2018

Reducing Sepsis Mortality: A Cloud-Based Alert Approach

Janet A. Zink
Virginia Commonwealth University

Reducing Sepsis Mortality: A Cloud-Based Alert Approach

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

Janet A. Zink
MS in Management Information Systems, Nova Southeastern University, 2003
BS in Medical Technology, Florida Atlantic University, 1996

Director: Dr. Jonathan P. DeShazo
Associate Professor, Department of Health Administration

Virginia Commonwealth University
Richmond, Virginia
December, 2018

Acknowledgement

I would like to thank everyone involved in assisting me in bringing this project to fruition. I am very appreciative of the encouragement from my family, in particular my brother Bryan, whose personal integrity and warm support has helped bolster me throughout the process. I would also like to acknowledge my nieces Katherine, Kristyn, Kayla, and Hannah, who always inspire me to see the world with fresh eyes, and I am very grateful to be an aunt, mentor and friend to each of them. My close friends Erin, Tina, Aysé, and Kaye also deserve mention for uplifting me across the decades and miles.

Dr. Jonathan DeShazo, my dissertation committee chair, has been indispensable as a colleague, collaborator, and advisor. His seasoned guidance and expertise in informatics has assisted me in the refinement and direction of the manuscript. Committee member Dr. Jessica Mittler's expertise in statistical methods and overall composition was similarly appreciated. Likewise, I am indebted to Dr. Robert Rooney for his unwavering belief in me and my potential, which has inspired me greatly in my academic career. Everyone who has provided aid, including dissertation committee members, professors, my cohort mates, data analysts, administrative staff, and many others also deserve thanks.

Table of Contents

List of Tables

List of Figures

List of Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
AMI	Acute myocardial infarction
ARRA	American Recovery and Reinvestment Act
BIG	Biorepository for Integrative Genomics
CDS	Clinical Decision Support
COPD	Chronic Obstructive Pulmonary Disease
CPOE	Computerized Physician (or Prescriber) Order Entry
ED	Emergency Department
EMR	Electronic Medical Record
HCI	Human-Computer Interaction
HHS	U.S. Department of Health & Human Services
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health
HR	Heart rate
IBM	International Business Machines
ICD	International Classification of Diseases
MAP	Mean arterial pressure
MEWS	Modified Early Warning Score
ICU	Intensive Care Unit
RCT	Randomized Controlled Trial
RR	Respiratory rate
SBP	Systolic blood pressure
SIRS	Systemic Inflammatory Response Syndrome
SSC	Surviving Sepsis Campaign
TREWScore	Targeted Early Warning System Score
VCU	Virginia Commonwealth University
VTE	Venous thromboembolism
WBC	White blood cell
WHO	World Health Organization

Abstract

REDUCING SEPSIS MORTALITY: A CLOUD-BASED ALERT APPROACH

By Janet A. Zink, Ph.D.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2018

Major Director: Dr. Jonathan P. DeShazo
Associate Professor, Department of Health Administration

Sepsis is a fatal whole-body inflammation caused by severe infection. Every year, about a quarter of a million Americans are stricken with severe sepsis, and up to 50 percent of them die as a direct result. Factors such as increased life expectancy, antibiotic resistance, and broader use of immunosuppressive agents have caused the number of cases to continue to rise by eight percent per year. Therefore, timely recognition of sepsis is crucial to the initiation of evidence-based therapeutic measures that can prevent the eventual breakdown of organ systems, shock, and resultant death.

The aim of this study is to examine the impact of a cloud-based clinical decision support (CDS) alerting system for systemic inflammatory response syndrome (SIRS), a precursor to sepsis, and sepsis itself, on adult patient and process outcomes at Virginia Commonwealth University (VCU) Health System. The two main hypotheses are: 1) the implementation of cloud-

based SIRS and sepsis alerts will lead to lower sepsis-related mortality and lower average length of stay, and 2) the implementation of cloud-based SIRS and sepsis alerts will lead to more frequent ordering of the Sepsis Initial Resuscitation PowerPlan (order set bundle) and more recording of sepsis diagnoses. To measure these outcomes, data were collected from September 2013 through December 2016 after the implementation of a sepsis cloud-based alerting system within the Cerner EMR. A pre-implementation group diagnosed with sepsis within the year leading up to the alert intervention consisted of 1,551 unique inpatient visits, and the three-year post-implementation sample size was 9,711 visits, for a total cohort of 11,262 visits over the course of four years. Logistic regression and multiple linear regression were used to test the hypotheses.

Linking cloud-generated SIRS and sepsis alerts with clinical outcomes fills a unique gap in the informatics literature. It does so by measuring the clinical performance of an evidence-based alerting method for promoting maximally effective prevention and treatment practices to combat sepsis-related mortality. Study results showed that, post-alert activation, sepsis-related mortality was slightly higher after the implementation of SIRS alerts, but the presence of sepsis alerts did not have a significant relationship to mortality. The average length of stay and the total number of recorded sepsis diagnoses were higher after the implementation of both SIRS and sepsis alerts, while ordering of the Sepsis Initial Resuscitation PowerPlan was lower. There is preliminary evidence from this study that more sepsis diagnoses are made as a result of alert adoption, suggesting that clinicians can consider the implementation of cloud-based SIRS and sepsis alerts in order to capture a higher number of sepsis diagnoses.

Chapter 1: Introduction

Overview

According to a report issued by the Agency for Healthcare Research and Quality (AHRQ), certain healthcare IT applications, including those that provide clinical decision support (CDS) to medical providers, lead to better patient outcomes in terms of reduced patient length of stay and lower rates of hospital-related mortality (Berner, 2009). As Brokel et al. (2011) point out, automated CDS alerts can increase adherence to protocols and bolster surveillance and monitoring for disease conditions. Sucher, Moore, Todd, Sailors & McKinley (2008) similarly state that CDS alerts offer a method to standardize treatment, test interventions, and certify quality of care improvements.

Sepsis is a common and potentially life-threating complication of infection, with a sudden onset and subsequent rapid progression ("Sepsis Fact Sheet", 2017). With 751,000 new cases each year, and 215,000 resultant fatalities, timely diagnosis of sepsis is crucial to condition management (Guerra, Mayfield, Meyers, Clouatre, & Riccio, 2013). A key driver of inpatient mortality is sepsis, and it is the tenth most common cause of death in the U.S. (Guerra et al., 2013). It is also only one of two infectious conditions listed in the top 15 causes of death (Melamed & Sorvillo, 2009). Severe sepsis occurs when sepsis causes organ malfunction, such as kidney, lung, liver, or heart failure, and inadequate blood flow to various parts of the body (Maggio & Carvahlo, 2017; Wiedemann, 2007). A trend analysis conducted by (Dombrovskiy,

Martin, Sunderram, & Paz, 2007) revealed that during the period from 1993 to 2003, the rate of patients hospitalized for severe sepsis nearly doubled, and that the resultant mortality rate had likewise increased. As the U.S. population ages, this scenario is expected to become even more common. For example, those between 65 and 70 years of age have a 5-fold higher chance than average of being hospitalized for pneumonia, the most common infectious cause of severe sepsis (Yende, Iwashyna, & Angus, 2014).

From a financial perspective, severe sepsis costs the United States an average of $22,100 per case. Even higher expenditures were associated with neonates, intensive care unit (ICU) patients, surgical patients, and those with multiple organ failure (Angus et al., 2001). By 2011, sepsis-related costs had amounted to more than $20 billion, and 5.2 percent of the total expenditures for all hospitalizations annually ("Sepsis Study Comparing", 2014). Per the AHRQ, it was the single-most expensive condition to treat in 2011, out of a list of 20, including acute myocardial infarction and pneumonia (Torio & Andrews, 2013). Sands et al. (1997) also noted that a substantial portion of severe sepsis cases develop outside ICUs. As per their study of eight academic medical centers, these accounted for 41% of the incidents of diagnosed sepsis.

A systematic international overview of hospital-treated and severe sepsis, spanning a period of 36 years, concluded that hospital-related mortality averaged 17% and 26% for sepsis and severe sepsis, respectively (Fleischmann et al., 2016). The meta-analysis was based on 27 studies of high-income countries. Fleischmann et al. also asserted that an annual sepsis rate of 31.5 million, a severe sepsis rate of 19.4 million, and at least 5.3 million deaths were extrapolated to the rest of the world, based on a population of 7.2 billion. According the authors, this may even be a significant underestimate, as valid studies on sepsis epidemiology in low to middle-income countries are generally not available. Some of the increase seen in diagnosed

sepsis cases may be due, in certain countries, to the growing use of coding favorable to reimbursement for sepsis (Singer et al., 2016).

The Sepsis Definitions Task Force (Sepsis-3), as convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, has worked to improve sepsis diagnostic criteria in order to hasten the recognition and early intervention for patients at risk. It recognizes that even patients who survive sepsis struggle with long-term physical, psychological, and cognitive dysfunction (Singer et al., 2016). There is also evidence of immune system disruption, which renders the patient more vulnerable to dying, even several years later ("Sepsis Fact Sheet", 2017). The one-year survival rate of those who suffer from a bout of severe sepsis is 34% (Linner et al., 2013). Providing immediate goal-directed therapy upon diagnosis is essential to reducing sepsis-related mortality from the accompanying infection and eventual organ dysfunction and shock (Rivers & Ahrens, 2008). According to Rivers et al. (2008), therapeutic intervention within six hours of a diagnosis of severe sepsis or severe septic shock has significant short and long-term benefits, including the restoration of oxygen balance and prevention of cardiac circulatory collapse. Timely management of symptoms can mitigate the development of sepsis for those patients most at risk (Singer et al., 2016).

This study will examine CDS alerts for systemic inflammatory response syndrome (SIRS), a precursor to sepsis, and sepsis itself as to their effectiveness in reducing sepsis-related mortality at Virginia Commonwealth University (VCU) Health System. These are specialized CDS alerts that clinicians, defined as physicians or nurses, see as they are working in the computerized charting system, or electronic medical record (EMR). Continual real-time assessment of newly entered vital signs and laboratory results that have been designated as SIRS and sepsis criteria occurs via the cloud, a type of internet-based computing. A separate algorithm

then determines if the patient has SIRS or sepsis based on these physiological and lab data elements, and immediately generates a pop-up alert in the patient's EMR chart for any clinician that has a designated relationship with the patient.

Background

Timely diagnosis is crucial to the management of sepsis, and the initiation of early goal-directed therapy is imperative to reducing sepsis-related mortality. Internationally, there are tens of millions of cases per year, and increasing lifespans continue to drive the burden of sepsis-related mortality upward (Melamed & Sorvillo, 2009). Patients in intensive care units are particularly susceptible as they are subject to multiple invasive procedures and already experiencing immunosuppression (Moore et al., 2010). Those hospitalized for sepsis are on average more than eight times as likely to die during their hospitalization, and incidence rates more than doubled from 2000 through 2008. (Hall et al., 2011). Reducing mortality requires both quick recognition and uniform and consistent application of evidence-based measures. The Surviving Sepsis Campaign (SSC), a committee of 30 international organizations with expertise on sepsis, convened in 2012 in order to achieve a consensus on comprehensive recommendations for sepsis treatment. One of their strongest recommendations included resuscitation of the patient within these first six hours after sepsis has been identified (Dellinger et al., 2013). Reliance on manual identification of these patients means missing many critical opportunities for intervention (Guerra et al., 2013).

CDS alerts, usually developed locally by hospital information technology staff, have had varying levels of success in improving outcomes due to the timing and complexity involved in the onset of SIRS and sepsis. To address this, Cerner Healthcare Corporation developed a cloud-based SIRS and sepsis detection algorithm that continually crawls (i.e. searches) the clinical

database looking for values aligning with established criteria for SIRS and sepsis. It gathers patient data and discerns patterns for the purpose of proactive risk identification. This data is comprised of laboratory test and vital sign orders that are placed at recommended evidence-based intervals. When the system finds three signs of SIRS, a SIRS alert is generated. When at least two signs of SIRS and one sign of organ dysfunction are found, sepsis alerts are generated (see Table 1 for a comprehensive list of criteria). The algorithm will always evaluate the most recent result for any qualifying criterion, and it uses more stringent physiologic values for sepsis than the conventional standard. The qualifying heart rate (HR) is greater than 95 versus 90, the respiratory rate is greater than 22 versus 20, and three of four SIRS criteria or two of four with one indicator of organ dysfunction is used rather than two or more. (Kaplan & Pinksy, 2011). While they are signed into PowerChart, clinicians receive SIRS and sepsis alerts (see Appendices A & B) on qualifying patients for whom they are responsible. When the patient presents with SIRS, a rapid pattern of deterioration emerges and they may soon progress on to sepsis, septic shock, and death, once the initial indicators have appeared. SIRS and sepsis are identified by the algorithm when criteria in Table 1 are found in the EMR.

Table 1

SIRS & Sepsis Alert Criteria used by the VCU Health System

Criteria for SIRS and Sepsis Alerts	
(Ranges may change based on patient's age)	
SIRS Alert - The patient must meet at least three SIRS criteria:	Sepsis Alert - The patient must meet at least two SIRS criteria and one Organ Dysfunction criterion:
Temp (>38.3°C or <36°C)	Lactic Acid Level (>2.0 mmol/L)
HR (>95 bpm)	SBP (<90 mmHg)
RR (>22 b/min)	MAP (<65 mmHg)
Glucose Level (>180 mg/dL or <50 mg/dL)	Creatinine Level (0.5 mg/dL increase)
WBC (>12 K/CMM or <4 K/CMM)	Total Bilirubin (>2 mg/dL)
Bands (>10% immature neutrophils)	

In this study, the clinically-activated SIRS or sepsis alert is the intervention that the relevant clinicians received. The delivery method was Cerner's Discern Notify alerting functionality. When a clinician signs in to PowerChart, the EMR used for charting, a relationship, i.e. assignment, is automatically established with all of the patients on the clinician's designated unit. If a patient meets the criteria established for a SIRS or sepsis alert, based on the continuously running sepsis-detection algorithm, a flashing red exclamation point icon appears in the lower right-hand corner of the chart. This occurs each time a clinician that is linked with the patient signs in. The clinician must then click on the icon in order to expand the alert on the screen and read the instructions on how to proceed, otherwise the red exclamation point will persist until the alert is acknowledged by clicking on it. The alerts themselves contain patient identifying information such as name, medical record number, birthdate, location, and the clinical criteria that generated the alert (See Appendices A & B). There are also numbered steps for the clinician to take, including reassessing vital signs, contacting the physician, documenting actions taken, and escalating to the Chief of Staff in the event of a non-timely response by the covering provider. The addition of an associated therapeutic PowerPlan, called Sepsis Initial Resuscitation, is recommended. It is a Cerner order set bundle specific to a plan of care. The plan includes initial evaluative laboratory tests, a chest x-ray, oxygen therapy, and various medications including continuous infusions, antimicrobials, vasoactive agents, and corticosteroids (See Appendix C).

Prior to the alert implementation, VCU Health System collected alert data via a "silent mode" process for six months, which coincided with the latter half of the pre-implementation period. Clinicians did not see any real alerts generated in the EMR during this time. This was an important step that was done in order validate the alert algorithm's sensitivity and specificity, so

that feedback could be incorporated, and reference ranges adjusted if needed. The only changes made were to exclude patients in surgery and recovery room suites for the periods they were in those areas. Once the "silent mode" alert evaluation process was complete, the alerts were turned on in the production environment. The alerts were switched on concurrently for all inpatient units, with the exception of pediatrics.

Study Aim

The overarching aim of this prospective study was to determine whether the implementation of a Cerner cloud-based SIRS and sepsis alerting system, customized for VCU Health System by the primary investigator (PI), resulted in a significant reduction of sepsis-related mortality. The alerts were also anticipated to lead to lower average length of stay due to earlier sepsis-related intervention and treatment. Additionally, more timely diagnoses of sepsis and higher consistent application of interventional order set protocols were anticipated.

Process Model

Figure 1 displays a process model developed by the primary investigator that depicts the progression from the EMR-based algorithmic evaluation, to the alerts, and then on to the anticipated outcomes. First, all VCU Health System inpatients aged 18 and over are continually screened by the cloud-based sepsis algorithm. The system-generated laboratory and physiological values, as delineated in Table 1, trigger either a SIRS or sepsis alert. The SIRS alert will continue to be triggered every 24 hours as long as the patient qualifies for it, and the sepsis alert is triggered every 48 hours per patient, per user. Should the patient be treated successfully for either SIRS or sepsis, the alerts will not continue to be generated. Once a particular SIRS or sepsis alert is opened by an assigned clinician, it will not appear again for the same user. The same alert will be displayed to another clinician if it has not been viewed and

dismissed by clicking on the red exclamation point in the lower right-hand corner of the chart. When an alert appears on the screen, the clinician is expected to read the intervention content, take the appropriate therapeutic actions as outlined, and then dismiss the alert by clicking on the "X" in the upper right-hand corner (see Appendices A & B).

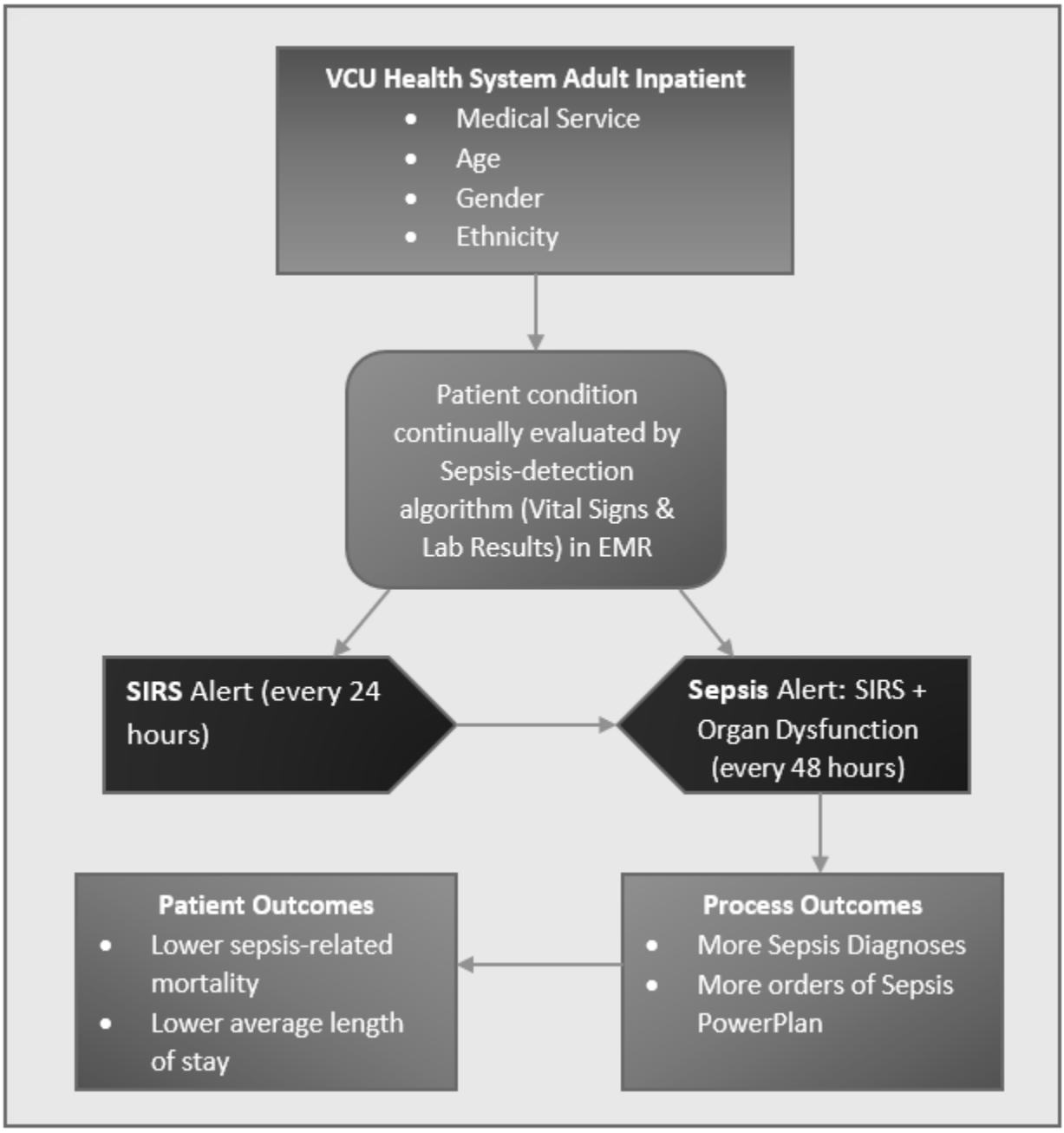


Figure 1. Process Model of Interventions and Outcomes Relating to Sepsis Early Detection

No orders are generated automatically. Placing them via the Sepsis Initial Resuscitation PowerPlan or individually is at the physician's discretion. The therapeutic recommendations contained within the Sepsis PowerPlan are intended to be administered within the "golden six hour" window for life-sustaining treatment (Singer et al., 2016). Both alerts will still appear regardless of any previous PowerPlans ordered on the patient's chart. The appearance of the SIRS alert is intended to allow clinicians adequate time to evaluate and treat the patient well before the onset of sepsis. If the SIRS alert is properly addressed from a treatment perspective, then a sepsis alert might never be generated, but this is not guaranteed as patient presentation of symptoms may vary. The sepsis alert can be considered the fail-safe, final call to action. A patient who had a SIRS alert and then also qualifies for a sepsis alert will receive both.

It is anticipated that the SIRS and sepsis alerts will lead to improvements in certain process outcomes. These include the ordering of the Sepsis PowerPlan on the patient's chart and the recording of a correct diagnosis of sepsis in the EMR. As a result, improved patient outcomes are then expected in the terms of reduction of sepsis-related mortality and average length of stay, compared to before the implementation of the alerts. The two study hypotheses in the next section follow from the model.

Study Hypotheses

Reducing sepsis-related mortality requires both early recognition and uniform and consistent application of evidence-based intervention protocols. Identification of an anatomical infection site within six hours of the presentation of sepsis symptoms is crucial to successful intervention and treatment (Rivers et al., 2001). If the physician does not identify sepsis within this onset period, it is often too late to save the patient (Rivers & Ahrens, 2008). Castellanos-Ortega et al. (2010) found that septic shock-related mortality rose by 7.6% with each hour that

interventional measures were delayed. The majority of sepsis-related deaths occur in patients that were initially admitted to the hospital with less severe sepsis. Rivers et al. (2001) also found that when early-goal directed therapy for treating sepsis was employed, the in-hospital mortality rate was 30.5% as compared to 46.5% for those treated with standard therapy. At Mount Sinai hospital in New York, a vital-signs triggered CDS alert resulted in a 40% reduction in sepsis mortality in 2012. According to Liu et al. (2014), standardizing care for those with less severe sepsis could result in a reduction in mortality, as performance improvement initiatives have primarily centered on severe sepsis. Lower sepsis-related mortality is therefore anticipated due to successful earlier intervention, as a consequence of alert implementation, while the patient is still in the hospital.

Patients with sepsis also had an average length of stay that was 11 days longer than the average hospital stay, according to Hall, Williams, DeFrances, and Golosinskiy (2011). A study examining the cost of 30-day readmissions following hospitalization with sepsis found that the mean length of stay was lengthier than that of acute myocardial infarction (AMI), heart failure, chronic obstructive pulmonary disease (COPD), and pneumonia (Mayr et al., 2017). After implementation of a triage model for severe sepsis called Sepsis Alert in a university hospital in Malmo, Sweden, median length of stay was lowered significantly, from nine to seven days (Rosenqvist, Fagerstrand, Lanbeck, Melander, & Åkesson, 2017). Likewise, Austrian, Jamin, Doty, and Blecker (2017) demonstrated a significant length of stay reduction from 10.1 to 8.6 days following the implementation of an ED sepsis advisory alert. It is theorized that the alerts will reduce length of stay due to earlier patient intervention and treatment, prior to the onset of sepsis. The patient might therefore spend less time in the hospital to recover and be subsequently

discharged as a consequence of the aversion of or resolution of sepsis. Based on these assumptions regarding sepsis-related mortality and length of stay, it is therefore hypothesized:

H_1: The implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to lower sepsis-related mortality and lower average length of stay.

There has been positive attribution of early sepsis recognition to timely and consistent application of interventional order set protocols. Such order set protocols may bundle initial fluid resuscitation, maintenance IV fluids, antibiotic therapy, glucose management, and steroid utilization together (Dellinger et al., 2013). According to Howell and Davis (2017), the most vital component of sepsis therapy is management of the infection. The faster antimicrobials are ordered and administered, the lower the attendant risk of infectious complications. An SSC performance improvement initiative conducted a 7.5-year study that found increasing compliance with the use of recommended order set bundles was correlated to a 25% relative risk reduction for sepsis-related mortality (Levy et al., 2014). More frequent ordering of the Sepsis PowerPlan is anticipated due to the higher awareness generated by the alerts, with a direct reference to ordering the plan contained within the alert instructions for physicians (See Appendix B).

The implementation of the alerts is also expected to lead to more frequent instances of physician-recorded sepsis diagnoses on the patient's chart within the EMR due to more timely and accurate recognition of the specific symptoms of sepsis. According to Rivers and Ahrens (2008), the use of sepsis alerting systems based on SSC-recommended scoring models has shown promise in assisting clinicians with diagnosing sepsis. Thus, the following is postulated:

H_2: The implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to more ordering of the Sepsis Initial Resuscitation PowerPlan (order set bundle) and more

recording of sepsis diagnoses.

The purpose of this study is to examine the impact of SIRS and sepsis alert implementation on the patient outcomes of sepsis-related mortality and length of stay, and the process outcomes of ordering the Sepsis Initial Resuscitation PowerPlan and a recording a sepsis diagnosis within the EMR.

Chapter Summary and Overview of Remaining Chapters

This chapter has laid out the case for improving sepsis-related process and patient care outcomes. It highlighted the tremendous costs, both physical and financial, borne by individuals and the healthcare system, as sepsis-related disability and mortality continue to rise. Additionally, the case for evidence-based sepsis intervention protocols is made, with CDS alerts suggested as a viable method for improving patient outcomes, which include sepsis-related mortality, length of stay, use of a standardized order set, and a recorded sepsis diagnosis.

The remaining four dissertation chapters provide a detailed literature review, methods used to test the proposed hypotheses, and lastly, the analysis results with an in-depth discussion of conclusions. In Chapter 2, literature relevant to this study is scrutinized and synthesized to provide a detailed background on related studies. This review underscores the need for undertaking this research. Topics investigated in more detail include the role of CDS in the EMR, CDS implementation use cases, sepsis-related intervention protocols, and previously studied CDS sepsis informatics efforts. The chapter ends with a rationale for the study and the knowledge gap it could fill in the biomedical informatics literature. In Chapter 3, methods for the study are outlined including research design, variable measurement, sampling strategy, data sources, and data analysis. Chapter 4 reports specific findings for each hypothesis based on statistical analyses of the data, and then the key features, implications, limitations, and possible

directions for further research are discussed in Chapter 5. In conclusion, report references are listed along with appendices for items cited in the text.

Chapter 2: Literature Review

Overview

In order to understand how this study aids in furthering research related to CDS alert interventions, this chapter begins by providing a general overview of how CDS works as a subsystem within the EMR. It also describes the transformative prospects for the technology, as well as its current limitations and challenges. This is followed by a review of the literature that covers various types of CDS implementations, including those that are sepsis-related. Manual and paper-based sepsis intervention protocols and their more recent translation into CDS applications are also examined. Finally, this chapter summarizes deficits in current knowledge and the potential for this research study to provide additional insights that can be used as feedback for the further refinement of sepsis-related CDS alerts.

CDS Systems Defined

CDS systems provide a means for clinicians to proactively interact with electronic medical records. Rather than just presenting the user with a static presentation of data, a CDS system of rules and alerts can provide guidance, recommendations, and warnings to influence and corroborate a clinician's diagnostic accuracy in terms of prevention, early detection, and individualized treatment of maladies (Downing, Boyle, Brinner, & Osheroff, 2009). Adopting a suite of CDS rules and alerts can alert clinicians to all sorts of potential errors, including prescribing the wrong drug or dose of drug, missing important orders that need to be signed, or

choosing a medication or medium to which a patient is allergic (Berner, 2009). CDS systems have primarily been implemented in larger for-profit and non-profit healthcare systems. By way of observation, they have been nearly unilaterally adopted in academic medical centers, which is where the majority of research has been conducted to date. Furthermore, in order to facilitate and hasten the adoption of CDS, some researchers advocate the creation of a collaborative international CDS knowledge base (Cresswell, Bates, Phansalkar, & Sheikh, 2010).

According to the Department of Health & Human Services (HHS), the U.S. has topped the goal of 50% adoption of EMRs amongst physician practices and 80% of eligible hospitals from 2012 - 2013, largely due to provisions outlined in the American Reinvestment and Recovery Act (ARRA) stimulus bill of 2009. $19.2 billion was set aside under the Health Information Technology for Economic and Clinical Health (HITECH) to stimulate the adoption of EMRs, and at this point more than half of eligible providers have received Medicare or Medicaid incentive payments for demonstrating Meaningful Use Stage I (U.S. Department of Health & Human Services, 2013). At least one CDS rule had to be implemented in order to meet the Stage I requirements (Romano & Stafford, 2011).

A typical CDS system utilized in a healthcare setting provides clinicians with alerts customized to its specific workflows and is knowledge-driven, as it mines for clinical data at the individual patient level. Most CDS is included as part of the overall EMR suite that healthcare systems purchase from a vendor, and typically requires some degree of manual manipulation in order to be appropriate for a particular environment (Berner, 2009). It is generally comprised of three components: a knowledge base (clinical data), an engine (programming and user interface), and specific outputs (targeted advice) (Wright, Print, & Merrie, 2011). From a technical perspective, a CDS programmer uses a series of linked, branching Boolean logic statements

according to a heuristic function, employing calculations, algorithms, and grouping elements that draw upon existing information from a clinical repository (Downing et al., 2009) to create a CDS rule.

Complexity is inherent in the adoption of CDS, and three categories of major challenges have been identified by Sittig et al. (2007): improving the effectiveness of CDS interventions, creating new CDS interventions, and disseminating existing CDS knowledge. The implementation of CDS has been difficult for healthcare organizations due to numerous factors, including a lack of demonstrated interventional evidence-based value models, no standardized clinical database architecture, and wide variations in CDS content development. Additionally, Wright et al. (2011) have noted that studies on CDS outcomes often relate to technology-led initiatives within healthcare systems, rather than clinical needs that have been carefully elucidated.

One of the major limitations to the effectiveness of CDS as a catalyst for improved care is low alert acceptance rates, in terms of how the user responds to the presented information, either heeding the advice proffered by taking the recommended course of action, such as placing orders, or rejecting it. Seidling et al. (2011) found that the graphical display attributes were the most important determinant of user alert acceptance. In general, alerts should be categorized by clinical risk or severity with the use of text, color, shape, and position. Contemporaneous alerts should be shown together, and information that requires action should be clearly delineated. Textual information was less impactful to acceptance, but more influential when detailed information and direction was given regarding drug-drug interactions, for example (Phansalkar et al., 2010). Also per Seidling et al. (2011), mandatory interaction with an alert can lead to lower user satisfaction and overreliance on them for accurate knowledge and action in general. Clinical

informatics is drawing on human-computer interaction (HCI) design principles to improve graphical user interfaces, and these should inform the design and placement of CDS alerts as well (Phansalkar et al., 2010).

By way of experience, frequency of alerting is another CDS user acceptance impediment; it can engender frequent clinician overriding or ignoring of the alert recommendations. Thus, it is generally recommended that alerts that mandate user acknowledgement should be kept as minimal as possible (Phansalkar et al., 2010). A balance needs to be struck between providing information in the right manner and frequency in order to effect maximum clinical impact (Seidling et al., 2011).

CDS System Implementations

There have been mixed outcomes stemming from implementations of both standard vendor-provided and institutionally custom-developed CDS alerts. For example, Barnes-Jewish hospital in St. Louis, Missouri, created a real-time predictive algorithm to identify patients on general medical wards that were experiencing clinical deterioration that put them at a higher risk for death, to identify them for transfer into the ICU. With a limited number of ICU beds available, this would ensure that they were used for the patients that most needed them. After validating and running the algorithm in 2011, the team found that the real-time alerts were highly specific for clinical deterioration and correlated with a longer length of stay. Unfortunately, notifying the clinicians of the algorithm-identified patients via pager alerts was not associated with improved outcomes (Bailey et al., 2013).

There have been several attempts to apply CDS successfully in the pharmacy and therapeutics realm. Vanderbilt University Medical Center created a custom CDS advising system to recommend dosing and monitoring strategies for aminoglycoside (amikacin and tobramycin)

orders, and integrated it into their computerized prescriber order entry (CPOE) system. Clinician selection of initial drug doses and administration intervals was improved and so were the serum drug concentrations, as compared to standard dosing within the institution. However, peak concentrations and nephrotoxicity rates showed no deviation from standard practice (Cox, Nelsen, Waitman, McCoy, & Peterson, 2011).

At the University of Illinois Medical Center at Chicago, a vendor-provided CDS system was customized and implemented to prompt clinicians to fill out a form documenting the administration of venous thromboembolism (VTE) prophylaxis upon admission. Clinicians then began to receive alerts in cases of inadequate prophylactic measures. A year post-implementation, the researchers measured prophylactic compliance rates, bleeding events, and diagnoses of hospital-acquired VTE. They found that VTE risk had been significantly lowered in the general medical population, but not hospital-wide. A higher percentage of patients had received pharmacologic intervention, but there was no change in the amount of bleeding events (Galanter et al., 2010).

CDS has also been demonstrated to be a cost-effective and scalable clinical intervention strategy when integrated with an EMR. Per Calvert et al. (2017), an algorithm-driven CDS biomarker tool for sepsis screening called InSight has been demonstrated to reduce the costs related to severe sepsis cases by $560,000 per year in a 50-bed ICU. Additionally, Olenik, Zimbro, Ver Schneider, and Jones (2017) found that average patient costs per stay were $1145 less for patients identified by a sepsis sniffer algorithm within the first four hours of admission. Likewise, in a large medical group in Minnesota, Gilmer et al. (2012) have shown that diabetic patients had costs significantly lowered when a "Diabetes Wizard" form was employed that provided clinical indicators, recommendations for treatment, and safety alerts. Intervention costs

were $120 per patient during the first year, and fell to $76 in subsequent years, with clinical impact estimated to be equivalent to that of more expensive condition management or education programs.

Research on CDS system effectiveness has shown that the process of care and patient outcomes are oftentimes not improved as a result of integration with a facility's EMR or CPOE application (Mollon et al., 2009). A Canadian team, as reported by Roshanov et al. (2013), conducted a meta-regression of 162 randomized trials to ascertain which features distinguished efficacious CDS systems from those that were not. Those systems deemed effective had to improve all primary, or at least half of secondary, outcomes of care for certain patient states, such as blood pressure, clinical events, and quality of life. Factors associated with success included having decision support provided outside of the EMR as a standalone application, requiring providers to supply an override reason when not following CDS advice, and CDS that offered advice directly to patients as well. Overall, medical care was improved 52-64% across studies, and of those that were appraised for impact on patient outcomes, 15-31% demonstrated a positive influence.

Looking forward, cutting-edge CDS systems are beginning to be offered in the artificial intelligence realm, utilizing IBM's Watson technology. This is accomplished by having nearly instantaneous access to an endless volume of diagnostic information from the internet, including academic journals and medical reference texts, that no one human could ever hope to master in a lifetime. Such systems, like the Oncology Expert Advisor as implemented at The University of Texas MD Anderson Cancer Center, can provide the most appropriate diagnostic responses based on the patient's clinical presentation. Thus far, the advisor has appropriately recommended appropriate courses of cancer treatment more than 80% of the time (Takahashi et al., 2014).

Seemingly, there is ample room for growth and improvement in CDS strategies as new technologies are incorporated into EMRs.

Sepsis-Related Intervention Protocols

Select studies within the last decade have examined the correlation between evidence-based early intervention protocols and sepsis clinical outcomes. These efforts have focused on identification of sepsis patients by manual observation methods. Rivers and Ahrens (2008) delineate quality improvement initiatives and highlight the use of evidence-based protocol screening tools like paper checklists and tracking forms. Christiana Care Health System created and implemented a "Sepsis Alert" handout packet that incorporated a care management guideline for nursing, a treatment algorithm in the form of a flowchart, and an order set bundle. This resulted in a 49.4% reduction in sepsis-related mortality rates from 2005-07 (Zubrow et al., 2008). Powers and Burchell (2010) describe similar intervention protocols based on general, inflammatory, hemodynamic, organ dysfunction, and tissue perfusion variables, with concomitant mortality reduction of up to 16%.

Sepsis Informatics and CDS

CDS specifically designed to aid with early sepsis detection has been the next step in the evolution of sepsis intervention protocols. For example, Methodist Hospital in Houston implemented a computerized CDS sepsis database. Their mandatory manual sepsis-screening tool in combination with the computerized CDS protocol lowered mortality from 35.1% to 23.3% over the course of two years. The three-step tool, developed in conjunction with a literature review and multidisciplinary local expert consensus for the surgical intensive care unit (SICU), was intended to involve the entire bedside clinician team (Moore et al., 2009). They attributed the results to early identification and timely, consistent application of interventional

protocols (Moore, Turner, Todd, McKinley, & Moore, 2010). Additionally, Sawyer et al. (2011) associated a real-time sepsis-screening pager alert to prompt and appropriate clinician interventions among non-intensive care unit (ICU) patients.

Another approach cited as successful by Moorman, Xiao, Griffin, and Lake (2005) involved an online sepsis prediction system for premature infants based on heart rate characteristic (HRC) abnormalities. Nearest-neighbor models were first trained and tested on HRC and lab data from over 300 patients. Resulting analyses that were developed using various combinations of demographic, laboratory, and physiological sepsis-related parameters were highly significantly associated with an imminent sepsis diagnosis, prior to signs of clinical illness appearing.

Likewise, Meurer et al. (2009) delineate the results of a simple timed alerting system developed at the University of Michigan Medical Center. Its intent was to identify elderly emergency department (ED) patients at high risk of infection, or evidence of two or more SIRS criteria, during their stay in the ED. They concluded that the tool was able to detect infection in this patient population with low sensitivity but high specificity, and that it might have better clinical care and research utility with additional optimization.

Berger, Birnbaum, Bijur, Kuperman, and Gennis (2010) reported that an automated alert was associated with higher rates of lactate testing in sepsis patients in the ED with greater than two SIRS criteria, but that it did not alter mortality rates. Furthermore, Herasevich, Pieper, Pulido, and Gajic (2011) implemented what they termed a “septic shock sniffer” to be used to enroll ICU patients at the Mayo Clinic into a time-sensitive clinical echocardiography in severe sepsis study. The near real-time alerting system paged a research coordinator regarding potentially qualifying patients. A resultant positive prognostic value of 34% was sufficient to

positively double enrollment compared to the pre-implementation period. A few years later, the system was further developed and refined as a clinical intervention. The initial design, informed by manual chart review of adults with severe sepsis/septic shock that had been admitted to the ICU, was translated into an automated surveillance algorithm integrated into their EMR. This was done by recursive data partitioning, in order to realize iterative improvements based on feedback from previous runs. They found being positive for SIRS, having low systolic blood pressure, and a suspected infection were the cluster of items that had the best predictive value, and indicated that a prospective study would be needed to clinically validate the sniffer (Harrison et al., 2015).

Another near real-time EMR notification alerting system implemented in an academic ED was described by Nelson, Smith, Jared, and Younger (2011). Physiologic vital signs, confirmed first by nurses, were collected at predetermined intervals and evaluated. Approximately 50% of the patients alerted had already experienced the sepsis-related interventions under study, namely increases in ordering of lactate tests, blood cultures, chest x-rays, and antibiotic administration. It was determined that the alerting algorithm increased the performance of some of the targeted interventions, but it did not show a high positive predictive value. Additionally, Back, Jin, and Lee (2014) constructed an inpatient sepsis risk assessment algorithm called the Auto-SepRAS, which was implemented in a university hospital in Seoul, South Korea. It was updated daily with seven variables extracted from the EMR and classified patients into low, medium, or high sepsis risk categories in order to help tailor care strategies depending on the risk group to which they were assigned.

More recently, Olenik et al. (2017) assessed an in-house developed CDS sniffer algorithm at an integrated healthcare delivery system consisting of 12 southeastern US hospitals

with a variety of EMRs. The algorithm evaluated manually entered results every 12 hours to help identify patients at high risk for sepsis by evaluating their clinical condition. Results showed an average length of stay of one day less when high sepsis risk was identified within four hours of admission, but there was no statistically significant effect demonstrated on sepsis-related mortality.

In terms of other approaches, Mani et al. (2014) developed a predictive modeling system from off-the-shelf EMR data for a neonatal patient population using machine learning techniques, which allow the system to automatically improve as it learns, without additional human programming. The sensitivity of the algorithms developed exceeded that of physicians when culture-negative sepsis cases were excluded from that population. A follow-up study may assess its utility in improving antibiotic use, however, there was no interactive alerting capability included, nor in the previously-described HRC model. Gultepe et al. (2014) detail another machine learning methodology used with adult patients at University of California Davis who met at least two SIRS criteria. Lactate level, sepsis occurrence, and mortality risk were able to be inferred from laboratory results and other heterogeneous patient data.

Furthermore, Johns Hopkins University researchers developed a supervised learning approach, a subset of machine learning that infers function from a designated data set, to train a system model that takes the censoring effects of clinical interventions, such as fluid administration, on patient outcomes into account. From there, they created a custom targeted early warning score (TREWScore) for early identification of those at risk for septic shock and concomitant organ failure (Henry, Hager, Pronovost, & Saria, 2015). The score was a research-based predictive tool not integrated into an EMR. It was compared to the previously used Modified Early Warning Score (MEWS), a more generalized version that has been used for

surgical inpatients, and a routine screening protocol for SIRS (Gardner-Thorpe, Love, Wrightson, Walsh, & Keeling, 2006). Their analysis of 16,234 distinct ICU patients, aged 15 years or over, from a publicly available data set of deidentified EHRs collected at Beth Israel Deaconess Medical Center in Boston, revealed that that not only did the TREWScore perform better versus the MEWS, but it achieved a sensitivity rate of 85%, higher than the routine protocol, while demonstrating a similar level of specificity as a predictive tool.

Finally, according to Vogel (2014), New York's Mount Sinai hospital had seen a reduction in sepsis mortality in the year 2012 as compared to 2011, with the rate dropping from 33% to 16%, putting it ahead of peer facilities. This was following its implementation of a non-cloud-based sepsis alert, triggered when vital signs that match criteria for early sepsis are entered into the chart, and prompting a bedside call by a nurse practitioner. The alert facilitated earlier identification and standardization of timely response protocols and patient transfers.

While the number of CDS studies has increased over the last couple of decades, little previous research has specifically correlated real-time, computerized interactive sepsis alerts with clinical outcomes, although momentum has been growing rapidly in this area within the last few years as the technology matures. Instead, computer-enabled screening forms and databases, alerts based on asynchronous or timed triggers, or near real-time alerts have been deployed, as cited in the previous examples in this section. The exceptions are Bailey et al. (2013), who explored the use of real-time alerts to notify clinicians regarding clinical deterioration, and Sawyer et al. (2011) who studied outcomes related to sepsis screening alerts.

Knowledge Gaps

Initially, identification of the at-risk sepsis patient was based on manual observation and the implementation of evidence-based protocols. Positive outcomes from CDS attempts for

sepsis identification and intervention are preliminary and some are solely prognostic and not clinically validated, with others being anecdotal yet promising (Moore et al., 2009). To date, there has been research relating to improving survival rates for sepsis, applications for clinical trial enrollment predictive modeling and simple alerting, as previously outlined. These have primarily been CDS systems that work at predetermined intervals and do not run on a real-time basis. The CDS systems evaluated here that do run in real-time are not based on custom cloud-based algorithms, as the CDS SIRS and sepsis alerts in this study do. Increasingly, machine learning methods have been employed, but the cloud-based crawler algorithm design is relatively new. As Despins (2017) has underscored in a systematic review of CDS sepsis detection systems, better patient outcomes can, but do not necessarily follow from earlier intervention, as study results have varied widely. The following research is intended to add to our knowledge of the literature as a process and patient outcomes evaluation of a unique real-time, cloud-based CDS alerting tool employed so that septic patient recognition and care are improved, and sepsis-related mortality is reduced.

Chapter Summary

EMR systems and to a somewhat lesser extent, CDS, have become ubiquitous in the healthcare organization landscape. This chapter described some of the many challenges inherent in creating effective CDS alerts in general considering the lack of standardized implementations, low user alert acceptance rates, and a dearth of foundational research to inform their design, in particular for sepsis alerts, among others. Research surrounding CDS implementations has thus far generated equivocal results, and there remains a gap between uncovering the aspects of the most impactful CDS alerting, refining it from a clinical perspective, and translating those findings into practice. Literature examining electronic sepsis-related CDS interventional

protocols is limited, yet it shows some early promise in reducing sepsis mortality and related complications.

Chapter 3: Methodology

Research Design

Non-probability, consecutive sampling was used for a prospective, pre-post study design. The study was prospective as it was planned prior to the implementation of alerts and the variables of interest were chosen up front to see how they would impact patient and process outcomes. The pre-implementation group consisted of patients diagnosed with sepsis in the EMR during an inpatient stay within the year preceding the alerts going live, from September 2012 through September 2013. The total post-implementation observation period spanned three years, from September 2013 through December 2016, and included interruptive, actionable alerts generated via Discern Notify. Discern is Cerner's alert generating system, which in this case is based on a patient's relationship to a designated clinician.

The research tested the study hypotheses by estimating the relationship between the SIRS and sepsis alerts and various patient-related and diagnostic factors for the post-implementation group as compared to a pre-implementation group. To test H_1, binary logistic regression was used to estimate the relationships between the each of the two independent variables, SIRS and sepsis alerts, and the dependent variable sepsis-related mortality. Multiple linear regression was used to test the relationships between SIRS and sepsis alerts and the dependent variable length of stay. For H_2, multiple linear regression was used to estimate the relationships between SIRS and sepsis alerts and the dependent variable Sepsis Initial Resuscitation PowerPlan, and binary

logistic regression was used to test the relationships between SIRS and sepsis alerts and the dependent variable sepsis diagnosis.

The study took place at VCU Health System's Main Hospital, an early adopter of the SIRS and sepsis alerts, in partnership with their primary healthcare information system vendor, Cerner Corporation. The hospital has 865 beds and is a regional referral center for the state and the region's only Level I Trauma Center.

Sampling Strategy

Consecutive sampling was used, as all patient visits meeting the inclusion criteria were selected. The sample size was calculated similarly to an earlier analysis done with an automated, non-cloud-based computerized sepsis alert delivered via pager for non-ICU patients, as reported by Sawyer et al. (2011). The researchers assumed post-alert intervention rates between 60% and 75%. For purposes of this research, these intervention rates are estimated at 70%, as VCU Health System alert algorithm is highly specific, with a low possibility of false negatives. It was calculated that at least 304 patients were needed to achieve a .80 power level with a two-sided significance level of .05, and 1,000 or more patients are an adequate sample size to provide a power level near 1.0. The total cohort size amounted to 11,262 unique patient visits, comprised of 9,087 individual patients.

A pre-implementation group was also obtained from the one-year period prior to the alerts going live. Patients that died in the hospital with a sepsis diagnosis or were discharged with a sepsis diagnosis during the 12 months preceding the cloud alert rollout comprised the pre-implementation group. The post-implementation group consisted of 9,711 unique visits. Only the patient visits meeting all the study group inclusion criteria as specified in Table 2 appeared in the queried results. This should diminish any concerns relating to selective reporting bias. If a patient

did not fall within VCU Health System's defined ranges for laboratory values and vital signs (see Table 1), then a SIRS or sepsis alert was not triggered. Test results were entered into the EMR manually by clinicians and automatically via peripheral systems such as chemistry analyzers and patient bedside monitors.

Table 2

Study Inclusion Criteria

Inclusion Criteria for Pre-Implementation Group (*N* = 1551)
Age: >= 18 *and* located in any inpatient (IP) unit *and* Sepsis Diagnosis present on chart
Inclusion Criteria for Post-Implementation Group (*N* = 9711)
Age: >= 18 *and* located in any inpatient (IP) unit *and* (Sepsis Diagnosis present on chart *or* at least one SIRS or Sepsis Alert triggered *or* Sepsis Initial Resuscitation PowerPlan ordered on chart)

Study Sample

The total number of SIRS and sepsis alerts averaged 2,319 per year over the three-year period from September 2013 through December 2016, while the number of unique patients receiving at least one of either alert averaged around 1492. The pre-implementation group that had been diagnosed with sepsis within the year leading up to the beginning of the study, from September 2012 through September 2013, consisted of 1,551 inpatient visits. The three-year post-implementation sample size was 9,711 inpatient visits. The total number of patient visits meeting the inclusion criteria was 11,262. Table 3 contains summary statistics of pre-implementation, post-implementation, and combined sample data.

Table 3

Summary Statistics of Group Characteristics

	Pre-Implementation Group	Post-Implementation Group	Combined Samples
Total number of patients	1551 (09/12–09/13)	9711 (09/13–12/16)	11262 (09/12–12/16)
Age (Mean)	56 years	55 years	55 years
Gender	Male = 54% Female = 46%	Male = 56% Female = 44%	Male = 56% Female = 44%
Ethnicity			
American Indian/Alaskan	<1%	<1%	<1%
Asian	1%	1%	1%
Black or African American	53%	50%	51%
Native Hawaiian/Other Pacific Islander	<1%	<1%	<1%
Other/Unknown	3%	4%	3%
White	43%	45%	45%
Medical Service (Count)	58 total services	36 total services	62 total services
Sepsis Mortality (% of Total)	21.10%	16.14%	16.83%
SIRS Alerts (One or more per patient visit)		1901 (42% of total)	1901
Sepsis Alerts (One or more per patient visit)		3290 (73% of total)	3290
Total number of patients receiving at least one SIRS or Sepsis Alert or both		4524	4524

Note. The Chi-square statistic (X2(2)) for a comparison of proportions between the pre-implementation and post-implementation groups on sepsis mortality is 23.51. The result is significant at $p < 0.0001$.

Variable Measurement

Table 4 relates each hypothesis to specific study variables and methods of analyses, while Table 5 briefly describes the independent, dependent, and control variables used in this study.

Independent Variables.

The independent variables chosen were SIRS alerts and sepsis alerts. In all analyses

Table 4

Hypotheses, Variables & Analyses

Hypothesis 1	Variables	Analyses
The implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to lower sepsis-related mortality and lower average length of stay.	IVs: SIRS alerts, Sepsis alerts DVs: Sepsis-related mortality, Length of stay (LOS) CVs: Medical Service, Age, Gender, Ethnicity	Logistic regression and multiple linear regression to model the relationship between each of the IVs and the DVs. CVs are held constant.

Hypothesis 2	Variables	Analyses
The implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to more ordering of the Sepsis Initial Resuscitation PowerPlan (order set bundle) and more recording of sepsis diagnoses.	IVs: SIRS alerts, Sepsis Alerts DVs: Ordering of Sepsis Initial Resuscitation PowerPlan, Sepsis diagnosis coding CVs: Medical Service, Age, Gender, Ethnicity	Logistic regression and multiple linear regression to model the relationship between each of the IVs and the DVs. CVs are held constant.

Table 5

Study Variables and Definitions

Dependent Variables	Definition	Analysis
Sepsis-related mortality	This categorical variable has the two possible responses of deceased (0) or alive when left the hospital (1). Deceased (0) represents inpatients who died in the hospital as a result of sepsis, prior to having the opportunity to be discharged.	H_1
Length of stay (LOS)	This continuous variable represents the number of days that the patient resides in an inpatient unit; the period ranging from admission to discharge (1 – 464 days).	H_1
Sepsis Resuscitation PowerPlan	This continuous variable represents the number of times the standard Sepsis Initial Resuscitation PowerPlan is ordered in the Cerner EMR per patient visit.	H_2
Sepsis diagnosis	This categorical variable represents the official ICD-9 or ICD-10 codes as recorded by a physician in the sepsis diagnostic category. The possible values are Yes (1) or No (0), representing the presence or absence of a recorded diagnosis code.	H_2

Table 5 - Continued

Independent Variables	Definition	Analysis
SIRS Alerts	This categorical variable represents the presence (1) or absence (0) of one or more SIRS alerts during the patient's visit. It was made categorical as a small number of patients with very high numbers of SIRS alerts as outliers caused skewness in the distribution. It is used in conjunction with the dependent variables *Sepsis-related mortality*, *Length of stay*, and *Ordering of Sepsis Initial Resuscitation PowerPlan*.	H_1 & H_2
Sepsis Alerts	This categorical variable represents the presence (1) or absence (0) of one or more sepsis alerts during the patient's visit. It was made categorical as a small number of patients with very high numbers of sepsis alerts as outliers caused skewness in the distribution. It is used in conjunction with the dependent variables *Sepsis-related mortality*, *Length of stay*, and *Ordering of Sepsis Initial Resuscitation PowerPlan*.	H_1 & H_2
SIRS Alerts	This continuous variable represents the number of unique SIRS alerts per patient visit, ranging from 1 – 17. It is used in conjunction with *Sepsis diagnosis* dependent variable only.	H_2
Sepsis Alerts	This continuous variable represents the number of unique sepsis alerts per patient visit, ranging from 1 - 34. It is used in conjunction with *Sepsis diagnosis* dependent variable only.	H_2
Control Variables	Definition	Analysis
Age	This continuous variable represents the adult patient's age, within a range of 18 to 120 years.	*All*
Gender	This categorical variable represents the gender as male (1) or female (0).	*All*
Ethnicity	This categorical variable represents coded ethnic categories in the Cerner EMR as Hispanic or Latino, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Unknown.	*All*
Medical Service	This categorical variable is a hospital-specific numeric code and description that represents a medical specialty, per inpatient stay.	*All*

except those that measure the recording of the sepsis diagnosis dependent variable, they were represented as binary, defined as the presence (1) or absence (0) of one or more alerts of either type during a patient visit. This operationalization was chosen as a small number of patients had a very high number of SIRS or sepsis alerts. For the sepsis diagnosis dependent variable analyses

only, the independent SIRS alerts and sepsis alerts variables were characterized as continuous, or the numeric value of SIRS or sepsis alerts per visit, as all patient visits used in the analyses had alerts (SIRS alerts range: 1 – 17; sepsis alerts range: 1 – 34).

Dependent Variables.

The dependent variables chosen were sepsis-related mortality, length of stay, ordering of the standard Sepsis Initial Resuscitation PowerPlan, and the recording of sepsis diagnosis. All of the dependent variables were linked together with the independent variables by way of a person identification number. Sepsis-related mortality was represented as binary categorical variable with the two possible responses of deceased in the hospital as a result of sepsis (0) or alive at discharge (1), as the study was not designed to track patients post-discharge. In order to measure total inpatient time from admission to discharge, the length of stay in whole days, as recorded in the EMR, was chosen as a continuous variable. The variable was classified as continuous as it is numeric and can take on any value within its range (1 – 464).

The Sepsis Initial Resuscitation PowerPlan is a predefined Cerner evidence-based order set bundle that includes the proper laboratory and medication response protocols, depending on the alert type and urgency. As a variable, it represents the number of times the PowerPlan is ordered in the Cerner EMR per patient visit, and was chosen to represent the clinician's interventional response to the alerts. Due to a high number of patient visits having no PowerPlan ordered, the original range of the variable was from zero to three, and the distribution skewed. Therefore, as a count variable representing a finite number of PowerPlans, it had to be converted from a discrete into a continuous variable, which was accomplished by first normalizing the data with a logarithmic transformation. This conversion was necessary in order for the variable to be

appropriate for the multiple linear regression analyses and consistent with the overall choice of using regression techniques for the study data.

Several related ICD-9 and ICD-10 codes characterize the binary categorical sepsis diagnosis variable (See Appendix D). ICD stands for "International Classification of Diseases." The possible values are Yes (1) or No (0), representing the presence or absence of a recorded sepsis diagnosis code. The global use of these codes for clinical diagnostic purposes is a World Health Organization (WHO) developed standard. The codes monitor disease and health condition incidence and prevalence. Selection of ICD-10 codes is mandatory for every patient, and done with the assistance of a "Problem and Diagnosis" tool within the Cerner EMR. Gaieski, Edwards, Kallan, and Carr (2013) found that the retrospective use of ICD-9 codes was highly accurate for identifying severe sepsis diagnoses.

Control Variables.

Factors commonly known to impact sepsis-related outcomes, such as age, gender and ethnicity, are included as control variables in all analyses (Sawyer et al., 2011). Standardized rates of mortality and hospitalization have frequently been stratified by age and gender because severe sepsis tends to affect the very young and the elderly more, and males more frequently than females (Dombrovskiy, Martin, Sunderram, & Paz, 2007). Angus et al. (2001) and Galanter et al. (2010) also adjusted for high-risk comorbidities, while racial and ethnic group disparities in sepsis-related mortality were found by Melamed and Sorvillo (2009). Medical service, or specialty, used by hospitalists to categorize patients upon admission into groups like surgery, telemetry, critical care, palliative care, rehab, etc., is also included as a control variable representing the clinical acuity and complexity of a patient, which can vary and is expected to be associated with particular medical conditions because the categories frequently overlap. Medical

services like critical care, for example, would be indicative of patients that are likely experiencing life-threatening organ-system failure.

Data Sources

The data were obtained from a real-world healthcare environment. This should provide valuable insight into the effectiveness of the proposed intervention, since de-identified health data were collected as a by-product that represents actual patient care. The large queries were run on a data warehouse, which is a copy of the Cerner production environment that is refreshed nightly. The databases are the property of VCU Health System as maintained by Cerner Corporation in their Kansas City, Missouri, Data Center. Data elements were retrieved as follows:

1. Length of stay, diagnosis, medical service, age, gender, ethnicity: Cerner Millennium Clinical Database (PowerInsight)
2. SIRS and sepsis alerts and sepsis order set bundles: Cerner HealtheIntent Discern Analytics 2 (DA2) Report

If there were any non-standard or undefined values contained in the fields that the algorithm draws upon, the patient would not have qualified for an alert. Therefore, there was a slight risk of missing a patient based an anomalous result being entered or auto-generated. Given that the algorithm was continually looking at new results, there was a high likelihood that any qualifying patient would get at least one, and probably multiple automated alerts during their stay. There were no missing variable values within the data, which can be attributed to these values being required data fields for every patient in Cerner. In addition, VCU Health System uses nationally recommended norms for laboratory value reference ranges. Standardization of data elements within the Cerner EMR means that data quality is reasonably high, as data must

conform to predefined parameters. System data elements are all defined and actualized in a similar manner, and testing methods and algorithmic content are consistent, enhancing the reliability and validity of the overall data. Although there may be minor variations in the reference ranges used by other academic hospitals to measure laboratory and physiologic criteria, they should not be large enough to impair the generalizability of results to those hospitals.

Existing patient information, including demographic and clinical data, was de-identified for purposes of this study. The Cerner clinical database queries were conducted securely on password-protected and encrypted cloud-based storage to ensure patient privacy. The Health Insurance Portability and Accountability Act (HIPAA) Privacy rule safeguarded patient confidentiality, yet ensured that the medical information needed to conduct this study was available for examination and analysis.

Data Analysis

Data collection and analysis took place three years after live implementation of the sepsis cloud alerting system. The data were retroactively gathered via clinical database queries, for the purpose of identifying all the eligible cases within a three-year interval. Therefore, the actual clinical data extraction process from the data warehouse took place once the alerts were active in the system for three years. The nature of the study itself was still prospective as the study was designed prior to the implementation of the alerts. The pre-implementation group consisted of 1,551 inpatient visits, each having a recorded sepsis diagnosis in the EMR in the year up leading up to the activation of the alert intervention. The three-year post-implementation group was comprised of 9,711 unique visits. The total cohort amounted to 11,262 unique patient visits.

Contingency tables were generated for the purpose of contrasting the pre- and post-implementation cohorts on the distribution frequency of sepsis-related mortality, whereas

comparisons of means and population proportions were done for average length of stay and Sepsis Initial Resuscitation PowerPlan, respectively. The pre-implementation cohort consisted of patient visits with a recorded sepsis diagnosis on the chart. As a recorded sepsis diagnosis was also one of the selection criteria for the post-implementation group, the whole post-implementation group (N = 9711) could not be used as a valid basis for comparison. The post-implementation group who received alerts (N = 4524) was made up of patient visits with one or more SIRS alerts, sepsis alerts, or both, and is a subset of the post-implementation cohort (N = 9711). The alerted post-implementation cohort used was not the sum of those who had one or more SIRS alerts (N = 1901) and one or more sepsis alerts (N = 3290) because some patients visits had both SIRS and sepsis alerts, and these were counted together as one instance.

In order to test the hypotheses, a total of eight separate regressions were run. Table 6 characterizes each analysis as it relates to its corresponding hypothesis. Multiple linear regression was an appropriate method to use for the four study analyses that used the continuous variables length of stay and Sepsis Initial Resuscitation PowerPlan. Binary logistic regression was used for the four analyses for which the dependent variables of interest, sepsis-related mortality and sepsis diagnosis, were categorical and dichotomous (Alexopoulos, 2010). The independent variables are the same for each hypothesis: SIRS and sepsis alerts. The same control variables were used in each analysis: age, gender, ethnicity and medical service.

For the dependent variable sepsis diagnosis, the two analyses only were conducted using patient visits that had one or more SIRS alerts (N = 1901) and one or more sepsis alerts (N = 3290; see Table 6), that is, observations only collected from the post-implementation period. This varied from the other six analyses that used the combined samples (N =11262). The use of only post-implementation data was due to the fact there were no alerts present in the pre-

Table 6

Descriptions of analyses

Subhypothesis	Sample	Method	Description	Outcome
The implementation of cloud-based **SIRS alerts** is associated with lower **sepsis-related mortality**.	Combined samples (*N* = 11262)	Binary logistic regression	No SIRS alerts compared to >0 alerts	Sepsis-related mortality probability: Deceased =0 Alive=1
The implementation of cloud-based **sepsis alerts** is associated with lower **sepsis-related mortality.**	Combined samples (*N* = 11262)	Binary logistic regression	No sepsis alerts compared to >0 alerts	Sepsis-related mortality probability: Deceased =0 Alive=1
The implementation of cloud-based **SIRS alerts** is associated with lower average **length of stay.**	Combined samples (*N* = 11262)	Multiple linear regression	No SIRS alerts compared to >0 alerts	LOS in days: Continuous
The implementation of cloud-based **sepsis alerts** is associated with lower average **length of stay**.	Combined samples (*N* = 11262)	Multiple linear regression	No sepsis alerts compared to >0 alerts	LOS in days: Continuous
The implementation of cloud-based **SIRS alerts** is associated with more ordering of the **Sepsis Initial Resuscitation PowerPlan.**	Combined samples (*N* = 11262)	Multiple linear regression	No SIRS alerts compared to >0 alerts	PowerPlans ordered: Continuous
The implementation of **cloud-based sepsis alerts** is associated with more ordering of the **Sepsis Initial Resuscitation PowerPlan**.	Combined samples (*N* = 11262)	Multiple linear regression	No sepsis alerts compared to >0 alerts	PowerPlans ordered: Continuous
The implementation of cloud-based **SIRS alerts** is associated with more recorded **sepsis diagnoses.**	Post-implementation group (*N* = 9711) subset with SIRS alerts (*N* = 1901)	Binary logistic regression	Impact of each additional SIRS alert on the dependent variable	Sepsis diagnosis probability: Y/N
The implementation of cloud-based **sepsis alerts** is associated with more recorded **sepsis diagnoses.**	Post-implementation group (*N* = 9711) subset with sepsis alerts (*N* = 3290)	Binary logistic regression	Impact of each additional sepsis alert on the dependent variable	Sepsis diagnosis probability: Y/N

Note. Subhypothesis variables are in boldface.

implementation group, which was selected solely on the basis of a recorded sepsis diagnosis being present in the patient's chart, and that the presence of a sepsis diagnosis on the chart was also used as one of the post-implementation group inclusion criteria. Sepsis-related mortality and average length of stay were hypothesized to be lower, and accurate diagnoses of sepsis and utilization of interventional order sets were projected to be higher after the implementation of the alerting system. The software application used to analyze all of the data was IBM Statistical Package for the Social Sciences (SPSS), version 24. A missing value analysis was also run, and no cases were found. All study data pulled from Cerner come from required fields.

Chapter Summary

This chapter provided a summary of the study's research design, namely that of a consecutive, prospective study with a pre-implementation group. It further went on to describe the technology behind the intervention, the clinical processes associated with it and the organization at which it took place. Additionally, variables and their respective measurements were outlined along with the sampling strategy, and the data sources were disclosed. Finally, the data analysis methodologies and their appropriateness for the study were covered.

Chapter 4: Results

This chapter presents the results of the study. In particular, it details the quantitative results for the two hypotheses, as described in Chapter 3, with contingency tables, comparisons of means and proportions, and binary and multiple linear regressions. A discussion of each analysis and the related conclusions are outlined. Finally, a summary of the results from the statistical tests performed to address the study hypotheses concludes this chapter.

H1: Association Between SIRS and Sepsis Alerts and Sepsis Mortality

Contingency Tables: Sepsis Mortality.

Contingency tables were created to summarize the relationship between the categorical variables of SIRS and sepsis alerts and sepsis mortality. A significance level of 0.05 was used. Table 7 displays the frequency distribution of SIRS alerts and sepsis mortality. As shown, 226 of the 1901 patient visits with at least one SIRS alert during their stay also died in the hospital due to sepsis. This represented 11.9% of the total number of patients with at least one SIRS alert. Of those without any SIRS alerts, 14.9% died. The Chi-square statistic ($X2(2) = 39.85$, $p < 0.00001$), a test used to compare the proportion of subjects in each of two groups who have a dichotomous outcome, had a *p*-value less than 0.05. This means there that is a statistically significant difference in sepsis mortality between the proportion of patients that had at least one SIRS alert that died, versus those that did not.

Table 8 displays the frequency distribution of sepsis alerts and sepsis mortality. Of the

Table 7

Contingency Table: SIRS Alerts and Sepsis Mortality

			Sepsis Mortality		
			No	Yes	Total
SIRS Alerts	No	Count	7692 (7786) [1.13]	1669 (1575) [5.59]	9361
		% of Total	68.3%	14.8%	83.1%
	Yes	Count	1675 (1581) [5.57]	226 (320) [27.55]	1901
		% of Total	14.9%	2.0%	16.9%
Total		Count	9367	1895	11262
		% of Total	83.2%	16.8%	100.0%

Note. The contingency table above provides the following information: the observed cell totals, (the expected cell totals), and [the Chi-square statistic for each cell]. The Chi-square statistic ($X^2(2)$) is 39.85. The *p*-value is < 0.00001. The result is significant at $p < 0.05$.

3290 patient visits with at least one sepsis alert during their stay, 553 experienced sepsis-related mortality. This is 4.9% of the total number of patients with at least one sepsis alert. The Chi-square statistic (X2(2) = 0.0011, p = 0.97) had a *p*-value greater than 0.05, meaning that there is no statistically significant difference between the proportion of patients that did or did not have at least one sepsis alert, that died from sepsis.

Regression Results: Sepsis Mortality.

Binary logistic regression analyses were conducted to evaluate the changes in sepsis

Table 8

Contingency Table: Sepsis Alerts and Sepsis Mortality

			Sepsis Mortality		
			No	Yes	Total
Sepsis Alerts	No	Count	6630 (6631) [0.00]	1342 (1341) [0.00]	7972
		% of Total	58.9%	11.9%	70.8%
	Yes	Count	2737 (2736) [0.00]	553 (554) [0.00]	3290
		% of Total	24.3%	4.9%	29.2%
Total		Count	9367	1895	11262
		% of Total	83.2%	16.8%	100.0%

Note. The contingency table above provides the following information: the observed cell totals, (the expected cell totals), and [the Chi-square statistic for each cell]. The Chi-square statistic ($X^2(2)$) is 0.0011. The *p*-value is 0.97. The result is not significant at $p < 0.05$.

mortality after employing SIRS and sepsis alerts within the EMR while controlling for medical service, age, gender, and ethnicity. A pre-implementation group, which included patients with a sepsis diagnosis from the year preceding the alert implementation, was combined with those in the post-alert group period that spanned three years, to form the complete cohort ($N = 11262$).

The logistic regression results for SIRS alerts and sepsis mortality are presented in Table 9. For the entire model, the omnibus tests of model coefficients, or Chi-square tests ($X^2(2) = 388.64$, $p < 0.001$) had a *p*-value less than the significance level of 0.05. The Nagelkerke R^2

result was 0.06, a value indicative of the impact of all of the variables within the model. The model explained only 6% of the overall variance in the prediction of sepsis mortality. Investigation of the individual associations showed that SIRS alerts (Wald = 19.60, $p < 0.001$) had a statistically significant relationship with sepsis mortality. SIRS alerts had a standardized beta coefficient of 0.34 and an odds ratio of 1.41:1. The odds ratio indicates that if one or more SIRS alerts was present on a patient, then he or she had 1.41 higher odds of dying due to sepsis-related complications than a patient who had no alerts.

Table 9

Association Between SIRS Alerts and Sepsis Mortality

	B	S.E.	Wald	df	Sig.	Odds Ratio
Age	0.03	0.00	265.35	1	0.00*	1.03
Gender	0.00	0.05	0.01	1	0.92	1.01
Race	0.10	0.02	35.98	1	0.00*	1.11
Medical Service	0.00	0.00	0.88	1	0.35	1.00
SIRS Alerts	0.34	0.08	19.60	1	0.00*	1.41
Constant	-3.96	0.15	743.86	1	0.00*	0.02

Note. $X^2(2) = 388.64$, $p < 0.001$, Nagelkerke $R^2 = 0.06$, $N = 11262$

a. Dependent variable: Sepsis Mortality
b. Covariates: Age, Gender, Race, Medical Service
c. Independent variable: SIRS Alerts
*Significant at a level less than or equal to 0.05

Results for sepsis alerts and sepsis mortality are displayed in Table 10. For the whole regression model, the Chi-square tests ($X^2(2) = 367.94$, $p < 0.001$) had a p-value less than the significance level of 0.05. However, the relationship between the sepsis alerts and the prediction

Table 10

Association Between Sepsis Alerts and Sepsis Mortality

	B	S.E.	Wald	df	Sig.	Odds Ratio
Age	0.03	0.00	283.50	1	0.00*	1.03
Gender	0.00	0.05	0.00	1	0.97	1.00
Race	0.10	0.02	36.94	1	0.00*	1.11
Medical Service	0.00	0.00	0.35	1	0.55	1.00
Sepsis Alerts	0.01	0.06	0.60	1	0.81	1.01
Constant	-3.70	0.13	781.98	1	0.00*	0.03

Note. $X^2(2) = 367.94$, $p < 0.001$, Nagelkerke $R^2 = 0.05$, $N = 11262$

a. Dependent variable: Sepsis Mortality
b. Covariates: Age, Gender, Race, Medical Service
c. Independent variable: Sepsis Alerts
*Significant at a level less than or equal to 0.05

of sepsis mortality was not statistically significant ($p = 0.81$). The Nagelkerke R^2 result was 0.05, a value denoting the small effect size of the model, all variables included. It explained 5% of the overall variance in the prediction of sepsis mortality.

The results of these logistic regression analyses do not support the first hypothesis that "the implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to lower sepsis-related mortality". It was demonstrated that the implementation of SIRS alerts in the EMR were associated with higher sepsis-related mortality, and sepsis alerts had no relationship to the number of sepsis deaths.

Comparison of Cohorts on Sepsis Mortality.

The post-implementation group who received alerts only ($N = 4524$) was compared with

the pre-implementation group (N = 1551) on the dependent variable sepsis mortality. Table 11 shows that 21.1% of those in the pre-implementation group that were diagnosed with sepsis died in the hospital, and 78.9% survived and were discharged. In contrast, of those in the post-implementation group (Table 12), 14.4% experienced sepsis-related inpatient mortality, and 85.6% were discharged after having their sepsis treated. The Chi-square statistic (X2(2) = 516.46, p = 0.000) for the pre-implementation group had a p-value of less than 0.05, as did the post-implementation group (X2(2) = 2291.87, p = 0.000), indicating that there was a statistically significant difference between the observed and expected values for both groups. Additionally, according to the two-sample t-test ($p < 0.001$), there was a statistically significant difference between the pre-implementation and alerts-only post-implementation cohort population means for sepsis-related mortality. These results differ from those of the logistic regression for the first hypothesis for SIRS alerts, in that there was slightly higher sepsis-related mortality seen post-implementation of the SIRS alerts. No significant result for the post-implementation cohort was obtained for sepsis alerts via logistic regression. These differences might be explained by the fact that the pre-implementation cohort consisted only of patient visits with a recorded sepsis diagnosis on the chart. As a recorded sepsis diagnosis was also one of the three selection criteria for the post-implementation group, the whole post-implementation cohort could not be used as a valid basis for comparison to the pre-implementation group.

H1: Association Between SIRS and Sepsis Alerts and Length of Stay

Regression Results: Length of Stay.

Multiple linear regression analyses were conducted to estimate the changes in length of stay after employing SIRS and sepsis alerts within the EMR, respectively, while controlling for medical service, age, gender, and ethnicity. A pre-implementation group, which included patients

Table 11

Sepsis-Related Mortality – Pre-Implementation Group

		Frequency	Percent	Cumulative Percent
Valid	No	1223	78.9	78.9
	Yes	328	21.1	100.0
	Total	1551	100.0	

Note. The Chi-square statistic ($X^2(2)$) is 516.46. The *p*-value is = 0.000. The result is significant at $p < 0.05$.

Table 12

Sepsis-Related Mortality – Post-Implementation Group

		Frequency	Percent	Cumulative Percent
Valid	No	3872	85.6	85.6
	Yes	652	14.4	100.0
	Total	4524	100.0	

Note. The Chi-square statistic ($X^2(2)$) is 2291.87. The *p*-value is = 0.000. The result is significant at $p < 0.05$. This group includes post-implementation patients who received a SIRS or sepsis alert, or both.

*The two-sample t-test result between the pre-implementation (Table 11) and post-implementation groups (Table 12) on Yes and No is $p < 0.001$. The result is significant at $p < 0.05$.

with a sepsis diagnosis from the year preceding the alert implementation, was combined with those in the post-alert group period that spanned three years, to form the complete cohort (N = 11262).

Multiple linear regression was chosen because the dependent variable, length of stay, is a continuous variable. It represents the total number of days that the patient spent in the hospital during their inpatient visit. The independent variables, SIRS and sepsis alerts, are categorical, classified as being either present (1) or absent (0) during the patient visit.

The multiple linear regression results for SIRS alerts and length of stay are presented in Table 13. The analysis revealed statistical significance ($F(5, 11256) = 35.27$, $p < 0.001$) for the entire model. The *R*-square value ($R^2 = 0.02$) equated to a low level, indicating a small combined effect size by the independent variables on the dependent variable. SIRS alerts ($B = 5.40$, t [11262] = 11.25, $p < 0.001$) had a statistically significant relationship with the length of stay. Investigation of the beta coefficient indicated that the presence of SIRS alerts was associated with in a longer length of stay in days. When at least one SIRS alert was present per patient visit, the length of stay was 5.40 days longer, on average, then when no SIRS alerts were present.

Results for sepsis alerts and length of stay are displayed in Table 14. Significant regression analysis results ($F(6, 11256) = 38.27$, $p < 0.001$) for the whole model are shown. The *R*-square value ($R^2 = 0.02$) again equated to a low level, indicating a small combined effect size by the independent variables on the dependent variable. The sepsis alert results ($B = 4.66$, t [11262] = 11.89, $p < 0.001$) were statistically significant. The beta coefficient indicates that employing individual sepsis alerts had a positive association with the length of stay in days. When at least one sepsis alert was present per patient visit, the length of stay was 4.66 days longer, on average, compared to those that had no sepsis alert.

The results of the multiple linear regression analyses did not support the first hypothesis that “the implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to lower average length of stay”. It was demonstrated that the implementation of SIRS and sepsis alerts in

Table 13

Association Between SIRS Alerts and Length of Stay

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	10.81	0.84		12.92	0.00*
Age	0.01	0.01	0.00	0.40	0.69
Gender	1.50	0.36	0.04	4.17	0.00*
Race	0.67	0.12	0.05	5.76	0.00*
Medical Service	-0.02	0.01	-0.01	-1.35	0.18
SIRS Alerts	5.40	0.48	0.11	11.25	0.00*

Note. $F(5, 11256) = 35.27$, $p < 0.001$, R-Square (R^2) = 0.02, $N = 11262$

a. Dependent Variable: Length of Stay in days
b. Covariates: Medical Service, Gender, Age, Race
c. Independent Variable: SIRS Alerts
*Significant at a level less than or equal to 0.05

the EMR was associated with a higher average length of stay.

Comparison of Cohorts on Length of Stay.

The post-implementation group who received any alerts only ($N = 4524$) was compared with the entire pre-implementation group ($N = 1551$) on the dependent variable length of stay to see whether support for the first hypothesis would be seen. As shown in Table 15, there was no statistically significantly difference ($p = 0.081$) in the mean length of stay in days between the pre-implementation group (16.39) and the post-implementation group (17.59). As with the cohort comparison of sepsis mortality on population means, the difference in results from those of the

Table 14

Association Between Sepsis Alerts and Length of Stay

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	11.13	0.83		13.39	0.00*
Age	-0.01	0.11	-0.01	-0.58	0.57
Gender	1.45	0.36	0.04	4.03	0.00*
Race	0.61	0.12	0.05	5.23	0.00*
Medical Service	-0.02	0.01	-0.01	-1.08	0.28
Sepsis Alerts	4.66	0.40	0.11	11.89	0.00*

Note. $F(6, 11256) = 38.27$, $p < 0.001$, R-Square (R^2) = 0.02, $N = 11262$

a. Dependent Variable: Length of Stay in days
b. Covariates: Medical Service, Gender, Age, Race
c. Independent Variable: Sepsis Alerts
*Significant at a level less than or equal to 0.05

multiple linear regressions run on length of stay may be due to the nature of the comparison groups. The pre-implementation cohort consisted only of patient visits with a recorded sepsis diagnosis on the chart. As a recorded sepsis diagnosis was also one of the three selection criteria for the post-implementation group, the whole post-implementation cohort could not be used as a valid basis for comparison to the pre-implementation group.

H2: Association Between SIRS and Sepsis Alerts and Sepsis Initial Resuscitation PowerPlan

Regression Results: Sepsis Initial Resuscitation PowerPlan.

Table 15

Comparison of Cohorts on Length of Stay in Days

		Pre-Implementation Group	Post-Implementation Group
N	Valid	1551	4524
	Missing	0	0
Mean		16.39	17.59
Std. Error of Mean		0.52	0.33
Median		10.00	11.00
Mode		3.00	4.00
Std. Deviation		20.38	22.49
Variance		415.44	506.67
Range		284.00	377.00
Minimum		0.00	0.00
Maximum		284.00	377.00

Note. The two-sample t-test result between groups is $p = 0.081$.
The result is not significant at $p < 0.05$.

Multiple linear regression analyses were conducted to assess changes in the ordering of the Sepsis Initial Resuscitation PowerPlan after employing SIRS and sepsis alerts within the EMR, respectively, while controlling for medical service, age, gender, and ethnicity. A pre-implementation group, which included patients with a sepsis diagnosis from the year preceding the alert implementation, was combined with those in the post-alert group period that spanned

three years, to form the complete cohort (N = 11262).

Multiple linear regression was chosen because the dependent variable, Sepsis PowerPlan use, is a continuous variable that represents the number of Sepsis Initial Resuscitation PowerPlans ordered on the chart of a patient during their visit. The original variable was log transformed from discrete to continuous in order to be appropriate for the analysis. The independent variables, SIRS and sepsis alerts, are categorical, classified as being either present (1) or absent (0) during the patient visit.

The multiple linear regression results for SIRS alerts and Sepsis PowerPlan use are presented in Table 16. The analysis for the whole model was statistically significant (F(6, 11256) = 1.70, p = 0.03). The R-square value (R^2 = 0.001) indicated a low effect size by the independent variables on the dependent variable. The SIRS alerts (B = -0.01, t [11262] = -2.15, p = 0.03) had a statistically significant relationship with PowerPlan use, according to their p-value. However, the presence of SIRS alerts was associated with fewer PowerPlans being ordered on the patient charts. Due to the initial logarithmic transformation of the PowerPlan variable, the exponentiated regression coefficient value (exp(B) = -1.01), as the geometric mean of the original variable, must be used for interpretation, as exponentiation is the inverse of the logarithmic function. The negative beta coefficient suggests an inverse relationship between the variables, meaning that when at least one SIRS alert was present per patient visit, 1.01 fewer PowerPlans were ordered.

Results for sepsis alerts and Sepsis PowerPlan use are shown in Table 17. The regression analysis displayed statistical significance (F(6, 11256) = 2.52, p = 0.03) for the entire model. Sepsis alerts (B = -0.01, t [11262] = -2.96, p < 0.001), like SIRS alerts, had a statistically significant relationship with PowerPlan use. As was the case with SIRS alerts, the presence of sepsis alerts was associated with fewer PowerPlans being ordered on the patient charts. The beta

Table 16

Association Between SIRS Alerts and Sepsis Initial Resuscitation PowerPlan

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	0.02	0.01		3.34	0.00*
Age	0.00	0.00	0.00	0.24	0.81
Gender	0.00	0.00	0.00	-0.12	0.91
Race	0.00	0.00	-0.01	-0.72	0.47
Medical Service	0.00	0.00	-0.02	-1.58	0.12
SIRS Alerts	-0.01	0.00	-0.02	-2.15	0.03*

Note. $F(5, 11256) = 1.70$, $p = 0.03$, R-Square (R^2) = 0.001, $N = 11262$

a. Dependent Variable: Sepsis Initial Resuscitation PowerPlan Ordered
b. Covariates: Medical Service, Gender, Age, Race
c. Independent Variable: SIRS Alerts
*Significant at a level less than or equal to 0.05

coefficient value was again negative, and exp(*B*) = -1.01, meaning that when there was at least one sepsis alert present on a patient visit, 1.01 fewer PowerPlans were ordered.

The results of these multiple linear regression analyses did not support the second hypothesis that "the implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to more ordering of the Sepsis Initial Resuscitation PowerPlan". It was demonstrated that the implementation of SIRS and sepsis alerts in the EMR was correlated with fewer PowerPlans being ordered by physicians.

Comparison of Cohorts on Sepsis Initial Resuscitation PowerPlan.

Table 17

Association Between Sepsis Alerts and Sepsis Initial Resuscitation PowerPlan

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	0.02	0.01		3.38	0.00*
Age	0.00	0.00	0.00	0.40	0.69
Gender	0.00	0.00	0.00	-0.09	0.93
Race	0.00	0.00	-0.01	-0.62	0.53
Medical Service	0.00	0.00	-0.02	-1.60	0.11
Sepsis Alerts	-0.01	0.00	-0.03	-2.96	0.00*

Note. $F(5, 11256) = 2.52$, $p = 0.03$, R-Square (R^2) = 0.001, $N = 11262$

a. Dependent Variable: Sepsis Initial Resuscitation PowerPlan Ordered
b. Covariates: Medical Service, Gender, Age, Race
c. Independent Variable: Sepsis Alerts
*Significant at a level less than or equal to 0.05

The post-implementation group who received any alerts only ($N = 4524$) was compared with the entire pre-implementation group ($N = 1551$) on the dependent variable Sepsis PowerPlan to see whether support for the second hypothesis would be seen. As shown in Table 18, there was a statistically significantly result for the *z*-score test, meaning that there is a difference between the two population proportions. For the pre-implementation group, the proportion is 0.014, and for the post-implementation group, it is 0.007. These results are similar to the multiple linear regression analysis run on the Sepsis PowerPlan variable, as there were a lower number of PowerPlans ordered post-alert implementation. As with previous cohort

Table 18

Comparison of Cohorts on Sepsis PowerPlan Ordered

	Pre-Implementation Group	Post-Implementation Group
Total number of PowerPlans ordered	22	32
Sample Size	1551	4524

Note. The *z*-score for two population proportions is 2.57. The *p*-value is 0.005. The result is significant at $p < 0.05$.

comparisons, the pre-implementation cohort consisted only of patient visits with a recorded sepsis diagnosis on the chart. As a recorded sepsis diagnosis was also one of the three selection criteria for the post-implementation group, the whole post-implementation cohort could not be used as a valid basis for comparison to the pre-implementation group.

H2: Association Between SIRS and Sepsis Alerts and Sepsis Diagnosis

Probability Tables: Sepsis Diagnosis.

First, Table 19 shows that the model using SIRS alerts predicted that 85.0 %, or 920 of intervention patient visits, would not have a sepsis diagnosis. It also predicted that 17.6%, or 144 intervention patient visits would have a sepsis diagnosis. Cases were classified as true events if the predicted probability equaled or exceeded 0.50. The overall percentage of correct Yes and No predictions was 56.0%.

Next, Table 20 displays the probabilities using sepsis alerts. It correctly predicted that 94.2%, or 1784 intervention patients would not be diagnosed with sepsis. It also predicted that

Table 19

Probability Table: SIRS Alerts and Sepsis Diagnosis

Observed			Predicted		
			Sepsis Diagnosis		Percentage Correct
		Total	No	Yes	
Sepsis Diagnosis	No	1082	920	162	85.0%
	Yes	819	675	144	17.6%
Overall Percentage		1901	1595	306	56.0%

Note. The classification cut-off value is 0.50.
N = 1901, post-implementation sample with SIRS alerts.

Table 20

Probability Table: Sepsis Alerts and Sepsis Diagnosis

Observed			Predicted		
			Sepsis Diagnosis		Percentage Correct
		Total	No	Yes	
Sepsis Diagnosis	No	1893	1784	109	94.2%
	Yes	1397	1290	107	7.7%
Overall Percentage		3290	3074	216	57.5%

Note. The classification cut-off value is 0.50.
N = 3290, post-implementation sample with sepsis alerts.

7.7%, or 107 intervention patients would be diagnosed with sepsis. The classification cut-off value again used was 0.50. The overall percentage of correct Yes and No predictions was 57.5%.

Regression Results: Sepsis Diagnosis.

Binary logistic regression analyses were conducted to evaluate the changes in sepsis diagnosis status after employing SIRS and sepsis alerts within the EMR, respectively, while controlling for medical service, age, gender, and ethnicity. The pre-implementation group was not included as it was comprised only of patient visits with a recorded sepsis diagnosis on the chart. As a recorded sepsis diagnosis was also one of the three selection criteria for the post-implementation group, the whole post-implementation cohort could not be used as a valid basis for comparison to the pre-implementation group. Therefore, the analysis for SIRS alerts only included patients who had received one or more SIRS alerts (N = 1901), and the analysis for sepsis alerts only included patients who had received one or more sepsis alerts (N = 3290).

Logistic regression was chosen since the dependent variable of sepsis diagnosis is a binary categorical variable with the two possible responses of Yes (1) or No (0). In these two analyses only, the independent variables, SIRS and sepsis alerts, are continuous. They are measured here as a count of the number of unique alerts per patient visit. Representing the variable as binary in this instance would have characterized it as a constant, i.e. all patients would have had a Yes (1) value. Therefore, it would have been a static value in the model, and not a meaningful variable.

The logistic regression results for SIRS alerts and sepsis diagnosis are presented in Table 21. For the entire model, the omnibus tests of model coefficients, or Chi-square tests ($X^2(2)$ = 30.23, $p < 0.001$) had a p-value less than the significance level of 0.05. The Nagelkerke R^2 result was 0.05, a value indicative of the impact of all of the variables within the model. It explained only 5% of the overall variance in the prediction of sepsis diagnosis. Beta coefficients and odds ratios were used to determine the individual associations. SIRS alerts (Wald = 25.14, $p < 0.001$) had a statistically significant relationship with sepsis diagnosis. SIRS alerts had a beta coefficient

Table 21

Association Between SIRS Alerts and Sepsis Diagnosis

	B	S.E.	Wald	df	Sig.	Odds Ratio
Age	0.01	0.00	21.49	1	0.00*	1.01
Gender	0.07	0.01	0.56	1	0.46	1.07
Race	-0.03	0.03	0.73	1	0.40	0.97
Medical Service	-0.01	0.00	14.30	1	0.00*	0.99
Number of SIRS alerts	0.20	0.04	25.14	1	0.00*	1.22
Constant	-0.85	0.22	14.78	1	0.00*	0.43

Note. $X^2(2) = 30.23$, $p < 0.001$, Nagelkerke $R^2 = 0.05$, $N = 1901$

a. Dependent variable: Sepsis Diagnosis
b. Covariates: Age, Gender, Race, Medical Service
c. Independent variable: SIRS Alerts
*Significant at a level less than or equal to 0.05

of 0.20 and an odds ratio of 1.22:1. This indicates that for each additional SIRS alert present on a patient, he or she had 1.22 higher odds of having had a sepsis diagnosis recorded in the EMR than those with one fewer SIRS alert.

Results for sepsis alerts are presented in Table 22. For the whole regression model, the Chi-square tests ($X^2(2) = 51.79$, $p < 0.001$) had a significant p-value of less than 0.05. The Nagelkerke R^2 result was 0.04, a value denoting the small effect size of the model, all variables included. It explained 4% of the overall variance in the prediction of sepsis diagnosis. Sepsis alerts (Wald = 38.13, $p < 0.001$) had a statistically significant relationship with sepsis diagnosis. Sepsis alerts had a beta coefficient of 0.27 and an odds ratio of 1.31:1. This indicates that per

Table 22

Association Between Sepsis Alerts and Sepsis Diagnosis

	B	S.E.	Wald	df	Sig.	Odds Ratio
Age	0.00	0.00	9.37	1	0.00*	1.01
Gender	-0.02	0.07	0.10	1	0.75	0.98
Race	-0.08	0.02	12.46	1	0.00*	0.92
Medical Service	-.010	0.00	14.82	1	0.00*	0.99
Sepsis Alerts	0.27	0.04	38.13	1	0.00*	1.31
Constant	-0.41	0.17	5.62	1	0.02	0.67

Note. $X^2(2) = 51.79$, $p < 0.001$, Nagelkerke $R^2 = 0.04$, $N = 3290$

a. Dependent variable: Sepsis Diagnosis
b. Covariates: Age, Gender, Race, Medical Service
c. Independent Variable: SIRS Alerts

each additional sepsis alert present on a patient, he or she had 1.31 higher odds of having had a sepsis diagnosis recorded compared to those with one fewer sepsis alert.

The results of these logistic regression analyses fully support the second hypothesis that "the implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to more frequent diagnoses of sepsis". It was demonstrated that the presence of additional SIRS and sepsis alerts in the post-implementation group was associated with more sepsis diagnoses being recorded by physicians.

Chapter Summary

The purpose of this study was to examine the impact of implementing cloud-based SIRS and sepsis alerts in the Cerner EMR. This chapter enumerated the results of each hypothesis. The

dependent variables tested, using logistic regression and multiple linear regression, included sepsis-related mortality, length of stay, sepsis diagnosis, and the ordering of the Sepsis Initial Resuscitation PowerPlan. The pre-implementation group was also compared to the post-implementation group on the dependent variables of length of stay and sepsis-related mortality. The interpretation of and key findings of these results, along with limitations and recommendations for future research, will be discussed in Chapter 5.

Chapter 5: Conclusion

Overview

This chapter summarizes and reviews the key findings and implications of the study. Also discussed will be limitations and recommendations for future research in the domain of CDS sepsis alerting. The primary purpose of this study was to estimate the impact of implementing real-time, cloud-based SIRS and sepsis alerts on inpatient sepsis-related mortality, length of stay, ordering of the Sepsis Initial Resuscitation PowerPlan, and sepsis diagnosis coding. As a process and patient outcomes evaluation of a unique CDS alerting tool, it was employed to improve recognition and care of those patients at risk for sepsis. A sample of 11,262 unique patient visits, along with the total number of occurrences of SIRS and sepsis alerts, were retrieved from a clinical data warehouse for the analysis. Two main hypotheses were examined. How these hypotheses were met and a discussion of related key results follows.

Hypothesis Results and Discussion

H_1: The implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to lower sepsis-related mortality and lower average length of stay.

The first major finding of this research is that patients having one or more SIRS alerts were correlated with having 1.41 higher odds of experiencing sepsis-related mortality than those with no alerts. Due to the post-implementation cohort patients being alerted on prior to the onset of sepsis, it was expected that mortality would be lower. However, Berger et al. (2010) had

previously found that the implementation of a computerized alert based on two SIRS criteria had left the mortality rate unchanged. A possibility that was not controlled for in this study is that patient mortality could be due to conditions unrelated to SIRS or sepsis. Per Long, Koyfman, and Bright (2015), there are several conditions that meet the criteria for SIRS and can therefore mimic sepsis. These include pulmonary embolism, anaphylaxis, colitis, and vasculitis, among others. If they are not ruled out, higher mortality rates may result.

Secondly, it was found that the presence of one or more sepsis alerts did not have a statistically significant impact on sepsis-related mortality in-house. This is in contrast to the reduced mortality rate found in previous sepsis CDS alert studies by Zubrow et al. (2008), Powers and Burchell (2010), Moore et al. (2010), and Vogel (2014). As the post-implementation cohort consisted of patient visits, it might be deduced that multiple visits by the same patients over the three-year study period ultimately ended in their death, as the outcomes tend to deteriorate with each admission for patients that have had already sepsis and survived it (Yende & Angus, 2007). There were stricter physiologic criteria used to define sepsis in this study algorithm, compared with all the other studies cited in the literature review that use the more liberal criteria as outlined by the Sepsis Definitions Task Force (Singer et al., 2016), that would make the results of this study less comparable to those that used the stricter criteria. It was also not clear in those studies as to how mortality rate was assessed, or over what period of time. Again, this makes it more difficult to correlate the results of this study, which only assessed sepsis mortality in-house, with others. Patients who were discharged, after being treated for sepsis, may have had either a higher or lower survival rate due to delayed sequelae. Fewer than half of severe sepsis patients are still alive within one year, as the subsequent mortality rate for these patients is high (Yende & Angus, 2007). Due to post-discharge information not being able

to be obtained for this study, in terms of subsequent health status or mortality, these factors could not be accounted for and therefore not measured. Despite adjusting for acuity with the medical service control variable in this study, the most clinically severe patients may have tended to have more SIRS or sepsis alerts, so any improvement due to the presence of the alerts may have been skewed lower by the deaths of those in the worst condition.

Support for H_1, however, was found via a comparison of population means between the pre-implementation cohort (N = 1551) and the post-implementation cohort with one or more SIRS or sepsis alerts, or both (N = 4524), for sepsis-related mortality. Inpatient deaths due to sepsis were 6.7% lower in the post-implementation group. This difference between this result and those of the regression analysis, where SIRS alerts were associated with a slightly higher sepsis-related mortality, might be explained due to the post-implementation group only being comprised of those who received one or more SIRS or sepsis alerts, or both (N = 4524), and not the combined regression analysis sample (N = 11262) made up of patient visits with one or more SIRS and sepsis alerts, those diagnosed with sepsis, and those with a Sepsis PowerPlan ordered. The comparison of population means results could indicate that the alerts were more impactful on sepsis mortality than indicated by the regression results, as patients in the combined sample that were diagnosed with sepsis by a clinician and not alerted on may not have met the officially defined VCU Health System criteria for SIRS and sepsis. This could mean that the metrics used by clinicians to identify sepsis differed from those of the alerts, and if the patient was not truly septic, then sepsis-related mortality might not reasonably follow.

The next major finding pertains to the second part of H_1, the impact of the alerts on length of stay. Results indicated that both SIRS and sepsis alerts were associated with a higher average length of stay, not a lower one. This is similar to the results obtained by Bailey et al.

(2013) at Barnes-Jewish hospital in St. Louis, where the median length of stay was found to be statistically longer for pager-alerted patients, at 7.01 vs. 2.94 days for non-alerted patients ($p < 0.001$). As so at Barnes-Jewish, it could be postulated that patients who deteriorated clinically over time generated more alerts, and may have accounted for these higher average lengths of stay.

It had been originally theorized that alerts would reduce the overall length of stay due to more timely intervention and evidenced-based treatment, preventing sepsis from occurring, with the patient discharged sooner than if they became septic. However, even if the patient's sepsis has been managed with antibiotic therapy (Howell & Davis, 2017), they may still need more time in the hospital to recover than a non-septic patient. Likewise, the patients with the most sepsis alerts might well remain alive and in an inpatient status longer due to successful interventions. Other factors to consider that might impact the length of stay, in spite of the medical service variable being controlled for, include varying aspects of the patient population in terms of admission diagnosis and socioeconomic status, a different mix of illnesses, and changes in medication protocols, some of which may be less effective for the treatment of septic patients. Medical service can change during an inpatient stay, and is not directly correlated to specific diseases or patient types as defined by VCU Health System. For this study, the medical service assigned upon admission was used. Using medical service to represent clinical complexity may not have adequately controlled for patient acuity. If a score or index had been used to calculate clinical complexity in this study and controlled for, the overall results may have been more in line with the projected hypotheses.

As with sepsis-related mortality, the pre-implementation cohort ($N = 1551$) was compared to the alerts-only post-implementation cohort ($N = 4524$) by a comparison of means,

for length of stay. The mean length of stay in days was 1.2 days longer for those in the post-implementation group than those in the sepsis-diagnosed pre-implementation group, which was not a statistically significant result. The difference in results between this analysis and that of the regression on length of stay may again be due to the use of the combined samples (N = 11262) for the latter.

H_2: The implementation of cloud-based SIRS and sepsis alerts in the EMR will lead to more ordering of the Sepsis Initial Resuscitation PowerPlan and more recording of sepsis diagnoses.

The major finding with regard to the initial part of H_2 is that SIRS and sepsis alerts were associated with fewer orders of the Sepsis Initial Resuscitation PowerPlan. This did not lend support to the second hypothesis, suggesting that SIRS and sepsis alerts may not sufficiently spur physicians to order more Sepsis PowerPlans. Based on my observations at VCU Health System, it could be surmised that while they may have indeed heeded the instructions provided in the alerts when prompted, physicians still preferred to choose their own mix of orders, placing individual orders for fluids, medications, and lab work outside the pre-configured Sepsis PowerPlan. They might also have realized, prior to an alert appearing, that the patient had SIRS or was septic. Within the Cerner EMR, physicians also have the option to save a customized version of a plan, a behavior frequently associated with PowerPlans, but the study was not able to take this into account due to the unobtainable nature of the customized PowerPlan data. A method for tracking physician-customized PowerPlans might therefore yield a more accurate view of how frequently they are ordered. Another possibility is that they did not know how or where to locate the Sepsis PowerPlan. In that case, better instructions, or a link to the PowerPlan

itself, could have been included in the alert text body. Sepsis PowerPlans may also need to be more widely promoted at VCU Health System as a standard of care.

Prior to alert implementation, there were very few patients on whom there was a standard Sepsis PowerPlan ordered, so it already suffered from a low usage rate. Only 22 unique patient visits in the pre-implementation group (N = 1551) and 32 patient visits in the alerts-only post-implementation group (N = 4524) had Sepsis PowerPlans ordered. It could be expected that this trend might continue, particularly if individually placed orders or customized PowerPlans were continuing to be used, as previously theorized. PowerPlans may also not have been ordered if the alerts were ignored due to alert fatigue (Phansalkar et al., 2010). Alert fatigue is not only a factor due to multiple SIRS or sepsis alerts on a patient being possible throughout their stay, but the coexistence of many other types of interruptive, real-time alerts employed in the EMR at VCU Health System.

Additionally, a global quality improvement study conducted by Rhodes et al. (2015) determined that SSC-recommended order set bundle (akin to PowerPlans) compliance was associated with a 40% reduction in the hospital-associated mortality rate for the 3-hour bundle and a 36% reduction for the 6-hour bundle. Hence, low compliance in ordering Sepsis PowerPlans in this study may have also contributed somewhat to the lack of reduction in the mortality rate (first half of H_1).

The pre-implementation cohort (N = 1551) was also compared to the alerts-only post-implementation cohort (N = 4524) via a comparison of population proportions, for the Sepsis PowerPlan variable. There was a statistically significant result, indicating that there was a difference between the two population means, with the post-implementation group having a proportionally lower number of PowerPlans ordered.

Relating to the second half of $H_{2,}$ statistically significant results indicated that the implementation of both cloud-based SIRS and sepsis alerts was associated with more diagnoses of sepsis. This suggests that alerts could have contributed to the higher amount of sepsis diagnosis codes being documented. However, the recording of an active diagnosis on the patient's chart is a core measure of Stage 1 of Meaningful Use, which was implemented at VCU Health System in 2012, and could also be responsible for the increased recording of their diagnoses.

Study Limitations

There are several possible limitations to this study. The pre-implementation group used could only be identified by the presence of a recorded sepsis diagnosis on the patient's chart, which may have made it not as suitable as a basis for comparison to the post-implementation group that included all patients diagnosed with sepsis as well as those who had SIRS and sepsis alerts or a Sepsis PowerPlan ordered, even if no sepsis diagnosis was present in the EMR. Prior to the implementation of the alerts, this was ascertained to be the best way to identify septic patients. As all data were extracted from a data warehouse, order set bundles equivalent to a Sepsis PowerPlan, such as those customized and saved by individual physicians, were not able to be identified and counted. This would have required individual chart reviews, which were not feasible given the size of the study cohort. Additionally, use of the control variable medical service might not have been an exact substitute for the patient's clinical acuity, but it was the closest fit based on the data available. VCU Health System also serves a large uninsured, indigent population, and this may have influenced alerting outcomes due to a prevalence of generally unhealthier patients, particularly if clinical complexity was not adequately controlled

for. Other academic medical centers and hospitals may have different patient populations, depending on the areas they serve.

Also of note, the Cerner algorithm used by VCU Health System employs slightly more acute physiologic criteria for sepsis than the conventional standard. The qualifying heart rate (HR) is greater than 95 versus 90, the respiratory rate is greater than 22 versus 20, and three of four SIRS criteria or two of four with one indicator of organ dysfunction is used rather than two or more. (Kaplan & Pinksy, 2011). Perhaps due to these refinements, Erlichman, Trach, Patel, Maheshwari, and Seckel (2014) found that the Cerner sepsis detection algorithm had a positive predictive value for sepsis only slightly higher than that of its SIRS criteria. Estimations of sensitivity and specificity of the Cerner algorithm across multiple geographic regions and facility types were found to be 83% and 92%, respectively (Amland & Hahn-Cover, 2016). Further adjustments to the algorithm are always being made, and may bring it more in line with nationally recommended standards. Implications based on the more stringent criteria used in this study may therefore be more pertinent to other hospitals that use the Cerner sepsis algorithm for SIRS and sepsis alerting, than those that use an algorithm from another vendor, or one that is custom-developed. Hospitals that use the more liberal nationally-recommended criteria may not benefit directly from the results of this study, while those that use the stricter criteria may see a higher number of sepsis diagnoses being made, as was found here.

False-positive alerts may happen on occasion, and false negatives will result in no alerting, with the attendant risk of not realizing the need for rapid intervention. False-positive results can also lead to alert fatigue (Despins, 2017). Clinicians are responsible for properly assessing the patient in a timely manner once an alert is generated. If the alerts are not taken as seriously by clinical staff due to alert fatigue, they may be less likely to take the next logical

intervention step, such as calling a physician or rechecking vital signs (Bailey et al., 2013). Although unlikely, if any vital signs or laboratory tests have been entered or resulted incorrectly, or have changed within a short period of time, then the alert may or may not be warranted. This could have diluted the impact of the alerts. False-positive alerts, false-negative alerts, and alert fatigue might have led to delays in the recording of sepsis diagnoses or ordering of PowerPlans, or assured that they never occurred at all, due to inaccurate information or a lack thereof. With the data obtained for this study, it was not possible to estimate the impact of those erroneous alerts or alert fatigue. The influence of any or all of these limitations should be considered as they pertain to the conclusions, with the pre- and post-implementation cohort differences, inability to accurately assess the number of PowerPlan orders, and stricter alert criteria of the study algorithm being the most salient.

Implications

Adopting CDS alerting technology to identify sepsis risk sooner than by manual observation, by alleviating some of the weight on staff, may engender better patient outcomes by allowing clinicians to prioritize care of septic patients. A patient being diagnosed with SIRS or sepsis via an alert sooner can be treated more quickly. Clinician awareness and responsiveness to the alerts themselves may increase if alert fatigue is mitigated by better alert design. More adherence to alert advice may also lead to enhanced patient outcomes, particularly for sepsis-related mortality. Healthcare systems could potentially consider adding this technology as part of an evidence-based medicine protocol for ameliorating mortality, as there is preliminary evidence from this study that more sepsis diagnoses are made as a result of alert adoption. Hospitals also need to be aware that any technology adds additional risk, so it needs to be considered and implemented carefully in light of mixed results from not only this study, but many others here

cited from the literature. This research suggests that clinicians and clinical informaticists can therefore consider the implementation of cloud-based SIRS and sepsis alerts if they want to capture more sepsis diagnoses.

As supported by not only this study, but several cited in the literature review, alerts geared toward sepsis-related interventions demonstrate varying levels of success in increasing diagnostic awareness of sepsis or reducing sepsis-related mortality and average length of stay, their effectiveness dependent upon specific physiologic parameters, clinician notification methods, and venues in which they are employed. Further study of specific patient populations in multiple healthcare setting types, with stratification for high-risk comorbidities and improved alerting technology is recommended for fostering increased understanding of how to best use CDS for lightening the burden of sepsis-related mortality. Despite hopes that targeted healthcare IT applications such as CDS would lead to improved patient outcomes through more immediate syndrome recognition, rapid intervention, and treatment standardization (Brokel et al., 2011), particularly in terms of reduced length of stay and lower mortality rates (Berner, 2009), the promise has yet to be fully realized.

Future Research Recommendations

This study looks at all adult inpatients, so it could alternatively explore specific chronically ill patient subpopulations, such as those in ICUs. Those patients tend to have a higher incidence of sepsis, along with several comorbidities, thus a comorbidity index might be used as a control variable. This could help determine whether to adjust alerting criteria to be more in line with Surviving Sepsis Campaign (SSC)-recommended reference ranges for vital signs and laboratory results, in order to gauge alert effectiveness in reducing mortality in certain high-risk populations, as the expected reduction in sepsis related mortality was not seen in the overall

patient population. Pediatric and elderly patient populations, who are more vulnerable to sepsis post-infection, might also be examined in order to see if the more stringent criteria in the alerts results in lower sepsis-related mortality (Angus et al., 2001). Comparisons between medical services, such as general medical and surgery, might also be instructive regarding sepsis mortality rates, due to the varying nature of patient makeup and treatments for sepsis. Patients diagnosed with sepsis could also be tracked longitudinally, post-discharge, in order to obtain more accurate mortality rates, as those that expire shortly after discharge due to sepsis are not captured and counted in inpatient studies. Measuring other literature-supported variables may also provide more insight into the impact of the alerts, such as time to antibiotic treatment (Rosenqvist, et al., 2017), factors influencing practitioner performance (Garg et al., 2005), and cost effectiveness (Calvert et al., 2017).

Gaieski, Edwards, Kallan, and Carr (2013) discovered that national estimates for the incidence and mortality rate of severe sepsis vary depending on how they are measured. They did find that the retrospective use of ICD-9 codes was highly sensitive for the diagnosis of severe sepsis, which would suggest its use as a sepsis diagnosis proxy be continued. Per the literature, a preponderance of research on sepsis alerting has been conducted in academic medical centers. Studies at medical centers thus far, including this one, have produced equivocal results regarding the patient outcomes of sepsis-related mortality and length of stay, and the process outcomes of recorded sepsis diagnoses and bundle order set usage. It would therefore be recommended the effectiveness of SIRS and sepsis alerts be measured in other settings, such as healthcare facilities in the private and not-for-profit domains, due to variations in patient demography such as income and illness acuity in cities, suburbs, and rural areas. Such studies might help in obtaining a more accurate overall view of how effective these alerts are in various populations.

In addition, Rhodes et al. (2015) determined that overall compliance rates with the SSC-recommended order set bundles (akin to PowerPlans) were low, at 19% for the 3-hour bundle and 36% for the 6-hour bundle. VCU Health System also suffered from low order set bundle (Sepsis PowerPlan) use. Thus, in order to fully understand whether the needed evidence-based protocols for sepsis treatment were followed, tracking physician-customized order sets, individual groupings of sepsis-related orders, or their equivalents, by chart reviews or other means may prove a better way to measure their overall uptake and consequently, develop strategies for improving clinician responsiveness.

As the human and financial costs of sepsis-related mortality remain unacceptably high, SIRS and sepsis alerts are worth a continued investment for any healthcare facility with a compatible EMR. Although investing in and deploying sophisticated, real-time algorithmic SIRS and sepsis alerts does not necessarily result in improved patient and process outcomes, they should continue be used in order to accurately ascertain their effectiveness in those terms. Increased use of the sepsis algorithm will also provide more data for additional studies that can address its impact on sepsis-related mortality. While speculation on the existing literature can inform current clinical practice, better-designed studies measuring outcome variables more accurately can be constructed to determine where and why alerts are or are not working.

Conclusion

VCU Health System provided a singular setting in which real-time, state-of-the art, uniquely customized cloud-based SIRS and sepsis alerts were employed on a large, general, adult inpatient population. The study examined the impact of SIRS and sepsis CDS alerts upon the patient outcomes of sepsis-related mortality and length of stay, and the process outcomes of recorded sepsis diagnoses and ordered Sepsis PowerPlans. Although results were mixed, they

provide a basis for comparison for additional studies involving similar types of CDS sepsis detection algorithms, and even though alerting criteria can vary slightly per institution, it should not be enough to significantly alter overall outcomes. Each research study design can build upon the lessons learned from previous studies, engendering more effective research in terms of independent, dependent, and control variable choice and measurement.

References

Alexopoulos, E. C. (2010). Introduction to multivariate regression analysis. *Hippokratia*, *14*(Suppl 1), 23–8.

Amland, R. C., & Hahn-Cover, K. E. (2016). Clinical Decision Support for Early Recognition of Sepsis. *American Journal of Medical Quality*, *31*(2), 103–110.

Angus, D. C., Linde-Zwirble, W. T., Lidicker, J., Clermont, G., Carcillo, J., & Pinsky, M. R. (2001). Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine*, *29*(7), 1303–1310.

Austrian, J. S., Jamin, C. T., Doty, G. R., & Blecker, S. (2017). Impact of an emergency department electronic sepsis surveillance system on patient mortality and length of stay. *The Journal of the American Medical Informatics Association*, *25*(5), 523–529.

Back, J., Jin, Y., & Lee, S. (2014). Development and Validation of an Automated Sepsis Risk Assessment System. *Research in Nursing & Health, 39*, 317– 327.

Bailey, T. C., Chen, Y., Mao, Y., Lu, C., Hackmann, G., Micek, S. T., … Kollef, M. H. (2013). A trial of a real-time Alert for clinical deterioration in Patients hospitalized on general medical wards. *Journal of Hospital Medicine*, *8*(5), 236–242.

Berger, T., Birnbaum, A., Bijur, P., Kuperman, G., & Gennis, P. (2010). A Computerized Alert Screening for Severe Sepsis in Emergency Department Patients Increases Lactate Testing but Does Not Improve Inpatient Mortality. *Applied Clinical Informatics,* 394-407.

Berner, E.S. (2009). Clinical Decision Support Systems: State of the Art. Agency for Healthcare Research and Quality. Retrieved from

http://healthit.ahrq.gov/images/jun09cdsreview/09_0069_ef.html

Brokel, J. M., Schwichtenberg, T. J., Wakefield, D. S., Ward, M. M., Shaw, M. G., & Kramer, J. M. (2011). Evaluating Clinical Decision Support Rules as an Intervention in Clinician Workflows with Technology. *CIN: Computers, Informatics, Nursing, 2*(1), 36-42.

Calvert, J., Hoffman, J., Barton, C., Shimabukuro, D., Ries, M., Chettipally, U., … Das, R. (2017). Cost and mortality impact of an algorithm-driven sepsis prediction system. *Journal of Medical Economics*, *20*(6), 646–651.

Castellanos-Ortega, A., Suberviola, B., García-Astudillo, A., Holanda, M.S., Ortiz, F. Llorca, J., & Delgado-Rodríguez, M. (2010). Impact of the Surviving Sepsis Campaign protocols on hospital length of stay and mortality in septic shock patients: Results of a three-year follow-up quasi-experimental study. *Critical Care Medicine*, *38*(4), 1036–1043.

Cox, Z. L., Nelsen, C. L., Waitman, L. R., McCoy, J. A., & Peterson, J. F. (2011). Effects of clinical decision support on initial dosing and monitoring of tobramycin and amikacin. *American Journal of Health-System Pharmacy*, *68*(7), 624–632.

Cresswell, K.M., Bates, D.W., Phansalkar, S., & Sheikh, A. (2011). Opportunities and challenges in creating an international centralized knowledge base for clinical decision support systems in ePrescribing. *BMJ Quality and Safety*, *20*, 625-30.

Dellinger, R. P., Levy, M. M., Rhodes, A., Bs, M. B., Annane, D., Gerlach, H., … Beale, R. J. (2013). Surviving Sepsis Campaign. *Critical Care Medicine*, *41*(2), 580–637.

Despins, L.A. (2017). Automated Detection of Sepsis Using Electronic Medical Record Data: A Systematic Review. *Journal for Healthcare Quality*, *39*, 322-333.

Dombrovskiy, V. Y., Martin, A. A., Sunderram, J., & Paz, H. L. (2007). Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis

from 1993 to 2003. *Critical Care Medicine*, *35*(5), 1244–50.

Downing, G.J., Boyle, S.N., Brinner, K.M., & Osheroff, J.A. (2009). Information Management to enable personalized medicine: stakeholder roles in building clinical decision support. *BMC Medical Informatics and Decision Making*, *9*(44).

Erlichman, P., Trach, L., Patel, B., Maheshwari, V., & Seckel, M. (2014). Sensitivity and Positive Predictive Value of Cerner EMR Based Sepsis Recognition Tool. *Critical Care Medicine*, *42*(12), 2014.

Fleischmann, C., Scherag, A., Adhikari, N. K. J., Hartog, C. S., Tsaganos, T., Schlattmann, P., … Reinhart, K. (2016). Assessment of global incidence and mortality of hospital-treated sepsis current estimates and limitations. *American Journal of Respiratory and Critical Care Medicine*, *193*(3), 259–272.

Gaieski, D. F., Edwards, J. M., Kallan, M. J., & Carr, B. G. (2013). Benchmarking the incidence and mortality of severe sepsis in the United States. *Critical Care Medicine*, *41*(5), 1167–1174.

Galanter, W. L., Thambi, M., Rosencranz, H., Shah, B., Falck, S., Lin, F. J., … Lambert, B. (2010). Effects of clinical decision support on venous thromboembolism risk assessment, prophylaxis, and prevention at a university teaching hospital. *American Journal of Health-System Pharmacy*, *67*(15), 1265–1273.

Gardner-Thorpe, J., Love, N., Wrightson, J., Walsh, S., & Keeling, N. (2006). The value of Modified Early Warning Score (MEWS) in surgical in-patients: A prospective observational study. *Annals of the Royal College of Surgeons of England*, *88*(6), 571–575.

Garg, A. X., Adhikari, N. K., McDonald, H., Rosas-Arellano, M. P., Devereaux, P. J., Beyene, J., ... Haynes, R. B. (2005). Effects of Computerized Clinical Decision Support Systems on

Practitioner Performance and Patient Outcomes: A Systematic Review. *The Journal of the American Medical Association*, *293*(10), 1223-1238.

Guerra, W. F., Mayfield, T. R., Meyers, M. S., Clouatre, A. E., & Riccio, J. C. (2013). Early Detection and Treatment of Patients with Severe Sepsis by Prehospital Personnel. *The Journal of Emergency Medicine*, *44*(6), 1116-1125.

Gultepe, E. Green, J. P., Nguyen, H., Adams, J., Albertson, T., & Tagkopoulos, I. (2013). From vital signs to clinical outcomes for patients with sepsis: a machine learning basis for a clinical decision support system. *The Journal of the American Medical Association, 21*, 315–325.

Gilmer, T. P., O'Connor, P. J., Sperl-Hillen, J. M., Rush, W. A., Johnson, P. E., Amundson, G. H., … Ekstrom, H. L. (2012). Cost-Effectiveness of an Electronic Medical Record Based Clinical Decision Support System. *Health Services Research*, *47*(6), 2137–2158.

Hall, J. H., Williams, S. N., DeFrances, C. J., & Golosinskiy, A. (2011). Inpatient Care for Septicemia or Sepsis: A Challenge for Patients and Hospitals. *NCHS Data Brief. 62.*

Harrison, A. M., Thongprayoon, C., Kashyap, R., Chute, C. G., Gajic, O., Pickering, B. W., & Herasevich, V. (2015). Developing the surveillance algorithm for detection of failure to recognize and treat severe sepsis. *Mayo Clinic Proceedings*, *90*(2), 166–175.

Henry, K. E., Hager, D. N., Pronovost, P. J., & Saria, S. (2015). A targeted real-time early warning score (TREWScore) for septic shock. *Science Translational Medicine*, *7*(299), 299ra122.

Herasevich, V., Pieper, M. S., Pulido, J., & Gajic, O. (2011). Enrollment into a time sensitive clinical study in the critical care setting: results from computerized septic shock sniffer implementation. *The Journal of the American Medical Association*. *18*, 639-644.

Howell, M. D., & Davis, A. M. (2017). Management of Sepsis and Septic Shock. *The Journal of the American Medical Association*, *315*(8), 801–810.

Kaplan, L. J., & Pinsky, Michael, R. (2011). Systemic Inflammatory Response. Retrieved from http://emedicine.medscape.com/article/168943-overview

Levy, M. M., Rhodes, A., Phillips, G. S., Townsend, S. R., Schorr, C. A., Beale, R., … Dellinger, R. P. (2014). Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Intensive Care Medicine*, *40*(11), 1623–1633.

Long, B., Koyfman, A., & Bright, J. (2015, December 1). Mimics of Sepsis: What do ED Physicians Need to Know? Retrieved from http://http://www.emdocs.net/mimics-of-sepsis/

Liu, V., Escobar, G. J., Greene, J. D., Soule, J., Whippy, A., Angus, D. C., & Iwashyna, T. J. (2014). Hospital deaths in patients with sepsis from 2 independent cohorts. *The Journal of the American Medical Association*, *312*(1), 90–2.

Maggio, P.M., & Carvahlo, C. (2017). Sepsis, Severe Sepsis, and Septic Shock. Retrieved from http://www.merckmanuals.com/home/infections/bacteremia,-sepsis,-and septic-shock/sepsis,-severe-sepsis,-and-septic-shock

Mani, S., Ozdas, A., Aliferis, C., Varol, H. A, Chen, Q., Carnevale, R., ... Weitkamp, J. (2014). Medical decision support using machine learning for early detection of late-onset neonatal sepsis. *The Journal of the American Medical Association. 21*, 326–336.

Mayr, F. B., Talisa, V. B., Balakumar, V., Chang, C.-C. H., Fine, M., & Yende, S. (2017). Proportion and Cost of Unplanned 30-Day Readmissions After Sepsis Compared With Other Medical Conditions. *The Journal of the American Medical Association*, *317*(5), 530.

Meurer, W. J., Smith, B. L., Losman, E. D., Sherman, D., Yaksich, J. D., Jared, D. J., ... Younger, J. G. (2009). Real-Time Identification of Serious Infection in Geriatric Patients

Using Clinical Information System Surveillance. *Journal of the American Geriatrics Society*. *57*, 40–45.

Melamed, A., & Sorvillo, F. J. (2009). The burden of sepsis-associated mortality in the United States from 1999 to 2005: an analysis of multiple-cause-of-death data. *Critical Care*, *13*(1), R28.

Mollon, B., Chong, J. J., Holbrook, A. M., Sung, M., Thabane, L., & Foster, G. (2009). Features predicting the success of computerized decision support for prescribing: a systematic review of randomized controlled trials. *BMC Medical Informatics and Decision Making*, *9*, 11.

Moore, L. J., Jones, S. L., Kreiner, L. A., McKinley, B., Sucher, J. F., Todd, S. R., … Moore, F. A. (2009). Validation of a Screening Tool for the Early Identification of Sepsis. *Journal of Trauma-Injury Infection and Critical Care*, *66*(6), 1539–1547.

Moore, L. J., Turner, K. L., Todd, S. R., McKinley, B., & Moore, F. A. (2010). Computerized clinical decision support improves mortality in intra-abdominal surgical sepsis. *The American Journal of Surgery*, *200*, 839-844.

Moorman, R., Xiao, Y., Griffin, P., & Lake, D.E. (2005). Informatics monitoring to predict imminent sepsis. *Heart Rhythm*. *2*(5), S167.

Nelson, J. L., Smith, B. L., Jared, J. D., & Younger, J. G. (2011). Prospective Trial of Real-Time Electronic Surveillance to Expedite Early Care of Severe Sepsis. *Annals of Emergency Medicine*, 57(5), 500-504.

Olenik, E. M., Zimbro, K. S., Ver Schneider, P., & Jones, D. (2017). Predicting Sepsis Risk Using the “Sniffer” Algorithm in the Electronic Medical Record. *Journal of Nursing Care Quality*, *32*, 25-31.

Phansalkar, S., Edworthy, J., Hellier, E., Seger, D. L., Schedlbauer, A., Avery, A. J., & Bates, D.

W. (2010). A review of human factors principles for the design and implementation of medication safety alerts in clinical information systems. *The Journal of the American Medical Informatics Association*, *17*(5), 493–501.

Powers, K. A., & Burchell, P. L. (2010). Sepsis Alert: Avoiding the shock. *Nursing*, *40*(4), 35-38.

Rhodes, A., Phillips, G., Beale, R., Cecconi, M., Chiche, J. D., De Backer, D., … Levy, M. (2015). The Surviving Sepsis Campaign bundles and outcome: results from the International Multicentre Prevalence Study on Sepsis (the IMPreSS study). *Intensive Care Medicine*, *41*(9), 1620–1628.

Rivers, E. P., & Ahrens, T. (2008). Improving Outcomes for Severe Sepsis and Septic Shock: Tools for Early Identification of At-Risk Patients and Treatment Protocol Implementation. *Critical Care Clinics*, *23*, S1-S47.

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., & Tomlanovich, M. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *The New England Journal of Medicine*, *345*(19), 1368–1377.

Romano, M.J., & Stafford, R.S. (2011). Electronic Health Records and Clinical Decision Support Systems. *Archives of Internal Medicine*, *171*(10), 897-903.

Rosenqvist, M., Fagerstrand, E., Lanbeck, P., Melander, O., & Åkesson, P. (2017). Sepsis Alert – a triage model that reduces time to antibiotics and length of hospital stay. *Infectious diseases*, *49*(7), 507-513.

Roshanov, P. S., Fernandes, N., Wilczynski, J. M., Hemens, B. J., You, J. J., Handler, S. M., … Haynes, R. B. (2013). Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials. *BMJ*, *346*(February), f657.

Sands, K. E., Bates, D. W., Lanken, P. N., Graman, P. S., Hibberd, P. L., Kahn, K. L., … Platt, R. (1997). Epidemiology of sepsis syndrome in 8 academic medical centers. *The Journal of the American Medical Association*, *278*(3), 234–40.

Sawyer, A.M., Deal, E.N, Labelle, A.J., Witt, C., Thiel, S.W., Heard, K., … Kollef, M.H. (2011). Implementation of a real-time computerized sepsis alert in nonintensive care unit patients. *Critical Care Medicine, 39*, 469-473.

Seidling, H. M., Phansalkar, S., Seger, D. L., Paterno, M. D., Shaykevich, S., Haefeli, W. E., & Bates, D. W. (2011). Factors influencing alert acceptance: a novel approach for predicting the success of clinical decision support. *The Journal of the American Medical Informatics Association*, *18*(4), 479–84.

Sepsis Fact Sheet. (2017, February 1). Retrieved from https://www.nigms.nih.gov/education/pages/factsheet_sepsis.aspx

Sepsis Study Comparing Three Treatment Methods Shows Same Survival Rate. (2014, March 18). Retrieved from https://www.nigms.nih.gov/news/results/pages/20140318.aspx

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., … Angus, D. C. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *The Journal of the American Medical Association*, *315*(8), 801–10.

Sittig, D. F, Wright, A., Osheroff, J. A., Middleton, B, Teich, J. M., Ash, J. S., Campbell, E., … Bates, D.W. (2008). Grand challenges in clinical decision support. *Journal of Biomedical Informatics, 41,* 387-392.

Sucher, J. F., Moore, F. A., Todd, R. S., Sailors, M., & McKinley, B.A. (2008). Computerized clinical decision support: a technology to implement and validate evidence based guidelines. *The Journal of Trauma-Injury Infection & Critical Care, 64*, 520-537.

Takahashi, K., Kantarjian, H. M., Garcia-Manero, G., Stevens, R. J., Dinardo, C. D, Allen, J., ... Chin, L. (2014). MD Anderson's Oncology Expert Advisor powered by IBM Watson: A Web-based cognitive clinical decision support tool. *Journal of Clinical Oncology, 32,* 5s.

Torio, C. M., & Andrews, R. M. (2013). National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011. *Healthcare Cost and Utilization Project: Statistical Brief #160, 31*(1), 1–12.

U.S. Department of Health & Human Services. (2013). Doctors and hospitals' use of health IT more than doubles since 2012. Retrieved from http://www.hhs.gov/news/press/2013pres/05/20130522a.html

Vogel, L. (2014). EMR alert cuts sepsis deaths. *Canadian Medical Association Journal, 186*(2), E80.

Wiedemann, L.A. (2007). Coding Sepsis and SIRS. *Journal of AHIMA, 78*(4), 76-78.

Wright, D. M., Print, C. G., & Merrie, A. E. H. (2011) Clinical decision support systems: should we rely on unvalidated tools? *ANZ Journal of Surgery, 81*, 316-7.

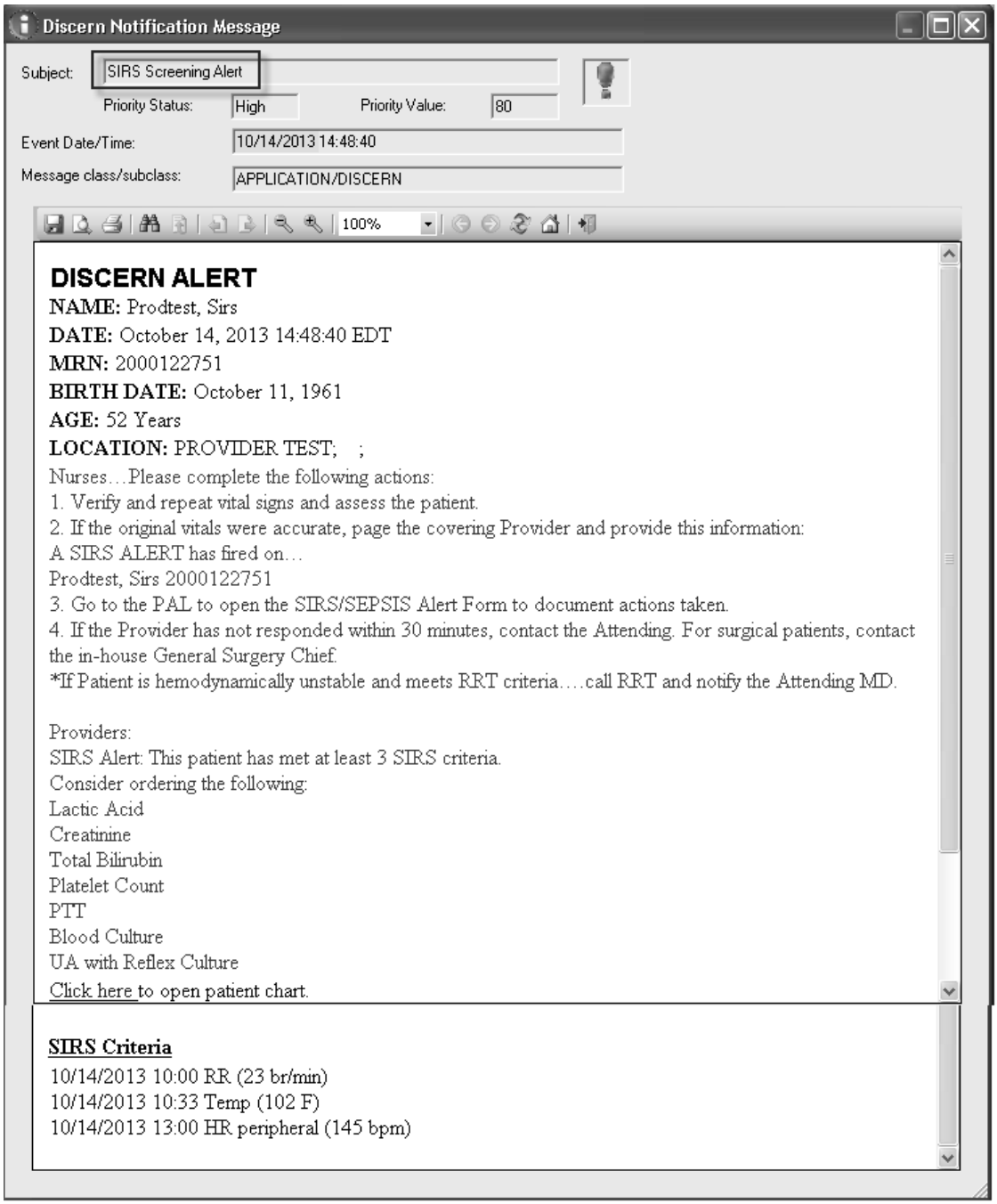
Yende, S., & Angus, D. C. (2007). Long-term outcomes from sepsis. *Current Infectious Disease Reports, 9*(5), 382–386.

Yende, S., Iwashyna, T. J., & Angus, D. C. (2014). Interplay between sepsis and chronic health. *Trends in Molecular Medicine, 20*(4), 234–238.

Zubrow, M. T., Sweeney, T. A., Fulda, G. J., Seckel, M. A., Ellicott, A. C., Mahoney, D. D.,… Farraj, M.B. (2008). Improving Care of the Sepsis Patient. *The Joint Commission Journal on Quality and Patient Safety, 34*(4), 187-191.

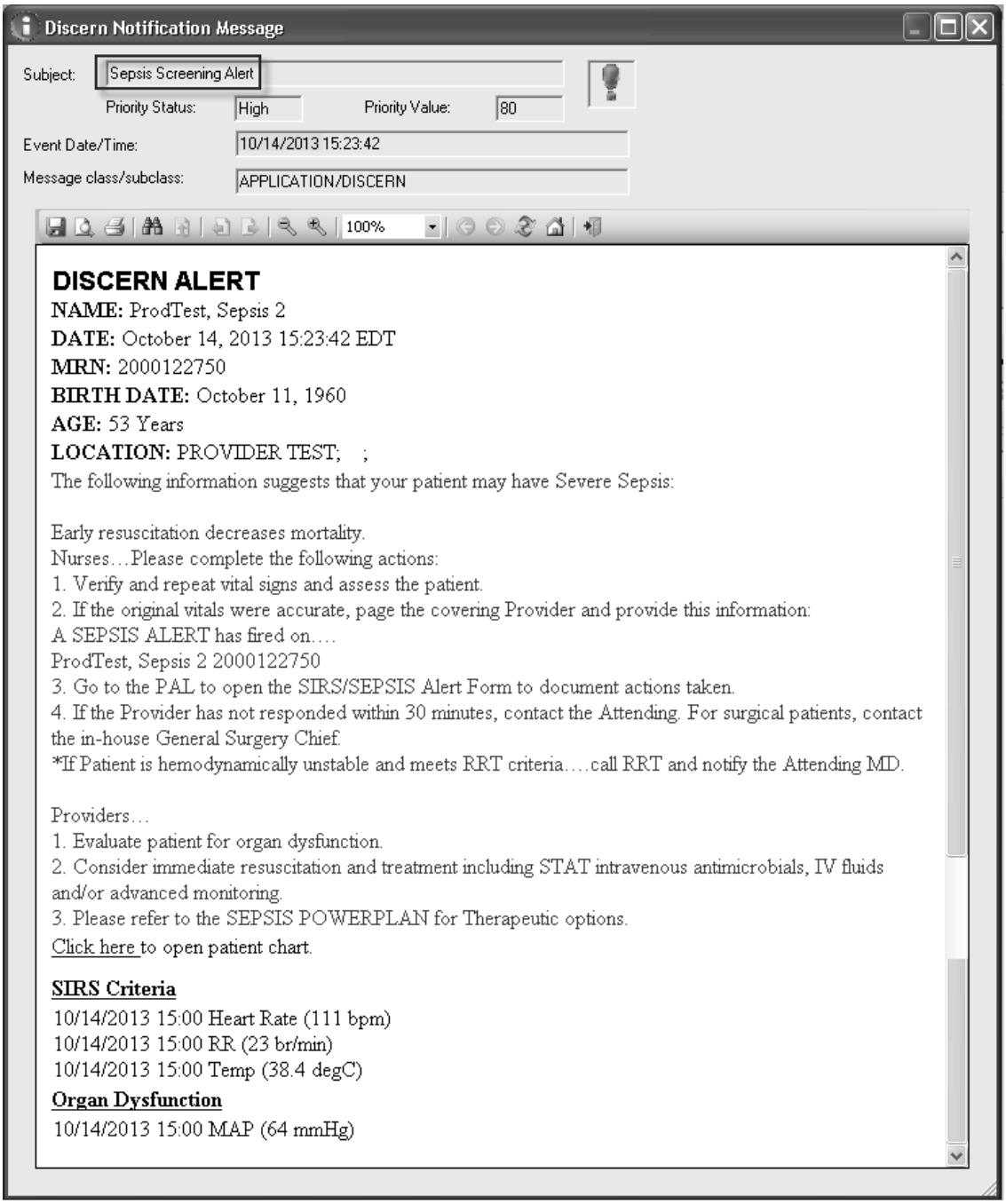
Appendix A

SIRS Screening Alert



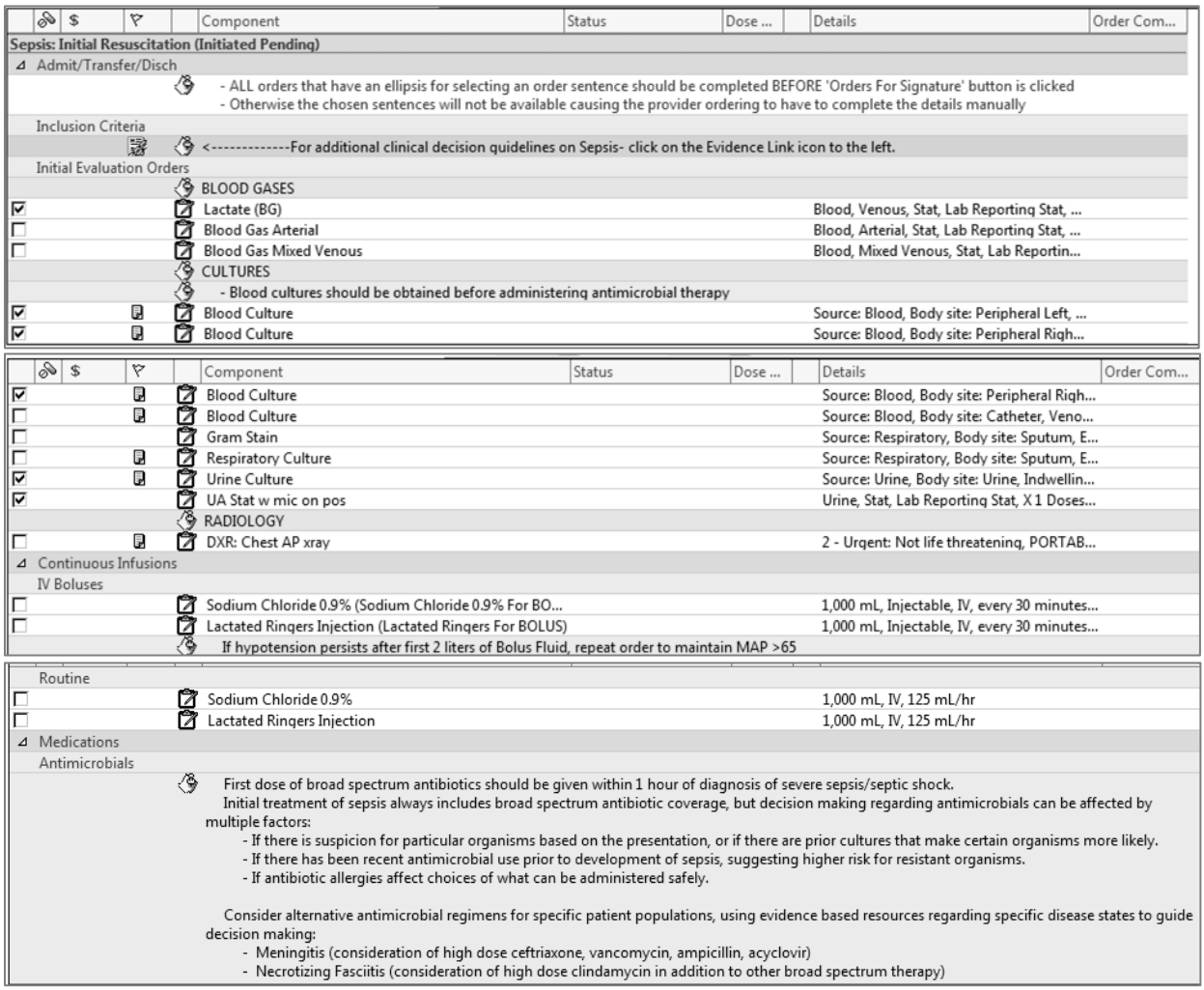
Appendix B

Sepsis Screening Alert



Appendix C

Sepsis Initial Resuscitation PowerPlan (Order Set Bundle)



	Component	Status	Dose ...	Details	Order Com...
Sepsis: Initial Resuscitation (Initiated Pending)					
Admit/Transfer/Disch					
	- ALL orders that have an ellipsis for selecting an order sentence should be completed BEFORE 'Orders For Signature' button is clicked - Otherwise the chosen sentences will not be available causing the provider ordering to have to complete the details manually				
Inclusion Criteria					
	<----------For additional clinical decision quidelines on Sepsis- click on the Evidence Link icon to the left.				
Initial Evaluation Orders					
	BLOOD GASES				
☑	Lactate (BG)			Blood, Venous, Stat, Lab Reportinq Stat, ...	
☐	Blood Gas Arterial			Blood, Arterial, Stat, Lab Reportinq Stat, ...	
☐	Blood Gas Mixed Venous			Blood, Mixed Venous, Stat, Lab Reportin...	
	CULTURES				
	- Blood cultures should be obtained before administering antimicrobial therapy				
☑	Blood Culture			Source: Blood, Body site: Peripheral Left, ...	
☑	Blood Culture			Source: Blood, Body site: Peripheral Righ...	

	Component	Status	Dose ...	Details	Order Com...
☑	Blood Culture			Source: Blood, Body site: Peripheral Righ...	
☐	Blood Culture			Source: Blood, Body site: Catheter, Veno...	
☐	Gram Stain			Source: Respiratory, Body site: Sputum, E...	
☐	Respiratory Culture			Source: Respiratory, Body site: Sputum, E...	
☑	Urine Culture			Source: Urine, Body site: Urine, Indwellin...	
☑	UA Stat w mic on pos			Urine, Stat, Lab Reporting Stat, X1 Doses...	
	RADIOLOGY				
☐	DXR: Chest AP xray			2 - Urgent: Not life threatening, PORTAB...	
Continuous Infusions					
IV Boluses					
☐	Sodium Chloride 0.9% (Sodium Chloride 0.9% For BO...			1,000 mL, Injectable, IV, every 30 minutes...	
☐	Lactated Ringers Injection (Lactated Ringers For BOLUS)			1,000 mL, Injectable, IV, every 30 minutes...	
	If hypotension persists after first 2 liters of Bolus Fluid, repeat order to maintain MAP >65				

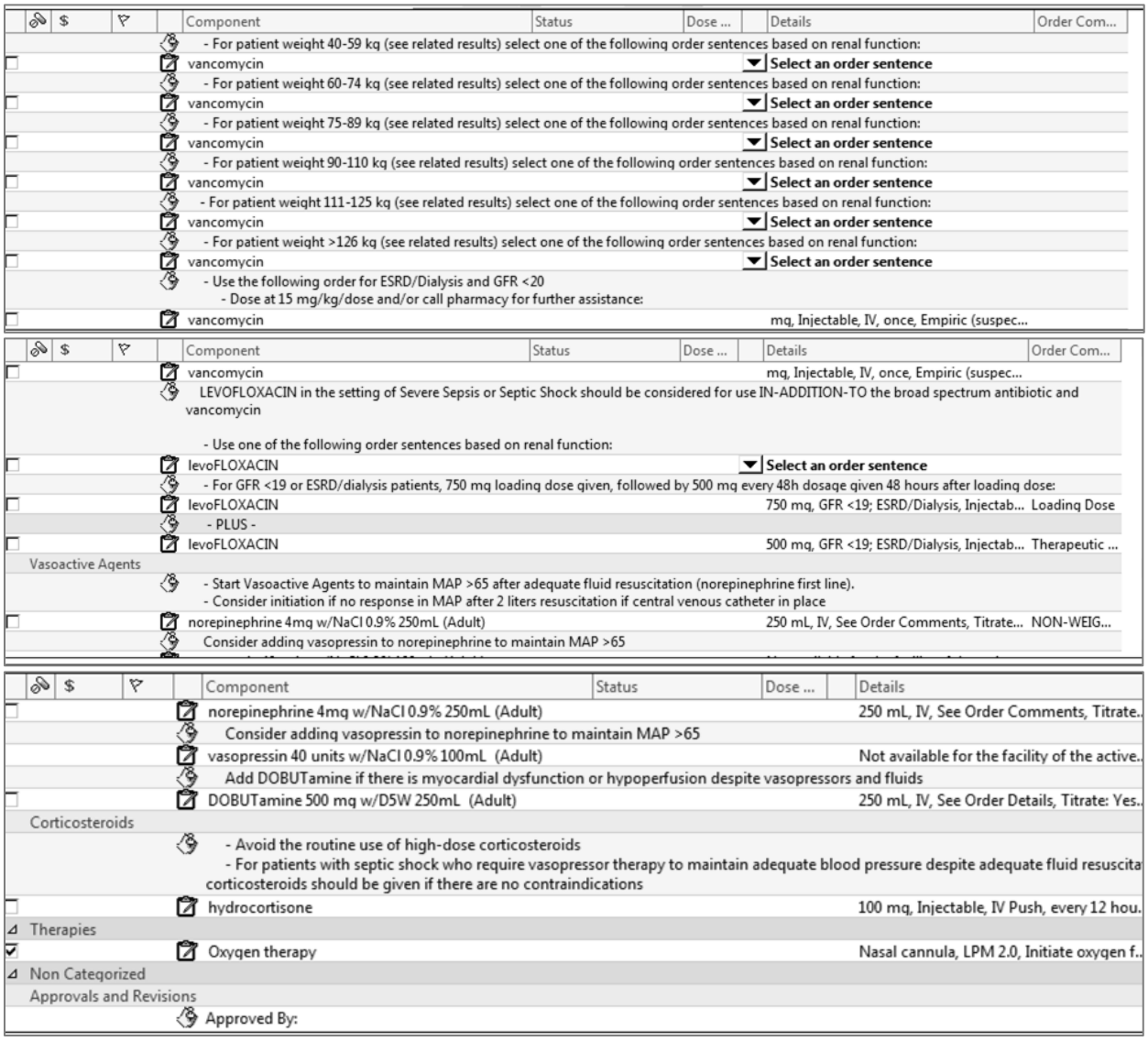
	Component	Status	Dose ...	Details	Order Com...
Routine					
☐	Sodium Chloride 0.9%			1,000 mL, IV, 125 mL/hr	
☐	Lactated Ringers Injection			1,000 mL, IV, 125 mL/hr	
Medications					
Antimicrobials					
	First dose of broad spectrum antibiotics should be given within 1 hour of diagnosis of severe sepsis/septic shock. Initial treatment of sepsis always includes broad spectrum antibiotic coverage, but decision making regarding antimicrobials can be affected by multiple factors: - If there is suspicion for particular organisms based on the presentation, or if there are prior cultures that make certain organisms more likely. - If there has been recent antimicrobial use prior to development of sepsis, suggesting higher risk for resistant organisms. - If antibiotic allergies affect choices of what can be administered safely. Consider alternative antimicrobial regimens for specific patient populations, using evidence based resources regarding specific disease states to guide decision making: - Meningitis (consideration of high dose ceftriaxone, vancomycin, ampicillin, acyclovir) - Necrotizing Fasciitis (consideration of high dose clindamycin in addition to other broad spectrum therapy)				

Appendix C - Continued

Sepsis Initial Resuscitation PowerPlan (Order Set Bundle)

Appendix C - Continued

Sepsis Initial Resuscitation PowerPlan (Order Set Bundle)



Component	Status	Dose ...	Details	Order Com...
- For patient weight 40-59 kg (see related results) select one of the following order sentences based on renal function:				
vancomycin			Select an order sentence	
- For patient weight 60-74 kg (see related results) select one of the following order sentences based on renal function:				
vancomycin			Select an order sentence	
- For patient weight 75-89 kg (see related results) select one of the following order sentences based on renal function:				
vancomycin			Select an order sentence	
- For patient weight 90-110 kg (see related results) select one of the following order sentences based on renal function:				
vancomycin			Select an order sentence	
- For patient weight 111-125 kg (see related results) select one of the following order sentences based on renal function:				
vancomycin			Select an order sentence	
- For patient weight >126 kg (see related results) select one of the following order sentences based on renal function:				
vancomycin			Select an order sentence	
- Use the following order for ESRD/Dialysis and GFR <20 - Dose at 15 mg/kg/dose and/or call pharmacy for further assistance:				
vancomycin			mg, Injectable, IV, once, Empiric (suspec...	

Component	Status	Dose ...	Details	Order Com...
vancomycin			mg, Injectable, IV, once, Empiric (suspec...	
LEVOFLOXACIN in the setting of Severe Sepsis or Septic Shock should be considered for use IN-ADDITION-TO the broad spectrum antibiotic and vancomycin - Use one of the following order sentences based on renal function:				
levoFLOXACIN			Select an order sentence	
- For GFR <19 or ESRD/dialysis patients, 750 mg loading dose given, followed by 500 mg every 48h dosage given 48 hours after loading dose:				
levoFLOXACIN			750 mg, GFR <19; ESRD/Dialysis, Injectab...	Loading Dose
- PLUS -				
levoFLOXACIN			500 mg, GFR <19; ESRD/Dialysis, Injectab...	Therapeutic ...
Vasoactive Agents				
- Start Vasoactive Agents to maintain MAP >65 after adequate fluid resuscitation (norepinephrine first line). - Consider initiation if no response in MAP after 2 liters resuscitation if central venous catheter in place				
norepinephrine 4mg w/NaCl 0.9% 250mL (Adult)			250 mL, IV, See Order Comments, Titrate...	NON-WEIG...
Consider adding vasopressin to norepinephrine to maintain MAP >65				

Component	Status	Dose ...	Details
norepinephrine 4mg w/NaCl 0.9% 250mL (Adult)			250 mL, IV, See Order Comments, Titrate...
Consider adding vasopressin to norepinephrine to maintain MAP >65			
vasopressin 40 units w/NaCl 0.9% 100mL (Adult)			Not available for the facility of the active...
Add DOBUTamine if there is myocardial dysfunction or hypoperfusion despite vasopressors and fluids			
DOBUTamine 500 mg w/D5W 250mL (Adult)			250 mL, IV, See Order Details, Titrate: Yes...
Corticosteroids			
- Avoid the routine use of high-dose corticosteroids - For patients with septic shock who require vasopressor therapy to maintain adequate blood pressure despite adequate fluid resuscita corticosteroids should be given if there are no contraindications			
hydrocortisone			100 mg, Injectable, IV Push, every 12 hou...
Therapies			
Oxygen therapy			Nasal cannula, LPM 2.0, Initiate oxygen f...
Non Categorized			
Approvals and Revisions			
Approved By:			

Appendix D

ICD-9 and ICD-10 Codes Used to Identify Sepsis

Type	ICD-9	ICD-10
Diagnosis	038.0	A40.0, A40.1, A40.3, A40.8, A40.9
Diagnosis	038.1	A41.2
Diagnosis	038.11	A41.01
Diagnosis	038.12	A41.02
Diagnosis	038.19	A41.1
Diagnosis	038.2	A40.3
Diagnosis	038.3	A41.4
Diagnosis	038.40	A41.50
Diagnosis	038.41	A41.3
Diagnosis	038.42	A41.51
Diagnosis	038.43	A41.52
Diagnosis	038.44	A41.53
Diagnosis	038.49	A41.59
Diagnosis	038.8	A41.81, A41.89, A42.7
Diagnosis	038.9	A41.9
Diagnosis	785.52	R65.21
Diagnosis	995.91	A02.1, A22.7, A26.7, A32.7, A40.0, A40.1, A40.3, A40.8, A40.9, A41.01, A41.02, A41.1, A41.2, A41.3, A41.4, A41.50, A41.51, A41.53, A41.53, A41.59, A41.81, A41.89, A41.9, A42.7, A54.86, B37.7
Diagnosis	995.92	R65.20, R65.21
Diagnosis	998.02	T81.12XA

Vita

Janet Anne Zink was born on September 19, 1969, in Teaneck, New Jersey, and is an American citizen. She graduated as salutatorian from Miramar High School, Miramar, Florida in 1987. She received her Bachelor of Science in Medical Technology from Florida Atlantic University, Boca Raton, Florida in 1996 and subsequently worked as a medical laboratory technologist and laboratory supervisor in hospitals throughout South Florida for seven years. She received a Master of Science in Management Information Systems from Nova Southeastern University, Ft. Lauderdale, Florida in 2003. Since then, she has worked with healthcare information systems in private, not-for-profit and academic settings. Positions held include systems analyst, solution architect, project manager and team lead. She is currently employed as the Informatics Manager of and a researcher with the Biorepository for Integrative Genomics (BIG) Initiative at the University of Tennessee Health Science Center.