76-2.45)
IPFS – mean (sd)		4.1 (3.7)	3.8 (3.5)	5.2 (4.0)	*Per unit change:* 1.05 (1.03-1.08) *Per change over entire range:* 2.66 (1.66-4.22)
Ejection fraction (%) – mean (sd)	14	42.7% (18.6)	42.6% (18.6)	42.7% (18.6)	*Per unit change:* 1.00 (1.00-1.01) *Per change over entire range:* 1.40 (0.91-2.14)
Systolic dysfunction: EF < 40%	14	761 (44.8%)	599 (45.1%)	168 (44.1%)	0.85 (0.70-1.05)

sd: standard deviation; IPFS: Inpatient Physiology Failure Score; EF: ejection fraction

APPENDIX I

MULTIVARIATE COX PROPORTIONAL HAZARD MODEL

Covariate	Model 1: Personal characteristics	Model 2: Past Medical History	Model 3: Home Medications	Model 4: ADL and Code Status	Model 5: Social Habits	Model 6: Severity of Illness	Final Model
Personal Characteristics							
Age*	0.90 (0.44-1.90)	1.09 (0.52-2.31)	0.69 (0.34-1.45)	0.59 (0.24-1.51)	0.75 (0.36-1.58)	0.69 (0.33-1.48)	0.72 (0.35-1.49)
Female	0.98 (0.71-1.35)	1.16 (0.92-1.46)	1.25 (0.99-1.58)	1.15 (0.91-1.45)	1.14 (0.90-1.45)	1.15 (0.91-1.46)	1.16 (0.92-1.46)
Unmarried	0.92 (0.67-1.27)	1.06 (0.84-1.33)	1.10 (0.87-1.39)	1.11 (0.88-1.40)	1.14 (0.90-1.43)	1.14 (0.90-1.43)	1.16 (0.90-1.43)
Caucasian	1.17 (0.68-2.21)						
Skilled nursing facility	1.75 (1.26-2.37)	1.43 (1.04-1.94)	1.49 (1.08-2.03)	1.15 (0.79-1.67)			
Unmarried female	1.15 (1.03-1.30)	1.13 (1.01-1.26)	1.01 (0.99-1.25)	1.12 (1.00-1.26)	1.12 (1.00-1.26)	1.11 (1.00-1.25)	1.11 (1.00-1.26)
Female in SNF	1.13 (0.96-1.32)						
Unmarried in SNF	1.10 (0.93-1.29)						
Transfer from another facility	0.90 (0.84-1.41)						
Southeastern MN residence	1.50 (1.19-1.48)	1.58(1.27-1.98)	1.73 (1.38-2.18)	1.65 (1.32-2.08)	1.63 (1.30-2.05)	1.63 (1.30-2.04)	1.64 (1.31-2.05)

APPENDIX J

COMPETING CAUSES AND DISTRIBUTION COMPARISONS FOR TIME TO THE FIRST ADVERSE EVENT PER PATIENT (EACH PATIENT COUNTED ONLY ONCE)

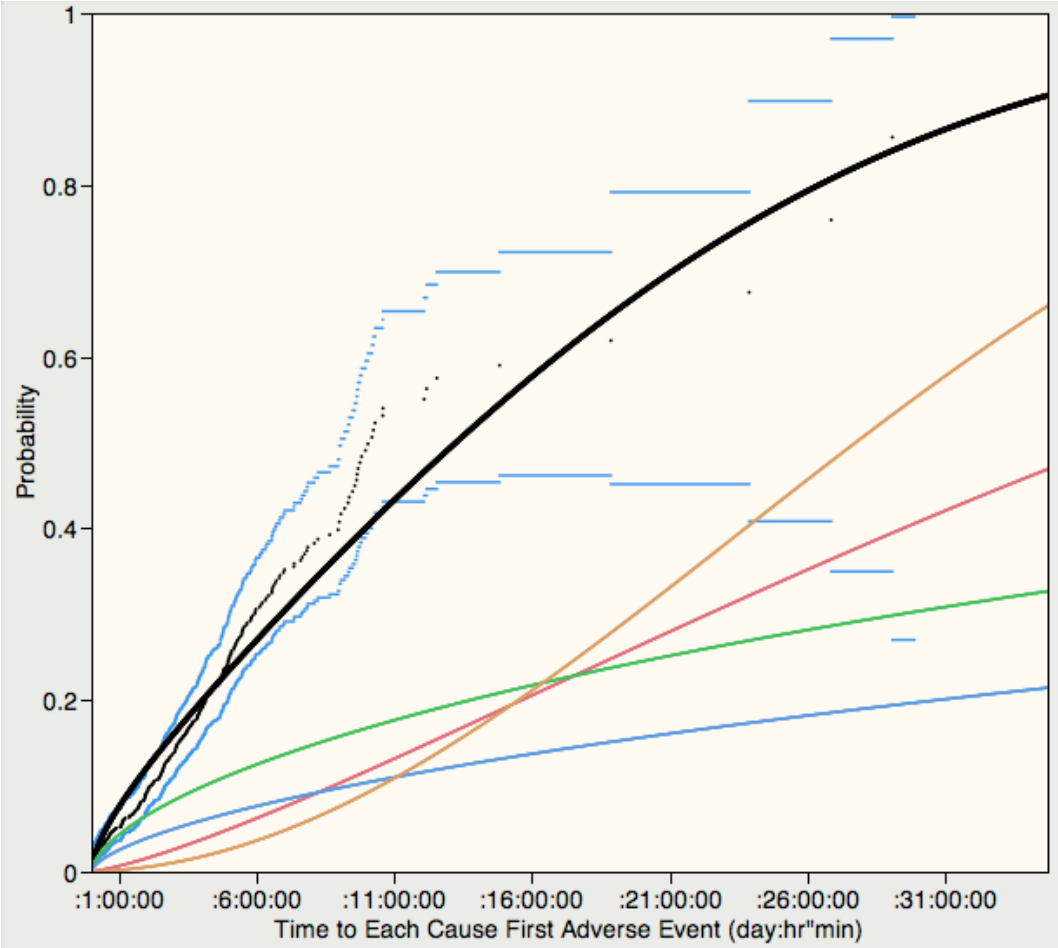


Figure J1: Competing cause distributions of time between admission and the first adverse event of each individual type and their aggregated distribution

Red: TH Weibull distribution of Infection causes
Green: TH Weibull distribution of medication causes
Blue: TH Weibull distribution of patient care causes
Orange: TH lognormal distribution of procedure causes

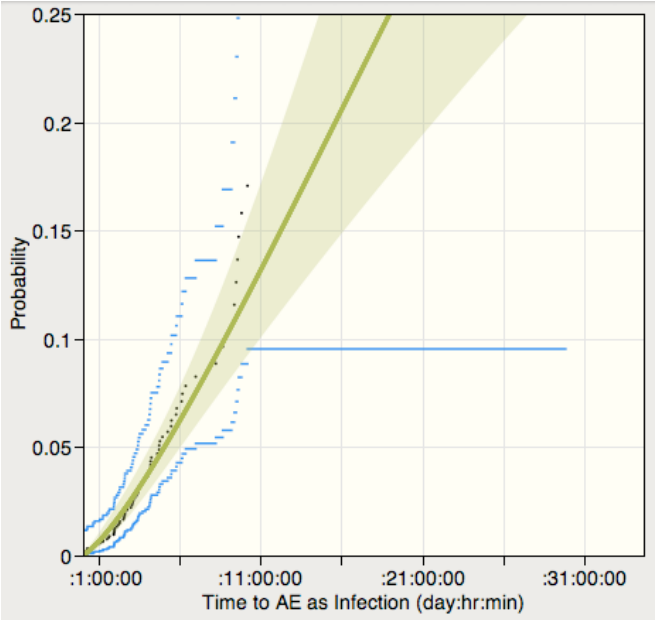


Figure J2: Threshold Weibull cumulative frequency distribution for those first adverse events (F(*t*) estimate) that are infections

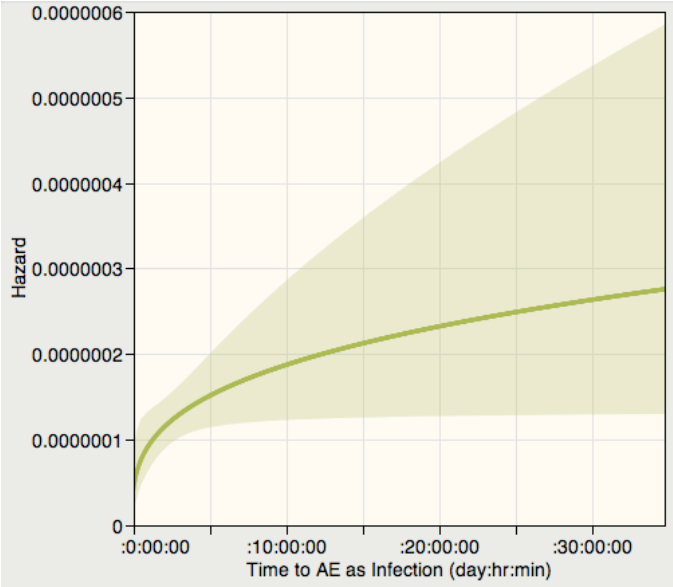


Figure J3: Hazard function (h(*t*)) for those first adverse events that are related to infectious control failures

Table J1: Distribution parameters and criterion for time from admission to portion of first adverse events that are infections

	Parameters			Criterion		
Distribution	Location	Scale	other	AICc	-2Log-Likelihood	BIC
Exponential		8271147.9		2405.82	2403.82	2411.27
Lognormal	17.1	2.49		2430.81	2401.80	2424.15
Weibull	15.6	0.88	α : 5812196.6 β : 1.1	2406.08	2402.07	2416.98
Threshold Weibull	15.0	0.76	α : 4264296 β : 1.3 threshold: -7948	2405.27	2399.25	2421.61

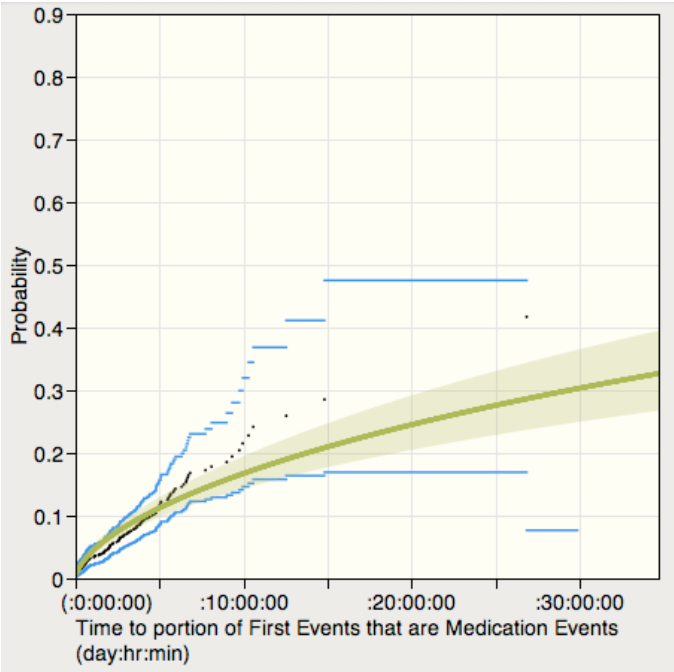


Figure J4: Threshold Weibull cumulative frequency distribution for the portion of first adverse events (F(*t*) estimate) that are medication events

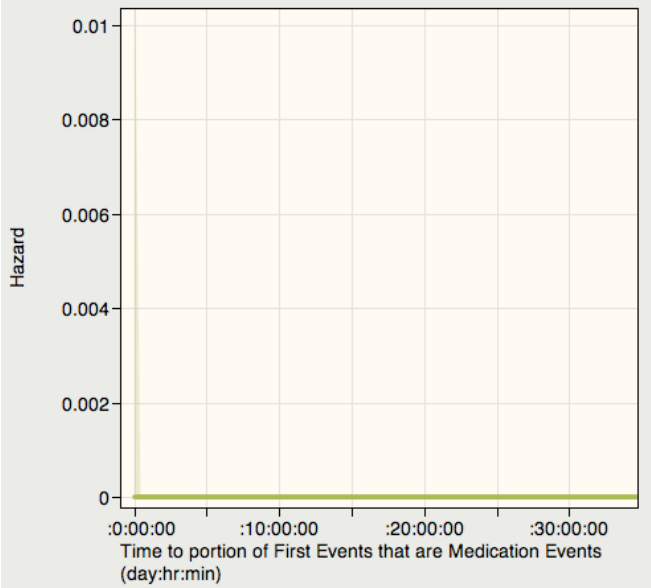


Figure J5: Hazard function (h(*t*)) for those first adverse events that are related to safe medication process failures

Table J2: Distribution parameters and criterion for time from admission to the portion of first adverse events that are medications adverse events

	Parameters			Criterion		
Distribution	Location	Scale	other	AICc	-2Log-Likelihood	BIC
Threshold	16.0	1.62	*threshold* : 60	5242.94	5236.93	5259.28
Weibull			α : 13428887			
			β : 0.62			
Weibull	16.0	1.40	α : 8673041.9	5342.78	5338.78	5353.68
			β : 0.70			
Exponential		5931833.3		5370.37	5368.37	5375.82
Lognormal	17.3	3.54		5380.90	5376.89	5391.79

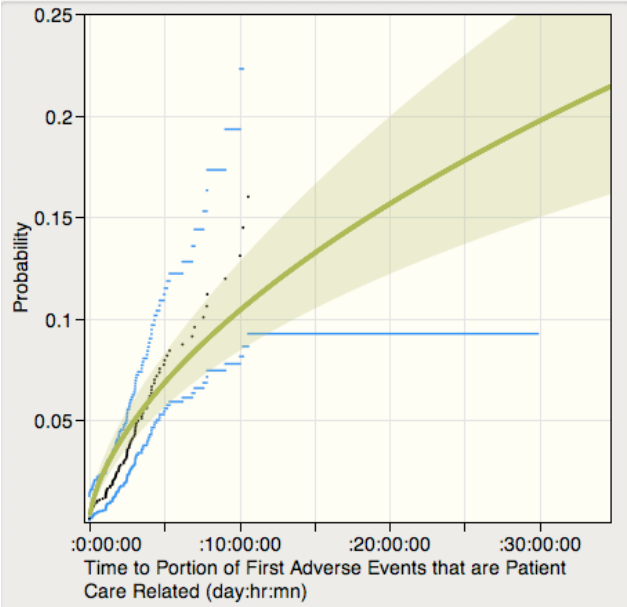


Figure J6: Threshold Weibull cumulative frequency distribution for the portion of first adverse events that are patient care events (F(*t*) estimate)

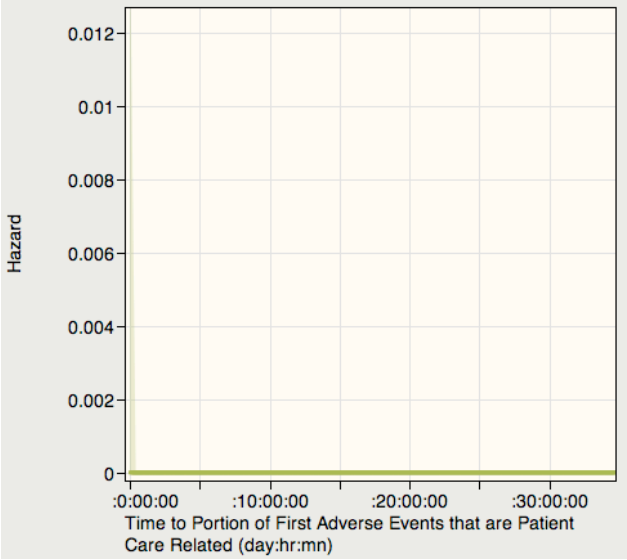


Figure J7: Hazard function (h(*t*)) for those first adverse events that are related to safe patient care process failures

Table J3: Distribution parameters and criterion for time from admission to the portion of first adverse events that are patient care adverse events

	Parameters			Criterion		
Distribution	Location	Scale	Other	AICc	-2Log-Likelihood	BIC
Threshold Weibull	17.0	1.58	*threshold* : 60.0 α : 28495684 β : 0.63	3179.92	3173.90	3196.26
Weibull	17.0	1.36	α : 15627633 β : 0.73	3276.30	3272.29	3287.19
Exponential		5931833.3		3287.98	3285.98	3293.43
Lognormal	18.68	3.78		3302.89	3298.88	3313.78

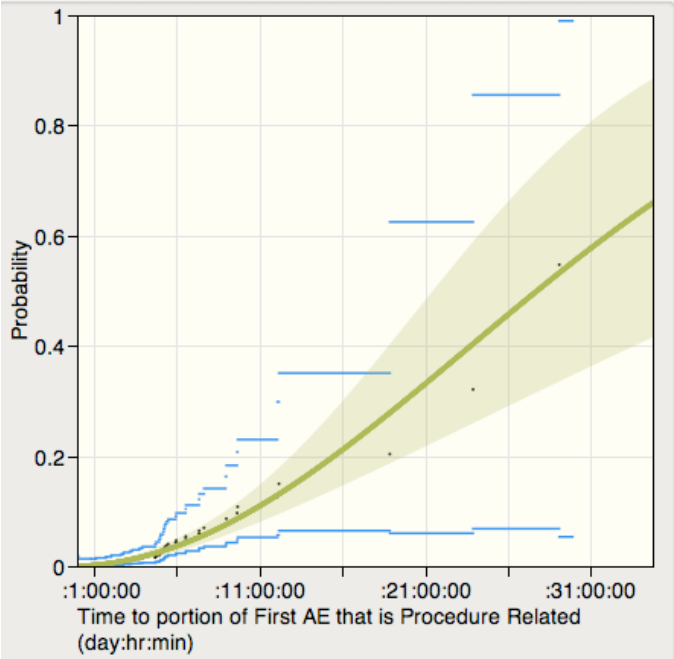


Figure J8: Threshold Weibull cumulative frequency distribution for the portion of first adverse events that are procedural events (F(*t*) estimate)

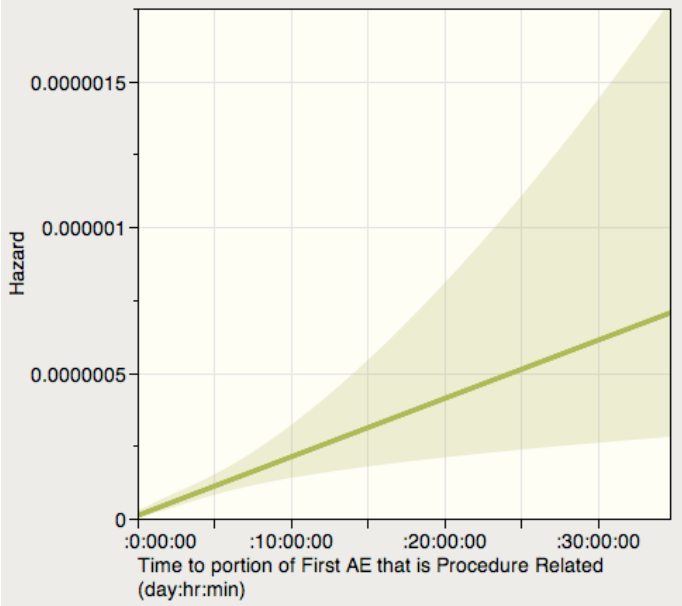


Figure J9: Hazard function (h(*t*)) for patient care injury prophylaxis failures

Table J4: Distribution parameters and criterion for time from admission to the portion of first adverse events that are procedural adverse events

	Parameters			Criterion		
Distribution	Location	Scale	Other	AICc	-2Log-Likelihood	BIC
Threshold Weibull	15.0	0.50	*threshold* : -441450 α : 2934501 β : 1.99	1513.55	1507.53	1529.89
Weibull	15.2	0.63	α : 3903327.1 β : 1.6	1520.26	1516.25	1531.15
Exponential		13346625		1533.80	1531.80	1539.25
Lognormal	16.71	1.99		1548.79	1544.79	1559.69

APPENDIX K

COMPETING CAUSES AND DISTRIBUTION COMPARISONS FOR TIME TO THE FIRST ADVERSE EVENT OF EACH TYPE (PATIENTS MAY HAVE MORE THAN ONE ADVERSE EVENT, BUT ONLY THE FIRST OF EACH TYPE IS INCLUDED

This analysis includes the first of every type of adverse event for each patient. There are a total of 485 AE representing SOPP failures included in these distributions (99 infections, 200 medication events, 131 patient care events and 55 procedural events). If a patient had more of one type of event (e.g. two medication events), only the first of that type was included.

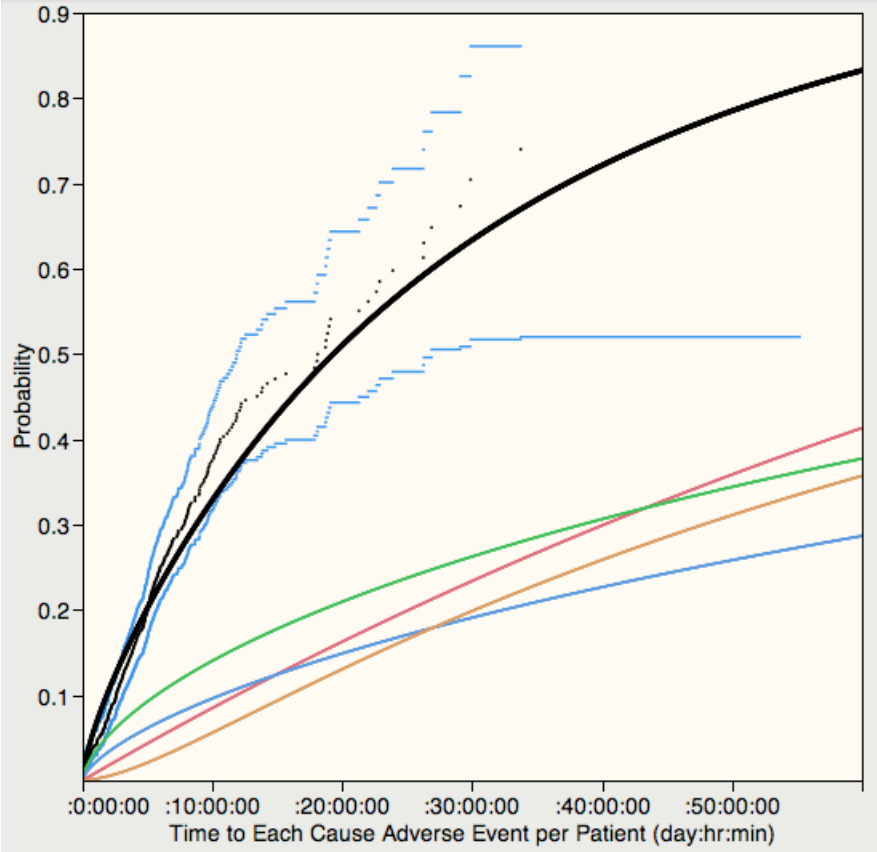


Figure K1: Competing cause distributions of time between admission and the adverse events of each individual type with their aggregated distribution (patients can be counted once in each type of AE)

Red: Exponential distribution of Infection causes; Green: TH Weibull distribution of medication causes; Blue: TH Weibull distribution of patient care causes; Orange: TH lognormal distribution of procedure causes

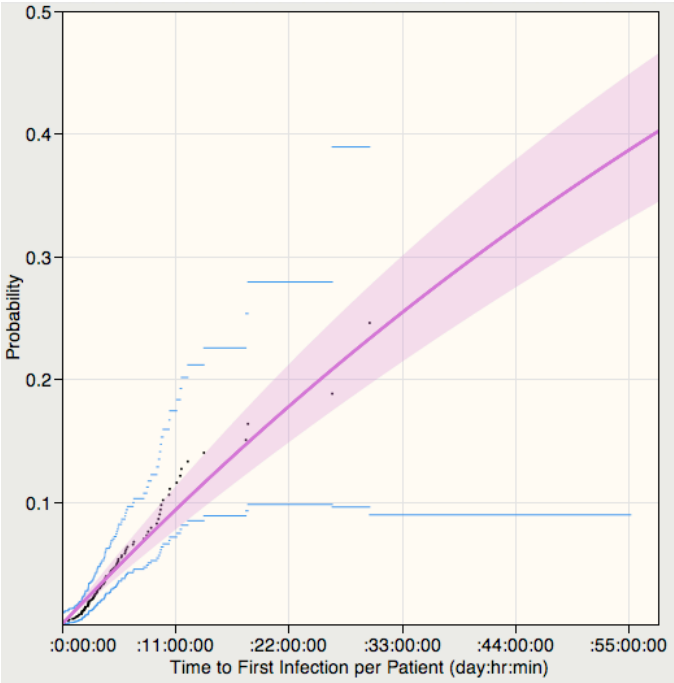


Figure K2: Exponential cumulative frequency distribution for first infection adverse events (F(*t*) estimate) experienced by HF patients

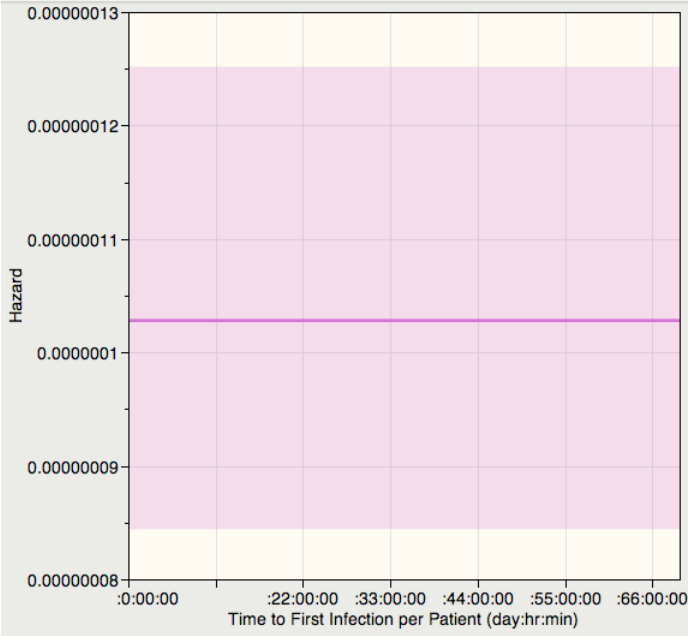


Figure K3: Hazard function (h(*t*)) for infection control SOPP failures

Table K1: Distribution parameters and criterion for time from admission to first infection control SOPP failures

	Parameters			Criterion		
Distribution	Location	Scale	other	AICc	-2Log-Likelihood	BIC
Exponential		9727193.9		3385.91	3383.91	3391.60
Lognormal	17.0	2.35		3410.62	3406.62	3422.01
Weibull	15.9	0.92	α : 7737859.2 β : 1.1	3386.66	3381.58	3404.05
Threshold Weibull	16.0	0.86	α : 6756526 β : 1.2 threshold: -2737	3387.59	3381.58	3404.68

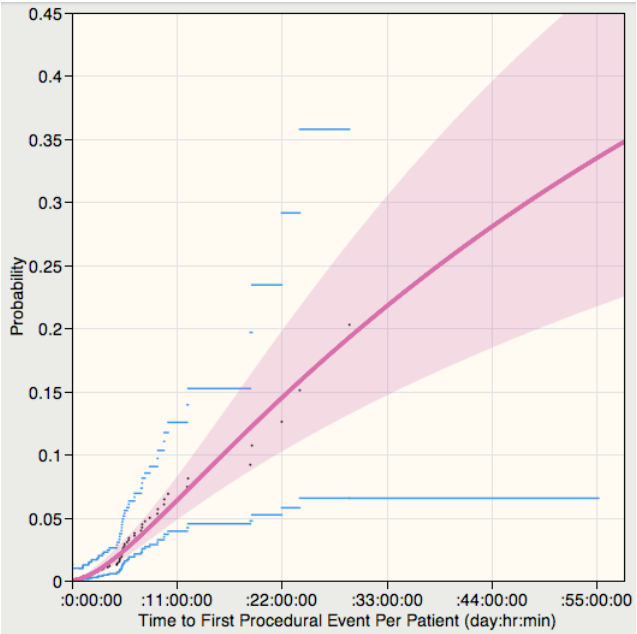


Figure K4: Threshold lognormal cumulative frequency distribution for first procedural adverse events (F(*t*) estimate) experienced by HF patients

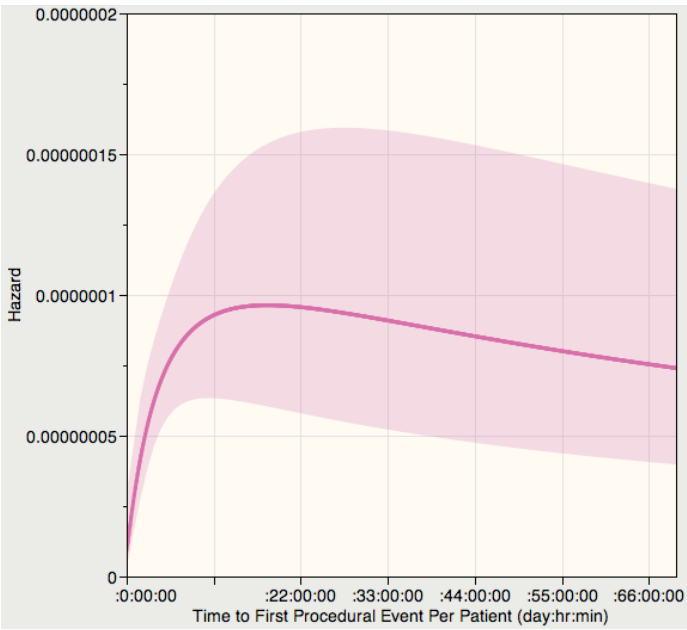


Figure K5: Hazard function (h(*t*)) for safe procedural SOPP failure

Table K3: Distribution parameters and criterion for time from admission to safe medication delivery SOPP failures

	Parameters			Criterion		
Distribution	Location	Scale	other	AICc	-2Log-Likelihood	BIC
Threshold Weibull	17.0	1.57	*threshold* : 60.0 α : 16739366 β : 0.64	6424.07	6418.06	6441.15
Weibull	16.0	1.41	α : 11866322 β : 0.71	6520.77	6516.77	6532.16
Exponential		4814961.0		6556.88	6555.48	6578.57
Lognormal	14.57	3.47		6562.84	6558.84	6574.24

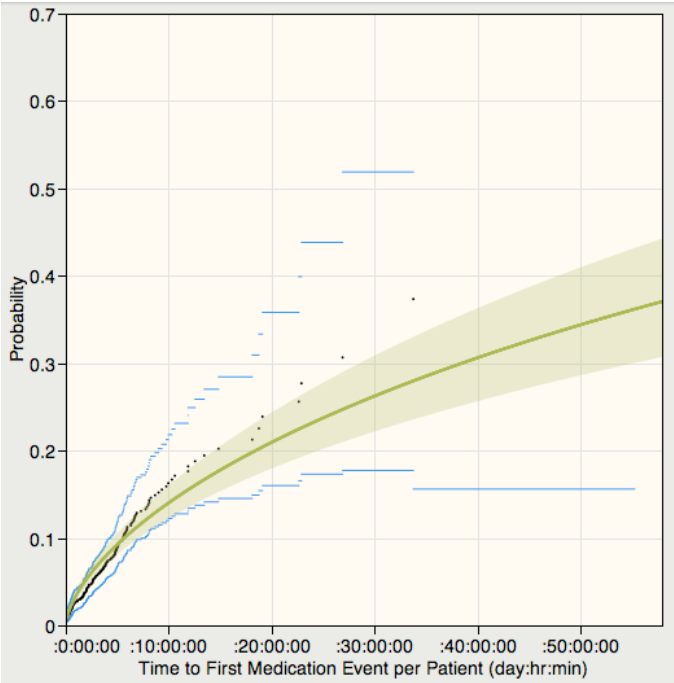


Figure K6: Threshold Weibull cumulative frequency distribution for first medication SOPP failure experienced by HF patients (F(*t*) estimate)

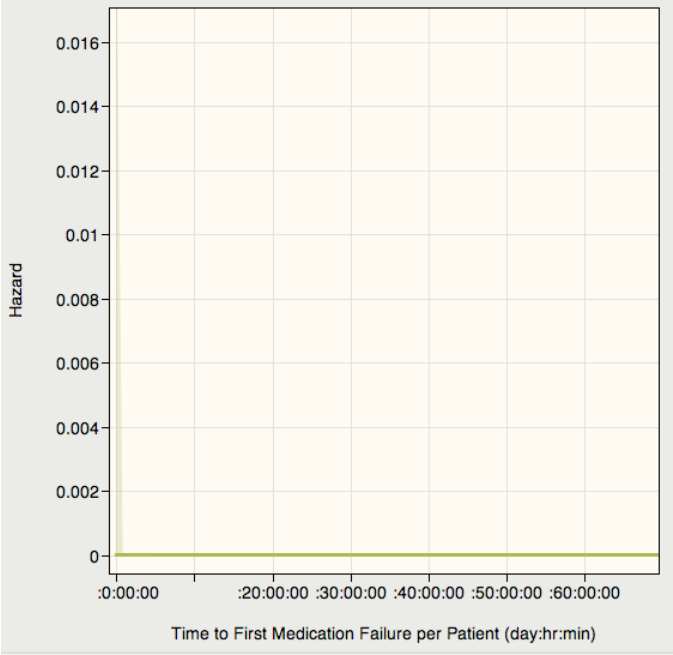


Figure K7: Hazard function (h(*t*)) for safe medication delivery SOPP failures

Table K3: Distribution parameters and criterion for time from admission to safe medication delivery SOPP failures

	Parameters			Criterion		
Distribution	Location	Scale	other	AICc	-2Log-Likelihood	BIC
Threshold Weibull	17.0	1.57	*threshold* : 60.0 α : 16739366 β : 0.64	6424.07	6418.06	6441.15
Weibull	16.0	1.41	α : 11866322 β : 0.71	6520.77	6516.77	6532.16
Exponential		4814961.0		6556.88	6555.48	6578.57
Lognormal	14.57	3.47		6562.84	6558.84	6574.24

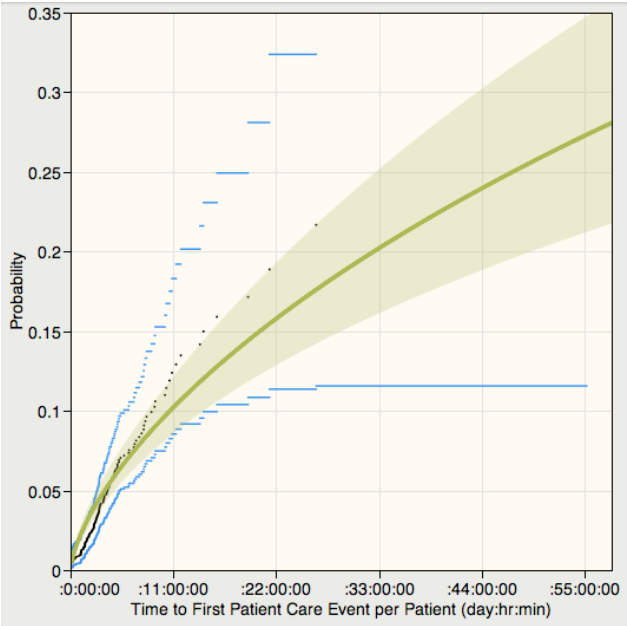


Figure K8: Threshold Weibull cumulative frequency distribution for first patient care injury prophyalxis SOPP failure experienced by HF patients (F(*t*) estimate)

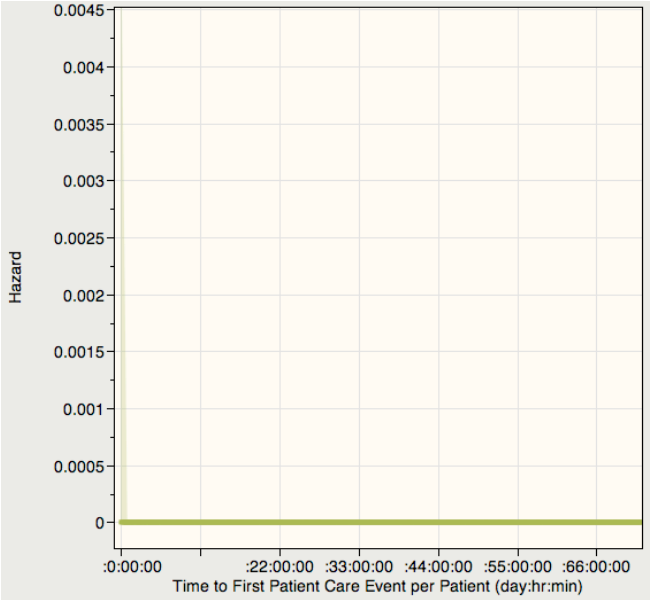


Figure K9: Hazard function (h(*t*)) for patient care injury and illness prophylaxis SOPP failures

Table K4: Distribution parameters and criterion for time from admission to procedural events

	Parameters			Criterion		
Distribution	Location	Scale	other	AICc	-2Log-Likelihood	BIC
Threshold Weibull	17.0	1.49	*threshold* : 60 α : 25998125 β : 0.67	4312.07	4306.06	4329.15
Weibull	17.0	1.27	α : 14733064 β : 0.77	4396.37	4392.38	4407.78
Exponential		7351085.5		4406.32	4404.31	4412.01
Lognormal	18.26	3.41		4432.33	4428.32	4443.72

APPENDIX L

ADMINISTRATION PERSPECTIVE: ANALYSIS OF FAILURES IN STANDARD POLICIES AND PROCEDURES FOR INFECTION CONTROL FOR HOSPITALIZED PATIENTS THROUGH DURATION OF STUDY (2005-2007)

Table L1: Parameters and fit criterion for Weibull distribution of time (days) between recurrent hospital acquired infections through period of study (2005-2007)

Parameters			Criterion		
Location	Scale	Other	AICc	-2Log-Likelihood	BIC
0.47	1.09	α : 1.59 β : 0.92	325.95	321.83	331.18

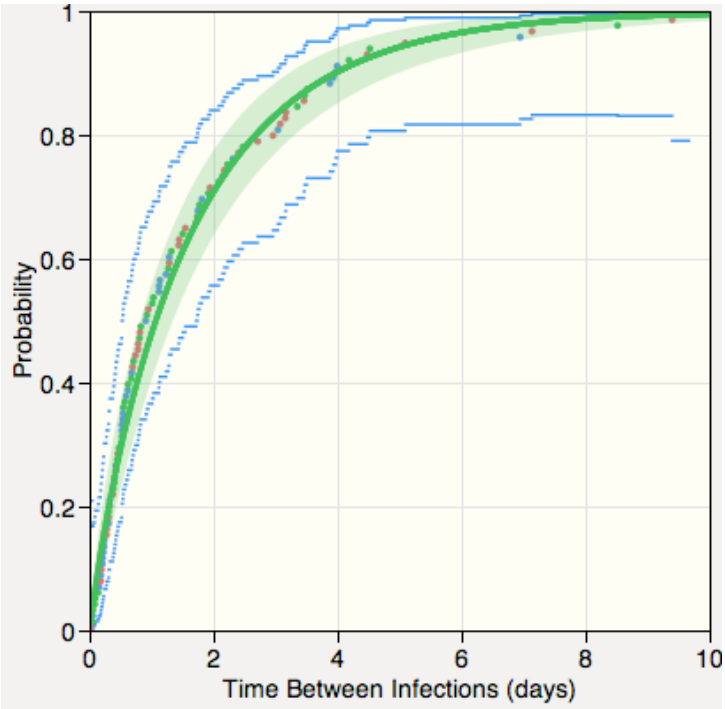


Figure L1: Weibull distribution of time (days) between recurrent hospital acquired infections through period of study (2005 – 2007)

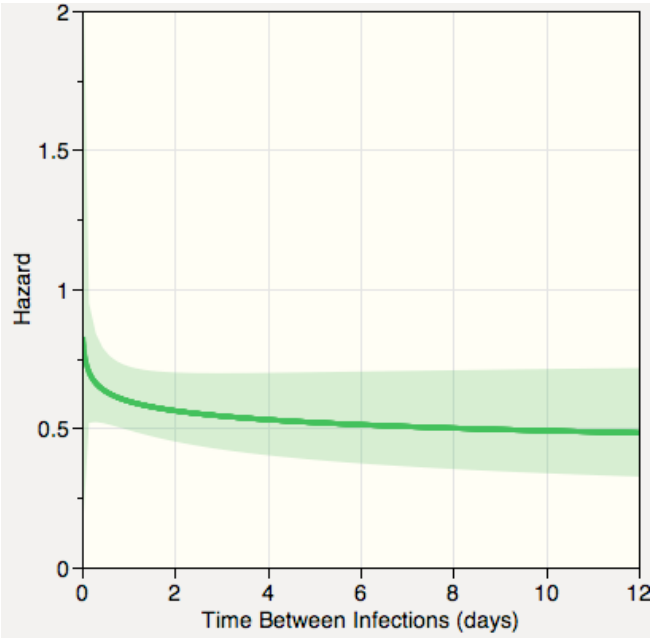


Figure L2: Hazard of recurrent failure of the standard operating procedures and policies for infection control during the period of study (2005 – 2007)

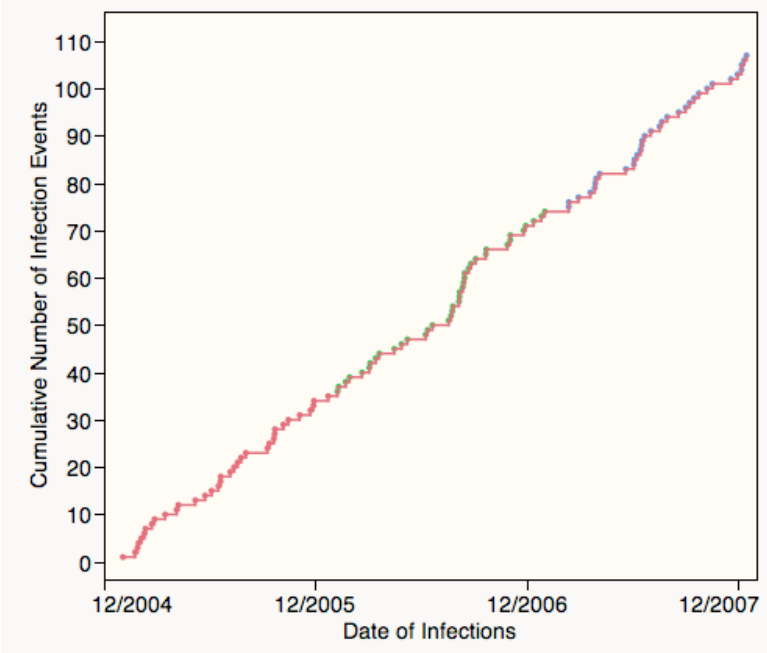


Figure L3: Cumulative failures of the standard operating procedures and policies for infection control during the period of study (2005-2007)

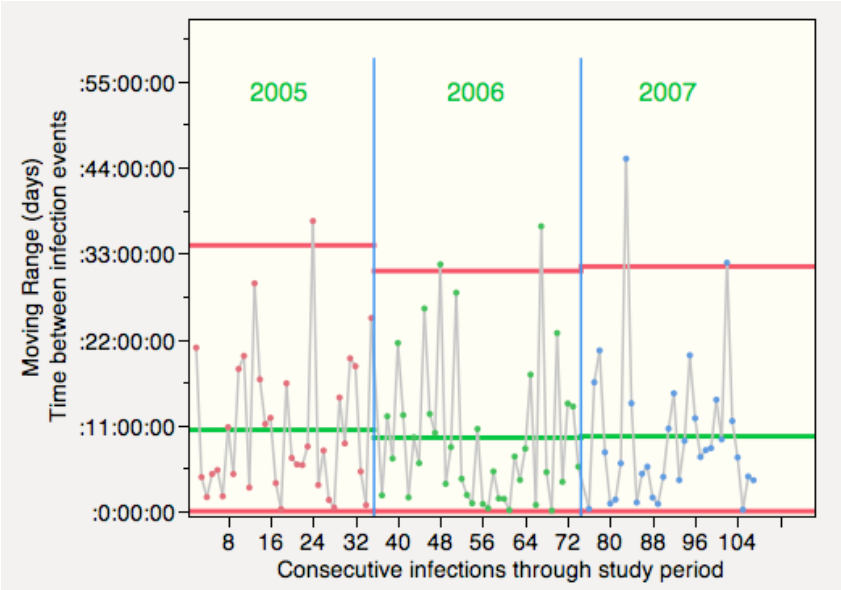
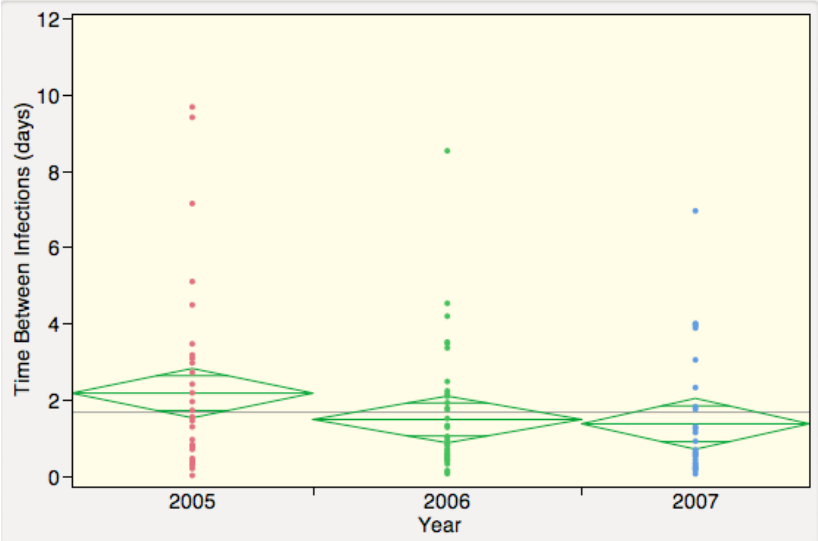


Figure L4: Moving range statistical process control of consecutive failures in the standard operating procedures and policies for infection control during the period of study by year (2005-2007)



Prob > F
0.17

Figure L5: ANOVA of time between failures of the standard operating procedures and policies for infection control during the period of study by year (2005-2007)

APPENDIX M

ANALYSIS OF FAILURES IN STANDARD POLICIES AND PROCEDURES FOR SAFE MEDICATION DELIVERY FOR HOSPITALIZED PATIENTS THROUGH TIME PERIOD OF STUDY (2005-2007)

Table M1: Parameters and fit criterion for threshold Weibull distribution of time (days) between recurrent medication events through period of study (2005-2007)

Parameters			Criterion		
Location	Scale	Other	AICc	-2Log-Likelihood	BIC
0.60	1.18	α : 1.83 β : 0.84 threshold: -4.44×10^{-16}	825.43	819.33	835.87

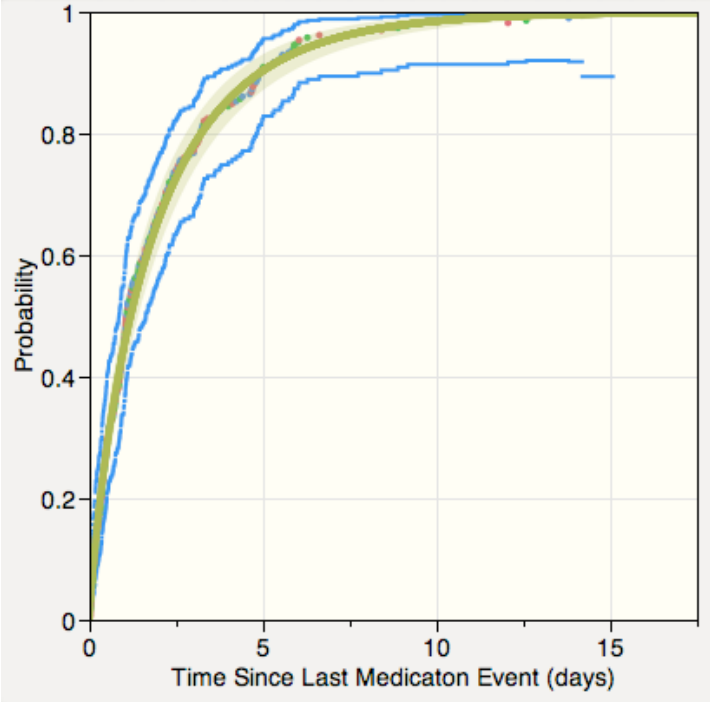


Figure M1: Threshold Weibull distribution of time (days) between recurrent medication events through period of study (2005-2007)

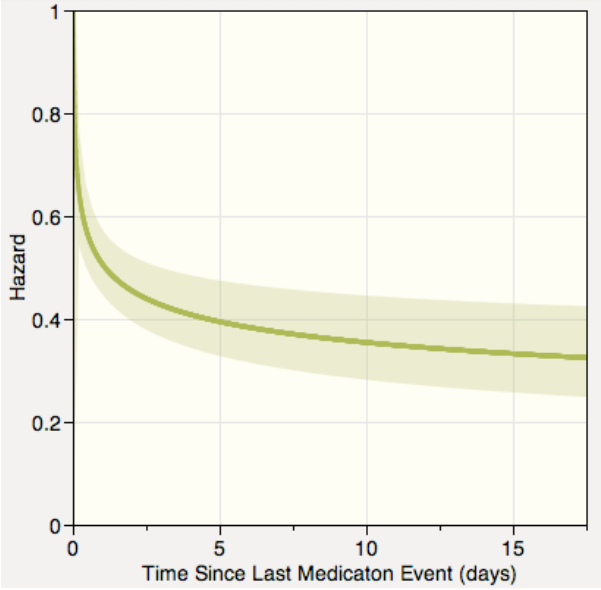


Figure M2: Hazard of recurrent failure of the standard operating procedures and policies for safe medication practices during the period of study (2005-2007)

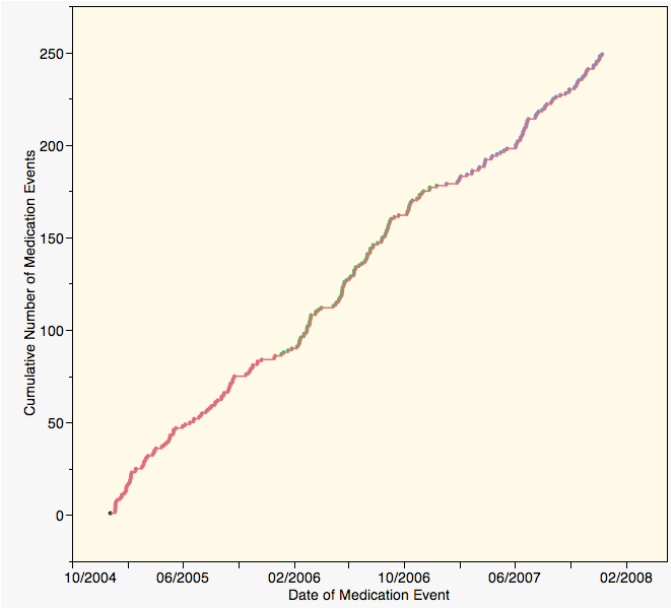


Figure M3: Cumulative failures of the standard operating procedures and policies for safe medication practices during the period of study (2005-2007)

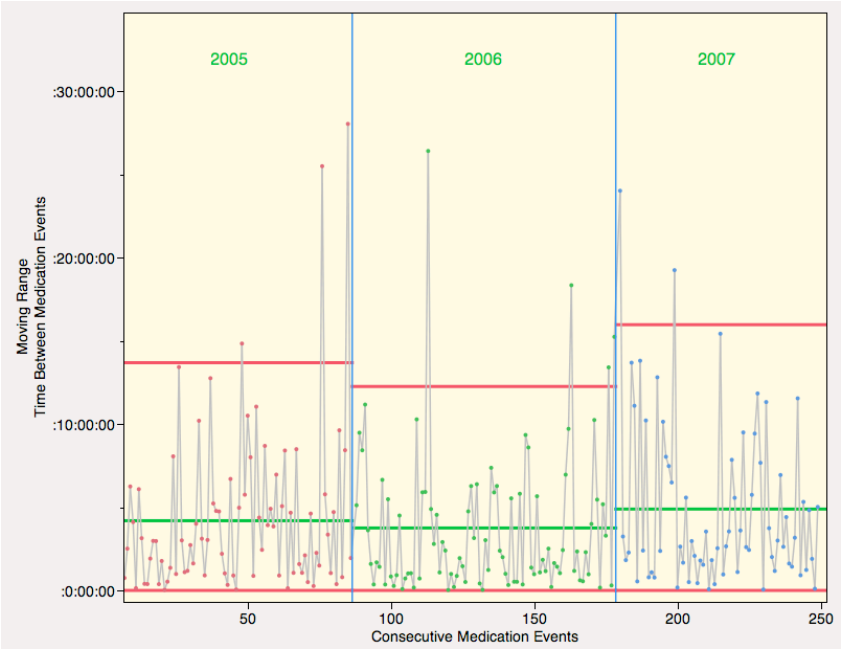


Figure M4: Moving range statistical process control of consecutive failures in the standard operating procedures and policies for safe medication practices during the period of study by year (2005-2007)

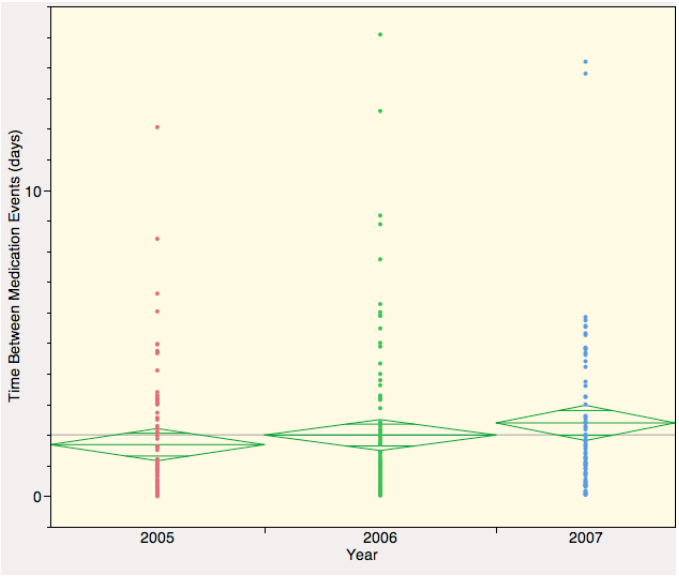


Figure M5: ANOVA of time between failures of the standard operating procedures and policies for safe safe medication practices during the period of study by year (2005-2007)

APPENDIX N

ANALYSIS OF FAILURES IN STANDARD POLICIES AND PROCEDURES FOR SAFE MEDICATION DELIVERY FOR HOSPITALIZED PATIENTS THROUGH TIME PERIOD OF STUDY (2005-2007)

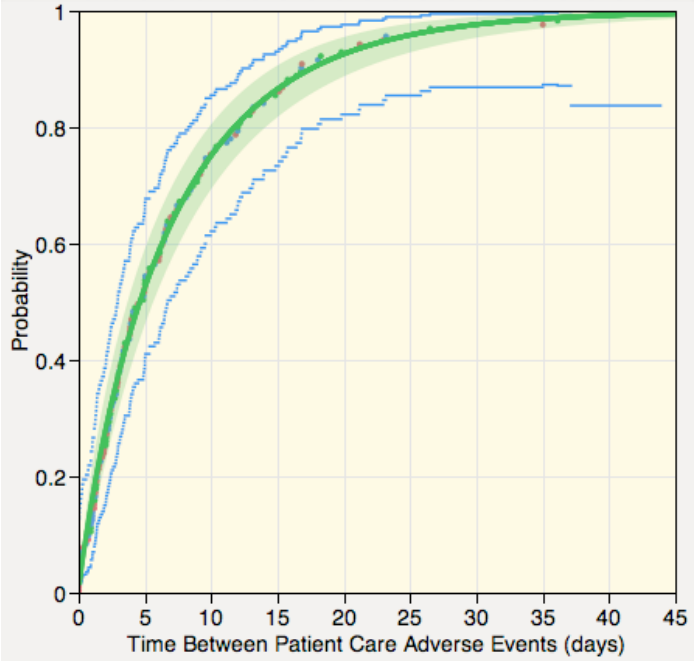


Figure N1: Weibull distribution of time (days) between recurrent patient care events through period of study (2005-2007)

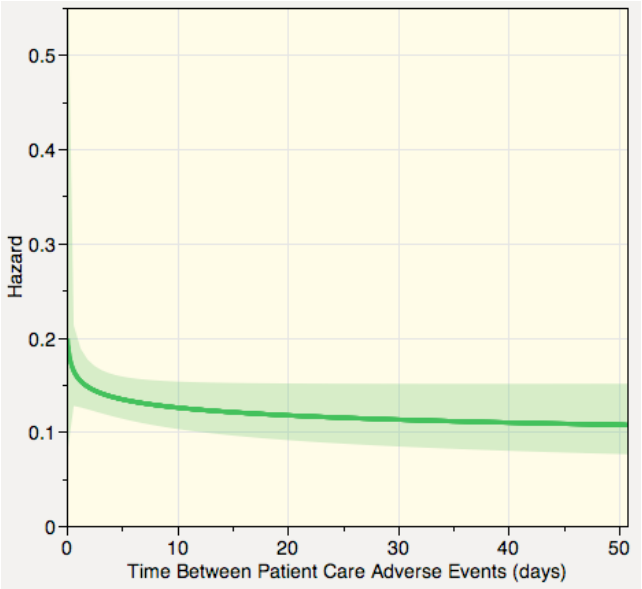


Figure N2: Hazard of recurrent failure of the standard operating procedures and policies for prophylaxis against patient care events during the period of study (2005-2007)

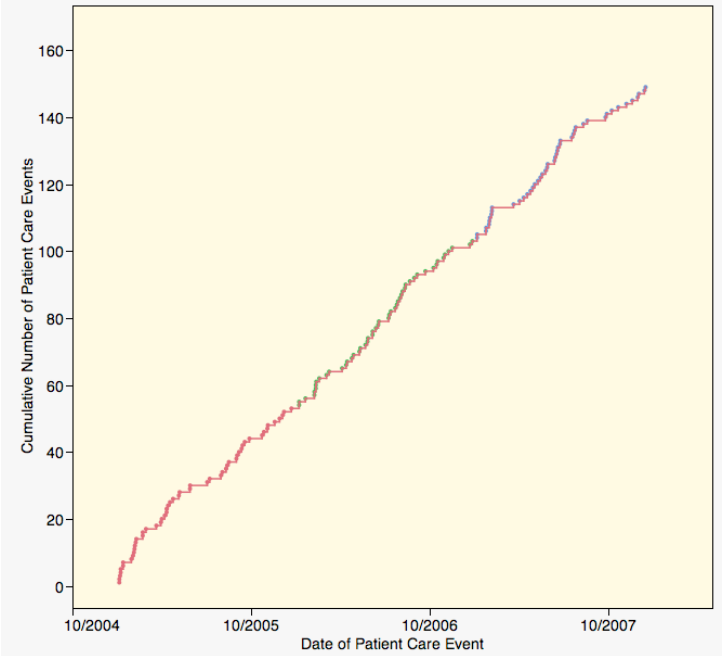


Figure N3: Cumulative failures of the standard operating procedures and policies for prophylaxis against patient care events during the period of study (2005-2007)

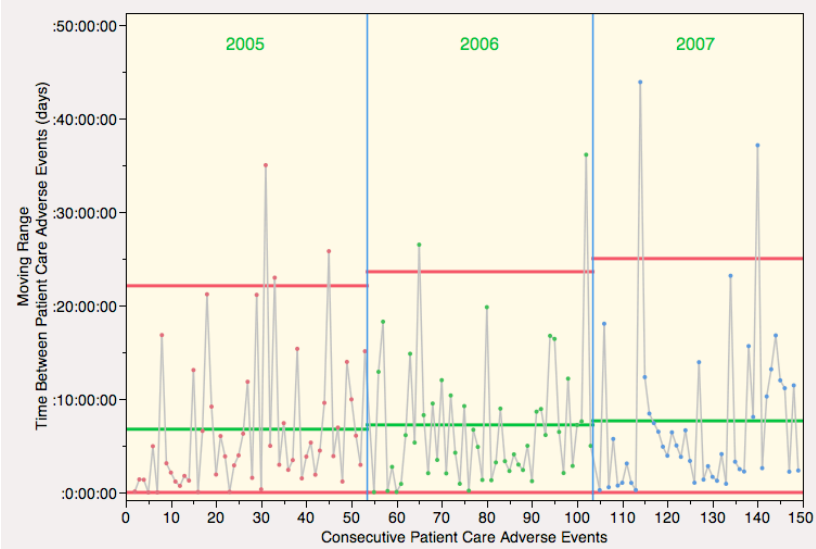


Figure N4: Moving range statistical process control of consecutive failures in the standard operating procedures and policies for prophylaxis against patient care events during the period of study (2005-2007)

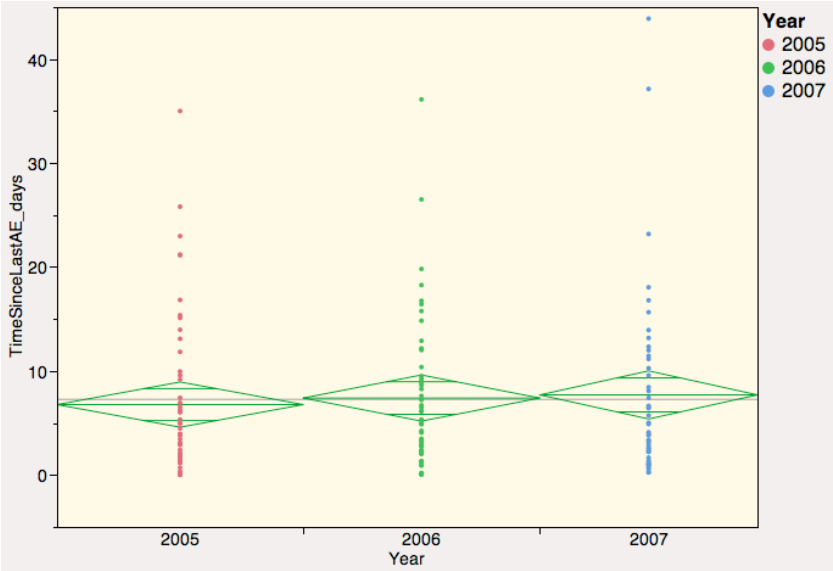


Figure N5: ANOVA of time between failures of the standard operating procedures and policies for prophylaxis against patient care events during the period of study by year (2005-2007)

APPENDIX O

ANALYSIS OF FAILURES IN STANDARD POLICIES AND PROCEDURES FOR SAFE PROCEDURES FOR HOSPITALIZED PATIENTS THROUGH TIME PERIOD OF STUDY (2005-2007)

Table O1: Parameters and fit criterion for Weibull distribution of time (days) between recurrent procedural events through period of study (2005-2007)

Parameters			Criterion		
Location	Scale	Other	AICc	-2Log-Likelihood	BIC
2.82	1.08	α : 16.81 β : 0.93	474.26	470.05	478.27

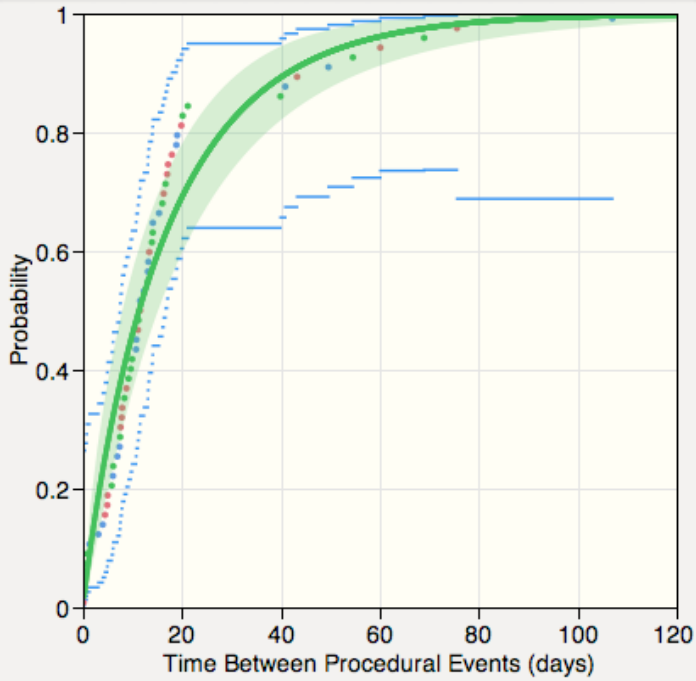


Figure O1: Hazard of distribution of time (days) between recurrent procedural events through period of study (2005 – 2007)

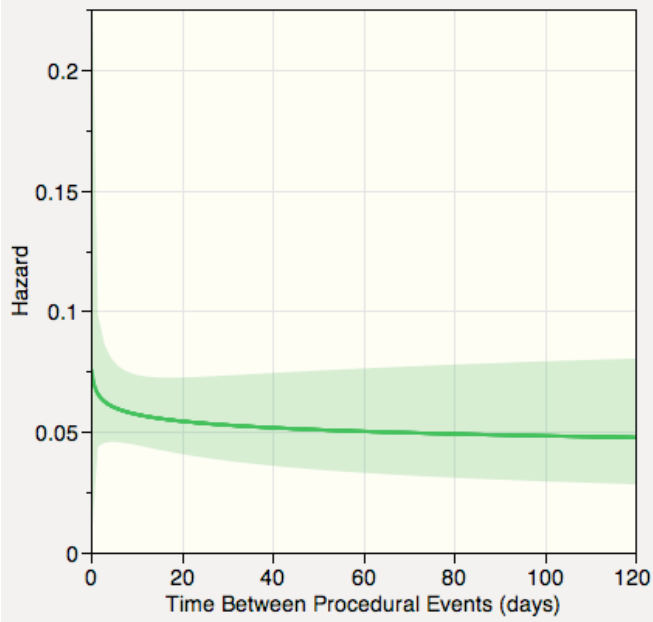


Figure O2: Hazard of recurrent failure of the standard operating procedures and policies for safe procedures during the period

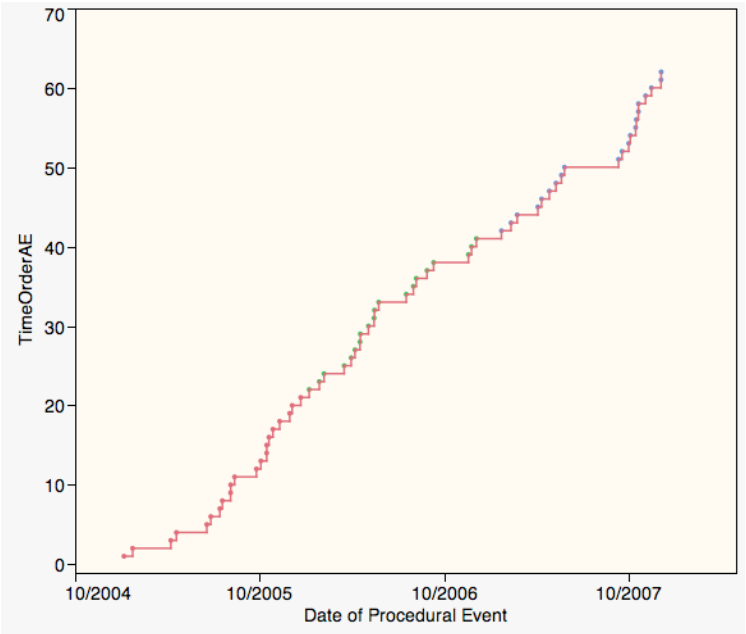


Figure O3: Cumulative failures of the standard operating procedures and policies for safe procedures during the period of study (2005-2007)

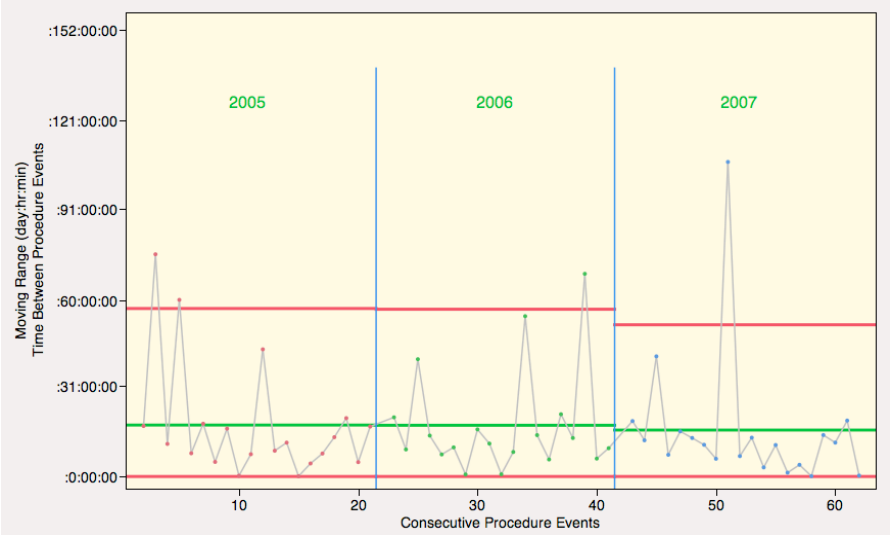


Figure O4: Moving range statistical process control of consecutive failures in the standard operating procedures and policies for safe procedures during the period of study by year (2005-2007)

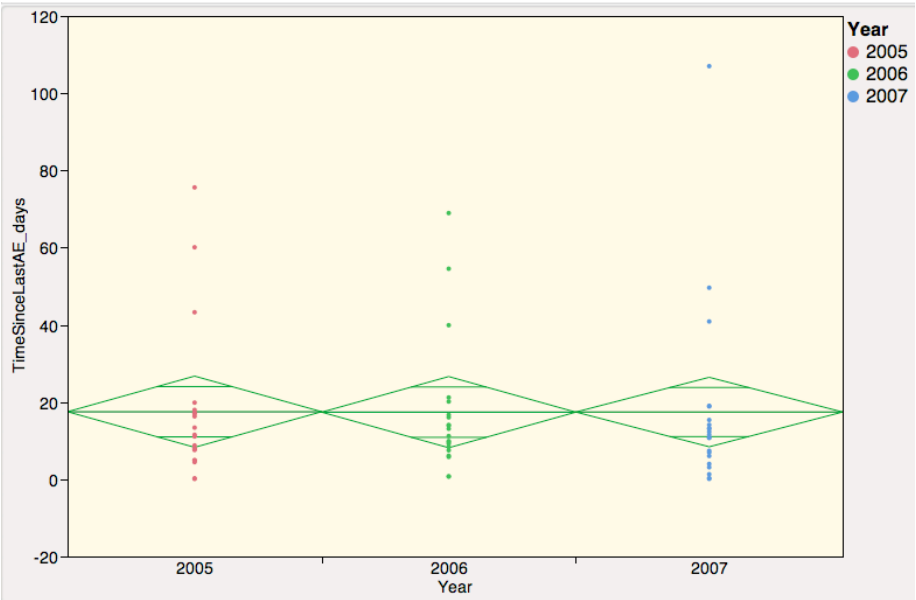


Figure O5: ANOVA of time between failures of the standard operating procedures and policies for safe procedures during the period of study by year (2005-2007)

BIOGRAPHICAL SKETCH

Jeanne M. Huddleston, MD, FACP, **FHM,** is the co-Director of the Health Care Systems Engineering Program at Mayo Clinic. She is a past President of the Society of Hospital Medicine, the founder of Hospital Medicine and its Fellowship at Mayo Clinic, Rochester, MN. She is a Chair of Mayo Clinic's Mortality Review Subcommittee, a multi-disciplinary group of providers that review every death in search of where the health care delivery system may have failed the providers and/or the patient. She received her MD degree in 1993 from the College of Human Medicine, Michigan State University. She completed her residency in internal medicine and advanced general medicine fellowship at Mayo Clinic. Dr. Huddleston is a Harvard Macy Scholar (both in the Physician Educator and the Leadership Programs) and alumnus of the Health Forum/AHA Patient Safety Leadership Fellowship. Dr. Huddleston is currently a NIH scholar (K12) funded to obtain Masters' Degrees in both Clinical Research and Industrial Engineering. This education will focus and intensify her scholarly translation of systems engineering to health care delivery in an effort to improve the value of the healthcare experience for patients, their families and the providers.