Checklist to Prevent MRSA Surgical Site Infections

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Abstract

Aims and Design: Methicillin-resistant *Staphylococcus aureus* (MRSA), accounts for an estimated 94,000 invasive infections and 19,000 deaths annually in the U.S. In order to prevent MRSA infections among veterans, the VA successfully implemented the VA MRSA Prevention Initiative that has reduced patient-to-patient transmission of MRSA. However, this Initiative does not prevent most MRSA surgical site infections (SSIs) because MRSA SSIs are usually caused by MRSA transferring from a patient's nose to their own surgical incision site. Cardiac surgery and total joint arthroplasty (TJA; e.g. hip or knee surgery) are among the most common operations performed by the VA and are associated with particularly high clinical and economic impact. In order to eliminate MRSA SSIs in the VA, the study group developed a checklist based on a meta-analysis of studies that assessed methods to prevent gram-positive SSIs among TJA and cardiac surgery patients. This SSI Checklist includes preoperatively testing a surgical patient's nose for asymptomatic MRSA colonization. If the patient is MRSA colonized, s/he will be treated with prophylactic nasal mupirocin ointment, chlorhexidine gluconate baths, and antibiotic prophylaxis with both cefazolin and vancomycin. The SSI Checklist will be implemented in 10 VA Medical Centers (VAMCs). A high-quality quasi-experimental study, with a qualitative process evaluation will be performed to assess the SSI Checklist. The goals of this project are 1) to assess the effectiveness and cost-effectiveness of the checklist to prevent MRSA SSIs among veterans undergoing TJA or cardiac surgery, and 2) to assess barriers and facilitators to checklist implementation.

Methods: This study includes both quantitative and qualitative components. In the quantitative component, the SSI Checklist will be implemented in 10 VAMCs for 3 years and outcomes will be compared between the intervention group and two control groups: 1) 5 years of historic data from the same 10 VAMCs, 2) 8 years (5 historic year and 3 intervention years) of concurrent data from other VAMCs that did not implement the SSI Checklist. Study endpoints will include: 1) MRSA SSIs as defined by the CDC; 2) SSIs caused by other pathogens; 3) cost per SSI prevented, cost per life-saved, cost per MRSA SSI prevented and cost per quality-adjusted life-year (QALY) saved. VA databases including VA National Surgical Quality Improvement Program (VASQIP), VA Decision Support System, VA Inpatient Evaluation Center (IPEC), Veterans' Informatics & Computing Infrastructure (VINCI) and Compensation and Pension Record Interchange (CAPRI)/VistA Web and local Iowa City CPRS/JLV will be used to collect data. Time series analysis and linear mixed effects models will be used for the statistical analysis. In the qualitative component, a process evaluation will be conducted at 6 different VAMCs, which includes collecting data before, during and after implementation, to examine the contextual factors and stakeholder perspectives that influence adoption of the SSI Checklist. Observations and semi-structured interviews will be conducted in Years 1 and 3, and surveys will be conducted in years 3 and 4, along with thematic content analysis, to examine facilitators and barriers to the implementation at the different study sites. The Consolidated Framework for Implementation Research will be used to guide the process evaluation and provide the foundation for a systematic evaluation of local contextual factors that influence implementation of the SSI Checklist. The products of this study include a validated SSI Checklist, a business-case analysis, an implementation toolkit, and a team experienced in checklist implementation for prevention of infections. At the end of this study period, the study team will meet with operational partners including National Infectious Disease Program Office (NIDS) and the MRSA / Multidrug-resistant Program Office (MDRO), and the National Center for Occupational Health and Infection Control (COHIC) to discuss implementing this checklist nationwide as part of the VA MRSA Prevention Initiative. This study has high potential to significantly decrease SSI, and in turn morbidity and mortality due to SSIs, in our Nation's Veterans.

List of Abbreviations

MRSA: Methicillin-resistant *Staphylococcus aureus*

SSIs: surgical site infections

TJA: total joint arthroplasty

VAMC: VA Medical Centers

QALY: quality-adjusted life-year

VASQIP: VA National Surgical Quality Improvement Program

IPEC: VA Inpatient Evaluation Center

VINCI: Veterans' Informatics & Computing Infrastructure

NIDS: National Infectious Disease Program Office

MDRO: MRSA / Multidrug-resistant Program Office

COHIC: National Center for Occupational Health and Infection Control

CAPRI: Compensation and Pension Record Interchange

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1.0 Study Personnel

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2.0 Introduction

A. Background

A.1 Clinical Impact of MRSA: A CDC National Healthcare Safety Network (NHSN) survey of 463 hospitals found that *S. aureus* was the second most common hospital pathogen, causing 10% of all hospital infections in 2006-2007. Moreover, 56% of *S. aureus* isolates were methicillin-resistant *S. aureus* (MRSA).[10] In 2005 there were an estimated 94,000 invasive MRSA infections and 19,000 deaths due to MRSA in the U.S.[1] Dr. Perencevich and colleagues completed a meta-analysis that found that patients infected with MRSA had twice the odds of mortality compared with patients infected with methicillin-susceptible *S. aureus* (MSSA).[11]

Recently, community-associated strains of MRSA emerged as important clinical pathogens. Community-associated MRSA strains are now known to cause infections in hospitals.[12,13] Thus, more patients acquire infections outside of traditional healthcare settings and are at risk for developing surgical infections if not detected prior to their surgery.

S. aureus (MRSA and MSSA), unlike most virulent pathogens, asymptomatically colonizes the nose and other body sites in approximately 30% of healthy individuals.[14] Prior nasal carriage is a very important risk factor for subsequent infections. For example, in a large multicenter study, 82% of patients who developed a bloodstream infection were colonized with a genetically identical strain in the nose.[15] Prior nasal colonization with *S. aureus* is a major risk factor for developing *S. aureus* surgical site infections (SSI)[16] and most patients who develop SSI with *S. aureus* carry a genetically identical strain in their nares.[17,18] *Thus, elimination of S. aureus and MRSA SSI requires interventions that prevent infections in those already colonized with the pathogen. VA has successfully implemented a program to reduce MRSA transmission in hospitals; however, the program does not prevent SSIs among patients colonized with MRSA prior to surgery.*

A.2. Burden of Surgical Site Infections: Post-operative infections, commonly called SSIs, are a serious threat to patient safety. Of the 20 million patients undergoing operations in the U.S. each year, as many as 2% to 5% (800,000-2,000,000 patients) acquire a SSI.[19,20] SSI rates after cardiac procedures and total joint arthroplasty (TJA) range from 0.4% to 5%.[20,21] Based on CDC definitions, SSIs can be divided into deep (severe) and superficial (mild) infections.

Of the 50,000 patients included in the VA National Surgical Quality Improvement Program (VASQIP) in 2006, 4% developed post-operative SSIs. In an abstract selected for an oral presentation at the 2012 HSR&D Annual Meeting, Drs. Schweizer and Vaughan Sarrazin reported that that among all VA surgical patients, the risk-adjusted costs were 1.61 times greater (95% CI: 1.53, 1.71; difference=$12,927) in deep SSIs and 1.22 times greater in superficial SSIs, compared to surgical patients without a SSI, after adjusting for patient- and hospital-level variables.[3] Others have reported that SSIs extend hospital stays by 7.5 days and are very costly.[4,5] Data from over 5,000 SSIs reported to the CDC NHSN in 2006-2007 reveal that most were caused by Gram-positive cocci, particularly *Staphylococcus aureus*.[10] About half of the isolates were antimicrobial resistant including MRSA strains and recent studies report that the percentage of SSIs caused by resistant organisms is increasing.[22] In TJA and cardiac surgery, deep SSIs have a particularly high clinical and economic impact.(Table A.1)

Table A.1: Poor Outcomes Associated with Cardiac and Total Joint Arthroplasty (TJA) SSIs

	Excess Hospital Length of Stay	Excess Mortality	Cost of Treatment	Clinical Impact Example
Cardiac SSI	8.7 to 32.2 days.[5]	22%[19]	$41,559[4]	Therapy for MRSA mediastinitis requires significant debridement with potential loss of the sternum, open-cleansing of the wound, prolonged antibiotic therapy and re-operation to stabilize the sternum with pedicle flap using the major pectoral muscle and omentum.[23,24]
TJA SSI	14 days[25]	Not	$100,000[6]	A prosthetic knee infection requires the removal of the infected implant and a 6-8

		significant[25]		weeks course of intravenous antibiotics followed by a re-implantation surgery, prolonged periods of immobilization, and months of physical therapy.

A.3. Successful Checklist Utilization: As medical care becomes more complex, checklists can effectively guide hospital staff to ensure that patients consistently receive evidence-based care. A checklist evaluated by the World Health Organization Safe Surgery Saves Lives Study Group was shown to significantly reduce inpatient complications and mortality due to surgical errors.[7] A checklist created by Pronovost et al., resulted in a sustained reduction in central-line associated infections by up to 66%.[8] A *New Yorker* article on the benefits of checklists stated, "If a new drug were as effective at saving lives as Peter Pronovost's checklist, there would be a nationwide marketing campaign urging doctors to use it."[26]

Since neither checklist specifically aims to prevent SSIs, more can be done to decrease rates of infections among surgical patients. Hospital staff in the preoperative clinic are often faced with competing demands such as performing a physical examination, electrocardiogram, and blood and urine testing. Therefore, they often do not think to follow the few easy steps to prevent MRSA SSIs. Our SSI checklist, which requires only minimal time during the preoperative clinic visit, has the ability to ensure that all patients are consistently tested for MRSA colonization and that colonized patients receive optimal preventive care in order to reduce the risk of MRSA SSIs.

A.4 Prevention of MRSA in VA: A Successful Bundled Approach: A VA bundle to prevent MRSA was created including: (1) collecting nasal swabs for all patients on admission, in-hospital transfer and discharge to test for MRSA; (2) contact precautions for patients known or found to be MRSA carriers; (3) efforts targeting improved hand-hygiene; and (4) efforts encouraging culture change.[28] After a pilot study in the VA Pittsburgh Healthcare System,[27] and through the hard work Drs. Gary Roselle and Martin Evans (see A.9 Operational Partners), the bundle was implemented in all acute-care units in 150 VA medical centers in October 2007. By most measures the VA MRSA Initiative was a success. In a high-profile study published in the New England Journal of Medicine, VA investigators found that MRSA infections declined by 62% in ICUs and 45% in non-ICUs after initiation of the VA MRSA Initiative. MRSA acquisition declined 17% in ICUs and 21% in non-ICU settings.[2]

However, the existing bundle does not target prevention of SSIs since it does not include components to prevent infections in those already colonized with MRSA prior to surgery. For example, while patients receive mandatory nasal swabs on admission to the hospital, frequently these swabs are collected after their surgery, when they are admitted for post-operative observation. This is too late to guide the use of the three proven therapies shown to reduce MRSA SSI: nasal decolonization with mupirocin ointment, skin decontamination with chlorhexidine gluconate (CHG), and adding vancomycin to the standard preoperative antibiotic therapy for MRSA carriers. Nasal decolonization is performed by applying a topical antimicrobial ointment called mupirocin to each nostril in order to prevent the spread of MRSA from a patient's nose to their surgical site. Preoperative antibiotic prophylaxis is recommended for all cardiac and orthopedic surgery patients to prevent SSIs. Current guidelines recommend prophylaxis with the antibiotic cefazolin although this antibiotic does not have activity against MRSA, while the antibiotic vancomycin is active against MRSA.[29]

A.5 Pilot Data: Developing an MRSA Prevention Checklist for Orthopedic and Cardiac Surgery: As part of an AHRQ funded contract (PI: Herwaldt, Co-investigators: Perencevich, Schweizer) we performed a systematic literature review and meta-analysis to determine the optimal bundle of interventions to prevent gram-positive

surgical site infections (including MRSA) among patients undergoing TJA and cardiac surgery. We decided *a priori* that the most important interventions to evaluate were nasal decolonization and antibiotic prophylaxis.

We searched 1,246 articles of which 33 trials were included in the meta-analysis. In summary, this meta-analysis found that preoperative nasal decolonization with mupirocin ointment was protective against gram-positive SSI (including MRSA SSI) among both TJA and cardiac surgery patients (Table A.2).

Table A.2: Meta-analysis results

Intervention	Overall Pooled RR (95% CI) [n]*	Cardiac Surgery Pooled RR (95% CI) [n]*	TJA Pooled RR (95% CI) [n]*	MSSA SSI Pooled RR (95% CI) [n]*	**MRSA SSI** **Pooled RR (95% CI) [n]***
Nasal Decolonization	0.41 (0.28,0.58) [14]	0.41 (0.30,0.55) [9]	0.35 (0.20, 0.62) [6]	0.38 (0.24, 0.61) [9]	0.22 (0.09, 0.59) [4]
Vancomycin Prophylaxis for all Surgical Patients	0.80 (0.52,1.21) [12]	0.80 (0.51,1.27) [9]	0.82 (0.38, 1.78) [5]	1.33 (0.58, 3.06) [5]	0.39 (0.16, 0.95) [8]
Surveillance Culture Directed Decolonization and Vancomycin Prophylaxis (Bundle)	0.42 (0.31,0.58) [7]	0.37 (0.18, 0.76) [2]	0.46 (0.31, 0.68) [5]	0.44 (0.24, 0.80) [5]	**0.24** **(0.12, 0.46) [6]**

*n, number of studies in each subset

Conversely, the meta-analysis found that giving all patients preoperative prophylaxis with vancomycin was not superior to preoperative prophylaxis with standard beta-lactam antibiotics at preventing gram-positive surgical site infections. *Finally, a bundle that included preoperative screening for S. aureus nasal colonization, decolonization of S. aureus carriers, and targeted vancomycin prophylaxis for only MRSA colonized patients was associated with a 4-fold decline (pooled RR=0.24) in rates of MRSA SSIs compared to standard of care.*[9]

We presented these results to an expert panel of surgeons and infectious disease physicians. Based on the results of the meta-analysis and the expert opinion of the panel, a checklist was developed that included preoperative screening, targeted decolonization, targeted vancomycin prophylaxis, and chlorhexidine bathing. The expert panel strongly encouraged chlorhexidine bathing for skin decontamination of all preoperative patients based on results from recent studies.[30,31] The panel's decision to provide vancomycin and cefazolin prophylaxis to MRSA carriers was based on both the meta-analysis and other studies which found that vancomycin is inferior to cefazolin at preventing non-MRSA infections.[32-34]

We are currently in the process of implementing the checklist at over 20 hospitals in the Hospital Corporation of America (HCA) system through an AHRQ efficacy trial and have implemented the same protocol as a checklist in the Iowa City VA orthopedic surgery setting this spring. Despite the strengths of this efficacy study, we will not have the qualitative data required to identify key barriers and facilitators to checklist implementation in the HCA hospitals. Significantly, the structures of care and patient populations in HCA and VA are sufficiently different that this checklist should be pilot tested in the VA before implementing it throughout the entire VA system, as implementation barriers and effectiveness will likely differ in VA.

The goal of this proposal is to evaluate the implementation of the checklist, which will inform the roll-out of the checklist protocol and to assess the effectiveness and cost-effectiveness across all involved VA Medical Centers (VAMCs).

A.6 SSI Checklist Description: 13% of veterans are colonized with MRSA on admission.[2] Yet, at the present time there is no standard protocol for pre-surgical decolonization or assurance of appropriate choice of preoperative antibiotics for colonized patients (vancomycin plus cefazolin). Currently, MRSA screening results are not available prior to surgery, thus these evidence-based practices for preventing MRSA SSIs cannot be provided to the most at-risk patient population—MRSA colonized patients. Identifying this population at high-risk for MRSA SSI and providing them with decolonization and appropriate prophylaxis could greatly reduce rates of MRSA SSIs.

We propose to implement a SSI Checklist to decrease MRSA SSIs in 11 VAMCs. The SSI Checklist, described in Figure A.1, will be implemented based on the individual patient's MRSA status. When a surgery is scheduled, the patient will be nasally screened for MRSA within 30 days prior to the operation. Ideally, the patient will be screened and the results will be known around one week prior to surgery, so that patients can receive mupirocin and CHG with enough time to receive five days of mupirocin decolonization therapy prior to surgery, but not so early that patients will forget to apply these agents. If the patient has a history of MRSA colonization or infection in the past year they will be considered MRSA positive and not screened but will still be decolonized and receive vancomycin.

In emergent surgery, all patients will receive one dose of mupirocin ointment at surgery and will receive antibiotic prophylaxis with vancomycin and cefazolin. These patients will receive mupirocin twice a day for five days unless surveillance determines that the patient is MRSA negative in which case mupirocin will be discontinued.

Figure A.1: SSI Checklist Description

Pre-operative Checklist for *MRSA Colonized Surgical Patients*

✓ Decolonize with 2% mupirocin ointment in the nose twice a day for 5 days
✓ Bathe with chlorhexidine gluconate on each of the 5 days prior to the surgery date
✓ Receive vancomycin and cefazolin as preoperative antibiotics

Pre-operative Checklist for Patients Who are *MRSA Negative* on Screening

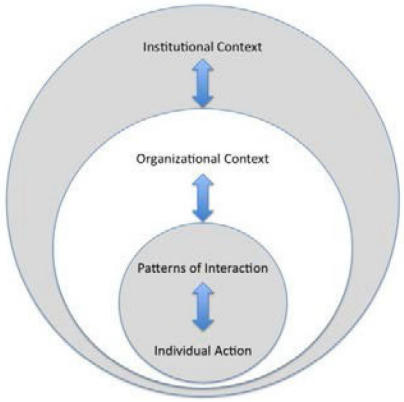
✓ Bathe with chlorhexidine gluconate the day before and morning of surgery
✓ Receive cefazolin as the preoperative antibiotic

A just-completed VA study of 4,200 pre-operative patients found that prior admission culture had only 20% sensitivity for predicting pre-operative MRSA carriage.[35] Thus, we decided to screen for MRSA colonization during the pre-operative outpatient evaluation visit, rather than rely solely on prior history of MRSA, in order to identify the 80% of MRSA colonized patients missed under current VA protocols. Of note, prior history was specific for MRSA colonization (specificity 99%), so those known to be MRSA positive from prior admissions can be safely treated as MRSA colonized without the need for additional cultures. All MRSA colonized patients can then receive mupirocin decolonization prior to surgery and have vancomycin added to their preoperative prophylactic antibiotics. Few, if any, VAs have implemented such a protocol.

The purpose of this research is to evaluate a SSI checklist. This checklist includes decolonizing a patient's nose and skin and optimizing antibiotics prior to surgery. At the time that we wrote it, the predominate product to decolonize patient's noses was mupirocin. However, in 2017, an FDA final monograph stated that nasal povidone-iodine may be used for pre-surgical decolonization. Nasal povidone-iodine should be able to overcome barriers to checklist implementation that we identified in Aim 3. We now plan to replace the nasal agent mupirocin with the nasal agent povidone-iodine at 3 participating medical centers (Iowa City VA, Minneapolis VA and Portland VA) to assess whether this overcomes the barriers to our SSI checklist.

A.7 Evaluation Framework: Our goal is to understand and improve the intervention implementation at the study sites and inform future infection prevention implementation efforts across VA. The Nested Theory of Structuration will be used to guide this study (Figure A.2).[36,37] This model suggests that efforts to improve process (and thus outcomes) must be directed across multiple levels and that team interactions shape and are themselves shaped by organizational structures, as well as individual action. To improve the process of care, it is necessary to understand and target the mutually reinforcing relationships between levels.[37] Thus we will use ethnographic observations, as outlined by Perlow, to understand the actions and levels of interactions between individual, team and facility-level factors.[36] For example, the Checklist in cardiac surgical patients will require compliance of the patient (individual action) in applying mupirocin and chlorhexidine baths, cardiology or cardiac surgery (team or organizational context) involvement in ordering the tests and decolonization agents and facility and VISN-level involvement in patient transfer and communication among staff at the sending and receiving facility (facility or institutional context).

Figure A.2: Nested Theory of Structuration adapted from Perlow et al.[36]



The qualitative component of the study will also use The Consolidated Framework for Implementation Research (CFIR), which is an organizing framework for assessing and better understanding where and why a process or intervention works.[38] The CFIR will be used to guide our assessment and systematic evaluation of local contextual factors that influence SSI checklist implementation.[38]

A.8 Benefits of the Proposed Approach: Three strengths of our proposed approach are: 1) the inclusion of an implementation focused process evaluation (Aim 3); 2) the VA-specific economic analysis (Aims 1 and 2); and 3) the use of a high-quality quasi-experimental study design with time-series analysis (Aims 1 and 2). Prior studies, including the ongoing AHRQ-funded SSI prevention study (PI: Herwaldt) that Drs. Perencevich and Schweizer are involved in as co-investigators, have not included a process evaluation. The inclusion of a systematic process evaluation with its products (e.g. implementation toolkit) will greatly enhance the likelihood of checklist adoption at the conclusion of the proposed research period and will also be VA-specific. It is important for VA to evaluate the checklist implementation, as factors such as facility transfer and integration into the existing VA MRSA initiative, are unique to VA.

The included VA-specific economic analysis will also aid in the adoption of the checklist and may

identify facilities or VISNs where it would be more cost-effective to implement the checklist. Given limited economic resources, it would be difficult to imagine VA-wide adoption of this potentially life-saving checklist without rigorous economic data.

Additionally, we plan to use a multisite, high-quality quasi-experimental (QE) study design, similar to that used by Pronovost et al., to evaluate the effectiveness of the SSI Checklist.[8] This will improve upon similar

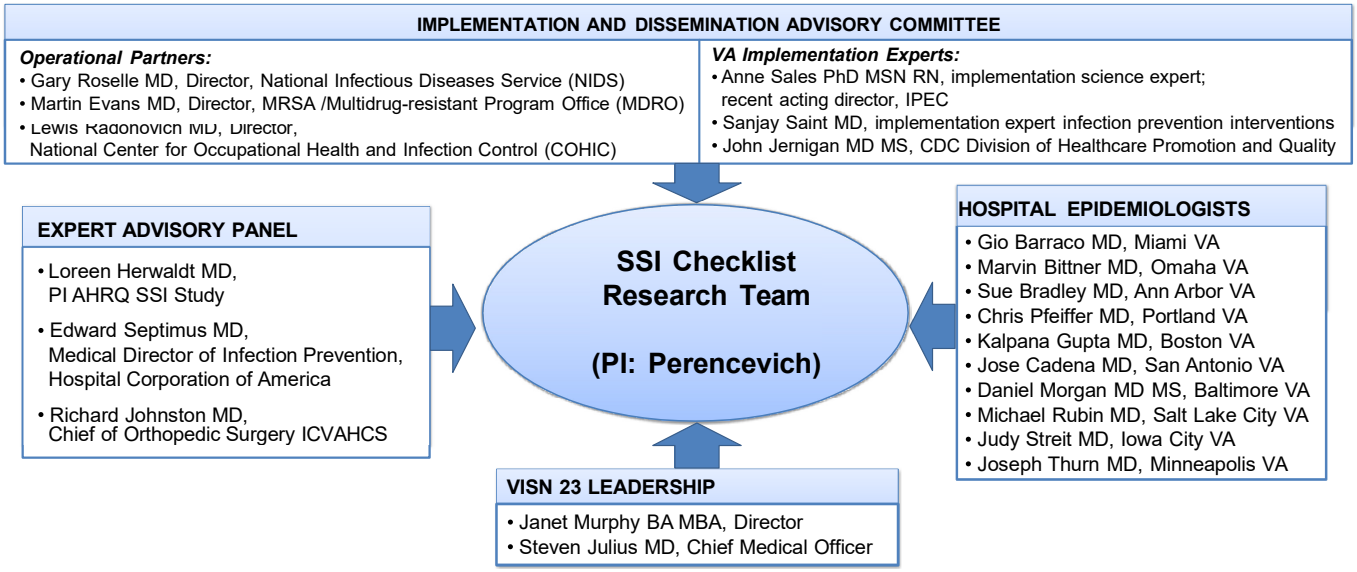
studies included in the meta-analysis, which only used simple single-center before-after QE study designs.[9] QE studies aim to evaluate interventions but do not use a randomized control group. In the simplest QE design, a population serves as its own control during a baseline period of observation. An intervention is then implemented, and a subsequent period of observation is completed. Changes in the outcome of interest are then compared before and after the time of the intervention. Such simple QE studies are subject to threats to internal validity including uncontrolled confounding and selection bias.

We will avoid these limitations by using a high-quality QE study design that includes: assessment of outcomes during a prolonged baseline period, use of nonequivalent control sites in which no intervention is implemented, and collecting data on confounding variables.[39] We will collect 5-years of baseline data and have all VA-sites not included in our 11-site study in a non-equivalent control group. We will also perform time-series analysis using segmented regression analysis. This is the optimal method to assess both changes in infection rates from the pre-intervention to the post-intervention period while also assessing for changing trends in outcome rates, while statistically adjusting for potential confounding.[40] In prior publications, we have extensively described the optimal design and analysis of QE studies in the investigation of infection-prevention interventions.[39-41]

A high-quality QE study design is a less expensive and more feasible alternative to randomized controlled trials (RCT) and cluster randomized trials (see section C.18), while benefiting from the high external validity (generalizability) that is typical of a well-designed QE study. To conduct this research we assembled an experienced team of experts in the design, conduct and analysis of quasi-experimental studies (Perencevich), MRSA prevention epidemiology including checklist development (Drs. Schweizer, Perencevich), cost-effectiveness (Perencevich) and qualitative implementation process focused evaluation of infection prevention interventions (Dr. Krein). We will also utilize the knowledge of an expert advisory panel.(Figure A.3)

A.9Operational Partner Collaboration: This project was designed in close consultation with the VA program offices that play key roles in MRSA prevention including Operational Partners from the National Infectious Disease Program Office (NIDS) and the MRSA / Multidrug-resistant Program Office (MDRO), the National Center for Occupational Health and Infection Control (COHIC), and VISN 23.(Figure A.3) This proposal has been shaped by continued discussions with our partners over the past 16 months, including an in-person meeting on August 8, 2011 in Cincinnati with Gary Roselle, MD (Director, NIDS), Martin Evans, MD (Director, MDRO), and Lewis Radonovich, MD (Director, COHIC). Drs. Roselle and Evans created the VA MRSA Initiative and are currently in charge of its implementation. They are in full support of our application and in implementing the SSI checklist alongside the VA MRSA Initiative once its effectiveness has been evaluated and potential barriers have been overcome.

Figure A.3 Operational Partners and Expert Advisors



Importantly, the investigators are already working with the operational partners. Dr. Perencevich is the Senior Associate for Infection Control Studies in COHIC, and has worked with COHIC, the NIDS, the Office of Quality and Safety, and the National Center for Patient Safety to develop a response to a recent VA OIG report, "Evaluation of MRSA Prevention Practices in VA Facilities." In addition, the project will benefit from the participation of 11 VA hospital epidemiologists who have agreed to be study investigators.

Finally, this proposal will benefit from an Implementation and Dissemination Advisory Committee that will include all mentioned operation partners two VA implementation experts, and Dr. John Jernigan, who has advised VA's MRSA Initiative for over 5 years starting with Pittsburgh's pilot study and through the recent long-term care study in VA CLCs.(see Figure A.3 and letters) We will have teleconferences with the Implementation and Dissemination Advisory Committee at project kickoff and at the end of each year of the study period.

B. Significance

B.1 Expanding the Scope of the Existing VA MRSA Initiative: Preventing MRSA Surgical Infections

By all accounts, the current VA MRSA Prevention Initiative has been hugely successful. However, the current program is not adequately resourced to prevent infections that manifest in patients already colonized with MRSA, even though 13% of veterans are MRSA colonized on admission.[2] This proposal seeks to eliminate MRSA SSIs in TJA (e.g., hip and knee surgery) and cardiac (e.g., bypass and valve replacement surgery) surgical patients.

We will assess the effectiveness of implementing a SSI checklist aimed at screening, decolonization, and optimization of pre-operative antibiotic selection. The checklist (Figure A.1, above) has already been developed through a systematic review of the literature and meta-analysis and utilization of an expert panel under an AHRQ-funded contract (PI: Herwaldt, co-Is Perencevich and Schweizer). Despite checklist evaluation at 21 hospitals through AHRQ, it is not being assessed at any VA hospitals. VA patients are very different than patients treated in private hospitals.

Veterans are more likely to be socially disadvantaged (e.g., minority, unmarried, lower education level, and lower income) compared to Medicare recipients.[42] This social disadvantage may influence a Veteran's ability to implement the at-home components of the checklist. However, VA also varies in its organizational structure and context. For example, the remarkable infrastructure that is already in place for the VA MRSA Prevention Initiative may allow for fewer barriers to implementation, since VA already screens all patients admitted to the hospital, and thus will have the necessary microbiology facilities. Additionally, cardiac surgery in VA is a unique enterprise where patients are often seen initially in local VAs and then referred to a large referral center within a VISN. For example, a focus of this proposal includes a VISN-level evaluation within VISN-23 (Iowa City, Omaha and Minneapolis). In VISN-23, all cardiac surgeries occur at the Minneapolis VA, so that unique communication and timing issues around decolonization and antibiotic selection may arise and require VA-specific responses. By including evaluation of checklist implementation in several VISN-23 facilities, factors that hinder the adoption of the checklist in the sending facilities (Iowa City and Omaha) and receiving facility can be identified and remediated. The implementation toolkit can include VISN-level instructions so that cardiac patients who are MRSA carriers can receive mupirocin and CHG at their home VAMC (e.g., Iowa City VAMC or Omaha VAMC) and receive preoperative prophylaxis with vancomycin and cefazolin at their surgery VAMC (e.g., Minneapolis VAMC).

B.2 Existing Guidelines and Protocols for MRSA Prevention in TJA and Cardiac Surgery: The current guidelines recommend antibiotic prophylaxis prior to major operations in order to prevent SSIs.[29] Guidelines also recommend preoperative prophylaxis with a beta-lactam antibiotic for cardiac and TJA procedures, unless patients are known to be at high-risk for MRSA infection, or if the facility-wide or operation-specific MRSA SSI rate is high. In those cases, anti-MRSA antibiotics such as vancomycin are recommended.[29] The addition of vancomycin to cefazolin prophylaxis for MRSA carriers is still considered appropriate prophylaxis according to guidelines, since cefazolin is provided with the vancomycin.

Yet, in the wake of rising fears over MRSA, there is debate as to whether vancomycin prophylaxis for all surgical patients should be implemented in order to prevent MRSA infections.[43] The argument against that strategy is that vancomycin may not be as effective against other gram-positive organisms compared to beta-lactam antibiotics.[32-34] Additionally, a recent VA study found that patients not colonized with MRSA who received vancomycin prophylaxis alone were more likely to develop a SSI compared to those who received beta-lactam prophylaxis.[44] Thus MRSA colonization status should be known before vancomycin antibiotic prophylaxis is given. Currently, this is not the case.

Recently, checklists and bundled interventions have greatly decreased the rates of specific HAIs such as central-line associated bloodstream infections and MRSA infections.[2,8] A bundled intervention that goes beyond current guidelines measures and includes nasal decolonization, skin decontamination, and targeted vancomycin prophylaxis would be expected to greatly reduce rates of MRSA SSIs. Currently, few hospitals have implemented nasal screening for *S. aureus* plus nasal decolonization to prevent *S. aureus* SSIs. Despite clinical trial data and guidelines, clinicians have not reached consensus. Therefore, practices are often inconsistent both within and across hospitals.[45] This is also the case in VA where currently patients might be documented as MRSA-positive in their electronic medical record, but are not routinely decolonized pre-operatively nor have vancomycin added to their prophylaxis. Thus, despite strong clinical evidence, as outlined in our meta-analysis and current consensus supporting the wider adoption of the components of the checklist in pre-operative surgical algorithms, barriers prevent their implementation.

B.3 Current Barriers to MRSA Checklist Adoption in VA: The current VA MRSA Prevention Initiative aims to prevent the spread of MRSA from colonized patients to uncolonized patients.[28] However the VA MRSA Initiative does not recommend decolonization for currently colonized patients. Since colonized veterans have 7 times higher odds of developing an MRSA infection compared to uncolonized veterans, MRSA infections will remain prevalent in VAMCs.[46] Based on our meta-analysis, the addition of decolonization of surgical patients to the VA MRSA Initiative could greatly reduce the number of MRSA colonized and infected surgical patients in the VA System.

Because the most expensive and time-consuming portion of the SSI Checklist is laboratory testing for MRSA colonization, which is already implemented at every VA for every admission, the addition of the SSI checklist to the existing MRSA Prevention Initiative is achievable. However, since swabbing should now occur before admission in those undergoing elective surgery, we anticipate barriers to checklist implementation.

Significant variation in the adoption of decolonization and optimal antibiotics in surgical prophylaxis exist. The variation and reasons for the variation represent significant barriers to the adoption of the evidence-based MRSA checklist. A recent survey conducted by the Infectious Disease Society of America's (IDSA) Emerging Infections Network (EIN) offers strong evidence that preoperative practices vary considerably.[45] Of 441 respondents, 47% did not decolonize any patients preoperatively. Also, 30% felt preoperative screening for all *S. aureus* should be the standard of care in the community, 22% felt screening for MRSA only should be the standard of care, 27% felt that screening should not be the standard of care, and 21% did not have an opinion. Thus, despite the evidence strongly supporting the use of preoperative MRSA screening and decolonization very few have adopted this clinically effective treatment. Even though VA screens on hospital admission, these tests are not routinely utilized preoperatively.

There is also concern that widespread use of mupirocin could cause mupirocin-resistant *S. aureus* strains to become common.[47] Furthermore, some argue that widespread mupirocin use may not prevent infections, since patients decolonized with mupirocin become recolonized within an average of 3 weeks.[48] Thus it is important to implement mupirocin decolonization only among the subsets of patients who would directly benefit. Surgical patients are an ideal population to provide mupirocin to because they are a distinct subset of patients at high-risk for MRSA infections and they are most at risk of a SSI within days or weeks of their incision.

Other potential barriers that we will assess in our process evaluation include patient compliance and healthcare worker buy-in; communication between the preoperative clinic, laboratory, pharmacy and anesthesiology; and increased costs and time needed to implement the checklist. These potential barriers are currently being addressed as the checklist is being implemented at the Iowa City VA and solutions such as the creation of standard order sets in CPRS to facilitate timely communication are underway.

Our standardized consensus-based checklist will help eliminate some of the problems described above and can be implemented widely by multiple mechanisms to ensure that providers follow the recommendations. Nevertheless, clinicians often do not implement evidence-based guidelines and implementation researchers who study the effectiveness of different improvement approaches have found that "one size does not fit all."[49,50] Thus, we aim to assess contextual factors and the specific mechanisms by which change occurs within health care organizations.[51]

In summary, we have shown that facilities need to optimize the process of administering pre-operative antimicrobials. Consensus-based standardized checklists will provide guidance on the timing, dose, and types of antimicrobials (see Appendix 1) to be administered in specific situations to help facilities achieve this goal. The SSI Checklist will also help facilities overcome issues related to pre-operative screening for MRSA and

decolonization. We expect SSI Checklist adoption in the individual facilities will drive change. The proposed SSI Checklist herein represents an exciting opportunity to contribute to the field on several levels while advancing the ultimate goal of reducing SSIs and improving patient safety on a broad scale.

B.4. Clinical Impact and Products: The goals of this project are to assess the effectiveness of implementing a checklist to prevent MRSA SSIs among Veterans undergoing TJA and cardiac surgery and identify and overcome barriers to the checklist adoption.The long-term objective of this application is to significantly reduce the number of SSIs in the entire VA System.

Once the proposed SSI checklist is shown to be effective in the 11 study sites, including the VISN-23 sites, and we have identified and overcome barriers to implementation, we plan to work with key stakeholders such as Dr. Martin Evans (Director MDRO), Dr. Gary Roselle (Director, NIDS) and Dr. Lewis Radonovich (Director, COHIC) to implement this SSI Checklist in all VAMCs as part of the VA MRSA Prevention Initiative. (See Letters of Support)

This likely cost-effective addition to the VA MRSA Prevention Initiative will reduce MRSA SSI and mortality and improve the quality of care for Veterans. The process evaluation will allow us to identify site and stakeholder specific strategies to facilitate checklist implementation broadly.

The products include:

1) an evidence-based SSI prevention checklist for TJA and cardiac surgery;

2) a facility-level and VISN-level business-case and cost-effectiveness analysis of the checklist; and

3) a VA-specific implementation quality improvement toolkit as developed in Aim 3.

3.0 Objectives

The goals of this project are 1) to assess the effectiveness and cost-effectiveness of the checklist to prevent MRSA SSIs among veterans undergoing TJA or cardiac surgery, and 2) to assess barriers and facilitators to checklist implementation. Along with our operational partners, the investigative team brings complementary expertise in quantitative and qualitative health services research methods, hospital epidemiology, infection control, and implementation science. The long-term goal is to develop an effective and easy-to-implement checklist, with an accompanying implementation toolkit, that can be incorporated into the current VA MRSA Prevention Initiative to prevent MRSA SSIs in the entire VHA System.

Specific Aim 1**:** Implement and evaluate the effectiveness and cost-effectiveness of a SSI checklist to reduce rates of MRSA SSIs among TJA patients.

Aim 1 VA Benefit: TJA is the most common surgery performed in VHA. Even small reductions in the rate of TJA SSIs could greatly reduce the number of veterans with a SSI.

Specific Aim 2: Implement and evaluate the effectiveness and cost-effectiveness of a SSI checklist to reduce

rate of MRSA SSIs among patients undergoing cardiac surgery.

Aim 2 VA Benefit: The rates of SSI after cardiac surgery are much higher than rates among other clean surgeries. In addition, mediastinitis is associated with high morbidity. A reduction in cardiac SSIs would decrease morbidity among many VA surgical patients.

Specific Aim 3: Identify and compare barriers and facilitators of implementing the SSI checklist across a diverse set of hospitals.

Aim 3 VA Benefit: If effective, the checklist can be implemented throughout VA as part of the MRSA Prevention Initiative. We will identify facilitators and modifiable barriers to ensure smooth implementation at other VA sites.

Hypotheses:

1) The SSI checklist will be effective at reducing MRSA SSIs among TJA and cardiac surgery patients.

2) Implementation of the checklist will be associated with an overall reduction in SSIs caused by all pathogens.

3) The SSI Checklist will be cost-saving since it will prevent many expensive SSIs.

4) Preoperative MRSA testing will be a modifiable barrier to implementing the SSI checklist.

4.0 Resources and Personnel

The central site will be the Iowa City VA Health Care System. Research staff at Iowa City will be the only staff performing chart reviews and the only site with access to study PHI. The nine other participating sites will contribute to efforts by observing processes that are currently in place for preventing SSIs, helping to implement the checklist, and collecting aggregate site-specific data such as number of surgeries performed.

There will be 11 sites included in this study and they are detailed in section 5.1, which includes table C.1, “sites selected for inclusion.”

Data analysts at the Iowa City VA will perform analysis and be responsible for data management. For this project, the Portland research team will assist with the qualitative data analysis. Data will be stored on the Iowa City VA server.

All patient and provider interviews at all sites will be conducted by Dr. Heather Reisinger or qualitative research team from Iowa City.

Table C.2 (in section 5.1) lists a Summary of Data Sources. Use of most of these requires Data Use Agreements, which will be obtained after IRB approval.

5.0 Study Procedures

5.1 Study Design

C.1 Overview: We plan to implement the SSI Checklist in 11 VA medical centers. The goals of this project are 1) to assess the effectiveness and cost-effectiveness of the checklist to prevent MRSA SSIs among veterans undergoing TJA or cardiac surgery (Aims 1&2), and 2) to assess barriers and facilitators to checklist implementation (Aim 3). Along with our operational partners, the investigative team brings complementary expertise in quantitative and qualitative health services research methods, hospital epidemiology and infection control, and implementation science. The overall goal is to develop an effective and easy-to-implement checklist, with an accompanying implementation toolkit, that can be incorporated into the current VA MRSA Prevention Initiative to prevent MRSA SSIs in the entire VHA System.

Roles of PI, LSIs, and site Ras:

The PI and other Iowa City study staff (research coordinators, data analysts), will be the only study staff to be working with the data from the sources listed in Table C2. LSIs will not have access to this data/PHI.

The LSI role will be principally to implement Aims 1 and 3 at each site. The LSIs, along with their research assistants at each site, will perform those duties outlined in Aim 3, such as working to connect providers at each site with the qualitative team. For Aim 1, LSIs will work with local healthcare staff to obtain “buy-in” for this project and work with Ras to train local staff on the intervention.

The local sites will receive funding from the grant to employ research assistants.

The LSIs/local site Ras will not conduct interviews, however the LSIs may participate in interviews and for that portion of the project be considered study participants.

Specifics of Role of RA at each site:

Research assistants/staff at each site will be engaged in research in the following ways:

1. Measurement of patient compliance in implementing the components of the checklist. A document entitled “Tool 3” is attached, which is a sample form for patient compliance monitoring for mupirocin and CHG that will be filled out during the patient intake on the day of surgery. The nursing staff will ask the patient these questions, and the research assistants will collect and analyze this data as research data. The data will be totally deidentified for analysis. The Ras will collect, analyze, manage, and store this data.

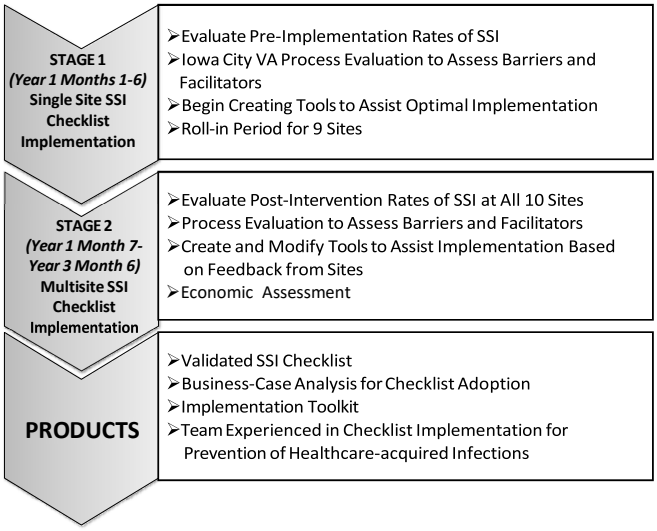
2. Identification of patients who will be undergoing surgical procedures via chart review and coordination with schedulers and nursing staff to ensure patients are scheduled early in the day in order to optimally receive components of the checklist as needed (ie medications) before they leave the pre-operative appointment. Ras will train schedulers and nurses on expectations for implementing the checklist and also for collecting compliance measures mentioned above.

3. Collection of infection data from Infection Control Practitioners (ICP). For several years, the VA MDRO/MRSA office has mandated collection of THA/TKA (TJA) surgical site infection data at all VA sites. Each site must monitor for surgical site infection (MRSA) at 30 days and 1 year post-operatively. Each month they must enter the number of procedures done and number that develop an MRSA SSI. This data is aggregate and lacks patient specific data such as whether the surgical site infection was deep or superficial. To collect that data and also SSI data from cardiac surgery we will also require each RA to provide us with SSI data from each site. The local VA infection preventionist already collects this data for TJA to upload to IPEC and collects this data for cardiac surgery at the

sites that perform cardiac surgery in this study. Identifiable information will be transmitted via secure VA network server connections to the Iowa City VA OI&T Research Server or the VINCI research environment after one year had passed. Thus, for the datasheet that captures Feb 2015 data, the SSI data won't be finalized until Feb 2016, so the data sheet will be sent in Feb 2016.

C.2 Implementation of the Checklist: In preparation for the proposed study, we are already in the process of implementing and evaluating the checklist at the Iowa City VA as a quality improvement process.(Stage 1, Figure C.1) Immediately upon receipt of funding, we will collect 5 years of baseline patient-level SSI data from all 11 sites using pre-existing VA datasets; these data will allow us to assess baseline SSI rates at each site and for various clinical service lines. We will then conduct initial meetings to establish site-specific processes for checklist implementation. Next, the SSI checklist will be implemented in all remaining 9 sites and evaluated.(Stage 2,Figure C.1) We will hold monthly training calls with each site during the first year of the study, then quarterly during the remainder of the study period.(see Table C.5 GANTT chart)

Figure C.1 Implementation Stages and Products



At each site, the site co-investigator (e.g., hospital epidemiologist) will work closely with the infection control professionals, chief of surgery, chief of pharmacy, and director of the hospital laboratory to plan for the roll-out of the checklist.(See letters of support) Decisions at the local level will need to address order set modification in CPRS, possible changes in screening and laboratory methods, utilization of decolonizing agents, and timing and dispensing of antibiotic regimens.

The products of this study (Figure C.1) include a business-case analysis for checklist adoption (C.14 Product 1, below) and an implementation toolkit (C.17 Product 2, below). The business-case analysis will provide justification for the implementation of this SSI Checklist. We hypothesize that the SSI Checklist will be cost-saving since it will prevent many expensive SSIs. The implementation toolkit will provide education materials (including brochures, videos, and CPRS templates) for patients, local facilities and VISNs on how to optimally implement the components of the SSI checklist. The toolkit components are part of quality improvement at each local site. Additional products include a validated SSI Checklist and a national, geographically diverse team experienced in checklist implementation for the prevention of healthcare-associated infections. This team can be utilized in order to evaluate other checklists or bundles to prevent healthcare-associated infections.

The following sections outline the specific issues that will need to be addressed in the effectiveness analysis and the process evaluation of the checklist.

C.3 Site Selection: This project will involve 11 VAMCs (Table C.1) that, in aggregate, performed an estimated 1 , 8 1 7 TJA procedures and 1,297 cardiac procedures each year.(See Letters of Support) Specifically, we sought to select hospitals to represent geographical variation and hospital size. In addition, we included all 3 tertiary care hospitals in VISN 23 because cardiac surgery is regionalized by VISN (e.g., Veterans from Iowa

City travel to Minneapolis for cardiac surgery), thus we needed to evaluate barriers and facilitators for the SSI Checklist at a VISN level as well as a facility level. The 8 sites for Aim 3 were selected to balance the need for depth of data in a single VISN (Iowa City, Minneapolis, and Omaha), geographic variation (Ann Arbor, Baltimore, Miami and Portland), and successful collaboration on previous projects (Baltimore, Iowa City, Portland – HSR&D IIR 09-099, Perencevich-PI). By implementing the SSI Checklist in each large acute care hospital in a single VISN (i.e. VISN-23), we will be able to examine the facilitators and barriers to implementation at a regional institutional level. Also, by implementing the SSI Checklist in geographically dispersed locations we will be able to address additional issues with checklist implementation as it is spread to other VAMCs in the VHA and in other regions of the country.

Table C.1: Sites Selected for Inclusion

Site	# TJA Procedures in 2011	# Cardiac Procedures in 2011	VISN 23	Aim 3 Process Evaluation
Ann Arbor VA	93	149		X
Baltimore VA	48	Not performed at this site		X
Boston VA	190	204		
Iowa City VA	162	Not performed at this site	X	X
Madison VA	331 *in 2014	96 *in 2014		X
Miami VA	139	162		X
Minneapolis VA	304	305	X	X
Omaha VA	147	Not performed at this site	X	X
Portland VA	132	204		X
Salt Lake City VA	146	56		
San Antonio VA	125	121		
Total	**1,817**	**1,297**		

C.4 Patient Selection: All patients who undergo TJA (e.g., hip or knee) or cardiac (e.g., bypass or valve) surgery from the beginning of the baseline period (January 2008) to the end of the intervention period (Year 4 of the study period) will be included in the study. These patients will be identified via ICD-9-CM procedure codes listed in Appendix 2. Patients will be excluded if they: have an ICD-9-CM diagnosis code consistent with endocarditis; have any documented infection before the surgical procedure; or undergo cardiac transplants or cardiac procedures performed using the percutaneous or thoracotomy approach. Patients undergoing hip and knee revisions will be excluded since they have a much higher risk of SSI. In addition, patients with documented allergies to mupirocin will be excluded. Those with allergies to CHG will not receive the CHG bathing, but will not be excluded.

C.5 Order set modification: Initial implementation will involve incorporating checklist items into the electronic medical record (CPRS) pre-operative clinic order set (e.g. swab processing, mupirocin and CHG ordering) with modifications to the peri-operative antibiotic order sets to include vancomycin added to existing antibiotic regimens if the patient is screen positive for MRSA. We have worked closely with Iowa City CPRS developers to create templates locally which we will then make available to each site to incorporate into their own CPRS

system.

C.6 Screening and laboratory methods: Ideally, patients will receive their nasal swab at the beginning of their preoperative clinic appointment and polymerase chain reaction (PCR) results will be known in time for patients to fill prescriptions for CHG and mupirocin (if needed) before the patient's appointment has ended. This is currently being done at the Iowa City VA by performing PCR on the swabs using the Cepheid Xpert SA Nasal Complete PCR machine that can accurately identify MRSA in 60-minutes. We recognize that not all sites will have access to the Cepheid PCR Machine. In this case, sites will use the same methods to detect MRSA as they use for the MRSA Prevention Initiative (PCR or CHROMagar) and we will work with the VA pharmacy to make sure MRSA positive patients receive mupirocin and chlorhexidine prior to their operation. These challenges will be identified and addressed as part of the evaluation conducted in Specific Aim 3.

C.7 Decolonizing agents: MRSA positive patients will receive both 2% mupirocin ointment and CHG from the pharmacy to be used for 5 days prior to surgery. As part of a toolkit developed in this study, each site will receive educational material targeting both patients and health-care workers including: 1) patient informational sheets with instructions for mupirocin and CHG use, 2) a form for patient compliance monitoring for mupirocin and CHG during the patient intake on the day of surgery, and 3) a video that instructs nurses in the preoperative clinic on how to obtain nasal swabs and educate patients on mupirocin and CHG. MRSA positive patients will be instructed to apply mupirocin at home twice per day for 5 days and use CHG (either bottles for baths or showers or CHG wipes) once a day for five days. MRSA negative patients will be instructed to use CHG the day before and morning of surgery. The toolkit materials are implemented as quality improvement at each local site.

The purpose of this research is to evaluate a SSI checklist. This checklist includes decolonizing a patient's nose and skin and optimizing antibiotics prior to surgery. At the time that we wrote it, the predominate product to decolonize patient's noses was mupirocin. However, in 2017, an FDA final monograph stated that nasal povidone-iodine may be used for pre-surgical decolonization. Nasal povidone-iodine should be able to overcome barriers to checklist implementation that we identified in Aim 3. We now plan to replace the nasal agent mupirocin with the nasal agent povidone-iodine at 3 participating medical centers (Iowa City VA, Minneapolis VA and Portland VA) to assess whether this overcomes the barriers to our SSI checklist.

C.8 Preoperative Antibiotics: MRSA negative patients will receive cefazolin prophylaxis. Prophylaxis with cefazolin (2 grams received <60 minutes before incision) is recommended by the Surgical Care Improvement Project (SCIP) guidelines and the American Society of Health System Pharmacists (ASHP) 2011 guidelines.[29] This is the current standard of care for patients undergoing TJA or cardiac surgery in VAMCs. MRSA positive patients will receive vancomycin (1 gram given over 60 minutes as recommended by ASHP) in addition to cefazolin (2 grams given <60 minutes before incision). The dual prophylaxis is recommended since vancomycin is inferior to cefazolin at preventing MSSA and Gram-negative surgical site infections.[32-34] Preoperative orders for cefazolin with or without vancomycin can be included in CPRS as soon as nasal colonization results are known.

Specific Aims 1 and 2: Implement and evaluate the effectiveness and cost-effectiveness of a SSI checklist to reduce rates of MRSA SSIs:

Aim 1. Among patients undergoing TJA surgery, and

Aim 2. Among patients undergoing cardiac surgery

C.9 Study Design: The quasi-experimental study design was chosen over the individual RCT design because we are implementing a SSI checklist at the population-level.[52] Two control groups will be utilized to measure the benefits of checklist adoption. The first control group will include the 5-year time period prior to checklist adoption in all 11 of the facilities under study. The second 'non-equivalent' control group will include all VA facilities not currently in the study by collecting SSI data through the VA National Surgical Quality Improvement Program (VASQIP) during the 8 year period (5 years pre-intervention and 3 years intervention). This will allow us to assess for secular trends that might bias our findings. For example, if SSIs are declining in VA independent of our checklist, we will be able to measure if declines after checklist-adoption were similar or greater than over-all VA trends. As the VA MRSA initiative began in 2007, we will collect data starting in FY08 or approximately 5 years prior to implementing the Checklist.

C.10 Data Sources: Rates of SSIs will be collected for both the pre-intervention and intervention period using the data sets described in Table C.2. Rates will be validated using infection control data from all 11 intervention sites. We will also work with the infection control practitioners and surgeons at each site to keep track of any other SSI prevention initiatives (e.g., change in patient warming protocol) implemented during the study period. Additional data from the data sets will be used to statistically adjust for confounding in the time series analysis.

Table C.2 Summary of Data Sources

Data Set	Description	Used to Identify SSIs?	Additional Data Collected
VA National Surgical Quality Improvement Program (VASQIP)	Aim: monitor & improve quality of surgical care in VA hospitals (data from 129 VAs)	Yes	Sex, transfer status (e.g., nursing home), length (time) of operation, Surgical Site Infection Risk Index including age, diabetes, dyspnea, use of steroids, alcoholism, smoking, recent radiotherapy, American Society of Anesthesiologists class, albumin, total bilirubin, emergency surgery, complexity, type of operation, wound classification[59]
VA Continuous Improvement in Cardiac Surgery Program (CICSP)	Clinical surgical registry for cardiac procedures (data from 44 VAs) Merged with VASQIP in 2009	Yes	
VA Inpatient Evaluation Center (IPEC)	Centralized infrastructure for MRSA coordinators to enter data for MRSA Initiative	Yes	Monthly rates of MRSA SSIs
Veterans' Informatics & Computing Infrastructure (VINCI)	Patient medical data including microbiology lab data	Yes	MRSA colonization, MRSA infections at other site, SSI causative organism (MRSA, gram positive, gram negative) of each SSI, length of postoperative stay, mortality, and readmission

VA Decision Support System	Includes encounter-specific data on costs incurred in the VA	No	Costs associated with SSI
Compensation and Pension Record Interchange (CAPRI)/VistA Web	Allows remote access to nationwide chart data	No	Chart reviews. This project includes multiple national sites. We will use CAPRI/VistA Web for national level access to Veterans' electronic health records. We will utilize CAPRI/VistA Web for three reasons: 1) find qualitative participants, 2) administrative data validation, and 3) review of charts for surgical data and medication compliance information.
Local Iowa City CPRS/JLV	Local Iowa City chart review	No	Local Iowa City chart reviews. We will utilize CPRS/JLV for 1) administrative data validation, and 2) review of charts for surgical data and medication compliance information.

C.11 Data Elements: Data used to assess effectiveness and cost-effectiveness will be collected retrospectively from VA resources. We will collect site-specific rates of SSI defined according to the CDC's National Healthcare Safety Network (NHSN) through the VASQIP (including CICSP) data base. VASQIP employs trained nurses at each VA site to perform manual chart review to confirm cases of SSI using CDC definitions. We will collect SSI numerator and denominator data as collected by the infection control programs at each VA in this proposal. Typically cardiac patients are followed for 30 days postoperatively to assess incidence of SSI while TJA patients are followed for a year postoperatively due to increased risk of later infections caused by implants.

The primary outcomes will be superficial and deep/organ space MRSA infections within 90-days postoperatively. We chose 90-days rather than 1 year since not all patients in the study will be able to be followed for 1 year due to the timing of the study. Since we will be able to follow 83% of the cohort for 1-year post-operatively, we will perform a secondary analysis in which we will include only patients who were followed for one year. However, it is unlikely that the 90-day analysis and 1 year analysis will differ significantly because over 75% of SSIs are detected within 30 days,[54] in fact most SSI manifest within 22 days.[55-57] Additionally, other SSI reporting systems such as the National Surgical Quality Improvement Program and the Society of Thoracic Surgeons systems employ 30-day postoperative surveillance regardless of implant. Additional secondary outcomes are Gram-positive SSI—which includes MSSA, and total SSI.

Outside of VA, most SSI are missed since they are superficial SSIs that manifest post-discharge in the outpatient setting;[55,58] however, this is not a significant issue in VA since medical records capture outpatient visits. Other secondary outcomes will include compliance with the entire bundle and individual bundle components. This will be established electronically, through measurement of mupirocin prescription, CHG prescription and swab collection, as well as utilizing the compliance information collected on patient intake on the day of surgery. We will also assess length of postoperative stay, mortality, and readmission.

Lastly we will test bacterial isolates from MRSA positive patients (and MSSA positive patients as our secondary outcome) at the 11 intervention sites. The VA is mandated to take nasal swabs from each patient preoperatively. For those patients who are MRSA and MSSA positive, we will have the bacterial isolates sent to the Iowa City site to be tested for resistance to mupirocin and CHG. We will also collect bacterial isolates from patients who experience ***Staphylococcus aureus*** **infections** during the study.
These isolates will also be tested for mupirocin and CHG resistance. Since resistance can develop in both MSSA and MRSA it is important to test both MRSA and MSSA isolates.

The purpose of this testing is to a) ensure our study checklist does not cause mupirocin or CHG resistance by b) determining if resistance was present at the initial nasal swab, or if resistance occurred after performance of study checklist.

Risk protection: For all project analyses, patients risk will be minimized by limiting access to data, maintaining study paper files in locked offices, and storing data on password-protected computers and on servers, which are secured in locked rooms by the Iowa City VA Medical Center Office of Information Resources Management. The servers can only be accessed by individuals with OIT-created network accounts. Data will be secured using network directory permissions assigned by OIT at the direction of the applicant and primary mentor; thus ensuring that only study personnel with the approval of the applicant (per IRB requirements) have access to identifiable human subject data. VINCI data will be maintained in a similar manner on VINCI platforms and protected by VINCI data managers. Data collection, management, and analyses will be compliant with VA data use agreements. In addition, reports of study findings will not identify individual patients.
Survey data will be scanned and uploaded directly to a secure server. Interviews will be recorded on encrypted recorders and files will be uploaded directly to a secure server. Recordings will be transcribed and reviewed for accuracy. All data (recordings, transcripts) will be stored on a secured server. Each participant will be assigned a unique study identifier which will be used on all data.
Subject identities (e.g., names, addresses, professional title) will be kept separate from the data and linkage information will only be available to the PI.

5.2 Recruitment Methods

We will perform analysis on all patients identified in VA databases (eg VASQIP) by ICD-9 procedure codes as undergoing TJA or cardiac surgery at VAMCs included AND not included in intervention group during 8 years evaluated, for a total of 113,000 surgeries at VA per year. So over the 8-year study period, there will be 904,000 patients included, plus the approximately 134 patients and healthcare workers interviewed at the sites and approximately 162 patients surveyed.

Recruitment and inclusion/exclusion:

Aims 1 and 2

All veterans who undergo total joint arthroplasty (e.g., hip or knee surgery) or cardiac (e.g., bypass or valve) surgery from the beginning of the baseline period (January 2008) to the end of the intervention period (Year 4 of the study period) will be included in the study. Veterans will be included regardless of age, race, gender, or underlying health status. Additionally, women and minorities will be included in this study. Inclusion and exclusion criteria are as follows:

Intervention Group Inclusion Criteria:

- Patients identified by the preoperative clinic staff and/or by *International Classification of Disease 9th Revision* (ICD-9) procedure codes as undergoing total joint arthroplasty or cardiac surgery at the 11 intervention VA Medical Centers during the intervention period (years 1-4 of grant)

Retrospective Control Group Inclusion Criteria:

- Patients identified in VA databases (e.g. VASQIP) by ICD-9 procedure codes as undergoing total joint arthroplasty or cardiac surgery at the 11 intervention VA Medical Centers during the 5 year preintervention period (2008-2013)

Concurrent Non-equivalent Control Group Inclusion Criteria:

- Patients identified in VA databases (e.g. VASQIP) by ICD-9 procedure codes as undergoing total joint arthroplasty or cardiac surgery at VA Medical Centers not included in the intervention group during the 8 years evaluated (5 years pre-intervention to match with the retrospective control group and 3 years of the intervention.)

Exclusion Criteria for all Patient Groups:

- Have an ICD-9 diagnosis code consistent with endocarditis;
- Have any documented infection before the surgical procedure;
- Undergo cardiac transplants or cardiac procedures performed using the percutaneous or thoracotomy approach
- Undergoing hip and knee revisions
- Documented allergies to mupirocin

We will not contact patients in order to collect outcomes. Instead, we will collect and evaluate data from electronic medical records and VA datasets (e.g., VASQIP) that are gathered for treatment purposes to assess rates of infection. The data that will be collected and evaluated for the study will be that which is normally collected during the pre-admission, peri-operative, and post-discharge periods.

Aim 3

Patient Surveys: We plan to survey approximately 162 patients. To identify these patients, chart review will be conducted by the Iowa City Qualitative Team and healthcare workers to find participating patients that match criteria. Surveys will be given to inpatients or mailed to recent inpatients, with a post-paid return envelope included. Summary of elements of consent will be included. If desired, the qualitative team will read the survey to the patient in person or over the telephone. They will be given the opportunity to ask questions and have all their questions answered. Participation in the survey will be an indication of consent. Patients will not be paid for the survey response.

Patient Semi-Structured Interviews: We plan to interview approximately 4 patients from each of the 8 process evaluation sites, for a total of 32 patients. We will obtain informed consent from these patients before interviewing them. To identify these patients, chart review will be conducted by the Iowa City Qualitative Team to find participating patients that match criteria. Then, a recruitment packet will be sent inquiring about willingness to participate in the interviews. The recruitment letter will let the patients know the Qualitative Team will be contacting them by phone to follow-up. The packet will include all study documents such as recruitment letter, informed consent, HIPAA authorization, form 10-3203 (for voice recording), and direct deposit forms for payments. To allow study participants the time to consider participating in the research study we will send study information to the potential participant with the option to opt-out in 2 separate mailers, prior to contacting the potential participant via phone. The first mailer will include the recruitment letter. The second mailer will include the informed consent, HIPAA authorization, form 10-3203 and direct deposit forms.
When we do call the patients, if they are interested in participating, research staff will go through the consent form, and other forms, with the subject and answer all questions about the study, and will emphasize the voluntary nature of the study. For those patients who agree to participate, interviews will be scheduled. All participants will receive information in both oral and written form regarding the risk and benefits of the project, confidentiality procedures, and study personnel to contact regarding questions and concerns (including contact numbers for the Central Institutional Review Board and a research compliance officer contact at Iowa City VA). The PI will be responsible for reviewing elements of consent before each point of data collection.
The patients who participate in qualitative interviews will be paid for their participation (not the healthcare workers). They will be paid $25 for their time. As dictated by federal regulations, patient-subjects will be paid via direct-deposit. Attached is OMB form 1510-0056 which patients will fill out.

When the subject understands the consent form, s/he will be instructed to sign and return it. During this initial call, an appointment for the interview phone-call will be made. This appointment will be at least 5 days in the future, to allow time for staff to receive signed consents and other documents.

Because patient interviews will be conducted over the telephone, this form along with the consent form will be sent in the mail and returned in the mail.

Research staff will attempt to reach each potential participant 3 times in the course of 3 weeks. If we do not reach the patient in that time, we will stop contacting him/her.

Healthcare Worker Semi-Structured Interviews

Approximately 110 healthcare workers and 32 patients will be interviewed.

With assistance from the Site Co-Investigator, the Research Coordinator will contact the healthcare workers and/or appropriate supervisors and inform them of the Qualitative Team's site visit. She will arrange a time for the semi-structured interviews. At the time of the interviews, the Qualitative Team will review the elements of consent with the interview participants. They will be given the opportunity to ask questions and have all their questions answered. Participation in the interview will be an indication of consent.

All participants will receive information in both oral and written form regarding the risk and benefits of the project, confidentiality procedures, and study personnel to contact regarding questions and concerns (including contact numbers for the University of Iowa Institutional Review Board). The PI will be responsible for reviewing elements of consent before each point of data collection.

The patients who participate in qualitative interviews will be paid for their participation (not the healthcare workers). They will be paid $25 for their time. As dictated by federal regulations, patient-subjects will be paid via direct-deposit. Attached is OMB form 1510-0056 which patients will fill out.

Because patient interviews will be conducted over the telephone, this form along with the consent form will be sent in the mail and returned in the mail.

5.3 Informed Consent Procedures

We will request a waiver of informed consent for all parts of the study except the semi-structured interviews (Aim 3). For the patient semi-structured interviews, we will obtain informed consent from patients before interviewing them. This will be done via the mail system, as the interviews will be conducted over the telephone. We will send patients a recruitment letter before calling them. When we do call the patients, if they are interested in participating, research staff will review elements of consent and answer all questions about t h e study, and will emphasize the voluntary nature of the study. Research team will ensure patient comfort with and understanding of the consent document.
Included with the informed consent document will be a document for consent of use of voice recording (attached). The participant will also have this form explained to him/her and return via mail.

For the healthcare worker semi-structured interviews, the qualitative team will review the elements of consent with the interview participants. They will be given the opportunity to ask questions and have all their questions answered. Participation in the interview will be an indication of consent.

For the patient surveys, the qualitative team will review the elements of consent with the interview participants in available. A written summary of the elements of consent will be available. Patients will be given the opportunity to ask questions and have all their questions answered. Participation in the survey will be an indication of consent.

All participants will receive information in both oral and written form regarding the risk and benefits of the project, confidentiality procedures, and study personnel to contact regarding questions and concerns (including contact numbers for the University of Iowa Institutional Review Board). The PI will be responsible for reviewing elements of consent before each point of data collection.

All consent procedures and interviews and surveys will be conducted by the Iowa City Qualitative Team. No investigators/research assistants from local sites will be performing interviews or surveys or consent procedures.

5.4 Inclusion/Exclusion Criteria

Persons involved in identifying patients who have or will undergo TJA or cardiac surgery at all sites are:

1. The Director of the Data Analysis Core at CADRE (Iowa City) will use VA databases, such as VASQIP, to identify patients using ICD-9 codes.
2. Research assistants at each site will have access to patient charts as well as to surgery schedules, and will work with surgery clinic schedulers to further identify patients receiving the intervention.

Intervention Group Inclusion Criteria:

- Patients identified by the preoperative clinic staff and/or by *International Classification of Disease 9th Revision* (ICD-9) procedure codes as undergoing total joint arthroplasty or cardiac surgery at the 11 intervention VA Medical Centers during the intervention period (years 1-4 of grant)

Retrospective Control Group Inclusion Criteria:

- Patients identified in VA databases (e.g. VASQIP) by ICD-9 procedure codes as undergoing total joint arthroplasty or cardiac surgery at the 11 intervention VA Medical Centers during the 5 year preintervention period (2008-2013)

Concurrent Non-equivalent Control Group Inclusion Criteria:

- Patients identified in VA databases (e.g. VASQIP) by ICD-9 procedure codes as undergoing total joint arthroplasty or cardiac surgery at VA Medical Centers not included in the intervention group during the 8 years evaluated (5 years pre-intervention to match with the retrospective control group and 3 years of the intervention.)

Exclusion Criteria for all Patient Groups:

- Have an ICD-9 diagnosis code consistent with endocarditis;
- Have any documented infection before the surgical procedure;
- Undergo cardiac transplants or cardiac procedures performed using the percutaneous or thoracotomy approach
- Undergoing hip and knee revisions
- Documented allergies to mupirocin

We will not contact patients in order to collect outcomes. Instead, we will collect and evaluate data from electronic medical records and VA datasets (e.g., VASQIP) that are gathered for treatment purposes to assess rates of infection. The data that will be collected and evaluated for the study will be that which is normally collected during the pre-admission, peri-operative, and post-discharge periods.

5.5 Study Evaluations

Participants will not be required to complete any procedures as part of the study. The only evaluation that some participants will participate in are the semi-structured interviews.

5.6 Data Analysis

Statistical Analysis of Effectiveness: We have written the standard reference for analyzing time-series outcome data collected during quasi-experimental studies of infection prevention and quality improvement interventions. We will utilize our recommended methods, which are similar to methods used in the Pronovost checklist study. Two control groups will be utilized to decrease the likelihood of bias. First, data on SSI rates among the participating VAMCs for five years prior to implementation of the checklist will be collected as a historic control group. Second, data on SSI rates for all VAMCs not included in the study will be collected from five years prior to the checklist to the end of the study period (non-equivalent controls) for a total of 8 years. This second control group will account for secular trends in SSI rates over time.

First, we will conduct simple tests using Fisher's exact test to compare pre-intervention MRSA SSI incidence rates to post-intervention MRSA SSI rates in the 11 intervention hospitals. This will be done for all studied operations, then we will analyze MRSA SSI rates among TJA patients and cardiac patients separately. Second, we will perform a similar analysis comparing MRSA SSI rates in the 11 intervention hospitals to MRSA SSI rates in the concurrent, nonequivalent

control group. Third, we will perform time-series analysis. Time-series regression analysis techniques will be used to determine whether implementation of the SSI Prevention Checklist is associated with decreased SSI incidence rates that are both statistically significant and clinically meaningful. The SSI rates are based on monthly counts, which might be assumed to follow a Poisson distribution or a negative binomial distribution. Time series techniques for these distributions have been recently developed. Such models are fit using the pseudo-likelihood. We will formulate models to assess whether the intervention is associated with a decreasing trend in SSI incidence, and if so, to characterize the nature of this trend. We will also analyze trends in hospital-specific SSI incidence rates. Post-intervention SSI counts for individual hospitals could contain a preponderance of zeros. To model count time series featuring an excess of zeros, it might be necessary to assume that the counts follow a zero-inflated Poisson distribution or zero-inflated negative binomial distribution.

Table C.3 Power Calculations Based on Conservative Estimates and Estimates from the Meta-Analysis

	Cardiac Operations (n=1,201 per year)[a]	TJA Operations (n=1,486 per year)[b]	Total (n=2,687 per year)
Conservative Power to Reduce MRSA SSIs (RR=0.4)	94%	85%	99%
Power to Reduce MRSA SSIs Based on Meta-Analysis (RR=0.24)	99%	99%	100%

Power calculations: Based on MRSA SSI rates from the literature this study will be sufficiently powered (>80%) to detect a relative difference in MRSA SSIs between the pre-intervention (5 years) and intervention periods (3 years) corresponding with a relative risk (RR) of 0.4 (2.5 fold decrease) for TJA procedures or cardiac procedures. Considering that the pooled RR for the meta-analysis of this bundle was 0.24 (4-fold decrease), the study should be sufficiently powered to detect a statistically significant decrease in MRSA SSIs. See Tables C.1(below) and C.3 (above) for sample sizes and power estimates. Thus, these studies are sufficiently powered to detect an absolute reduction in rates of cardiac MRSA SSIs from 1.15% to 0.46% and in rates of TJA MRSA SSIs from 0.70% to 0.28%.

Table C.1: Sites Selected for Inclusion

Site	# TJA Procedures in 2011	# Cardiac Procedures in 2011	VISN 23	Aim 3 Process Evaluation
Ann Arbor VA	93	149		X
Baltimore VA	48	Not performed at this site		X
Boston VA	190	204		
Iowa City VA	162	Not performed at this site	X	X
Madison VA	331 *in 2014, not included in power calc	96 *in 2014, not included in power calc		X
Miami VA	139	162		X
Minneapolis VA	304	305	X	X
Omaha VA	147	Not performed at this site	X	X
Portland VA	132	204		X
Salt Lake City VA	146	56		
San Antonio VA	125	121		
Total	**1,817**	**1,297**		

Aim 3:

Approximately 106 healthcare workers and 32 patients will be interviewed. We plan to survey approximately 162 patients.

All interviews will be audiorecorded on digital encrypted recorders or over the phone directly to a secure server. They will then be transcribed by our transcribers. All textual data (field notes and transcripts) will then be imported into MAXQDA, a qualitative data management and analysis software program.(2010)

The research study team will review field notes and transcripts and conduct an initial thematic content analysis. We will read a subset of transcripts and generate a preliminary codebook through a series of meetings. The thematic codes will include *a priori* codes for known barriers and facilitators to implementation, as well as inductive codes which are likely to emerge during data collection. The codebook will consist of top-level thematic codes, which will be used to "tag" textual data with the main themes. Top-level coding of thematic codes allows for comprehensive coding and more rapid turnaround of results, which can then be fed back in an iterative fashion to improve the implementation process. Particular attention will be paid to organizational and site-specific factors that may impact subsequent implementation. The factors will be discussed as a group and ideas for troubleshooting will be developed to improve the ongoing implementation effort as well as provide material for the implementation toolkit.

These observations and interview will occur in Years 1 and 3 to track how implementation is progressing and to examine facilitators and barriers to the implementation at the different study sites. These process evaluations will take place in 3 VISN-23 sites: Minneapolis VAMC, Omaha VAMC, and Iowa City VAMC; and 3 geographically diverse sites from other VISNs: Ann Arbor VAMC, Baltimore VAMC, Miami VAMC and Portland VAMC (and Madison VAMC, end of study only). Data will be collected during two site visits to each location (Years 1 and 3) and phone interviews with key informants.

Patient surveys will be conducted in years 3 and 4.

The guide for these semi-structured interviews and surveys will be developed based on the analysis of the pre-implementation observations and interviews. In addition to interviews with staff, patient interviews and patient surveys also will be conducted to evaluate patient perspectives about the checklist processes. In addition, patients will specifically be asked about the preoperative educational materials they receive (Table C.4) in an effort to improve their content and validity. The team who developed the first codebook will read a subset of the new transcripts and revisions to the codebook will be discussed. The revised codebook will be used to code the remaining transcripts and facilitate a thematic content analysis to identify critical barriers and facilitators to checklist implementation. For this project, the Portland research team will assist with the qualitative data analysis. Data will be stored on the Iowa City VA server.

Table C.4: Items Considered for Inclusion in Quality Improvement Toolkit
1. Educational sheets to inform patients on the use of mupirocin and chlorhexidine gluconate
2. A preoperative intake form in CPRS to track of compliance with mupirocin and CHG
3. Descriptions on how to program order sets in CPRS for pre-operative clinical visit MRSA screen test order
4. Clinical videos and brochures describing benefits and method for prescription of mupirocin and CHG, along with prophylaxis with vancomycin and cefazolin
5. Detailed description of the SSI Prevention Checklist

Thus, the iterative approach we have described will allow us to confirm key emerging themes related to implementation of the checklist as well as identify new issues as the checklist is implemented first in Iowa City and then subsequent facilities.

5.7 Withdrawal of Subjects

We do not anticipate any circumstances under which subjects would be withdrawn from research without their consent.

Subjects are entitled to decide to end their participation during an interview or survey without any loss of benefits to which they are entitled. Their interview or survey will be ended. If the participant would like to withdraw after the interview or survey has already occurred, for data collected prior to withdrawal, the study team may continue to review the data already collected for the study but cannot collect further information, except from public records.

6.0 Reporting

Due to the nature of our study, no adverse events or serious adverse events will occur at any sites. This is because all components of the SSI checklist are FDA approved and have been used to prevent SSIs in standard of care. This study is just evaluating whether standardized implementation of these FDA approved components can decrease the rates of surgical site infections. In this study, diagnosis or treatment of MRSA or other SSIs are not SAEs because these infections are expected to continue. Therefore these will not be reported to VA Central IRB or considered Unanticipated SAEs or UAPs. According to the *VHA Research Compliance Reporting Requirements* (VHA Handbook 1058.01,Transmittal Sheet, May 21, 2010), an ***adverse event*** is defined as "any untoward physical or psychological occurrence in a human subject participating in research" (page 2). All adverse events will be assessed to determine if they meet criteria for a serious adverse event. According to the *VHA Research Compliance Reporting Requirements* (VHA Handbook 1058.01, Transmittal Sheet, May 21, 2010), a ***serious adverse event*** is defined as "an adverse event in human research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect. An adverse event is also considered serious when medical surgical, behavioral, social, or other intervention is needed to prevent such an outcome" (page 5). Again, because we some patients to be diagnosed with MRSA or other SSIs, we will not consider or report these as Unanticipated SAEs or UAPs.

Investigators at each site will be responsible for adhering to requirements for reporting local serious unanticipated problems involving risks to participants as outlined below and in the protocol submitted with this application. The responsibilities of investigators at each site include:
1) Familiarizing herself with VA Central IRB requirements for reporting local SAE's, serious unanticipated problems, and protocol deviations/violations
2) Compliance with Central IRB policies for reporting SAE's and/or serious unanticipated problems involving risks to participants or others
2a) Alerting the VA Central IRB Local Site Liaison of the investigator's intent to submit a report to VA Central IRB
3) Reviewing the accuracy and completeness of all SAE's reported
4) Following up with research participants, as appropriate, until the incident is resolved
We will require that all such problems also be promptly reported to the PI and Co-PI of this research project. The Local Site Investigator will be responsible for submitting the reports to the Central IRB, after consultation and review with the PI and Co-PI to assure that the report conforms to all reporting requirements and that remedial steps have been undertaken, as appropriate. An electronic copy of the submitted report will be stored in a designated protected folder on the VA Iowa City secure server. The project coordinator will establish a database of submitted reports to monitor events occurring at any of the study's participating sites. Reports will be promptly reviewed by the study PI and Co-PI for potential patterns and for remedial counseling of research staff, should that be necessary.

This study poses minimal risk to patients; however, to ensure that the intervention does not pose a safety risk, we will employ a Data Safety Monitoring Plan. The study project team will evaluate SSI data quarterly. If SSI rates increase more than 20% above the baseline SSI rate we will immediately investigate why to ensure the safety of the patients and the validity and integrity of the data. We will also monitor increases in resistance to mupirocin and, if we see a 2-fold increase in mupircocin resistance above the baseline resistance of nasal swabs from MRSA-positive individuals, we will

immediately consult with our expert panel and discuss discontinuation of mupirocin as part of the checklist.

Reporting of Events to the VA Central IRB: This is a minimal risk study that does not involve an intervention with experimental treatments. Protocol violations due to human error might occur in the form of breaches to confidentiality and privacy. However, any SAE, serious unanticipated problem, and/or protocol violation occurring during the course of the study will be collected, documented, and reported by the Local Site Investigator to the VA Central IRB (after consultation and review with the PI and Co-PI) within the required time frame (5 business days after the study is made aware of the occurrence).

7.0 Privacy and Confidentiality

We will be obtaining, linking, and working with patient-level, individually identifiable data from VA administrative files and from VA's computerized medical records system. SSNs are included because they serve as patient medical record number in the VA medical records system.

Additionally, the bacterial isolates that will be shipped from local sites to Iowa City will be labeled with identifying information. Bacterial isolates are labeled with PHI at each site according to standard medical care protocols (typically first name, last name, and full social security number). In order to maintain specimen identity for full confidence of matching with subsequent administrative data, each site will submit the isolates labeled with their standard labeling. Specimens will be sent securely via FedEx and will be able to be tracked with tracking numbers. The specimens will be sent directly to Iowa City study staff and will be immediately placed in the designated research freezer by study staff. When specimens arrive and are tested, the results will be logged in a secure, password-protected spreadsheet which will contain identifiable information such as name and social security number. Again, this is necessary so that study staff may be sure to correctly match specimens with data regarding the course of each infection. Due to lab protocols it would be unfeasible to de-identify the specimens and attempt to identify them at a later date.

Only IRB approved team members and laboratory personnel have access to the specimens and results.

For all project analyses, patients risk will be minimized by limiting access to data, maintaining study paper files in locked offices, and storing data on password-protected computers and on servers, which are secured in locked rooms by the Iowa City VA Medical Center Office of Information Resources Management. The servers can only be accessed by individuals with OIT-created network accounts. Data will be secured using network directory permissions assigned by OIT at the direction of the applicant and primary mentor; thus ensuring that only study personnel with the approval of the applicant (per IRB requirements) have access to identifiable human subject data. VINCI data will be maintained in a similar manner on VINCI platforms and protected by VINCI data managers. Data collection, management, and analyses will be compliant with VA data use agreements. In addition, reports of study findings will not identify individual patients.

The PI, Study Coordinator at Iowa City and Data Analysts will have access to PHI. The local site study staff will not have access to PHI (beyond what they always have in their roles as physicians/hospital epidemiologists).

8.0 Communication Plan

All local sites will be engaged in research. All local sites will complete appropriate documentation to obtain approval of Central IRB with the help of the Iowa City study staff.

Study coordinators from all sites will participate in weekly or bi-weekly conference calls in order to stay informed of changes to protocol, informed consent, and HIPAA authorization. These meetings will also serve to update local sites about the event of any Serious Adverse Events, Unanticipated Problems, or interim results that may impact the conduct of the study.

In addition to meetings in which we discuss study procedures, site visits by Iowa City study staff will occur at certain intervals during the study, at which time adherence to IRB-approved protocol will be verified.

When the study reaches a point at which a local site is no longer needed to be engaged in research, the Iowa City study staff coordinator will notify local facility directors and local site investigators by telephone.

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