Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.


This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.
Multicenter Evaluation of The Effectiveness Of Source Control With Daily Chlorhexidine Skin Preparation In Reducing Nosocomial Infections Including MRSA and VRE

Sponsored by:
Centers for Disease Control and Prevention (CDC)
Sage Products, Inc.

Principal Investigator:
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# Protocol Synopsis

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<th>Multicenter evaluation of the effectiveness of source control with daily chlorhexidine skin preparation in reducing nosocomial infections including MRSA and VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Number:</td>
<td>CI06-003</td>
</tr>
<tr>
<td>Sponsor:</td>
<td>CDC and Sage Products, Inc.</td>
</tr>
<tr>
<td>Product:</td>
<td>2% Chlorhexidine Gluconate Cloth and Comfort™ Bath Washclothes</td>
</tr>
<tr>
<td>Primary Objectives:</td>
<td>To determine if daily bathing with chlorhexidine impregnated washcloths will reduce the incidence of MRSA and VRE within an Intensive Care Unit (ICU) or ward setting.</td>
</tr>
<tr>
<td>Study Design:</td>
<td>This is a cluster randomized, crossover, controlled trial with wards as the units of randomization. The trial will predominantly take place in ICU’s but may include any acute care ward that has active surveillance for MRSA and or VRE in place (i.e., Bone Marrow transplant units, Oncology wards, etc.) Units will be randomly assigned to utilize two bathing routines in a random order. Each bathing routine will be utilized on all admitted patients to the unit for a six month study period for a total study duration of 12 months. The two bathing routines will include either the use of the Comfort™ Bath Washcloth System (control) or the use of 2% Chlorhexidine Gluconate Cloth. Randomized units will either start with 2% Chlorhexidine Gluconate Cloth for six months and then switch to Comfort™ Bath Washcloth for the remaining six month period or the reverse order. Data collection will include all surveillance and clinical cultures for MRSA and or VRE and all bloodstream infections.</td>
</tr>
<tr>
<td>Number of Subjects:</td>
<td>Approximately 14 ICUs or acute care wards with 16,000 patients</td>
</tr>
<tr>
<td>Subject Population:</td>
<td>Males or Females, admitted to Intensive Care Units or acute care units</td>
</tr>
<tr>
<td>Number of Centers:</td>
<td>7 centers</td>
</tr>
<tr>
<td>Duration of Subject Participation:</td>
<td>Typically 1-90 days, or the duration of patient’s ICU or unit admission</td>
</tr>
<tr>
<td>Treatment:</td>
<td>Daily bathing with either: 1) Comfort™ Bath Washcloth or 2) 2% Chlorhexidine Gluconate Cloth</td>
</tr>
<tr>
<td>Assessments of Efficacy:</td>
<td>The primary efficacy endpoint will be the reduction in MRSA incidence during those study periods where the 2% Chlorhexidine Gluconate Cloth was utilized. Additional study endpoints include overall incidence of nosocomial bloodstream infections, nosocomial MRSA bloodstream infections, incidence of VRE and rate of chlorhexidine resistance among study isolates.</td>
</tr>
<tr>
<td>Safety:</td>
<td>Safety will be assessed through the monitoring of adverse events associated with bathing products to include any skin rashes or hypersensitivity reactions.</td>
</tr>
</tbody>
</table>
2. Study Sites and Participants

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University of Tennessee
Economic Analysis
  Todd Lee, M.D.
  Northwestern University
3. Introduction

Healthcare-associated infections are a significant source of morbidity and mortality among patients treated in U.S. healthcare institutions. One of the leading causes of nosocomial complications are bloodstream infections (BSIs) affecting between 87,500 and 350,000 patients annually with high attributable mortality and excess costs (1-6). Preliminary investigations have indicated that the use of chlorhexidine bathing in routine care of patients within the ICU might reduce the incidence of methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE) and nosocomial bacteremias. This prospective multi-centered trial entitled “Multicenter evaluation of the effectiveness of source control with daily chlorhexidine skin preparation in reducing nosocomial infections including MRSA and VRE” is intended to determine the possible benefits of daily bathing with chlorhexidine. This intervention aimed primarily at MRSA and VRE also has the potential to reduce other healthcare-associated infections including bacteremias and by its nature is a simple intervention that could be adopted by diverse US healthcare facilities. The trial will be co-supported by an industry sponsor, SAGE Products inc., the current manufacturers of a FDA approved washcloth product impregnated with 2% chlorhexidine and the Centers for Disease Control and Prevention (CDC).

4. Background and Significance

Infections among patients admitted to the intensive care unit are a significant health care problem in all hospitals. It is estimated that up to 20% of patients admitted to intensive care units develop an infection during their stay (1). These infections lead to increased length of stays, increased morbidity and, most concerning, increased mortality. Many of these infections are felt to be preventable and this has spurred recent interest in developing new strategies aimed at reducing their incidence.

The majority of infections reported in the intensive care unit are due to urinary tract infections, ventilator associated pneumonia and bloodstream infections (2). The majority are related to the presence of invasive devices (urinary catheters, mechanical ventilation and central venous catheters). Mortality is highest for catheter associated bloodstream infections where the attributable mortality rate averages between 30-35% but can be as high as 69% (3, 4). *Staphylococcus aureus* is the second leading cause of bloodstream infections and the leading cause of ventilator associated pneumonia. The increased incidence of MRSA is due in part to the rising prevalence of methicillin resistance among all staphylococcal isolates in the ICU. The rising incidence of MRSA infections in the ICU is concerning due to high costs associated with their care and high mortality rates. It is estimated that nosocomially acquired MRSA bloodstream infections are associated with a crude mortality of 22% and lead to $6,916 in excess costs (5). In summary, infections due to Staphylococci including MRSA are the predominant nosocomially acquired complication in the intensive care unit.

Another common multi-resistant pathogen seen within the intensive care unit is vancomycin resistant enterococcus (VRE). Between 1989 and 1993, the percentage of nosocomial enterococcal infections that were due to VRE increased from 0.3 to 7.9% (6). The percentage has continued to rise. In 2003, VRE was the cause of 27.5% of enterococcal infections among ICU patients. An increasing trend towards non-ICU patients having serious infections has been noted and most concerning there is a growing number of patients who have been documented to be colonized with both VRE and MRSA (7,8,46).
The increasing incidence of MRSA and VRE colonization and infection among ICU patients has been attributed to many factors including increased admission of patients already colonized with these pathogens to the ICU, prolonged carriage, poor compliance with handwashing and barrier precautions, delayed identification of colonized patients, and understaffing. The rising prevalence of MRSA and VRE within US hospitals has prompted a contentious debate about the best approach to combat these serious healthcare associated pathogens. Strategies that have been utilized to limit the spread of MRSA and VRE within ICU’s have included stricter attention to barrier precautions following identification of MRSA colonized patients as well as improved handwashing. One prominent strategy that has emerged as recommended by recent SHEA guidelines (9) suggests that hospitals should adopt more aggressive active surveillance culturing to identify unrecognized MRSA and VRE patients at the time of admission and periodically during their hospital stay. Under this “search and isolate” strategy, proponents argue that once reservoirs of MRSA and VRE within the hospital are identified, nosocomial transmission can be effectively eliminated through the use of strict barrier precautions and hand hygiene for these previously unidentified patients.

Despite the recommendations for the adoption of more widespread active surveillance culturing by the SHEA guidelines, most hospitals have not embraced this approach. A recent survey from the IDSA Emerging Infections Network indicated that 86% of infectious disease consultants supported contact precautions to control MRSA, but less than 46% supported routine use of active surveillance cultures and less than 28% of hospitals employed MRSA surveillance cultures (10). Reasons for this lack of enthusiasm for active surveillance culturing could include its attendant costs, the need for additional resources to maintain an active program, and the required high level of compliance with contact precautions and hand hygiene among healthcare personnel to make strict barrier precautions an effective containment strategy.

The “search and isolate” strategy has additional flaws that could limit its overall effectiveness. First, to be effective, this strategy requires high levels of compliance with barrier precautions and handwashing to reduce horizontal transmission. As the literature has documented, both are difficult to achieve in real world settings. Second the “search and isolate” strategy does little to eradicate colonization. In our study of MRSA patients admitted to a combined MICU/CCU we found that 55% of identified MRSA colonized patients remained colonized for the duration of their ICU stay (11). As long as patients remain colonized, the opportunity for transmission exists. We also know that colonization with MRSA is not a benign condition but associated with a risk for the development of serious infections during and after ICU admissions. Huang et al. followed ICU patients identified with MRSA for 18 months and found that 29% of these patients subsequently developed MRSA infection (12). Additional reports have indicated that the risk of subsequent MRSA infection among colonized ICU patients is over 30% (13,14). Barrier precautions and proper handwashing do little to reduce this risk. These considerations would suggest that additional strategies may be needed to address prolonged skin carriage with MRSA and VRE as a strategy to reduce the risk for horizontal transmission as well as the potential to reduce subsequent infections among colonized patients.

Previous studies in the prevention of catheter associated bloodstream infections have indicated that there are a number of modifiable risk factors for catheter-associated bloodstream infection (15). Most of these relate to proper sterile technique during the insertion and maintenance of central venous catheters (16). Proper site preparation with an effective skin disinfectant has been shown to be particularly important in reducing the incidence of subsequent catheter associated infections (17). It is now recognized that chlorhexidine is superior to other agents in site preparation. The use of chlorhexidine reduces residual skin organisms as well as inhibits their rebound growth and has been demonstrated to reduce CABSI in comparison to other skin
disinfectant products such as povidone-iodine. CDC guidelines now recommend that the preferential use of chlorhexidine containing skin disinfectants be used for site preparation prior to insertion (17).

The same properties that make chlorhexidine an effective agent in the prevention of CABSI have been utilized in selective settings to reduce the incidence of MRSA within the ICU. Chlorhexidine is an effective skin disinfectant that has been used successfully to eradicate MRSA skin colonization (18-20). The reduction in skin colonization with MRSA (skin asepsis) is thought to lead to reduced risk for horizontal transmission of MRSA within the ICU environment. The use of chlorhexidine has been used successfully in the control of a number of MRSA outbreaks within the ICU setting and in the community (21,22).

The role of chlorhexidine in reducing nosocomial infections highlights the importance of skin asepsis in the intensive care environment. Although the selective use of chlorhexidine as it relates to catheter site preparation and in the selective treatment of MRSA colonized patients during outbreaks has received preliminary study, there is little study of the potential utility of more wide scale use of chlorhexidine in daily bathing routines within the ICU and hospital. With daily bathing with chlorhexidine, there is the potential to reduce a number of nosocomial infections, including CABSI by reducing bacterial burdens on the skin. Reductions in resident bacteria on the skin could lead to reduced horizontal transmission of multiresistant bacterial pathogens and better outcomes following central line insertions. Daily bathing to produce a state of skin asepsis as such is an attractive theoretical means to reduce nosocomial infections because it represents a simple intervention that could be applied universally with relatively little effort.

The goal of the currently proposed study is to determine if universal use of a chlorhexidine-based bathing system for unit patients will decrease skin bacterial burden and lead to decreased transmission to wardmates resulting in reductions in the incidence of MRSA and VRE. Secondly, we hypothesize that reduced skin colonization with opportunistic bacterial pathogens will result in a reduction in the rate of catheter-associated bloodstream infections and overall bacteremias in comparison to regular bathing procedures.

5. Preliminary Studies

Chlorhexidine has long been recognized as an effective skin disinfectant. In use for over 30 years, chlorhexidine gluconate is used extensively as a surgical scrub, hand wash and skin cleanser. Chlorhexidine is rapidly active and has persistent activity for 2-5 days after application leading to excellent skin asepsis after use. Its use has been shown to lead to reduced infection after surgery when used as a perioperative skin preparation (23-25). The use of chlorhexidine in skin site preparation for central line insertion has been shown to lead to a two-fold reduction in the incidence of bloodstream infections in comparison to povidine-iodine (26,27). As such, chlorhexidine is recommended as one of the preferred agents for skin site preparation in the current CDC guidelines for catheter site care and use (17). Wider use of chlorhexidine in the prevention of nosocomial infections recently has included its incorporation into catheter material to prevent catheter associated bloodstream infections (28). Chlorhexidine has also been used during a number of nosocomial outbreaks of MRSA infections to provide skin asepsis and reduce horizontal transmission of MRSA between patients (21,22).

The use of chlorhexidine as a potential agent in the control of MRSA within the hospital environment has been an area of research at the McGuire VAMC during previous funding cycles for the CDC Prevention Epicenters. Preliminary work has examined the role of chlorhexidine in
reducing extra-nasal colonization with MRSA and the role of chlorhexidine at reducing MRSA transmission and infections within the intensive care unit.

Beginning in July of 2003, the effectiveness of chlorhexidine in reducing extranasal colonization with MRSA following a hospital wide adoption of chlorhexidine bathing for all identified MRSA patients was examined at the McGuire VAMC in Richmond, Virginia. Patients identified with MRSA were required to complete five days of daily bathing with chlorhexidine. Serial cultures were taken and the extent of MRSA colonization followed over time. Chlorhexidine was found to be a very effective agent in eradicating MRSA colonization. Table 1. presents the results of a cohort of patients that completed chlorhexidine bathing and had subsequent follow up cultures for up to three weeks.

<table>
<thead>
<tr>
<th>Site of MRSA Colonization</th>
<th>Patients with MRSA+ Initial Cultures</th>
<th>Patients with Follow up cultures</th>
<th>Patients with MRSA- follow up cultures</th>
<th>Percent cleared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extranasal Axilla</td>
<td>16 (17%)</td>
<td>10</td>
<td>8</td>
<td>80%</td>
</tr>
<tr>
<td>Perineum</td>
<td>35 (37.2%)</td>
<td>23</td>
<td>18</td>
<td>78.3%</td>
</tr>
<tr>
<td>Wound</td>
<td>5 (5.3%)</td>
<td>3</td>
<td>3</td>
<td>100%</td>
</tr>
</tbody>
</table>

Based on these preliminary results, a focused intervention to determine if the more widespread use of chlorhexidine bathing could reduce the incidence of MRSA in high risk patients in the Intensive Care Unit was undertaken. The study was a prospective evaluation of the selective use of mupirocin and chlorhexidine bathing for all patients identified with MRSA within a combined medical/coronary care unit. During a nine month baseline period, the baseline prevalence and incidence of MRSA was determined through an active surveillance program that included nasal cultures for MRSA on admission to the unit and continued surveillance of identified MRSA patients with surveillance cultures taken three times a week. No specific intervention other than the institution of contact precautions, barrier precautions and good hand hygiene for patients identified with MRSA was made during the baseline period. During the planned nine month intervention period all patients identified with MRSA were prescribed mupirocin for intranasal application for four days and received daily bathing with chlorhexidine for five days. The study took place between January 2003 and August 2004. The results of the study are presented in Table 2.

Table 2. Effectiveness of selective chlorhexidine bathing on MRSA incidence in the ICU (McGuire VAMC 1/03- 8/04)

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Admissions</th>
<th>Admission Prevalence</th>
<th>Prevalence per 1000 ICU pt days (range)</th>
<th>Incidence per 1000 pt ICU days (range)</th>
<th>Incidence per 1000 days at risk (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>845</td>
<td>11.00 %</td>
<td>29.33 (15.67-56.91)</td>
<td>6.62 (2.92-17.85)</td>
<td>8.45 (3.38-20.98)</td>
</tr>
</tbody>
</table>
The study has several important findings. The overall incidence of MRSA decreased 48% during the intervention period with 21 new MRSA cases detected during the baseline period and only 11 new MRSA cases during the intervention period. (Table 2). This resulted in a statistically significant difference in the incidence density [new cases of MRSA per 1000 patient days at risk] of 8.45 vs 4.05, \( p=0.048 \). Second, the prevalence of MRSA at unit admission was slightly lower in the intervention period and this was directly attributable to chlorhexidine bathing and intranasal mupirocin that occurred both within the hospital and on former ICU patients (Figure 1). 20/31 (65%) patients admitted to the unit with a previous history of MRSA had received chlorhexidine bathing prior to their admission and had negative surveillance cultures at the time of admission. Third, during the baseline period the majority of patients identified with MRSA were colonized for the duration of their ICU stay (55%). During the intervention period the duration of colonization with MRSA was substantially reduced. There were no reported problems attributed to the use of chlorhexidine bathing during the intervention. MRSA isolates collected during the study underwent susceptibility testing to chlorhexidine. Over 200 isolates were tested and there was no documented resistance to chlorhexidine using a breakpoint for MIC90 of 4 \( \mu g/ml \). There was no evidence of acquired resistance to chlorhexidine or changes in MICs among serial isolates collected from patients.

![Figure 1. MRSA Prevalence and Incidence following the introduction of chlorhexidine bathing for MRSA patients (1/2003-8/2004)](image-url)

In this study, the possible benefits of the addition of chlorhexidine bathing in an ICU with active surveillance culturing in place was studied. As such this study attempted to quantify the additional benefits of eradication of MRSA colonization in reducing MRSA incidence. The use of chlorhexidine bathing and mupirocin were a means to produce skin asepsis and eradicate a large reservoir of MRSA within the unit. The study examined the use of chlorhexidine in selected patients, as only patients identified with MRSA were the only patients who received chlorhexidine bathing. The study found this to be a very successful strategy resulting in a 48% decrease in the incidence of MRSA beyond that seen with active surveillance culturing alone. These results were striking as the study was not initiated as a result on any outbreak or
abnormally high rate of MRSA within the study unit, but as a planned prospective analysis prompted by a change in hospital policy.

These encouraging results led to a second pilot study. The second pilot study differed from the first in that all study ICU patients received chlorhexidine (universal bathing), not just the subset of patients identified as MRSA carriers by surveillance cultures. This study was a prospective, before-after, interventional design taking place within a combined medical/coronary care unit and surgical ICU that took place from January 2005 to December 2005. During a six-month baseline period, patients received bathing as usual. Baseline rates of MRSA prevalence and incidence were determined by ongoing surveillance that included admission cultures for MRSA, weekly prevalence culturing and clinical cultures. During the planned six month intervention period, all patients admitted to the unit received daily bathing with chlorhexidine. Bathing was in the form of a basin bed bath. Approximately 4 ounces of 4% chlorhexidine solution was added to a basin filled with warm water. Patients were then bathed according to standard nursing protocols for bed baths with special care to avoid contact with mucous membranes and the eyes. The results of the study were striking. The overall incidence of MRSA decreased 45% in the two ICUs (Table 3). The decrease in incidence was seen with similar rates of prevalence during both periods indicating a true decrease in incidence not related to burden of colonization within the units. The overall incidence of nosocomial bacteremias decreased 25% from 8.8/1000 patient days to 6.6/1000 patient days.

Table 3. Effect of Daily Chlorhexidine Bathing among Patients Admitted to a combined CCU/MICU and SICU at the McGuire VAMC (1/05-12/05)

<table>
<thead>
<tr>
<th></th>
<th>Baseline Period (1/05-6/05)</th>
<th>Intervention Period (7/05-12/05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA cases (no of cases on admission)</td>
<td>55</td>
<td>39</td>
</tr>
<tr>
<td>MRSA Prevalence (per 1000 patient days)</td>
<td>13.48</td>
<td>11.31</td>
</tr>
<tr>
<td>Incident MRSA cases (n)</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Incidence Density (new cases per 1000 patient days)</td>
<td>8.27</td>
<td>4.57</td>
</tr>
<tr>
<td>Incident Bacteremias (n)</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Bacteremia Incidence (new bacteremias per 1000 patient days)</td>
<td>8.8</td>
<td>6.6</td>
</tr>
</tbody>
</table>

In 2005, three additional CDC Prevention Epicenters (Washington University, Memorial Sloan Kettering, and Johns Hopkins) also completed pilot studies of the effect of universal bathing with chlorhexidine in the ICU and its effect on the incidence of MRSA, VRE and nosocomial bacteremias. These three studies had a similar design to the study completed at McGuire. All three studies were prospective, before-after, interventional designs. Each had a six month baseline period followed by a six month intervention where all admitted patients to the study units received chlorhexidine bathing daily. In addition to MRSA surveillance, surveillance for VRE was also completed in some units. Again this surveillance included admission cultures for VRE as well as ongoing surveillance while patients were admitted to the study units. The intent of these pilot studies was to determine the possible impact of daily chlorhexidine bathing on the incidence of MRSA, VRE and nosocomial bacteremias. These pilot studies were also designed to test the feasibility of a larger multi-center design and to independently confirm preliminary results seen at McGuire at other institutions.

The results of preliminary data analysis are encouraging. Memorial Sloan Kettering has demonstrated a 67% decrease in the incidence of MRSA and a 50% reduction in the incidence of VRE following the introduction of universal bathing with chlorhexidine (Table 3).
At Johns Hopkins University, the pilot study was completed in two separate ICUs. The overall incidence of VRE decreased 41% from 20.38 cases/1000 patient days to 12.06/1000 patient days. The overall incidence of incident bacteremias/fungemias decreased 44% from 2.74/1000 patient days to 1.53/1000 patient days (Table 4). More importantly, the reduction in bloodstream infections was noted among all organism types. Reductions were seen in the number of fungemias and bacteremias, including enterococci, gram positives, and gram negative organisms (Figure 2).

In summary, several pilot studies completed within the CDC Prevention Epicenters between 2002 and 2006 indicate that universal bathing with chlorhexidine may be a very effective modality to reduce the incidence of MRSA, VRE and nosocomial bacteremias.

As encouraging as the data from the second pilot study may be, there are several methodological limitations. First, the study was not designed as a multicenter randomized control trial. Each participating center conducted the pilot study as a stand-alone project and while the same definitions and similar methodologies were used, they were not identical. As an example, all of the studies have studied the use of chlorhexidine used in basin baths. Typically a four percent solution of chlorhexidine was added to a basin filled with water and patients were bathed by nursing personnel in bed. This method of basin baths is often inefficient; results in varied concentrations of chlorhexidine and cannot be completed on all patients, particularly

<table>
<thead>
<tr>
<th>Table 3. Effect of Daily Chlorhexidine Bathing among ICU Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Memorial Sloan Kettering (1/05-12/05)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td><strong>(1/05-6/05)</strong></td>
<td><strong>(7/05-12/05)</strong></td>
</tr>
<tr>
<td>MRSA Admission Prevalence</td>
<td>6.08%</td>
</tr>
<tr>
<td>MRSA Incidence (n)</td>
<td>15</td>
</tr>
<tr>
<td>MRSA Incidence (cases per 100 patient days)</td>
<td>5.73</td>
</tr>
<tr>
<td>VRE Admission Prevalence</td>
<td>17.63</td>
</tr>
<tr>
<td>VRE Incidence (n)</td>
<td>33</td>
</tr>
<tr>
<td>VRE Incidence (cases per 1000 patient days)</td>
<td>14.73</td>
</tr>
</tbody>
</table>
those with serious medical problems. As such compliance with bathing reported during pilot studies ranged from 70-95%. Secondly, the number of study patients from each institutions is small, and even if the results from individual institutions can be combined, there may be insufficient numbers (sample size and power) to detect a statistically significant reduction in BSIs. These methodologic issues suggest the need for a larger multicenter trial and ideally, the use of a product that would allow for standardized concentrations of chlorhexidine.

In 2002, SAGE Products, Inc., developed a new product to be used for bathing patients. Sage, Inc. is a large supplier of healthcare products to hospitals including the Comfort Bath® washcloth system (see Appendix). Many hospital systems use the Comfort Bath product that allows for simple bathing of patients without the need for soap, water or basins. The Comfort Bath washcloth system contains eight pre-moistened washcloths that are used to wipe and cleanse each area of the body. They are disposed of after use. The procedure requires no soap and water. In 2002 Sage developed a new washcloth impregnated with 2% chlorhexidine. These washcloths reduce the number of microorganisms on the skin and deliver residual antimicrobial activity for a prolonged period of time. In the first pilot trial of the effectiveness of the new chlorhexidine impregnated washcloth, Vernon et al examined 1787 patients admitted to a medical intensive care unit from October 2002 to December 2003 (29). They were able to document a reduction in the skin colonization with VRE for those cleansed with the new product as well as a 65% reduction in the incidence of VRE (26 per 1000 patient days to 9 per 1000 patient days). Additionally they noted reductions in the level of environmental contamination and the level of contamination of healthcare worker’s hands with VRE. This new product was well tolerated and resulted in higher compliance with daily bathing and also delivered standard concentrations of chlorhexidine. These data in combination with those previously generated in the CDC prevention Epicenters would indicate that this product would be an ideal candidate for further study of the effects of chlorhexidine bathing in a larger multicenter trial.

6. Research Design and Methods

6.1 Hypothesis:

A change in the regular bathing procedures to utilize products containing chlorhexidine will result in a reduction in the number of colonizing bacteria, including MRSA and VRE, on the skin of patients. Reduced colonization of the skin (skin asepsis) will lower the incidence of nosocomial transmission of bacteria in the ward and decrease incident cases of new bacteremias caused by these bacteria.

6.2 Design:

Prospective, cluster randomized, stratified, crossover trial of units. Units will serve as the as the units of randomization and as their own control. Units will be stratified by the presence of active surveillance culturing for MRSA and/or VRE at the time of study entry.

6.3 Study Setting:

The study will take place in two or more units per participating hospital. Approximately 14 units will be enrolled. Enrolled units will be predominantly intensive care units (ICUs) although additional units where active surveillance for MRSA and or VRE takes place will also be enrolled to include a Bone Marrow Transplant unit, a Burn unit and a Hematology Oncology ward. Study personnel will track blood culture data, patient-days, and MRSA and
VRE specific data per protocol. Units must have pre-existing active surveillance for MRSA and/or VRE in place at the time units undergo randomization in order to participate.

6.4 Participating Hospitals:

McGuire Veteran Affairs Medical Center (Coordinating Center)
Richmond, Virginia
  Principal Investigator: Michael Climo
  Co-Investigators: Edward Wong, Jane Cecil
Johns Hopkins University
Baltimore, Maryland
  Co-investigator: Trish Perl
Memorial Sloan Kettering
New York, New York
  Co-investigator: Kent Sepkowitz
Brigham and Women’s Hospital
Boston, Massachusetts
  Co-investigator: Debbie Yokoe
University of Iowa
Iowa City, Iowa
  Co-investigator: Loreen Herwaldt
Northwestern University
Chicago, Illinois
  Co-investigator: Maureen Bolon
Washington University
St. Louis, Missouri
  Co-investigator: Dave Warren

6.5 Intervention:

Selected units will be randomized to start with either Comfort Bath wash clothes or new chlorhexidine containing wash clothes. The unit of randomization will be a single unit. The units will utilize the randomized bathing procedure (Comfort Bath washcloths or washclothes impregnated with 2% chlorhexidine) for all patients admitted to the participating unit for a six month period of time and then switch to the alternative product for an additional six month period (figure 2). The periods that utilize the regular Comfort Bath wash clothes (control periods) will be compared to the periods in which the washcloths impregnated with chlorhexidine (Intervention period) are used for each ward. Patients will be bathed daily with data collection on the compliance with daily bathing. Data collection during the study will include all positive blood cultures, patient days for study units as well as additional data on MRSA and/or VRE colonization and infection among admitted patients.

Figure 3. Randomization Sceme
6.6 Outcome measures:

1. Overall rate of nosocomial BSI with significant bacterial pathogens during the control period in comparison to the rate during the use of chlorhexidine bathing.

   A. Specific rates will include:

      1) Number of MRSA bacteremias per 1000 patient days
      2) Number of VRE bacteremias per 1000 patient days
      3) Total number of bacteremias for all significant bacterial and fungal pathogens per 1000 patient days
      4) Number of bacteremias or fungemias for individual pathogens per 1000 patient days.

   B. Bacteremias will include only first significant bacteremia/fungemia for patients during each ICU or ward admission and will not include duplicate bacteremias during a single ICU or ward admission. Significant bacteremias will also only include bacteremias with organisms not considered to be skin contaminants (see organism key Appendix B for definition)

   C. Due to the large number of patients involved in this study and its prolonged nature we have elected not to collect line days for each unit or to characterize bloodstream infections as catheter associated or not catheter associated. Active surveillance of this nature is time consuming and unlikely to add additional information to the study as we are studying an intervention intended to reduce the overall rate of BSI within the study units. As such the denominator for all calculations will be total patient days. This is a reasonable surrogate measure of line days in the intensive care unit as up to 87% of all ICU associated BSI are catheter associated ().

2. Overall rate of incident cases of MRSA/VRE colonization and infection (incidence density) in the baseline period in comparison to the rate during the use of chlorhexidine bathing. Specific calculated rates will include:
A. Number of new MRSA/VRE positive patients per total number of patients. Monthly range and variance.

B. Number of new MRSA/VRE positive patients per 1,000 patient days. Monthly range and variance.

C. Number of new MRSA/VRE positive patients per 1,000 eligible patient days. Monthly range and variance. Eligible patient days are those days susceptible patients were at risk for acquisition of MRSA or VRE [Total patient days – total patient days for patients identified with MRSA or VRE] This denominator reflects the true incidence of colonization or infection.

6.7 Data collection:

6.71 Patient Specific Information:

Each patient admitted to the study unit during the study periods will be recorded and assigned a specific study number. The dates of admission, dates of discharge, study unit will be recorded and used to calculate length of stay and to determine the incidence of nosocomial infections based on microbiological data. Data entry will be entered into a password protected Access database. The Access database was developed during previous pilot work within the CDC prevention Epicenters (2003-2006) and has been used extensively by four centers (Johns Hopkins, McGuire, Memorial Sloan Kettering and Washington University) during their single institution evaluation of the effectiveness of chlorhexidine bathing. (see Appendix A). As with previous work completed within the CDC Epicenters, patient identifiers (in this case patient names and medical record number) will be removed from the database prior to submission to the coordinating center (McGuire). This data and research will not be used or disclosed to any persons or entity outside of the study institutions. All data collection files will be password protected and stored on computers belonging to study investigators. Personal health information will be maintained with the database during the collection of unit census data, microbiology data, and medical record review. All patients will be assigned a study identification number that is unique to each institution. Each participating institution will maintain a password protected code key file at their institution that will link study identifiers to patient identifiers. This code key will be accessible only to study investigators and study staff. Any hard copies of datasets will be stored in a locked filing cabinet. After all data are collected, analyzed, and published, linkage between patients and their unique identifier will be destroyed, with the exception of data collected through Infection Control Departments as part of hospital operations. Identified datasets related to infection control activities will be maintained at the primary institution according to hospital operations policy.

6.72 MRSA Screening:

Microbiological data on all MRSA surveillance performed within the study unit will be recorded for those units who have active surveillance in place. Active surveillance will be defined as cultures for MRSA within 48 hours of admission and at least once weekly while admitted to the unit or at time of discharge. Data entry will be entered into a password protected Access database. An incident case will be defined as any patient with a positive active surveillance or clinical culture > 48 hours after ICU admission in patients with either previous negative surveillance and clinical cultures or
no previous history of MRSA. Prevalent cases will be defined as any patient with positive active surveillance cultures or clinical cultures collected within 48 hours of admission. Weekly reports on compliance with admission surveillance cultures for all admitted patients will be monitored and reported during weekly teleconferences.

6.73 VRE Screening:

Microbiological data on all VRE surveillance performed within the study unit will be recorded for those units who have active surveillance in place. Active surveillance will be defined as cultures for VRE within 48 hours of admission and at least once weekly while admitted to the unit or at time of discharge. Data entry will be entered into a password protected Access database. Incident and prevalent cases will follow the same definitions as above for MRSA patients. Weekly reports on compliance with admission surveillance cultures for all admitted patients will be monitored and reported during weekly teleconferences.

6.74 Clinical Culture Data:

Microbiological data on all clinical cultures positive for MRSA or VRE will be entered into the Access database. These data will be compiled with surveillance data in order to determine prevalence and incidence rates for MRSA and VRE.

6.75 Blood culture data:

Data on all positive blood cultures will be collected for significant bacterial/fungal pathogens if they occurred >48 hours after unit admission and within 48 hours of discharge from the study unit. This will include all organisms with the exception of common skin contaminants and all coagulase negative staphylococci (see organism key Appendix B). Data collected will be entered into a password protected Access database. Incident bacteremias (or fungemias) will include only the first significant bacteremia with a significant bacterial or fungal organism during the unit admission and will not include duplicate organisms or subsequent infections as the primary aim of the study is to prevent incident cases.

6.76 Compliance Monitoring:

Confirmation of compliance with daily bathing will be collected by individual centers on a weekly basis during both the baseline and intervention periods. Compliance monitoring will consist of monitoring the use of Comfort Bath washcloth packages and new washcloth packages impregnated with 2% chlorhexidine during the week and ensuring that adequate supplies exist. The total quantity of washcloth packages used during the week will be entered into a compliance monitoring worksheet. For the purposes of this study, use of one washcloth package will be considered receipt of one patient bath. Oversight of the trial will not include direct observation of bathing. Previous work completed during pilot studies has indicated that the overwhelming majority of bathing occurs during the evening and late night shifts making it nearly impossible for research personnel to perform direct observation. Since the Comfort Bath washcloth package is designed to complete one patient bath it is reasonable to assume that use of one product will represent receipt of one bath. At the time of data analysis, the use of Comfort Bath washcloth packages and washcloth packages
impregnated with 2% chlorhexidine will be compared to the number of patients in the study unit to determine the approximate compliance with bathing.

6.77 Data Collection Forms

All data will be entered at the participating site into an Access Database (see Appendix A). Data will include basic demographic information on study patients as well as all culture information to include MRSA screening, VRE screening and blood culture data. The database will be password protected at the site. Definitions for all database fields are contained within Appendix C. Prior to submission to the coordinating center (McGuire), patient identifiers (name and medical record number) will be removed from the database.

6.8 Trial Oversight:

All principal investigators will serve on the steering committee for oversight of the trial. All investigators have participated previously in weekly teleconferences to develop, implement, and analyze multicenter projects during previous CDC Prevention Epicenter Funding (1999-2006). Oversight of this trial will follow a similar design with weekly teleconferences of the steering committee. At that time there will be weekly discussions of the progress report, reporting of compliance with active surveillance, reporting of compliance with bathing, and any adverse reactions or other weekly problems.

6.9 Statistical Analysis:

The effect of daily bathing with chlorhexidine impregnated washcloths on incidence density of BSI, MRSA, and VRE incidence will be modeled by means of Generalized Estimating Equations (GEEs) under the Poisson distribution family. Since each unit is observed twice under the study’s crossover design (once under the experimental and once under the control condition) and the targeted outcome is in the form of counts (here new cases or infections related to patient days of exposure), the GEE methodology is needed to model the count outcomes while accounting for the natural clustering effects induced by repeated observation of units.

Our study design requires three separate analyses based upon the type of surveillance (MRSA only, VRE only, or both) employed by the units. The analysis of BSI rates will use data from all units and will incorporate a three level fixed effect designating surveillance type. The analyses of MRSA and VRE rates, respectively, will be based on only those units engaging in the corresponding type of surveillance. In the latter analyses, a two level fixed effect for surveillance type will be incorporated (MRSA only versus both - or VRE only versus both).

The fundamental model in these analyses will specify treatment, order of presentation, and type of surveillance fixed main effects. Offsets in each model will be unit specific total patient days during the exposure periods. Even though the study design targets minimizing order and type of surveillance effects and neither are expected to be present in any magnitude, their possible effects will incorporated for control purposes. If either proves to be significant, their interactive effects with treatment will also be examined. Such interactive effects are likewise not expected to be present.
All significance tests in these analyses will be conducted given two-tailed alpha of .05. In addition, 95% confidence intervals estimating treatment and control rates as well as their ratio will be constructed. It should be noted that in this study, there can be no missing data and consequently no missing data issues. Analyses are planned to be conducted using the SAS System for Windows Genmod procedure (Version 9.1.3 or later).

6.10 Power considerations:

For power estimation, we have conservatively assumed that 12 units (4 units with both MRSA and VRE surveillance and 4 each using only one of the surveillance types) will be randomized under the study design. Based upon our prior experience with admission rate, length of stay and observed infection rates in such units, we anticipate an average incidence density rate (new cases of MRSA per 1000 patient days) of 8 per 1000 patient days for MRSA, an average incidence density of 15 per 1000 days for VRE, and an average incidence of 8 1000 patient days for new nosocomial BSIs a during each unit’s control exposure.

The following table shows power estimates corresponding to the test of treatment effect assuming six month exposures. Power estimations are based on 1000 iterations of data randomly drawn from Poison distributions and analyzed via GEE for the treatment effect assessed. Each cell in the table represents the power estimate for a specified combination of control rate and reduction rate due to treatment:

<table>
<thead>
<tr>
<th>Control Rate/1000 Patient Days:</th>
<th>BSI 7</th>
<th>BSI 8</th>
<th>BSI 9</th>
<th>MRSA 7</th>
<th>MRSA 8</th>
<th>MRSA 9</th>
<th>VRE 14</th>
<th>VRE 15</th>
<th>VRE 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction:</td>
<td>30%</td>
<td>98%</td>
<td>99%</td>
<td>94%</td>
<td>98%</td>
<td>98%</td>
<td>99%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>25%</td>
<td>94%</td>
<td>98%</td>
<td>99%</td>
<td>86%</td>
<td>88%</td>
<td>92%</td>
<td>98%</td>
<td>98%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Based upon prior research, we expect rate reductions to exceed 30%. As the table shows, the study should have at least 95% power to detect 30% or greater rate reductions and 85% or greater power to detect reductions as small as 25% in all three measured rate analyses. Hence, the study will be more than adequately powered. In fact, based on the number of enrolled units we estimate that we would be powered to detect a 30% reduction in MRSA, VRE and nosocomial bacteremias with incidence rates as low as 3.5/100 patient days, 4.5/100 patient days and 3.5/1000 patient days respectively during the control period.

6.11 Economic Analysis

In addition to understanding the effectiveness of the chlorhexidine impregnated washcloths it is important to estimate the cost-effectiveness of the interventions. We hypothesize that regular bathing utilizing products containing chlorhexidine will result in a reduction in the number of colonizing bacteria including MRSA and VRE on the skin of patients. The reduced colonization of the skin will lower the incidence of nosocomial transmission of bacteria in the ward and decrease incident cases of new bacteremias caused by these bacteria. Thus, the use of chlorhexidine impregnated washcloths may reduce the incidence of high cost MRSA and VRE infections in patients in intensive care units. Therefore it is
important to examine the cost-effectiveness of the use of chlorhexidine impregnated washcloths.

There are three potential scenarios that could exist with the use of the chlorhexidine impregnated washcloths, of which one is unlikely based on pilot data. First, the washcloths could reduce the rate of nosocomial infections enough to offset the increased costs associated with the use of the chlorhexidine impregnated washcloths in which case the new intervention would be considered cost-savings. The second scenario is that the washcloths will decrease the rate of nosocomial infections but increase the total costs of care where it is then important to determine the cost-effectiveness (value) of the washcloths. The final scenario, which again is less likely based on the pilot data, would be where the washcloths are less effective than current bathing practices and more costly where the chlorhexidine impregnated washcloths would be dominated by the current bathing practices. A final scenario that is a possibility in cost-effectiveness analyses is where the chlorhexidine impregnated washcloths would be less effective and be associated with lower costs. This scenario occurs infrequently when the new technology, chlorhexidine impregnated washcloths in this case, cost more than the previous standard of care.

To evaluate the cost-effectiveness of the chlorhexidine impregnated washcloths we will undertake two specific tasks:

1. Compare the costs in the intervention and control arms of the trial; and

2. Evaluate the cost-effectiveness of chlorhexidine impregnated washcloths compared to standard bathing practices by adapting a previously published model.

For the first task we will compare the hospitalization costs between the two arms of the study. For each of the study arms, we will determine the length of stay for each hospitalization, the rate of colonization and the rate of nosocomial infections. We will estimate the total cost of hospitalization for each individual included in the study. Because it is impractical to obtain billing data for each of the patients included in all of the institutions for the study we will estimate the hospitalization costs for individuals included in the trial. Using estimates reported in the literature or national averages may make the results more generalizable than relying on billing data from the eight institutions involved in the study. For the control arm, hospitalization costs will be a function of the length of stay, the average per diem cost for a hospitalization and the per diem costs associated with a nosocomial infection.

\[
\text{Total costs}_{\text{control}} = (\text{LOS}_{\text{no infection}} \times \text{per diem cost}_{\text{no infection}}) + (\text{LOS}_{\text{infection}} \times \text{per diem cost}_{\text{infection}})
\]

For the treatment arm, the hospitalization costs will be similar to that of the controls with the incremental costs associated with chlorhexidine impregnated washcloths included in the equation.

\[
\text{Total costs}_{\text{treatment}} = (\text{LOS}_{\text{no infection}} \times \text{per diem cost}_{\text{no infection}}) + (\text{LOS}_{\text{infection}} \times \text{per diem cost}_{\text{infection}}) + ((\text{Cost chlorhexidine washcloths} - \text{cost Comfort Bath washcloths}) \times \text{number of washcloths})
\]

The per diem costs for infections will be estimated using the same procedure we have used in previous work (30). For example, for VRE infections the per diem cost will be estimated
by combining total VRE cost estimates from Stosor and colleagues (31) ($83,897 – $56,707 = $27,190) with the length of stay data for VRE infections from Monteclavo et al. (32) (26.3 – 12.6 = 13.7 days) and adjusting to current year dollars ($27190/13.7 = $1984 per day [1995 $] * Medical care component of CPI = cost in current year dollars). Similar methods will be used to estimate MRSA and other nosocomial infection costs based on previously published cost estimates (5).

The difference in total hospital costs will be compared between the groups. Because cost data typically does not conform to the necessary assumptions of normality when comparing means, the costs will be compared using non-parametric bootstrap techniques (33,34). The bootstrap methods, as described by Barber and Thompson (33) and Desgangné (34) allow for the estimation of differences in costs and the calculation of confidence intervals for the difference. The non-parametric approach makes no underlying assumptions about the distribution of the data and yet compares the arithmetic means and differences in arithmetic means.

The bootstrap comparison will be done by sampling, with replacement, the costs from each of the groups until the original sample size in each arm is reached and calculating an average cost for each of these replicates. The difference in average costs will then be calculated between groups. This process will be repeated 1000 times to compare the average difference in hospitalization costs between control and intervention patients and the confidence interval surrounding the difference.

The second task will involve comparing the cost-effectiveness of the intervention with the control in terms of cost per life year saved. To complete this task, we will modify a previously published model in which we evaluated the cost-effectiveness of screening programs for VRE (30). The figures below show the structure of the model that will be easily adaptable to the comparison of the interventions rather than a screening program. To adapt the model, the two primary branches of the tree will be similar to the structure in the “No screen” branch in Figure 4 below. Both the intervention and control arms will have the same structure and the probabilities associated with the branches will come directly from the clinical trial. That is, the rate of colonization and infection for each arm of the decision tree will be based on the overall results from the clinical trial. The costs associated with each arm of the decision tree will be based on the hospitalization costs that were estimated above.

In addition to the decision-tree portion of the model there is also a Markov component of the model that accounts for the benefit of reducing colonization and infections within a unit (figure 5). This benefit is seen by reduced risk of nosocomial infections to patients in the unit that are not currently colonized. The Markov process will be adapted to not only include the rate of transmission of VRE but of other nosocomial infections.

The incremental cost-effectiveness ratio (ICER) will be calculated comparing the incremental costs and benefits associated with the intervention compared to the control. The formula for the ICER is:

\[
\text{ICER} = \frac{\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{control}}}{\text{Outcome}_{\text{intervention}} - \text{Outcome}_{\text{control}}}
\]

The outcome that will be used in the cost-effectiveness analysis is life years. The base case will be the mortality rate observed in each arm of the study to determine the life years saved attributable to the intervention. However, because we may not have sufficient power
to compare mortality in the study, we will also use the estimated risk of mortality associated with nosocomial infections in a sensitivity analysis. All analyses will be conducted from the perspective of the hospital. Additionally, we will conduct a fully probabilistic analysis on the decision model. Patients will move through the decision model based on the probability values at each of the nodes on the model. We compared the surveillance strategies with a probabilistic analysis of the analytic decision model, which involves assigning a distribution to the probability values at certain nodes of the model rather than a single value (35-37). The probability for the value is then chosen randomly from this distribution through Monte Carlo simulation. Using a probabilistic decision model incorporates uncertainty associated with the parameter estimates rather than relying on a single value to represent the estimate.

Results will be reported as cost per life year saved associated with the intervention compared to the controls. We will compute 95% confidence intervals for the incremental cost-effectiveness ratio, plot the results on cost-effectiveness planes and produce cost-effectiveness acceptability curves. In addition to the fully probabilistic analysis we will also conduct several sensitivity analyses. We will conduct one-way analyses on all variables included in the model. From the one-way analyses we will produce a funnel plot of the most influential parameters. We will also conduct two-way and multi-way sensitivity analyses on parameters that are thought to be correlated and co-vary with each other.

Figure 4. Decision tree
6.12 Chlorhexidine Resistance

Resistance to chlorhexidine is rare among both staphylococci and enterococci with reported MIC’s to chlorhexidine for staphylococci of 0.2 –3 μg/ml [0.00002-0.0003%] and for enterococci of 1-6 μg/ml [0.0004-0.0006%] (38-41). Previous studies have also indicated that following serial passage of both staphylococci and enterococci in the presence of chlorhexidine there are only minimal changes in MIC values and no evidence of reported high level resistance (38). Plasmid mediated resistance to antiseptics and disinfectants among staphylococci is well known. Most prevalent is the presence of the qacAB and qacCD gene families which encode proton dependent export proteins that confer resistance to a wide variety of disinfectants. Most prevalent among staphylococci is the qacA determinant found on the pSK1 family of conjugative plasmids that also typically encode resistance to a number of antimicrobials including β-lactamase (42). The presence of qacA results in substantial increases in MIC’s to quaternary ammonium compounds (QAC’s) but only a 2.5 fold increase in MIC’s to chlorhexidine (0.8 μg/ml to 2 μg/ml), corresponding to concentrations well below those seen in commercial preparations of chlorhexidine (38). Plasmid mediated resistance to chlorhexidine has not been described among enterococci. High level resistance to chlorhexidine among gram-negative bacterial organisms particularly Pseudomonas and Serratia has been reported (43-45). However many gram-negative organisms, fungal, and mycobacterial organisms remain susceptible to chlorhexidine.

With such widespread use of chlorhexidine that is anticipated during this proposed trial, we will test isolates for chlorhexidine resistance. Each participating center will ship isolates of staphylococci and enterococci collected within the study units to the coordinating center (McGuire VAMC). We will adopt a sampling strategy for testing given the large number of units and patients involved in the study. Each participating center will collect the first ten bacterial isolates (five MRSA and five VRE) from patients treated in the study during the calendar month and each month thereafter. Culture specimens will be labeled with a
unique Study number identifier corresponding to the identifier in the database form and as such will contain no unique identifiers contained within the 18 HIPAA identifiers. Over the twelve month duration of the study, we will collect 1,920 isolates of MRSA and VRE for testing. All isolates will be tested for susceptibility to chlorhexidine. MIC’s for chlorhexidine will be determined by an agar dilution method on Mueller-Hinton agar containing chlorhexidine diacetate (Sigma-Aldrich Inc., St. Louis, MO) in concentrations ranging from 1 to 16 μg/ml (corresponding to 0.0001% to 0.0016%). Although no standard definition exists for resistance to chlorhexidine, previous studies have indicated that most isolates of MRSA and VRE have MIC’s <8 μg/ml (0.0008%). For the purposes of this study, isolates with MIC>16 μg/ml will be considered resistant. Susceptibility to chlorhexidine will be compared between periods where chlorhexidine impregnated washcloths were in use to determine if acquired resistance to chlorhexidine developed following its wide-scale introduction. Although the primary goal of this testing is to determine any level of resistance to chlorhexidine among clinical isolates of MRSA and VRE, this effort will represent the largest survey of clinical isolates of MRSA and VRE for susceptibility to chlorhexidine completed to date.

7. Human Subjects Research Considerations

7.1 Human Subjects Involvement and Characteristics

This is a cluster randomized trial with an intervention that is based at the unit level. The “intervention” is examining two accepted bathing methods and the possible differences in the development of nosocomial infections based on the use of these products. Because both SAGE washcloth products are FDA approved products, we will be seeking a waiver of documentation of informed consent. All patients admitted to the units enrolled in this study will undergo bathing with two different bathing products (Comfort Bath Wash clothes or Wash clothes impregnated with 2% chlorhexidine) according to a randomization schedule. Both bathing products are FDA approved. The 2% chlorhexidine gluconate cloth is FDA approved as a patient perioperative skin preparation and for use to reduce bacteria that can potentially cause skin infection. It is for this latter use that this study will use the product. Comfort Bath Wash clothes are used extensively as a basin-less form of patient bathing. The study will determine potential differences between the use of the two products and the incidence of MRSA, VRE and nosocomial bacteremias. The proposed units are predominantly Intensive Care Units, Bone Marrow Transplant units and Hematology-Oncology wards. This indicates that the targeted patient population will be varied and will include a number of critically ill patients. Intensive care units that will participate will include surgical intensive care units, medical intensive care units and cardiology intensive care units. Patients in these units typically have a variety of medical conditions including post-surgical problems, myocardial infarctions, coronary artery disease and a number of infectious and complex medical care requiring intensive unit care. The expected age range of human subjects will be from 18-90 years of age as we will only be including units that serve adult populations. Both men and women will be included in the research. The proposed research will take place in six additional hospitals that include: Johns Hopkins University, Brigham and Women’s Hospital, Northwestern University, Washington University, Iowa University and Memorial Sloan Kettering.

7.2 Sources of Materials

Each patient admitted to study units during the study periods will be recorded and assigned a specific study number. The dates of admission, dates of discharge, study unit will be
recorded and used to calculate length of stay and to determine the incidence of nosocomial infections based on microbiological data. Additional data that will be collected include birth decade, gender, date of initiation of contact precautions and all microbiologic data for positive surveillance or clinical cultures for MRSA or VRE. All positive blood cultures will also be recorded. Data entry will be entered into a password protected Access database. The Access database was developed during previous pilot work within the CDC prevention Epicenters (2003-2006) and has been used extensively by four centers (Johns Hopkins, McGuire, Memorial Sloan Kettering and Washington University) during their single institution evaluation of the effectiveness of chlorhexidine bathing. (see Appendix A). As with previous work completed within the CDC Epicenters, patient identifiers (in this case patient names and medical record number) will be removed from the database prior to submission to the coordinating center (McGuire). This data and research will not be used or disclosed to any persons or entity outside of the study institutions. All data collection files will be password protected and stored on computers belonging to study investigators. Personal health information will be maintained with the database during the collection of unit census data, microbiology data, and medical record review. All patients will be assigned a study identification number that is unique to each institution. Each participating institution will maintain a password protected code key file at their institution that will link study identifiers to patient identifiers. This code key will be accessible only to study investigators and study staff. Any hard copies of datasets will be stored in a locked filing cabinet. After all data are collected, analyzed, and published, linkage between patients and their unique identifier will be destroyed, with the exception of data collected through Infection Control Departments as part of hospital operations. Identified datasets related to infection control activities will be maintained at the primary institution according to hospital operations policy.

7.3 Waiver of Informed Consent

This study will involve all adult patients admitted to the proposed study units. As such there is no recruitment strategy. It is intended to encompass all patients within the participating units. This study will be seeking waiver of informed consent in accordance with 45 CFR 46.116(d) based on the following:

1. The intended research presents no more than minimal risk to the patients. The intent is to study the potential differences between two accepted bathing products for patients and to determine if there is the potential to reduce nosocomial infections. Both products are FDA approved products and as such pose minimal risk to those patients involved. Bathing with chlorhexidine is an accepted procedure within the hospital and is often applied to selected patient populations within the hospital including pre-operative patients.

2. The activities within the proposal do not normally require informed consent. Bathing is an accepted practice within the hospital and does not require informed consent. Surveillance cultures are normally done in the course of many hospital surveillance activities and the standard of care is to require only verbal permission prior to collection.

3. This research could not be carried out without the waiver of consent. Given the large number of patients involved, the requirement for individual written informed consent would make the research impossible.
4. **The waiver of informed consent will not adversely affect the rights and welfare of patients.** The lack of informed consent will not ultimately affect the rights or welfare of the intended study participants.

5. **Whenever appropriate, subjects will be provided with additional pertinent information after their participation.** If there is any new information about the safety, utility or new research findings pertinent to the study participants, they will be immediately informed. In the case of severely ill patients, surrogates will be informed as dictated by local institutional policies.

7.4 Waiver of HIPAA Authorization

This clinical research study will be seeking waiver of written HIPAA authorization based on the following:

1. **Use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals.** We will keep all data in a secure Access database that is password protected and accessible only to dedicated research personnel. Data entry for individual patients will be coded and not include patient’s full name or complete social security number. All patients will be assigned a study identification number that is unique to each institution. As with previous work completed within the CDC Epicenters, patient identifiers (in this case patient names and medical record number) will be removed from the database prior to submission to the coordinating center (McGuire). Following this de-identification, the only protected health information contained within the database that will be forwarded to the coordinating center (McGuire) are the dates of admission and discharge dates from the study units. None of the other protected health Information identifiers are contained within the database. Personal health information will be maintained with the database during the collection of unit census data, microbiology data, and medical record review. Each participating institution will maintain a password protected code key file at their institution that will link study identifiers to patient identifiers. This code key will be accessible only to study investigators and study staff. Any hard copies of datasets will be stored in a locked filing cabinet. All data collection files will be password protected and stored on computers belonging to study investigators. After all data are collected, analyzed, and published, linkage between patients and their unique identifier will be destroyed, with the exception of data collected through Infection Control Departments as part of hospital operations. Identified datasets related to infection control activities will be maintained at the primary institution according to hospital operations policy. During the course of the study, information collected will not be disclosed to anyone other than the study personnel. This data and research will not be used or disclosed to any persons or entity outside of the study institutions.

2. **The research cannot practicably be conducted without the waiver.** Given the large number of involved patients, the research cannot be completed easily without the waiver.

3. **The research could not practicably be conducted without access to and use of the protected health information.** Accurate determination of lengths of stays and total patient days for all involved study participants will require access to dates of admission and discharge (protected health information). Without this information the research can not be practically conducted.

7.5 Protection Against Risk.
The study site Principal Investigator is responsible for the preparation and submission of all documents and periodic reports required by the local IRB. All protocol amendments affecting the safety and welfare of study participants must be approved by the IRBs prior to implementation. All investigators and participating sites will be in full compliance with human subjects and HIPAA requirements. This study protocol will be submitted to the Centers for Disease Control for IRB approval and the CDC may defer to local center’s IRB for human subject research protection oversight. The sponsoring institution and participating institutions promise that the study will be conducted to good clinical practice guidelines, applicable laws and regulations, and will report to investigators and regulatory authorities significant findings that could affect the safety and well being of research subjects. All study investigators and staff have been trained in human subjects research and HIPAA regulations.

Monitoring of any unexpected adverse effects or serious adverse events related to study procedures will be the responsibility of local investigators and are to be reported immediately to the steering committee as well as appropriate IRB. All unexpected adverse events and serious events are to be reported and sent to the steering committee at the coordinating center (McGuire) within five working days on the adverse event form (see Appendix H.)

For the purposes of this research protocol unexpected adverse events and serious adverse events will be defined as follows:

**Unexpected adverse event:** Any adverse reaction or experience that is not listed in the current labeling for the drug product or investigators brochure. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. Known adverse reactions to chlorhexidine containing topical products include irritation, sensitization, and generalized allergic reactions especially in the genital area. Chlorhexidine should be kept out of the ears and eyes. "Unexpected," as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

**Serious adverse drug event.** Any adverse reaction or experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 7.6 Potential Risks

This clinical research involves minimal risk to the patients involved since it involves only the use of two FDA approved bathing products. Potential recognized risks of bathing with chlorhexidine include local skin irritation, allergic reaction and irritation of mucous membranes. Chlorhexidine is not to be used in children. This research only involves adult patients aged 18 years or older.
7.7 Potential Benefits Of The Proposed Research To The Subjects And Others

The intent of this study is to demonstrate that the routine use of chlorhexidine in bathing practices will lead to reduced skin colonization with resistant bacteria including MRSA and VRE. This reduction can lead to significant declines in the incidence of MRSA and VRE and nosocomial bacteremias. Such reductions could have profound effects on associated health care costs and mortality. Since the intervention that is proposed is of minimal risk to the involved patients the potential benefits far outweigh any potential risk to individual patients.

7.8 Importance Of The Knowledge To Be Gained

MRSA and VRE are serious nosocomial pathogens associated with high morbidity and mortality for involved patients. In addition, nosocomial bacteremias are the leading cause of death among intensive care unit patients. Novel interventions that reduce these complications would greatly benefit large populations within our healthcare systems. If changes in bathing practices prove to be effective in reducing these complications, this would represent a simple intervention that could be applied broadly to all hospitals.

7.9 Inclusion of Women and Minorities

The proposed clinical research will involve all adult patients admitted to participating units. There will be no exclusion of any gender, racial or ethnic minority. Racial or ethnic origin of patients in previous pilot studies completed to date was not accurately determined (this information was not collected). This does not compromise the scientific objectives of the research, since the proposed intervention it is to be applied universally and race, ethnic origin and gender have no bearing on the intended effect. Although exact demographics for the targeted study populations are not readily available, we have estimated the distribution of gender and racial and ethnic groups to be enrolled based on prior studies done in the ICU environment.

7.10 Inclusion of Children

This clinical research will involve the enrollment of children. However it will only involve children from the age of 18-20 and as dictated by local policies for admission to the participating units. All of the proposed study units currently only admit adult patients. For most of the participating units this includes patients >18 years of age. Since the definition of children for the purpose of this application include any patient < 21 years of age, we will be enrolling children.

8. Literature Cited.


9. Appendices

Appendix A. Example of Access Database Data Entry Form
Appendix B. Classification of Bloodstream Infections
Appendix C. Definitions of all Entry fields in Access Database
Appendix D. Sage Comfort Bath™ Product Brochure
Appendix E. Sage, Inc. Chlorhexidine Impregnated Washcloth Product Brochure
Appendix F. MSDS – Sage Comfort Bath™
Appendix G. MSDS – SAGE 2% Chlorhexidine Gluconate Cloth
Appendix H. Unexpected Adverse Event Reporting Form
## Appendix A. Example of Access Database Data Entry Forms

### Chlorhexidine Intervention: MRSA and VRE

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicenter</td>
<td></td>
</tr>
<tr>
<td>StudyID</td>
<td>1</td>
</tr>
<tr>
<td>MRN</td>
<td>#Name? Last Name: #Name? First Name: #Name?</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Age at First Unit Admit</td>
<td></td>
</tr>
<tr>
<td>First MRSA Institutional Culture Date</td>
<td></td>
</tr>
<tr>
<td>First VRE Institutional Culture Date</td>
<td></td>
</tr>
</tbody>
</table>

#### Unit Admission

<table>
<thead>
<tr>
<th>Unit Name</th>
<th>Unit Admit Date</th>
<th>Unit Discharge Date</th>
<th>Precautions on Admit</th>
<th>StudyID</th>
<th>Cultures Prior to Unit Admit</th>
<th>Cultures During Unit Admit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>Present —, Pre-Unit Cultures</td>
<td>Present —, Unit Cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

STOP
<table>
<thead>
<tr>
<th>Specimen Date</th>
<th>Specimen Site</th>
<th>MRSA Result</th>
<th>VRE Result</th>
<th>Organism</th>
<th>StudyID</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/31/10</td>
<td>Surf (Name)</td>
<td>Yes</td>
<td>Not Eval</td>
<td>S. aureus (MRSA)</td>
<td>23</td>
</tr>
</tbody>
</table>

Enter the MOST RECENT VRE/MRSA positive test in the year prior to the unit admission.
Enter ALL POSITIVE MRSA/VRE microbiologic tests within the study period spanning from the date of this unit admission through 2 days beyond this unit discharge (surveillance and clinical tests).

Enter ALL NEGATIVE surveillance tests sent for MRSA/VRE in the same period as above.
Appendix B. List of Microbiologic Classification of Blood Stream Infections

<table>
<thead>
<tr>
<th>No.</th>
<th>BSI Classification</th>
<th>Organism</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>NO GROWTH/ NEGATIVE</td>
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</tr>
<tr>
<td>1</td>
<td>Achromobacter species</td>
<td>Corynebacterium, others</td>
</tr>
<tr>
<td>2</td>
<td>Acinetobacter baumannii</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>3</td>
<td>Acinetobacter calcoaceticicus</td>
<td>Diphtheroids</td>
</tr>
<tr>
<td>4</td>
<td>Acinetobacter 1wofli</td>
<td>Enterobacter aerogenes</td>
</tr>
<tr>
<td>5</td>
<td>Acinetobacter, others</td>
<td>Enterobacter cloacae</td>
</tr>
<tr>
<td>6</td>
<td>Actinomyces species</td>
<td>Enterobacter, others</td>
</tr>
<tr>
<td>7</td>
<td>Aeromonas species</td>
<td>Enterococcus faecalis (vanco-sensitive)</td>
</tr>
<tr>
<td>8</td>
<td>Alcaligenes species</td>
<td>Enterococcus faecalis (vanco-resistant)</td>
</tr>
<tr>
<td>9</td>
<td>Aspergillus species</td>
<td>Enterococcus faecium (vanco-sensitive)</td>
</tr>
<tr>
<td>10</td>
<td>Bacillus anthracis</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Bacillus cereus</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Bacillus subtilis</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Bacillus, others</td>
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</tr>
<tr>
<td>14</td>
<td>Bacteroides fragilis</td>
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</tr>
<tr>
<td>15</td>
<td>Bacteroides, others</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Blastomyces dermatitidis</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Branhamella catarrhalis</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Burkholderia cepacia</td>
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</tr>
<tr>
<td>19</td>
<td>Campylobacter species</td>
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</tr>
<tr>
<td>20</td>
<td>Candida albicans</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Candida glabrata</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Candida kruzei</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Candida lusitaniae</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Candida parapsilosis</td>
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</tr>
<tr>
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<td>Candida tropicalis</td>
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</tr>
<tr>
<td>26</td>
<td>Candida, others</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Citrobacter diversus</td>
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<tr>
<td>28</td>
<td>Citrobacter freundii</td>
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</tr>
<tr>
<td>29</td>
<td>Citrobacter koseri</td>
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<tr>
<td>30</td>
<td>Citrobacter, others</td>
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</tr>
<tr>
<td>31</td>
<td>Clostridium difficile</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Clostridium perfringens</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Clostridium, others</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td><strong>Coagulase negative staph (CNS)</strong></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Coccidioides immitis</td>
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</tr>
<tr>
<td>36</td>
<td>Corynebacterium group G-2</td>
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</tr>
<tr>
<td>37</td>
<td>Corynebacterium jeikeium</td>
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<tr>
<td>38</td>
<td>Corynebacterium, others</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Cryptococcus neoformans</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Diphtheroids</td>
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</tr>
<tr>
<td>41</td>
<td>Enterobacter aerogenes</td>
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</tr>
<tr>
<td>42</td>
<td>Enterobacter cloacae</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Enterobacter, others</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Enterococcus faecalis (vanco-sensitive)</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Enterococcus faecalis (vanco-resistant)</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Enterococcus faecium (vanco-sensitive)</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Enterococcus faecium (vanco-resistant)</td>
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<tr>
<td>48</td>
<td>Enterococcus gallinarum</td>
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<tr>
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<td>Enterococcus, others</td>
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</tr>
<tr>
<td>50</td>
<td>Escherichia coli</td>
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</tr>
<tr>
<td>51</td>
<td>Flavobacterium species</td>
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</tr>
<tr>
<td>52</td>
<td>Fungus</td>
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<tr>
<td>53</td>
<td>Fusarium species</td>
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<tr>
<td>54</td>
<td>Fusobacterium species</td>
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</tr>
<tr>
<td>55</td>
<td>Gram-negative cocci unspecified</td>
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</tr>
<tr>
<td>56</td>
<td>Gram-negative rod unspecified</td>
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</tr>
<tr>
<td>57</td>
<td>Gram-positive cocci unspecified</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>Gram-positive rod unspecified</td>
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</tr>
<tr>
<td>59</td>
<td>Haemophilus species</td>
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<tr>
<td>60</td>
<td>Histoplasma capsulatum</td>
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<tr>
<td>61</td>
<td>Klebsiella oxytoca</td>
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<tr>
<td>62</td>
<td>Klebsiella pneumoniae</td>
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<tr>
<td>63</td>
<td>Klebsiella, others</td>
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</tr>
<tr>
<td>64</td>
<td>Lactobacillus species</td>
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</tr>
<tr>
<td>65</td>
<td>Listeria monocytogenes</td>
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<td>Malassezia furfur</td>
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</tr>
<tr>
<td>67</td>
<td>Micrococcus species</td>
<td></td>
</tr>
<tr>
<td>68</td>
<td>Moraxella catarrhalis</td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>Morganella morganii</td>
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</tr>
<tr>
<td>70</td>
<td>Neisseria gonorrhoeae</td>
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<tr>
<td>71</td>
<td>Neisseria meningitidis</td>
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</tr>
<tr>
<td>72</td>
<td>Neisseria, others</td>
<td></td>
</tr>
<tr>
<td>73</td>
<td>Nocardia species</td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>Other (not listed elsewhere)</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>Pasteurella multocida</td>
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</tr>
<tr>
<td>76</td>
<td>Peptostreptococcus species</td>
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<td>Porphyromonas species</td>
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<td>Prevotella species</td>
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<td>Propionibacterium species</td>
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<td>Proteus mirabilis</td>
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<td>81</td>
<td>Proteus vulgaris</td>
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<td>Proteus, others</td>
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<td>Providencia species</td>
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<td>Pseudomonas aeruginosa</td>
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<td>Pseudomonas, others</td>
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<td>Serratia marcescens</td>
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<tr>
<td>88</td>
<td>Sporothrix schenckii</td>
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<tr>
<td>89</td>
<td>Staphylococcus aureus (methicillin-sensitive)</td>
<td></td>
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<tr>
<td>90</td>
<td>Staphylococcus aureus (methicillin-resistant)</td>
<td></td>
</tr>
<tr>
<td>91</td>
<td><strong>Staphylococcus capitis</strong></td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>Staphylococcus coagulase negative</td>
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</tr>
<tr>
<td>93</td>
<td>Staphylococcus epidermidis</td>
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<td>Staphylococcus haemolyticus</td>
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<td>Staphylococcus hominis</td>
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<td>96</td>
<td>Staphylococcus saprophyticicum</td>
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<td>Staphylococcus warneri</td>
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<td><strong>Staphylococcus, others</strong></td>
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<td>Stenotrophomonas maltophilia</td>
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<tr>
<td>100</td>
<td>Streptococcus group A (pyogenes)</td>
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<tr>
<td>101</td>
<td>Streptococcus group B (agalactiae)</td>
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</tr>
<tr>
<td>102</td>
<td>Streptococcus group D (bovis)</td>
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</tr>
<tr>
<td>103</td>
<td>Streptococcus pneumoniae</td>
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<tr>
<td>104</td>
<td>Streptococcus viridans</td>
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</tr>
<tr>
<td>105</td>
<td>Streptococcus, alpha hem</td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>Streptococcus, beta hem</td>
<td></td>
</tr>
<tr>
<td>107</td>
<td>Streptococcus, others</td>
<td></td>
</tr>
<tr>
<td>108</td>
<td>Torulopsis glabrata</td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>Yeast</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Underlined organisms represent common skin contaminants for the purpose of assigning a BSI classification. Organisms in **bold** represent coagulase-negative staphylococcus species.
Appendix C. Definitions of all Entry fields in Access Database

Demographics Form

1. **Epicenter**: Drop list for participating centers in study
2. **Start Date**: Starting date of study period
3. **End Date**: Last date of study period
4. **Study ID**: sequential ID number given to study patients
5. **MRN**: Medical record of study patient used during data entry for tracking and accuracy. Field is removed prior to data submission to coordinating center
6. **Last Name**: Last name of study patient used during data entry for tracking and accuracy. Field is removed prior to data submission to coordinating center
7. **First Name**: First name of study patient used during data entry for tracking and accuracy. Field is removed prior to data submission to coordinating center
8. **Gender**: Gender of study participant
9. **First MRSA Institutional Culture Date**: Date of the first recorded positive culture for MRSA at the institution for the study participant
10. **First VRE Institutional Culture Date**: Date of the first recorded positive culture for VRE at the institution for the study participant
11. **Age at First Unit Admit**: Age of the study participant at the time of unit admission. Age is chosen from drop down list that is listed in decades; 1) <18, 2) 18-35, 3) 36-45, 4) 46-55, 5) 56-65, 6) 66-75, 7) 76-85, and 8) >85.

Unit Subform

12. **UnitID**: Numbering system for ICU admissions, each admission is given a unique unit ID number, all study ID are patient specific and thus each study ID may have multiple unit ID numbers. Autonumbered on Dataview sheet.
13. **Unit name**: Name of study unit, up to two units in study per participating institution
14. **Unit Admit Date**: Date of admission to study unit
15. **Unit Discharge date**: Date of discharge from study unit
16. **Study ID**: Sequential ID number given to study patients
17. **Precautions on Admit**: Was patient placed on contact precautions on admission, (yes or no, checkbox)
18. **Cultures Prior to Unit Admission**: Were there cultures for MRSA or VRE present prior to admission to study unit (present or none)? Present prompts entry into Pre-Admit Cultures subform

19. **Cultures During to Unit Admission**: Were there any cultures taken during study unit admission (none or present)? Cultures include any cultures positive for MRSA, VRE and all positive blood cultures. Present prompts entry into Cultures subform

Pre-Admit culture form

20. **Specimen Site**: Site of most recent MRSA or VRE culture prior to admission

21. **Specimen Date**: Date of most recent MRSA or VRE culture prior to admission

22. **MRSA Result**: Result of most recent MRSA culture prior to admission (yes, no, not eval)

23. **VRE Result**: Result of most recent VRE culture prior to admission (yes, no, not eval)

24. **Organism**: MRSA or VRE, on this form should only reflect results of MRSA and VRE culturing prior to admission.

25. **StudyID**: Sequential ID number given to study patients generated on demographics form.

Cultures subform

26. **Specimen Site**: Site of MRSA or VRE culture during study unit admission. Data on all blood cultures is also entered into this field by selecting blood culture as specimen site.

27. **Specimen Date**: Date of MRSA or VRE culture during study unit admission

28. **MRSA Result**: Result of MRSA culture during study unit admission (yes, no, not eval)

29. **VRE Result**: Result of VRE culture during study unit admission (yes, no, not eval)

30. **Organism**: MRSA or VRE, on this form should only reflect results of MRSA and VRE culturing during study unit admission.

31. **StudyID**: Sequential ID number given to study patients generated on demographics form.
Comfort Bath®
Cleansing Washcloths

Full-body bathing
made easier!
Comfort Bath’s rinse-free
washcloths thoroughly
 cleanse and nourish with
 aloe and vitamin E, so they
 leave skin feeling clean, soft
 and moisturized.

The ultimate in rinse-free bathing!
Thick, ultra-soft washcloths are
premoistened with a rinse-free, aloe and
vitamin E formula. Warm and soothing, they
make full-body cleansing and moisturizing
easy in just one step. Just warm Comfort
Bath in a microwave or warmer. No rinsing.
No mess. No more time-consuming,
uncomfortable basin baths!

Using Comfort Bath also provides an
opportunity to observe skin condition from
head to toe. It also eliminates potential
contamination from dirty basins and hospital
tap water during bathing.

America’s number one basinless bathing
brand, Comfort Personal Cleansing® products
are trusted by more US hospitals than all
other brands combined.
Comfort Bath® Cleansing Washcloths

- Our patent-weight, Texcel® polyester blend washcloths are as thick as the laundered kind. With the softness of the line, they feel good even to fragile skin, yet they have superior strength and durability.
- Maximum amount of rinse-free cleansing solution and moisturizers, infused with aloe and vitamin K, they renew and soften skin.
- Eliminates potential contamination from dirty hospital and home water during bathing.
- Dermatologist-tested formula proven hypoallergenic, gentle and non-irritating. Can be used on all body areas including the face.
- Formula’s pH is closest to normal, healthy skin. It won’t dry skin like soap and water can.
- Saves nursing time, increases patient and nursing satisfaction. Safer and more comfortable than a bath tub.
- Replaces soaps, lotions, hot water, basins, laundered washcloths and towel reduces laundry and linen replacement.
- Fully isolated, reusable packaging. Washcloths stay warm throughout the bath, when warmed in our commercial-grade microwave or microwave.
- Latex-free product contains USP purified water.

For customizable protocols, performance improvement plans, educational materials and more, visit www.sageproducts.com/education

A better way to bathe

A recent hospital study. 90% of patients who received a bath bath said it was neither warm or comfortable. 96% did not even feel clean after the bath. Meanwhile, 98% of patients preferred Comfort Bath. Over 90% said their skin felt soft, and 97% said it was warm, comfortable and easy to use.

In another study, Comfort Bath was preferred by 100% of nurses. In fact, all nurses noted that Comfort Bath was easy to administer and left their patients clean and satisfied.

ORDERING INFORMATION

FRAGRANCE FREE COMFORT BATH®
1 kg/2.2 lb package
Reorder #7655

FRAGRANCE FREE COMFORT BATH®
1 kg/2.2 lb package
Reorder #7905

COMFORT BATH®
1 kg/2.2 lb package
Reorder #7915

COMFORT BATH®
1 kg/2.2 lb package
44 package case
Reorder #7000

3909 Three Oaks Road, Cary, Illinois 60013 • www.sageproducts.com • 800-323-2220

SAGE Product & Co
Introducing an entirely new FDA-APPROVED alcohol-free CHG formula

SAGE® 2% CHLORHEXIDINE GLUCONATE CLOTH PATIENT PREOPERATIVE SKIN PREPARATION in the first and only FDA-APPROVED applicator cloth.
Surgical Site Infections: Prevalence, Cost & Mortality

There are approximately 60 million inpatient and ambulatory surgical procedures performed in the U.S. annually. For surgery patients, SSIs are the leading hospital-acquired infection at 36% and the third most common hospital-acquired infection overall. Surgical site infections occur after 2.6% to 5% of procedures, translating to at least 1.3 million SSIs annually. Patients who develop SSIs “…are twice as likely to die. 60% more likely to spend time in an ICU, and more than five times more likely to be readmitted to the hospital.” SSIs also increase length of stay by 7 to 10 days and account for $25,546 in average costs.

In a study of elderly patients,SSI due to S. aureus was responsible for a more than 5-fold increase in mortality, more than 12 additional hospital days, and excess costs of more than $40,000.

In a 7-year, 479-patient study, methicillin-resistant S. aureus (MRSA) in a surgical wound resulted in over a 12-fold increase in mortality compared to patients without an SSI. For patients with an SSI, mean costs were $38,770 higher than those without infection. For MRSA SSIs, mean costs were $84,020 higher.

- 2.6% to 5% of surgical procedures result in surgical site infections.
- 7 to 10-day increase in length of stay.
- $25,546 average increase in cost.
CHLORHEXIDINE GLUCONATE
Fast-acting, Broad-spectrum, Persistent

“One of the most important attributes of CHG is its persistence.”

“...One of the most important attributes of CHG is its persistence. It has strong affinity for the skin, remaining chemically active for at least 6 hours. Indeed, it probably has the best persistent effect of any agent currently on the market.”

CHG is the only preoperative skin prep agent that the CDC recognizes as having “excellent” activity against gram-positive bacteria as well as “excellent” residual activity.
SAGE® 2% CHLORHEXIDINE GLUCONATE CLOTHS
An entirely new FDA-approved, alcohol-free CHG formula in the first and only FDA-approved applicator cloth

Addressing a known risk factor for surgical site infections: microorganisms on the skin

**UNIQUE 2% CHG FORMULA**
Sage’s unique, patent-pending formulation is rinse-free, quick-drying, and proven to provide rapid bactericidal action. It contains no alcohol or harsh detergents, eliminating immobility concerns and reducing the potential to dry out skin.

- Fast-acting and broad-spectrum. Effective against a wide range of microorganisms, significantly reducing their number on intact skin.
- Extremely persistent. Demonstrates continued antimicrobial activity for up to 6 hours after application.
- Free of alcohol and harsh detergents. Contains surfactants to loosen dirt and debris. Soaks skin with moisturizers and humectants.

**UNIQUE, ONE-STEP APPLICATOR CLOTH**
Now, skin prep can truly be achieved in one step. Sage’s non-abrasive, textured cloth distributes a uniform dose of CHG to the skin. It provides a skin-friendly yet effective scrub to remove debris and organic matter—while allowing CHG to cover the area to be prepped.

- Delivers a uniform dose of CHG. Each cloth contains 500mg.
- No drip, run or pooling associated with other skin prep products.
- Large 7.5 in. x 7.5 in. cloth makes it easier to prep body contours and hard-to-reach areas.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Sage 2% CHG Cloth</th>
<th>Pathogen</th>
<th>Sage 2% CHG Cloth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>✓</td>
<td>Pseudo monoica</td>
<td>✓</td>
</tr>
<tr>
<td>Including MRSA</td>
<td></td>
<td>Haemophilus influenzae</td>
<td>✓</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>✓</td>
<td>Other gram-positive cocci</td>
<td>✓</td>
</tr>
<tr>
<td>Including VRE</td>
<td></td>
<td>Group D streptococci</td>
<td>✓</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>✓</td>
<td>Non-enterococci</td>
<td>✓</td>
</tr>
<tr>
<td>Pasteurella agglutinosa</td>
<td>✓</td>
<td>Other gram-positive cocci</td>
<td>✓</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td></td>
<td>Bacillus fragilis</td>
<td>✓</td>
</tr>
</tbody>
</table>

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**LOG_{10} REDUCTION STUDY RESULTS**

In this study, the Sage 2% CHG Cloths met both criteria outlined in the FDA TFIR for effectiveness testing of a Surgical Preoperative Skin Preparation.

Sage 2% CHG Cloths to the Inguinal Site

![Graph showing reduction in Log_{10} reduction](image)

Baseline = 6.15 log

10 minutes: 3.1
20 minutes: 2.6
4 hours: 1.7

Sage 2% CHG Cloths to the Abdominal Site

![Graph showing reduction in Log_{10} reduction](image)

Baseline = 3.36 log

10 minutes: 3.1
20 minutes: 2.5
4 hours: 2.0

**ORDERING INFORMATION**

- **Sage® 2% Chlorhexidine Gluconate Cloths**
  - 2 cloths per package, cloth size: 2.5" x 2.5"
  - 90 packages/case
  - Reorder #9705
  - Reorder #9706

- **Dispenser Bracket**
  - 20 cases
  - Reorder #9700

- **Dispenser Tray**
  - 20 cases
  - Reorder #9701

1-800-323-2220  •  www.sagproducts.com
Sage Products: The Interventional Patient Hygiene Company

What is Interventional Patient hygiene?
Sage Products has a core belief in prevention—that evidence-based interventions will lead to improved outcomes. Our goals are to promote a positive patient hygiene intervention between caregivers and patients, achieve improved clinical outcomes, reduce adverse events and increase satisfaction. We are realizing those goals by focusing on the basics of nursing care. With our industry-leading brands and commitment, we are pioneering the drive toward Interventional Patient Hygiene.

Visit our FREE Clinical Education Website!
www.sageproducts.com/education
Sage's unique site provides FREE information that can help your facility improve care— including Performance Improvement Plans, Evidence-Based Protocols, Clinical Studies, Customizable Resources and more!

- Reducing VAP Risk Factors
- Preventing Skin Breakdown
- Improving Patient Hygiene

SAGE PRODUCTS INC
3905 Zion Cross Road • Cary, Illinois 60013
www.sageproducts.com • www.sagefooter.com
800.303.2220
Appendix F. MSDS - Comfort Bath® Wash cloth

MATERIAL SAFETY DATA SHEET

Manufactured by: Sage Products Inc.
3900 Three Oaks Road
Cary, IL 60013

Telephone:
Product Info 815 455 4700
Tech Info 815 455 4700
Emergency 800 424 5200

1 PRODUCT IDENTIFICATION

Product Name: Comfort Bath™ PBS Wipe Solution
(Finish-free soap and lotion cleansing).

Product Numbers: 7413-X, 7600, 7600-K, 7813*, 7813-K*, 7813-W*, 7814*, 7855, 7870,
7875, 7900, 7900-EU*, 7900D*, V7900, 7904, 7911, 7913*, 7915, 7916,
7926, 7927*, 7950*, 7955, 7950*, 7970, 7982, 7998

Sage Item Number:

Chemical Family: Aqueous mixture.

Formula: Proprietary.

DOT Hazard: Not listed.

* = Obsolete

Chemical Hazard Rating:
- Health: 0
- Flammability: 0
- Reactivity: 0

2 INGREDIENTS / HAZARDS CLASSIFICATION

NON-HAZARDOUS SOLUTION AS PER OSHA’S HAZARD COMMUNICATIONS STANDARD (29 CFR 1910.1200)

3 PHYSICAL AND CHEMICAL DATA

- Boiling Point: Not determined.
- Specific Gravity: 1.007-1.0178 @ 25°C
- Vapor Pressure: Not determined.
- Vapor Density (Air=1): Not determined.
- pH Value: 4.0 - 6.0
- Volatility: Negligible.
- Solubility in Water: Complete.
- Appearance & Odor: Clear, light straw color. Clean, fresh-like, characteristics of fragrance.

4 FIRE AND EXPLOSION HAZARD DATA

- Flash Point: Non-flammable. Ref. Setaflash Closed Tester, ASTM D-3278 @ ambient. No flash up at 105°C (221°F) - limit of instrument. Will not burn or propagate flame.
- Extinguishing Media: Use appropriate extinguishing media according to the class of material burning around this solution.
5 REACTIVITY DATA

STABILITY: STABLE
Hazardous Polymerization: Will not occur.
Incompatibilities: None known

Decomposition Products May Include: None known

6 HEALTH HAZARD DATA

EMERGENCY FIRST AID PROCEDURES: HANDLE IN ACCORDANCE WITH GOOD INDUSTRIAL HYGIENE AND SAFETY PRACTICES.

Ingestion: Non-toxic. Seek medical attention immediately if overdose has been taken.
Eye Contact: Non-irritating.
Skin Contact: Non-irritating. (Ref.: FDA Primary Dermal and Eye Irritation tests).

7 SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED: CONTAIN ALL SPILLED MATERIAL, ABSORB MATERIAL WITH INERT MATERIAL AND PLACE IN DRY CONTAINERS FOR DISPOSAL.

Waste Disposal Method: Dispose of in accordance with all local, state and federal regulations.

8 SPECIAL PROTECTION INFORMATION

Respiratory Protection: Not usually required.
Protective Gloves: Not usually required. For unusually prolonged exposure use chemical resistant, gauntlet type or equivalent.
Eye Protection: Not usually required, but wear chemical splash goggles or face shield when condition requires.

9 SPECIAL PRECAUTIONS

For Chemical Emergency: Domestic North America (800) 424-9300
Spill, Leak, Fire, Exposure, or Accident: International, Call (703) 522-3087 (Collect Calls Accepted)
Call CHEMTREC Day or Night

10 PREPARATION OF MSDS

Prepared by Safety Department on: October 22, 1996
This data was prepared from current, reliable sources; however, Sage Products Inc. makes no warranty regarding its accuracy. Because of conditions beyond our control, it is the user’s responsibility to determine safe conditions for usage.

Rev. #10: 05/26/06

Sage MSDS #13
MATERIAL SAFETY DATA SHEET

Manufactured by: Sage Products Inc.
3906 Three Oaks Road
Cary, IL 60013

Telephone: (815) 495-4700
Product Info (815) 495-4700
Tech Info (815) 495-4700
Emergency (800) 424-9300
(Chemtrec)

1 PRODUCT IDENTIFICATION

Product Name: 2% Chlorhexidine gluconate* Cloth
* Equivalent to 500 mg Chlorhexidine gluconate per cloth
Product Number: 9601-X, 9602-X, 9605, 9606, 9705, 9706, 9707
Sage Item Number: BS8426
Product Type: Topical Antimicrobial Cloth
Chemical Family: N/A

Chemical Hazard Rating:
- Health 0
- Flammability 0
- Reactivity 0

2 HAZARDOUS INGREDIENTS

THE HAZARD COMMUNICATION STANDARD REQUIRES THAT SUCH MIXTURES BE ASSUMED TO PRESENT THE SAME HEALTH HAZARD AS DO COMPONENTS THAT CONSTITUTE AT LEAST 1% OF THE MIXTURE (0.1% FOR CARCINOGENS), ALTHOUGH OSHA HAS NOTED THAT THE HAZARDS OF INDIVIDUAL COMPONENTS MAY BE ALTERED BY INCLUDING THEM IN A MIXTURE.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>CAS Registry No.</th>
<th>PEL/TLV</th>
<th>% Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine gluconate</td>
<td>13472-51-0</td>
<td>Not established</td>
<td>2</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>57-55-6</td>
<td>Not established</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Glycerin</td>
<td>56-81-5</td>
<td>Not established</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Polyester Fiber</td>
<td>25036-59-9</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

SOME OF THE INGREDIENTS IN THIS MIXTURE ARE TRADE SECRETS (TS).


N/A = Not Applicable
3 PHYSICAL DATA

Boiling Point: N/A Specific Gravity: N/A
Vapor Pressure: N/A Vapor Density (Air = 1): N/A
Freezing Point: N/A Flash Point: > 212 °F
Auto-ignition Temp: Not Known Lower Explosive Limit: None
Solubility in Water: N/A Upper Explosive Limit: None
Appearance & Odor: White polyester cloth with mild odor

4 FIRE AND EXPLOSION HAZARD DATA

FLASH POINT METHOD:

Estimated Flammable Limits in Air: Non-Flammable
Extinguishing Media Includes: Foam or water
Special Fire Fighting Procedures: Use a self-contained breathing apparatus in close proximity to fire.
Unusual Fire & Explosion Hazards: Treat as a solid that burns with low smoke density

5 REACTIVITY DATA

STABILITY: STABLE
Hazardous Polymerization: Will not occur.
Incompatibilities: None known
Decomposition Products May Include: CO, CO2

Sage MSDS 131 2
6 HEALTH HAZARD DATA

IMMEDIATE HEALTH HAZARD DATA:

Skin Absorption: Not likely. Product does not absorb well through skin.

Ingestion: Not likely. Considered non-toxic. If cloth is swallowed seek medical attention.

Inhalation: Not considered an inhalation hazard.

Skin: Not expected to present a skin hazard under anticipated conditions of normal use. If irritation occurs, discontinue use.

Ear: Hazardous to middle ear, with perforated eardrum. Seek medical attention.

Eyes: Keep out of eyes. If contact occurs rinse promptly and thoroughly with water and seek medical attention.

EMERGENCY FIRST AID PROCEDURES:

Ingestion (swallowing): N/A

Inhalation (breathing): N/A

Skin Contact: Flush with water, if irritation persists, get medical attention.

Eye Contact: Flush with water for fifteen minutes, get medical attention.

7 SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED.

Procedures: Wipe dry any surfaces.

Waste Disposal Method: Place in appropriate container and dispose of with all federal, state and local ordinances.

8 SPECIAL HANDLING/PROTECTION INFORMATION

Inhalation: N/A

Skin: If handling for long periods, wear protective gloves. Wash after handling product.

Eyes: Keep out of eyes. If product contacts eye(s), flush with plenty of water, if irritation persists, seek medical attention.

Storing: Store at room temperature.
9 SPECIAL PRECAUTIONS

For Chemical Emergency

Spill, Leak, Fire, Exposure, Domestic North America (800) 424-9300
or Accident International, Call (703) 527-3887 (Collect Calls
Call CHEMTREC Day or Night Accepted)

10 PREPARATION OF MSDS

Prepared by Safety Department on: 7/6/05

This data was prepared from current, reliable sources, however, Sage Products Inc.
makes no warranty regarding its accuracy. Because of conditions beyond our control, it
is the user’s responsibility to determine safe conditions for usage.

Date Issued: 7/8/05  Revisions: 3rd: 5/16/06
ADVERSE EVENT SUBMISSION FORM

The Principal Investigator must promptly report to the IRB, in writing, any unanticipated side effects, hazards, or other problems involving risks to subjects or others. Promptly report all adverse events considered to be related to research procedures to the Steering Committee.

Date:
Principal Investigator: Climo, Michael
Protocol#: CI06-003
Protocol Title: Multicenter Evaluation of The Effectiveness of Source Control With Daily Chlorhexidine Skin Preparation in Reducing Nosocomial Infections Including MRSA and VRE

Sponsor: SAGE Products, Inc., and Center for Disease Control and Prevention
Research Coordinator(s):
Phone: Fax:

Report Type: [ ] Initial [ ] Follow-up
Subject Identifier # (study ID number, do not list medical record number or other personal identifier):
AE Date:
AE Description (brief):

Is the adverse event a previously described complication that is listed in the “Risk” section of the Investigator’s Brochure [ ] Yes [ ] No

<table>
<thead>
<tr>
<th>This is a (an):</th>
<th>The opinion of the Principal Investigator is that the relationship of the research procedure is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Unanticipated/Unexpected Event</td>
<td>[ ] Unrelated  [ ] Probably not related  [ ] Possibly related  [ ] Probably related  [ ] Related</td>
</tr>
<tr>
<td>(Any untoward event that is not identified with the current investigator brochure or study protocol)</td>
<td>[ ] Other:</td>
</tr>
<tr>
<td>[ ] Serious Adverse Event</td>
<td></td>
</tr>
<tr>
<td>(Any untoward medical occurrence that results in death, is life-threatening, requires patient hospitalization, prolongs existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital abnormality)</td>
<td></td>
</tr>
</tbody>
</table>

INVESTIGATOR SIGNATURE          DATE
(Sub-investigator may sign if the investigator is unavailable (i.e. out of the country)
Multicenter Evaluation of The Effectiveness Of Source Control With Daily Chlorhexidine Skin Preparation In Reducing Nosocomial Infections Including MRSA and VRE

Funded by:
Centers for Disease Control and Prevention (CDC)
Sage Products, Inc.

Principal Investigator:
Michael Climo, M.D.
Hunter Holmes McGuire Veteran Affairs Medical Center
Virginia Commonwealth University Medical Campus
Richmond, Virginia

Version 1.3
April 18, 2007
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### Protocol Synopsis

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<thead>
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<th>PROTOCOL TITLE:</th>
<th>Multicenter evaluation of the effectiveness of source control with daily chlorhexidine skin preparation in reducing nosocomial infections including MRSA and VRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTOCOL NUMBER:</td>
<td>CI06-003</td>
</tr>
<tr>
<td>SPONSOR:</td>
<td>CDC and Sage Products, Inc.</td>
</tr>
<tr>
<td>PRODUCT:</td>
<td>2% Chlorhexidine Gluconate Cloth and Comfort&lt;sup&gt;®&lt;/sup&gt; Bath Washclothes</td>
</tr>
<tr>
<td>PRIMARY OBJECTIVES:</td>
<td>To determine if daily bathing with chlorhexidine impregnated washcloths will reduce the incidence of MRSA and VRE within an Intensive Care Unit (ICU) or ward setting.</td>
</tr>
<tr>
<td>STUDY DESIGN:</td>
<td>This is a cluster randomized, crossover-controlled trial with wards as the units of randomization. The trial will predominantly take place in ICU’s but may include any acute care ward that has active surveillance for MRSA and or VRE in place (i.e., Bone Marrow transplant units, Oncology wards, etc.) Units will be randomly assigned to utilize two bathing routines in a random order. Each bathing routine will be utilized on all admitted patients to the unit for a six month study period for a total study duration of 12 months. The two bathing routines will include either the use of the Comfort&lt;sup&gt;®&lt;/sup&gt; Bath Washcloth System (control) or the use of 2% Chlorhexidine Gluconate Cloth. Randomized units will either start with 2% Chlorhexidine Gluconate Cloth for six months and then switch to Comfort™ Bath Washcloth for the remaining six month period or the reverse order. Data collection will include all surveillance and clinical cultures for MRSA and or VRE and all bloodstream infections.</td>
</tr>
<tr>
<td>NUMBER OF SUBJECTS:</td>
<td>Approximately 14 ICUs or acute care wards with 16,000 patients</td>
</tr>
<tr>
<td>SUBJECT POPULATION:</td>
<td>Males or Females, admitted to Intensive Care Units or acute care units</td>
</tr>
<tr>
<td>NUMBER OF CENTERS:</td>
<td>7 centers</td>
</tr>
<tr>
<td>DURATION OF SUBJECT PARTICIPATION:</td>
<td>Typically 1-90 days, or the duration of patient’s ICU or unit admission</td>
</tr>
</tbody>
</table>
| TREATMENT: | Daily bathing with either:  
  1) Comfort<sup>®</sup> Bath Washcloth or  
  2) 2% Chlorhexidine Gluconate Cloth |
| ASSESSMENTS OF EFFICACY: | The primary efficacy endpoint will be the reduction in MRSA incidence during those study periods where the 2% Chlorhexidine Gluconate Cloth was utilized.  
Additional study endpoints include overall incidence of nosocomial bloodstream infections, nosocomial MRSA bloodstream infections, incidence of VRE and rate of chlorhexidine resistance among study isolates. |
| SAFETY: | Safety will be assessed through the monitoring of adverse events associated with bathing products to include any skin rashes or hypersensitivity reactions. |
2. Study Sites and Participants

**McGuire Veteran Affairs Medical Center**
Coordinating Center
1201 Broad Rock Boulevard
Richmond, Virginia 23249
Principal Investigator:
  Michael Climo
  Office: (804) 675 5018
  Cell: (804) 350-3487
  Fax: (804) 675 5437
  E-mail: Michael.climo@va.gov

Co-investigator:
  Edward Wong, M.D.
  Office: (804) 675-6792
  Fax: (804) 675 5437
  e-mail: Edward.wong@va.gov

Co-investigator:
  Jane Cecil, M.D.
  Office: (804) 675-5470
  Fax: (804) 675 5437
  e-mail: jane.cecil@va.gov

Research Coordinator
  Christine Harper, RN
  Office: (804) 675-5000 ext 3873
  Fax: (804) 675 5437
  e-mail: christine.harper@va.gov

**Brigham and Women’s Hospital**
Harvard School of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts
Co-investigator:
  Deborah Yokoe, M.D., MPH
  181 Longwood Avenue, Channing Laboratory, Boston, MA 02115
  Office: (617) 525-2689
  Fax: (617) 731-1541
  e-mail: dyokoe@partners.org

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3. Introduction

Healthcare-associated infections are a significant source of morbidity and mortality among patients treated in U.S. healthcare institutions. One of the leading causes of nosocomial complications are bloodstream infections (BSIs) affecting between 87,500 and 350,000 patients annually with high attributable mortality and excess costs (1-6). Preliminary investigations have indicated that the use of chlorhexidine bathing in routine care of patients within the ICU might reduce the incidence of methicillin-resistant S. aureus (MRSA), vancomycin-resistant enterococci (VRE) and nosocomial bacteremias. This prospective multi-centered trial entitled “Multicenter evaluation of the effectiveness of source control with daily chlorhexidine skin preparation in reducing nosocomial infections including MRSA and VRE” is intended to determine the possible benefits of daily bathing with chlorhexidine. This intervention aimed primarily at MRSA and VRE also has the potential to reduce other healthcare-associated infections including bacteremias and by its nature is a simple intervention that could be adopted by diverse US healthcare facilities. The trial will be co-supported by an industry sponsor, SAGE Products inc., the current manufacturers of a FDA approved washcloth product impregnated with 2% chlorhexidine and the Centers for Disease Control and Prevention (CDC).

4. Background and Significance

Infections among patients admitted to the intensive care unit are a significant health care problem in all hospitals. It is estimated that up to 20% of patients admitted to intensive care units develop an infection during their stay (1). These infections lead to increased length of stays, increased morbidity and, most concerning, increased mortality. Many of these infections are felt to be preventable and this has spurred recent interest in developing new strategies aimed at reducing their incidence.

The majority of infections reported in the intensive care unit are due to urinary tract infections, ventilator associated pneumonia and bloodstream infections (2). The majority are related to the presence of invasive devices (urinary catheters, mechanical ventilation and central venous catheters). Mortality is highest for catheter associated bloodstream infections where the attributable mortality rate averages between 30-35% but can be as high as 69% (3, 4). Staphylococcus aureus is the second leading cause of bloodstream infections and the leading cause of ventilator associated pneumonia. The increased incidence of MRSA is due in part to the rising prevalence of methicillin resistance among all staphylococcal isolates in the ICU. The rising incidence of MRSA infections in the ICU is concerning due to high costs associated with their care and high mortality rates. It is estimated that nosocomially acquired MRSA bloodstream infections are associated with a crude mortality of 22% and lead to $6,916 in excess costs (5). In summary, infections due to Staphylococci including MRSA are the predominant nosocomially acquired complication in the intensive care unit.

Another common multi-resistant pathogen seen within the intensive care unit is vancomycin resistant enterococcus (VRE). Between 1989 and 1993, the percentage of nosocomial enterococcal infections that were due to VRE increased from 0.3 to 7.9% (6). The percentage has continued to rise. In 2003, VRE was the cause of 27.5% of enterococcal infections among ICU patients. An increasing trend towards non-ICU patients having serious infections has been noted and most concerning there is a growing number of patients who have been documented to be colonized with both VRE and MRSA (7,8,46).
The increasing incidence of MRSA and VRE colonization and infection among ICU patients has been attributed to many factors including increased admission of patients already colonized with these pathogens to the ICU, prolonged carriage, poor compliance with handwashing and barrier precautions, delayed identification of colonized patients, and understaffing. The rising prevalence of MRSA and VRE within US hospitals has prompted a contentious debate about the best approach to combat these serious healthcare associated pathogens. Strategies that have been utilized to limit the spread of MRSA and VRE within ICU’s have included stricter attention to barrier precautions following identification of MRSA colonized patients as well as improved handwashing. One prominent strategy that has emerged as recommended by recent SHEA guidelines (9) suggests that hospitals should adopt more aggressive active surveillance culturing to identify unrecognized MRSA and VRE patients at the time of admission and periodically during their hospital stay. Under this “search and isolate” strategy, proponents argue that once reservoirs of MRSA and VRE within the hospital are identified, nosocomial transmission can be effectively eliminated through the use of strict barrier precautions and hand hygiene for these previously unidentified patients.

Despite the recommendations for the adoption of more widespread active surveillance culturing by the SHEA guidelines, most hospitals have not embraced this approach. A recent survey from the IDSA Emerging Infections Network indicated that 86% of infectious disease consultants supported contact precautions to control MRSA, but less than 46% supported routine use of active surveillance cultures and less than 28% of hospitals employed MRSA surveillance cultures (10). Reasons for this lack of enthusiasm for active surveillance culturing could include its attendant costs, the need for additional resources to maintain an active program, and the required high level of compliance with contact precautions and hand hygiene among healthcare personnel to make strict barrier precautions an effective containment strategy.

The “search and isolate” strategy has additional flaws that could limit its overall effectiveness. First, to be effective, this strategy requires high levels of compliance with barrier precautions and handwashing to reduce horizontal transmission. As the literature has documented, both are difficult to achieve in real world settings. Second the “search and isolate” strategy does little to eradicate colonization. In our study of MRSA patients admitted to a combined MICU/CCU we found that 55% of identified MRSA colonized patients remained colonized for the duration of their ICU stay (11). As long as patients remain colonized, the opportunity for transmission exists. We also know that colonization with MRSA is not a benign condition but associated with a risk for the development of serious infections during and after ICU admissions. Huang et al. followed ICU patients identified with MRSA for 18 months and found that 29% of these patients subsequently developed MRSA infection (12). Additional reports have indicated that the risk of subsequent MRSA infection among colonized ICU patients is over 30% (13,14). Barrier precautions and proper handwashing do little to reduce this risk. These considerations would suggest that additional strategies may be needed to address prolonged skin carriage with MRSA and VRE as a strategy to reduce the risk for horizontal transmission as well as the potential to reduce subsequent infections among colonized patients.

Previous studies in the prevention of catheter associated blood stream infections have indicated that there are a number of modifiable risk factors for catheter-associated bloodstream infection (15). Most of these relate to proper sterile technique during the insertion and maintenance of central venous catheters (16). Proper site preparation with an effective skin disinfectant has been shown to be particularly important in reducing the incidence of subsequent catheter associated infections (17). It is now recognized that chlorhexidine is superior to other agents in site preparation. The use of chlorhexidine reduces residual skin organisms as well as inhibits their rebound growth and has been demonstrated to reduce CABSII in comparison to other skin.
disinfectant products such as povidone-iodine. CDC guidelines now recommend that the preferential use of chlorhexidine containing skin disinfectants be used for site preparation prior to insertion (17).

The same properties that make chlorhexidine an effective agent in the prevention of CABSI have been utilized in selective settings to reduce the incidence of MRSA within the ICU. Chlorhexidine is an effective skin disinfectant that has been used successfully to eradicate MRSA skin colonization (18-20). The reduction in skin colonization with MRSA (skin asepsis) is thought to lead to reduced risk for horizontal transmission of MRSA within the ICU environment. The use of chlorhexidine has been used successfully in the control of a number of MRSA outbreaks within the ICU setting and in the community (21,22).

The role of chlorhexidine in reducing nosocomial infections highlights the importance of skin asepsis in the intensive care environment. Although the selective use of chlorhexidine as it relates to catheter site preparation and in the selective treatment of MRSA colonized patients during outbreaks has received preliminary study, there is little study of the potential utility of more wide scale use of chlorhexidine in daily bathing routines within the ICU and hospital. With daily bathing with chlorhexidine, there is the potential to reduce a number of nosocomial infections, including CABSI by reducing bacterial burdens on the skin. Reductions in resident bacteria on the skin could lead to reduced horizontal transmission of multiresistant bacterial pathogens and better outcomes following central line insertions. Daily bathing to produce a state of skin asepsis as such is an attractive theoretical means to reduce nosocomial infections because it represents a simple intervention that could be applied universally with relatively little effort.

The goal of the currently proposed study is to determine if universal use of a chlorhexidine-based bathing system for unit patients will decrease skin bacterial burden and lead to decreased transmission to ward mates resulting in reductions in the incidence of MRSA and VRE. Secondarily, we hypothesize that reduced skin colonization with opportunistic bacterial pathogens will result in a reduction in the rate of catheter-associated bloodstream infections and overall bacteremias in comparison to regular bathing procedures.

5. Preliminary Studies

Chlorhexidine has long been recognized as an effective skin disinfectant. In use for over 30 years, chlorhexidine gluconate is used extensively as a surgical scrub, hand wash and skin cleanser. Chlorhexidine is rapidly active and has persistent activity for 2-5 days after application leading to excellent skin asepsis after use. Its use has been shown to lead to reduced infection after surgery when used as a perioperative skin preparation (23-25). The use of chlorhexidine in skin site preparation for central line insertion has been shown to lead to a two-fold reduction in the incidence of bloodstream infections in comparison to povidone-iodine (26,27). As such, chlorhexidine is recommended as one of the preferred agents for skin site preparation in the current CDC guidelines for catheter site care and use (17). Wider use of chlorhexidine in the prevention of nosocomial infections recently has included its incorporation into catheter material to prevent catheter associated bloodstream infections (28). Chlorhexidine has also been used during a number of nosocomial outbreaks of MRSA infections to provide skin asepsis and reduce horizontal transmission of MRSA between patients (21,22).

The use of chlorhexidine as a potential agent in the control of MRSA within the hospital environment has been an area of research at the McGuire VAMC during previous funding cycles for the CDC Prevention Epicenters. Preliminary work has examined the role of chlorhexidine in
reducing extra-nasal colonization with MRSA and the role of chlorhexidine at reducing MRSA transmission and infections within the intensive care unit.

Beginning in July of 2003, the effectiveness of chlorhexidine in reducing extranasal colonization with MRSA following a hospital wide adoption of chlorhexidine bathing for all identified MRSA patients was examined at the McGuire VAMC in Richmond, Virginia. Patients identified with MRSA were required to complete five days of daily bathing with chlorhexidine. Serial cultures were taken and the extent of MRSA colonization followed over time. Chlorhexidine was found to be a very effective agent in eradicating MRSA colonization. Table 1. presents the results of a cohort of patients that completed chlorhexidine bathing and had subsequent follow up cultures for up to three weeks.

Table 1. Effect of chlorhexidine bathing on extranasal MRSA colonization

<table>
<thead>
<tr>
<th>Site of MRSA Colonization</th>
<th>Patients with MRSA+ Initial Cultures</th>
<th>Patients with Follow up cultures</th>
<th>Patients with MRSA- follow up cultures</th>
<th>Percent cleared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extranasal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axilla</td>
<td>16 (17%)</td>
<td>10</td>
<td>8</td>
<td>80%</td>
</tr>
<tr>
<td>Perineum</td>
<td>35 (37.2%)</td>
<td>23</td>
<td>18</td>
<td>78.3%</td>
</tr>
<tr>
<td>Wound</td>
<td>5 (5.3%)</td>
<td>3</td>
<td>3</td>
<td>100%</td>
</tr>
</tbody>
</table>

Based on these preliminary results, a focused intervention to determine if the more wide scale use of chlorhexidine bathing could reduce the incidence of MRSA in high-risk patients in the Intensive Care Unit was undertaken. The study was a prospective evaluation of the selective use of mupirocin and chlorhexidine bathing for all patients identified with MRSA within a combined medical/coronary care unit. During a nine month baseline period, the baseline prevalence and incidence of MRSA was determined through an active surveillance program that included nasal cultures for MRSA on admission to the unit and continued surveillance of identified MRSA patients with surveillance cultures taken three times a week. No specific intervention other than the institution of contact precautions, barrier precautions and good hand hygiene for patients identified with MRSA was made during the baseline period. During the planned nine-month intervention period all patients identified with MRSA were prescribed mupirocin for intranasal application for four days and received daily bathing with chlorhexidine for five days. The study took place between January 2003 and August 2004. The results of the study are presented in Table 2.

Table 2. Effectiveness of selective chlorhexidine bathing on MRSA incidence in the ICU (McGuire VAMC 1/03- 8/04)

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Admissions</th>
<th>Admission Prevalence</th>
<th>Prevalence per 1000 ICU pt days (range)</th>
<th>Incidence per 1000 pt ICU days (range)</th>
<th>Incidence per 1000 days at risk (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>845</td>
<td>11.00 %</td>
<td>29.33 (15.67-56.91)</td>
<td>6.62 (2.92-17.85)</td>
<td>8.45 (3.38-20.98)</td>
</tr>
</tbody>
</table>
The study has several important findings. The overall incidence of MRSA decreased 48% during the intervention period with 21 new MRSA cases detected during the baseline period and only 11 new MRSA cases during the intervention period. (Table 2). This resulted in a statistically significant difference in the incidence density [new cases of MRSA per 1000 patient days at risk] of 8.45 vs 4.05, p=0.048. Second, the prevalence of MRSA at unit admission was slightly lower in the intervention period and this was directly attributable to chlorhexidine bathing and intranasal mupirocin that occurred both within the hospital and on former ICU patients (Figure 1). 20/31 (65%) patients admitted to the unit with a previous history of MRSA had received chlorhexidine bathing prior to their admission and had negative surveillance cultures at the time of admission. Third, during the baseline period the majority of patients identified with MRSA were colonized for the duration of their ICU stay (55%). During the intervention period the duration of colonization with MRSA was substantially reduced. There were no reported problems attributed to the use of chlorhexidine bathing during the intervention. MRSA isolates collected during the study underwent susceptibility testing to chlorhexidine. Over 200 isolates were tested and there was no documented resistance to chlorhexidine using a breakpoint for MIC90 of 4 \( \mu \text{g/ml} \). There was no evidence of acquired resistance to chlorhexidine or changes in MICs among serial isolates collected from patients.

In this study, the possible benefits of the addition of chlorhexidine bathing in an ICU with active surveillance culturing in place were studied. As such this study attempted to quantify the additional benefits of eradication of MRSA colonization in reducing MRSA incidence. The use of chlorhexidine bathing and mupirocin were a means to produce skin asepsis and eradicate a large reservoir of MRSA within the unit. The study examined the use of chlorhexidine in selected patients, as only patients identified with MRSA were the only patients who received chlorhexidine bathing. The study found this to be a very successful strategy resulting in a 48% decrease in the incidence of MRSA beyond that seen with active surveillance culturing alone. These results were striking as the study was not initiated as a result on any outbreak or
abnormally high rate of MRSA within the study unit, but as a planned prospective analysis prompted by a change in hospital policy.

These encouraging results led to a second pilot study. The second pilot study differed from the first in that all study ICU patients received chlorhexidine (universal bathing), not just the subset of patients identified as MRSA carriers by surveillance cultures. This study was a prospective, before-after, interventional design taking place within a combined medical/coronary care unit and surgical ICU that took place from January 20005 to December 2005. During a six-month baseline period, patients received bathing as usual. Baseline rates of MRSA prevalence and incidence were determined by ongoing surveillance that included admission cultures for MRSA, weekly prevalence culturing and clinical cultures. During the planned six-month intervention period, all patients admitted to the unit received daily bathing with chlorhexidine. Bathing was in the form of a basin bed bath. Approximately 4 ounces of 4% chlorhexidine solution was added to a basin filled with warm water. Patients were then bathed according to standard nursing protocols for bed baths with special care to avoid contact with mucous membranes and the eyes. The results of the study were striking. The overall incidence of MRSA decreased 45% in the two ICUs (Table 3). The decrease in incidence was seen with similar rates of prevalence during both periods indicating a true decrease in incidence not related to burden of colonization within the units. The overall incidence of nosocomial bacteremias decreased 25% from 8.8/1000 patient days to 6.6/1000 patient days.

Table 3. Effect of Daily Chlorhexidine Bathing among Patients Admitted to a combined CCU/MICU and SICU at the McGuire VAMC (1/05-12/05)

<table>
<thead>
<tr>
<th></th>
<th>Baseline Period (1/05-6/05)</th>
<th>Intervention Period (7/05-12/05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA cases (no of cases on admission)</td>
<td>55</td>
<td>39</td>
</tr>
<tr>
<td>MRSA Prevalence (per 1000 patient days)</td>
<td>13.48</td>
<td>11.31</td>
</tr>
<tr>
<td>Incident MRSA cases (n)</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Incidence Density (new cases per 1000 patient days)</td>
<td>8.27</td>
<td>4.57</td>
</tr>
<tr>
<td>Incident Bacteremias (n)</td>
<td>36</td>
<td>23</td>
</tr>
<tr>
<td>Bacteremia Incidence (new bacteremias per 1000 patient days)</td>
<td>8.8</td>
<td>6.6</td>
</tr>
</tbody>
</table>

In 2005, three additional CDC Prevention Epicenters (Washington University, Memorial Sloan Kettering, and Johns Hopkins) also completed pilot studies of the effect of universal bathing with chlorhexidine in the ICU and its effect on the incidence of MRSA, VRE and nosocomial bacteremias. These three studies had a similar design to the study completed at McGuire. All three studies were prospective, before-after, interventional designs. Each had a six-month baseline period followed by a six-month intervention where all admitted patients to the study units received chlorhexidine bathing daily. In addition to MRSA surveillance, surveillance for VRE was also completed in some units. Again this surveillance included admission cultures for VRE as well as ongoing surveillance while patients were admitted to the study units. The intent of these pilot studies was to determine the possible impact of daily chlorhexidine bathing on the incidence of MRSA, VRE and nosocomial bacteremias. These pilot studies were also designed to test the feasibility of a larger multi-center design and to independently confirm preliminary results seen at McGuire at other institutions.

The results of preliminary data analysis are encouraging. Memorial Sloan Kettering has demonstrated a 67% decrease in the incidence of MRSA and a 50% reduction in the incidence of VRE following the introduction of universal bathing with chlorhexidine (Table 3).
At Johns Hopkins University, the pilot study was completed in two separate ICUs. The overall incidence of VRE decreased 41% from 20.38 cases/1000 patient days to 12.06/1000 patient days. The overall incidence of incident bacteremias/fungemias decreased 44% from 2.74/1000 patient days to 1.53/1000 patient days (Table 4). More importantly, the reduction in bloodstream infections was noted among all organism types. Reductions were seen in the number of fungemias and bacteremias, including enterococci, gram positives, and gram negative organisms (Figure 2).

| Table 3. Effect of Daily Chlorhexidine Bathing among ICU Patients
| Memorial Sloan Kettering (1/05-12/05) |
|-------------------------------------|-------------------------------------|
|                                    | Baseline (1/05-6/05) | Intervention (7/05-12/05) |
| MRSA Admission Prevalence           | 6.08%                  | 7.10%                     |
| MRSA Incidence (n)                  | 15                     | 4                         |
| MRSA Incidence (cases per 100 patient days) | 5.73                  | 1.59 (p=0.024)            |
| VRE Admission Prevalence            | 17.63                  | 14.52                     |
| VRE Incidence (n)                   | 33                     | 17                        |
| VRE Incidence (cases per 1000 patient days) | 14.73                 | 7.42 (p=0.020)            |

In summary, several pilot studies completed within the CDC Prevention Epicenters between 2002 and 2006 indicate that universal bathing with chlorhexidine may be a very effective modality to reduce the incidence of MRSA, VRE and nosocomial bacteremias.

As encouraging as the data from the second pilot study may be, there are several methodological limitations. First, the study was not designed as a multicenter randomized control trial. Each participating center conducted the pilot study as a stand-alone project and while the same definitions and similar methodologies were used, they were not identical. As an example, all of the studies have studied the use of chlorhexidine used in basin baths. Typically a four percent solution of chorhexidine was added to a basin filled with water and patients were bathed by nursing personnel in bed. This method of basin baths is often inefficient; results in varied concentrations of chlorhexidine and cannot be completed on all patients, particularly
those with serious medical problems. As such compliance with bathing reported during pilot studies ranged from 70-95%. Secondly, the number of study patients from each institution is small, and even if the results from individual institutions can be combined, there may be insufficient numbers (sample size and power) to detect a statistically significant reduction in BSIs. These methodologic issues suggest the need for a larger multicenter trial and ideally, the use of a product that would allow for standardized concentrations of chlorhexidine.

In 2002, SAGE Products, Inc., developed a new product to be used for bathing patients. Sage, inc. is a large supplier of healthcare products to hospitals including the Comfort Bath® washcloth system (see Appendix). Many hospital systems use the Comfort Bath product that allows for simple bathing of patients without the need for soap, water or basins. The Comfort Bath washcloth system contains eight pre-moistened washcloths that are used to wipe and cleanse each area of the body. They are disposed of after use. The procedure requires no soap and water. In 2002 Sage developed a new washcloth impregnated with 2% chlorhexidine. These washcloths reduce the number of microorganisms on the skin and deliver residual antimicrobial activity for a prolonged period of time. In the first pilot trial of the effectiveness of the new chlorhexidine impregnated washcloth, Vernon et al examined 1787 patients admitted to a medical intensive care unit from October 2002 to December 2003 (29). They were able to document a reduction in the skin colonization with VRE for those cleansed with the new product as well as a 65% reduction in the incidence of VRE (26 per 1000 patient days to 9 per 1000 patient days). Additionally they noted reductions in the level of environmental contamination and the level of contamination of healthcare worker’s hands with VRE. This new product was well tolerated and resulted in higher compliance with daily bathing and also delivered standard concentrations of chlorhexidine. These data in combination with those previously generated in the CDC prevention Epicenters would indicate that this product would be an ideal candidate for further study of the effects of chlorhexidine bathing in a larger multicenter trial.

6. Research Design and Methods

6.1 **Hypothesis:**

A change in the regular bathing procedures to utilize products containing chlorhexidine will result in a reduction in the number of colonizing bacteria, including MRSA and VRE, on the skin of patients. Reduced colonization of the skin (skin asepsis) will lower the incidence of nosocomial transmission of bacteria in the ward and decrease incident cases of new bacteremias caused by these bacteria.

6.2 **Design:**

Prospective, cluster randomized, stratified, crossover trial of units. Units will serve as the as the units of randomization and as their own control. Units will be stratified by the presence of active surveillance culturing for MRSA and/or VRE at the time of study entry.

6.3 **Study Setting:**

The study will take place in two or more units per participating hospital. Approximately 14 units will be enrolled. Enrolled units will be predominantly intensive care units (ICUs) although additional units where active surveillance for MRSA and or VRE takes place will also be enrolled to include a Bone Marrow Transplant unit, a Burn unit and a Hematology Oncology ward. Study personnel will track blood culture data, patient-days, and MRSA and
VRE specific data per protocol. Units must have pre-existing active surveillance for MRSA and/or VRE in place at the time units undergo randomization in order to participate.

6.4 **Participating Hospitals:**

McGuire Veteran Affairs Medical Center (Coordinating Center)
Richmond, Virginia
   - Principal Investigator: Michael Climo
   - Co-Investigators: Edward Wong, Jane Cecil
Johns Hopkins University
Baltimore, Maryland
   - Co-investigator: Trish Perl
Memorial Sloan Kettering
New York, New York
   - Co-investigator: Kent Sepkowitz
Brigham and Women’s Hospital
Boston, Massachusetts
   - Co-investigator: Debbie Yokoe
University of Iowa
Iowa City, Iowa
   - Co-investigator: Loreen Herwaldt
Northwestern University
Chicago, Illinois
   - Co-investigator: Maureen Bolon
Washington University
St. Louis, Missouri
   - Co-investigator: Dave Warren

6.5 **Intervention:**

Selected units will be randomized to start with either Comfort Bath wash clothes or new chlorhexidine containing wash clothes. The unit of randomization will be a single unit. The units will utilize the randomized bathing procedure (Comfort Bath washcloths or washclothes impregnated with 2% chlorhexidine) for all patients admitted to the participating unit for a six month period of time and then switch to the alternative product for an additional six month period (figure 3). The periods that utilize the regular Comfort Bath wash clothes (control periods) will be compared to the periods in which the washcloths impregnated with chlorhexidine (Intervention period) are used for each ward. Patients will be bathed daily with data collection on the compliance with daily bathing. Many skin care moisturizers that contain anionic emulsifiers may adversely affect the residual antibacterial effect of chlorhexidine and should be avoided during routine care during periods in which chlorhexidine is in use. Skin care products that are known to be compatible with chlorhexidine include: Aquaphor® Original Formula Ointment, Lubriderm® Dry Skin Care Lotion, Eucerin® Original Lotion, Vaseline® 100% Pure Petroleum Jelly, PROVON® Moisturizing Lotion. Participating study units will be asked to utilize one of these products for skin care during the proposed study. Data collection during the study will include all positive blood cultures, patient days for study units as well as additional data on MRSA and/or VRE colonization and infection among admitted patients.
6.6 Outcome measures:

1. Overall rate of nosocomial BSI with significant bacterial pathogens during the control period in comparison to the rate during the use of chlorhexidine bathing.

   A. Specific rates will include:
      
      1) Number of MRSA bacteremias per 1000 patient days
      2) Number of VRE bacteremias per 1000 patient days
      3) Total number of bacteremias for all significant bacterial and fungal pathogens per 1000 patient days
      4) Number of bacteremias or fungemias for individual pathogens per 1000 patient days.

   B. Bacteremias will include only first significant bacteremia/fungemia for patients during each ICU or ward admission and will not include duplicate bacteremias during a single ICU or ward admission. Significant bacteremias will also only include bacteremias with organisms not considered to be skin contaminants (see organism key Appendix B for definition)

   C. Due to the large number of patients involved in this study and its prolonged nature we have elected not to collect line days for each unit. Active surveillance of this nature is time consuming and unlikely to add additional information to the study as we are studying an intervention intended to reduce the overall rate of BSI within the study units. As such the denominator for all calculations will be total patient days. This is a reasonable surrogate measure of line days in the intensive care unit as up to 87% of all ICU associated BSI are catheter associated (1). Bloodstream infections will be characterized as catheter associated or not catheter associated.

2. Overall rate of incident cases of MRSA/VRE colonization and infection (incidence density) in the baseline period in comparison to the rate during the use of chlorhexidine bathing. Specific calculated rates will include:
A. Number of new MRSA/VRE positive patients per total number of patients. Monthly range and variance.

B. Number of new MRSA/VRE positive patients per 1,000 patient days. Monthly range and variance.

C. Number of new MRSA/VRE positive patients per 1,000 eligible patient days. Monthly range and variance. Eligible patient days are those days susceptible patients were at risk for acquisition of MRSA or VRE [Total patient days – total patient days for patients identified with MRSA or VRE] This denominator reflects the true incidence of colonization or infection.

6.7 Data collection:

6.71 Patient Specific Information:

Each patient admitted to the study unit during the study periods will be recorded and assigned a specific study number. The dates of admission, dates of discharge, study unit will be recorded and used to calculate length of stay and to determine the incidence of nosocomial infections based on microbiological data. Data entry will be entered into a password protected Access database. The Access database was developed during previous pilot work within the CDC prevention Epicenters (2003-2006) and has been used extensively by four centers (Johns Hopkins, McGuire, Memorial Sloan Kettering and Washington University) during their single institution evaluation of the effectiveness of chlorhexidine bathing. (see Appendix A). As with previous work completed within the CDC Epicenters, patient identifiers (in this case patient names and medical record number) will be removed from the database prior to submission to the coordinating center (McGuire). This data and research will not be used or disclosed to any persons or entity outside of the study institutions. All data collection files will be password protected and stored on computers belonging to study investigators. Personal health information will be maintained with the database during the collection of unit census data, microbiology data, and medical record review. All patients will be assigned a study identification number that is unique to each institution. Each participating institution will maintain a password protected code key file at their institution that will link study identifiers to patient identifiers. This code key will be accessible only to study investigators and study staff. Any hard copies of datasets will be stored in a locked filing cabinet. After all data are collected, analyzed, and published, linkage between patients and their unique identifier will be destroyed, with the exception of data collected through Infection Control Departments as part of hospital operations. Identified datasets related to infection control activities will be maintained at the primary institution according to hospital operations policy.

6.72 MRSA Screening:

Microbiological data on all MRSA surveillance performed within the study unit will be recorded for those units who have active surveillance in place. Active surveillance will be defined as cultures for MRSA within 48 hours of admission and at least once weekly while admitted to the unit or at time of discharge. Data entry will be entered into a password protected Access database. An incident case will be defined as any patient with a positive active surveillance or clinical culture > 48 hours after ICU
admission in patients with either previous negative surveillance and clinical cultures or no previous history of MRSA. Prevalent cases will be defined as any patient with positive active surveillance cultures or clinical cultures collected within 48 hours of admission. Weekly reports on compliance with admission surveillance cultures for all admitted patients will be monitored and reported during weekly teleconferences.

6.73 VRE Screening:

Microbiological data on all VRE surveillance performed within the study unit will be recorded for those units who have active surveillance in place. Active surveillance will be defined as cultures for VRE within 48 hours of admission and at least once weekly while admitted to the unit or at time of discharge. Data entry will be entered into a password protected Access database. Incident and prevalent cases will follow the same definitions as above for MRSA patients. Weekly reports on compliance with admission surveillance cultures for all admitted patients will be monitored and reported during weekly teleconferences.

6.74 Clinical Culture Data:

Microbiological data on all clinical cultures positive for MRSA or VRE will be entered into the Access database. These data will be compiled with surveillance data in order to determine prevalence and incidence rates for MRSA and VRE.

6.75 Blood culture data:

Data on all positive blood cultures will be collected for significant bacterial/fungal pathogens if they occurred >48 hours after unit admission and within 48 hours of discharge from the study unit. This will include all organisms with the exception of common skin contaminants and all coagulase negative staphylococci (see organism key Appendix B). Data collected will be entered into a password protected Access database. Incident bacteremias (or fungemias) will include only the first significant bacteremia with a significant bacterial or fungal organism during the unit admission and will not include duplicate organisms or subsequent infections, as the primary aim of the study is to prevent incident cases.

6.76 Mupirocin Use:

Each Study patient will have information about the concurrent use of mupirocin use during the admission recorded. This information is being collected to determine if concurrent mupirocin use affects the clearance of MRSA from the study population. Use of any mupirocin during the admission will be recorded in the Access Database.

6.77 Compliance Monitoring:

Confirmation of compliance with daily bathing will be collected by individual centers on a weekly basis during both the baseline and intervention periods. Compliance monitoring will consist of monitoring the use of Comfort Bath washcloth packages and new washcloth packages impregnated with 2% chlorhexidine during the week and ensuring that adequate supplies exist. The total quantity of washcloth packages used during the week will be entered into a compliance monitoring worksheet. For the purposes of this study, use of one washcloth package will be considered receipt of
one patient bath. Oversight of the trial will not include direct observation of bathing. Previous work completed during pilot studies has indicated that the overwhelming majority of bathing occurs during the evening and late night shifts making it nearly impossible for research personnel to perform direct observation. Since the Comfort Bath washcloth package is designed to complete one patient bath it is reasonable to assume that use of one product will represent receipt of one bath. At the time of data analysis, the use of Comfort Bath washcloth packages and washcloth packages impregnated with 2% chlorhexidine will be compared to the number of patients in the study unit to determine the approximate compliance with bathing.

6.78 Data Collection Forms

All data will be entered at the participating site into an Access Database (see Appendix A). Data will include basic demographic information on study patients as well as all culture information to include MRSA screening, VRE screening and blood culture data. The database will be password protected at the site. Definitions for all database fields are contained within Appendix C. Prior to submission to the coordinating center (McGuire), patient identifiers (name and medical record number) will be removed from the database.

6.8 Trial Oversight:

All principal investigators will serve on the steering committee for oversight of the trial. All investigators have participated previously in weekly teleconferences to develop, implement, and analyze multicenter projects during previous CDC Prevention Epicenter Funding (1999-2006). Oversight of this trial will follow a similar design with weekly teleconferences of the steering committee. At that time there will be weekly discussions of the progress report, reporting of compliance with active surveillance, reporting of compliance with bathing, and any adverse reactions or other weekly problems.

6.9 Statistical Analysis:

The effect of daily bathing with chlorhexidine impregnated washcloths on incidence density of BSI, MRSA, and VRE incidence will be modeled by means of Generalized Estimating Equations (GEEs) under the Poisson distribution family. Since each unit is observed twice under the study’s crossover design (once under the experimental and once under the control condition) and the targeted outcome is in the form of counts (here new cases or infections related to patient days of exposure), the GEE methodology is needed to model the count outcomes while accounting for the natural clustering effects induced by repeated observation of units.

Our study design requires three separate analyses based upon the type of surveillance (MRSA only, VRE only, or both) employed by the units. The analysis of BSI rates will use data from all units and will incorporate a three level fixed effect designating surveillance type. The analyses of MRSA and VRE rates, respectively, will be based on only those units engaging in the corresponding type of surveillance. In the latter analyses, a two level fixed effect for surveillance type will be incorporated (MRSA only versus both - or VRE only versus both).

The fundamental model in these analyses will specify treatment, order of presentation, and type of surveillance fixed main effects. Offsets in each model will be unit specific total
patient days during the exposure periods. Even though the study design targets minimizing
order and type of surveillance effects and neither are expected to be present in any
magnitude, their possible effects will incorporated for control purposes. If either proves to
be significant, their interactive effects with treatment will also be examined. Such
interactive effects are likewise not expected to be present.

All significance tests in these analyses will be conducted given two-tailed alpha of .05. In
addition, 95% confidence intervals estimating treatment and control rates as well as their
ratio will be constructed. It should be noted that in this study, there can be no missing data
and consequently no missing data issues. Analyses are planned to be conducted using the
SAS System for Windows Genmod procedure (Version 9.1.3 or later).

6.10 Power considerations:

For power estimation, we have conservatively assumed that 12 units (4 units with both
MRSA and VRE surveillance and 4 each using only one of the surveillance types) will be
randomized under the study design. Based upon our prior experience with admission rate,
length of stay and observed infection rates in such units, we anticipate an average
incidence density rate (new cases of MRSA per 1000 patient days) of 8 per 1000 patient
days for MRSA, an average incidence density of 15 per 1000 days for VRE, and an
average incidence of 8 1000 patient days for new nosocomial BSIs a during each unit’s
control exposure.

The following table shows power estimates corresponding to the test of treatment effect
assuming six-month exposures. Power estimations are based on 1000 iterations of data
randomly drawn from Poison distributions and analyzed via GEE for the treatment effect
assessed. Each cell in the table represents the power estimate for a specified combination
of control rate and reduction rate due to treatment:

<table>
<thead>
<tr>
<th>Control Rate/1000 Patient Days:</th>
<th>BSI 7</th>
<th>BSI 8</th>
<th>BSI 9</th>
<th>MRSA 7</th>
<th>MRSA 8</th>
<th>MRSA 9</th>
<th>VRE 14</th>
<th>VRE 15</th>
<th>VRE 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction:</td>
<td>30%</td>
<td>98%</td>
<td>99%</td>
<td>94%</td>
<td>98%</td>
<td>98%</td>
<td>99%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>25%</td>
<td>94%</td>
<td>98%</td>
<td>99%</td>
<td>86%</td>
<td>88%</td>
<td>92%</td>
<td>98%</td>
<td>98%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Based upon prior research, we expect rate reductions to exceed 30%. As the table shows,
the study should have at least 95% power to detect 30% or greater rate reductions and
85% or greater power to detect reductions as small as 25% in all three measured rate
analyses. Hence, the study will be more than adequately powered. In fact, based on the
number of enrolled units we estimate that we would be powered to detect a 30% reduction
in MRSA, VRE and nosocomial bacteremias with incidence rates as low as 3.5/100 patient
days, 4.5/100 patient days and 3.5/1000 patient days respectively during the control period.

6.11 Economic Analysis

In addition to understanding the effectiveness of the chlorhexidine impregnated washcloths
it is important to estimate the cost-effectiveness of the interventions. We hypothesize that
regular bathing utilizing products containing chlorhexidine will result in a reduction in the number of colonizing bacteria including MRSA and VRE on the skin of patients. The reduced colonization of the skin will lower the incidence of nosocomial transmission of bacteria in the ward and decrease incident cases of new bacteremias caused by these bacteria. Thus, the use of chlorhexidine impregnated washcloths may reduce the incidence of high cost MRSA and VRE infections in patients in intensive care units. Therefore it is important to examine the cost-effectiveness of the use of chlorhexidine impregnated washcloths.

There are three potential scenarios that could exist with the use of the chlorhexidine impregnated washcloths, of which one is unlikely based on pilot data. First, the washcloths could reduce the rate of nosocomial infections enough to offset the increased costs associated with the use of the chlorhexidine impregnated washcloths in which case the new intervention would be considered cost-savings. The second scenario is that the washcloths will decrease the rate of nosocomial infections but increase the total costs of care where it is then important to determine the cost-effectiveness (value) of the washcloths. The final scenario, which again is less likely based on the pilot data, would be where the washcloths are less effective than current bathing practices and more costly where the chlorhexidine impregnated washcloths would be dominated by the current bathing practices. A final scenario that is a possibility in cost-effectiveness analyses is where the chlorhexidine impregnated washcloths would be less effective and be associated with lower costs. This scenario occurs infrequently when the new technology, chlorhexidine impregnated washcloths in this case, cost more than the previous standard of care.

To evaluate the cost-effectiveness of the chlorhexidine impregnated washcloths we will undertake two specific tasks:

1. Compare the costs in the intervention and control arms of the trial; and

2. Evaluate the cost-effectiveness of chlorhexidine impregnated washcloths compared to standard bathing practices by adapting a previously published model.

For the first task we will compare the hospitalization costs between the two arms of the study. For each of the study arms, we will determine the length of stay for each hospitalization, the rate of colonization and the rate of nosocomial infections. We will estimate the total cost of hospitalization for each individual included in the study. Because it is impractical to obtain billing data for each of the patients included in all of the institutions for the study we will estimate the hospitalization costs for individuals included in the trial. Using estimates reported in the literature or national averages may make the results more generalizable than relying on billing data from the eight institutions involved in the study. For the control arm, hospitalization costs will be a function of the length of stay, the average per diem cost for a hospitalization and the per diem costs associated with a nosocomial infection.

\[
\text{Total costs}_{\text{control}} = (\text{LOS}_{\text{no infection}} \times \text{per diem cost}_{\text{no infection}}) + (\text{LOS}_{\text{infection}} \times \text{per diem cost}_{\text{infection}})
\]

For the treatment arm, the hospitalization costs will be similar to that of the controls with the incremental costs associated with chlorhexidine impregnated washcloths included in the equation.
Total costs_{treatment} = (\text{LOS}_{\text{no infection}} \times \text{per diem cost}_{\text{no infection}}) + (\text{LOS}_{\text{infection}} \times \text{per diem cost}_{\text{infection}}) + ((\text{Cost chlorhexidine washcloths} - \text{cost Comfort Bath washcloths}) \times \text{number of washcloths})

The per diem costs for infections will be estimated using the same procedure we have used in previous work (30). For example, for VRE infections the per diem cost will be estimated by combining total VRE cost estimates from Stosor and colleagues (31) ($83,897 – $56,707 = $27,190) with the length of stay data for VRE infections from Monteclavo et al. (32) (26.3 – 12.6 = 13.7 days) and adjusting to current year dollars ($27190/13.7 = $1984 per day \[1995\] \times \text{Medical care component of CPI = cost in current year dollars}). Similar methods will be used to estimate MRSA and other nosocomial infection costs based on previously published cost estimates (5).

The difference in total hospital costs will be compared between the groups. Because cost data typically does not conform to the necessary assumptions of normality when comparing means, the costs will be compared using non-parametric bootstrap techniques (33,34). The bootstrap methods, as described by Barber and Thompson (33) and Desgangné (34) allow for the estimation of differences in costs and the calculation of confidence intervals for the difference. The non-parametric approach makes no underlying assumptions about the distribution of the data and yet compares the arithmetic means and differences in arithmetic means.

The bootstrap comparison will be done by sampling, with replacement, the costs from each of the groups until the original sample size in each arm is reached and calculating an average cost for each of these replicates. The difference in average costs will then be calculated between groups. This process will be repeated 1000 times to compare the average difference in hospitalization costs between control and intervention patients and the confidence interval surrounding the difference.

The second task will involve comparing the cost-effectiveness of the intervention with the control in terms of cost per life year saved. To complete this task, we will modify a previously published model in which we evaluated the cost-effectiveness of screening programs for VRE (30). The figures below show the structure of the model that will be easily adaptable to the comparison of the interventions rather than a screening program. To adapt the model, the two primary branches of the tree will be similar to the structure in the “No screen” branch in Figure 4 below. Both the intervention and control arms will have the same structure and the probabilities associated with the branches will come directly from the clinical trial. That is, the rate of colonization and infection for each arm of the decision tree will be based on the overall results from the clinical trial. The costs associated with each arm of the decision tree will be based on the hospitalization costs that were estimated above.

In addition to the decision-tree portion of the model there is also a Markov component of the model that accounts for the benefit of reducing colonization and infections within a unit (figure 5). This benefit is seen by reduced risk of nosocomial infections to patients in the unit that are not currently colonized. The Markov process will be adapted to not only include the rate of transmission of VRE but of other nosocomial infections.

The incremental cost-effectiveness ratio (ICER) will be calculated comparing the incremental costs and benefits associated with the intervention compared to the control. The formula for the ICER is:
ICER = \( \frac{\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{control}}}{\text{Outcome}_{\text{intervention}} - \text{Outcome}_{\text{control}}} \)

The outcome that will be used in the cost-effectiveness analysis is life years. The base case will be the mortality rate observed in each arm of the study to determine the life years saved attributable to the intervention. However, because we may not have sufficient power to compare mortality in the study, we will also use the estimated risk of mortality associated with nosocomial infections in a sensitivity analysis. All analyses will be conducted from the perspective of the hospital. Additionally, we will conduct a fully probabilistic analysis on the decision model. Patients will move through the decision model based on the probability values at each of the nodes on the model. We compared the surveillance strategies with a probabilistic analysis of the analytic decision model, which involves assigning a distribution to the probability values at certain nodes of the model rather than a single value (35-37). The probability for the value is then chosen randomly from this distribution through Monte Carlo simulation. Using a probabilistic decision model incorporates uncertainty associated with the parameter estimates rather than relying on a single value to represent the estimate.

Results will be reported as cost per life year saved associated with the intervention compared to the controls. We will compute 95% confidence intervals for the incremental cost-effectiveness ratio, plot the results on cost-effectiveness planes and produce cost-effectiveness acceptability curves. In addition to the fully probabilistic analysis we will also conduct several sensitivity analyses. We will conduct one-way analyses on all variables included in the model. From the one-way analyses we will produce a funnel plot of the most influential parameters. We will also conduct two-way and multi-way sensitivity analyses on parameters that are thought to be correlated and co-vary with each other.
Figure 4. Decision tree

Figure 5. Markov process of the model

6.12 Chlorhexidine Resistance
Resistance to chlorhexidine is rare among both staphylococci and enterococci with reported MIC's to chlorhexidine for staphylococci of 0.2 –3 μg/ml [0.00002-0.0003%] and for enterococci of 1-6 μg/ml [0.0004-0.0006%] (38-41). Previous studies have also indicated that following serial passage of both staphylococci and enterococci in the presence of chlorhexidine there are only minimal changes in MIC values and no evidence of reported high-level resistance (38). Plasmid mediated resistance to antiseptics and disinfectants among staphylococci is well known. Most prevalent is the presence of the qacAB and qacCD gene families that encode proton dependent export proteins that confer resistance to a wide variety of disinfectants. Most prevalent among staphylococci is the qacA determinant found on the pSK1 family of conjugative plasmids that also typically encode resistance to a number of antimicrobials including ß-lactamase (42). The presence of qacA results in substantial increases in MIC's to quaternary ammonium compounds (QAC's) but only a 2.5 fold increase in MIC's to chlorhexidine (0.8 μg/ml to 2 μg/ml), corresponding to concentrations well below those seen in commercial preparations of chlorhexidine (38). Plasmid mediated resistance to chlorhexidine has not been described among enterococci. High level resistance to chlorhexidine among gram-negative bacterial organisms particularly Pseudomonas and Serratia has been reported (43-45). However many gram-negative organisms, fungal, and mycobacterial organisms remain susceptible to chlorhexidine.

With such widespread use of chlorhexidine that is anticipated during this proposed trial, we will test isolates for chlorhexidine resistance. Each participating center will ship isolates of staphylococci and enterococci collected within the study units to the coordinating center (McGuire VAMC). We will adopt a sampling strategy for testing given the large number of units and patients involved in the study. Each participating center will collect the first ten bacterial isolates (five MRSA and five VRE) from patients treated in the study during the calendar month and each month thereafter. Culture specimens will be labeled with a unique Study number identifier corresponding to the identifier in the database form and as such will contain no unique identifiers contained within the 18 HIPAA identifiers. Over the twelve month duration of the study, we will collect 1,920 isolates of MRSA and VRE for testing. All isolates will be tested for susceptibility to chlorhexidine. MIC’s for chlorhexidine will be determined by an agar dilution method on Mueller-Hinton agar containing chlorhexidine diacetate (Sigma-Aldrich Inc., St. Louis, MO) in concentrations ranging from 1 to 16 μg/ml (corresponding to 0.0001% to 0.0016%). Although no standard definition exists for resistance to chlorhexidine, previous studies have indicated that most isolates of MRSA and VRE have MIC's <8 μg/ml (0.0008%). For the purposes of this study, isolates with MIC>16 μg/ml will be considered resistant. Susceptibility to chlorhexidine will be compared between periods where chlorhexidine impregnated washcloths were in use to determine if acquired resistance to chlorhexidine developed following its wide-scale introduction. Although the primary goal of this testing is to determine any level of resistance to chlorhexidine among clinical isolates of MRSA and VRE, this effort will represent the largest survey of clinical isolates of MRSA and VRE for susceptibility to chlorhexidine completed to date.

7. Human Subjects Research Considerations

7.1 Human Subjects Involvement and Characteristics

This is a cluster-randomized trial with an intervention that is based at the unit level. The “intervention” is examining two accepted bathing methods and the possible differences in the development of nosocomial infections based on the use of these products. Because
both SAGE washcloth products are FDA approved products, we will be seeking a waiver of
documentation of informed consent. All patients admitted to the units enrolled in this study
will undergo bathing with two different bathing products (Comfort Bath Wash clothes or
Wash clothes impregnated with 2% chlorhexidine) according to a randomization schedule.
Both bathing products are FDA approved. The 2% chlorhexidine gluconate cloth is FDA
approved as a patient perioperative skin preparation and for use to reduce bacteria that can
potentially cause skin infection. It is for this latter use that this study will use the product.
Comfort Bath Wash clothes are used extensively as a basin-less form of patient bathing.
The study will determine potential differences between the use of the two products and the
incidence of MRSA, VRE and nosocomial bacteremias. The proposed units are
predominantly Intensive Care Units, Bone Marrow Transplant units and Hematology-
Oncology wards. This indicates that the targeted patient population will be varied and will
include a number of critically ill patients. Intensive care units that will participate will include
surgical intensive care units, medical intensive care units and cardiology intensive care
units. Patients in these units typically have a variety of medical conditions including post-
surgical problems, myocardial infarctions, coronary artery disease and a number of
infectious and complex medical care requiring intensive unit care. The expected age range
of human subjects will be from 18-90 years of age as we will only be including units that
serve adult populations. Both men and women will be included in the research. The
proposed research will take place in six additional hospitals that include: Johns Hopkins
University, Brigham and Women's Hospital, Northwestern University, Washington
University, Iowa University and Memorial Sloan Kettering.

7.2 Sources of Materials

Each patient admitted to study units during the study periods will be recorded and assigned
a specific study number. The dates of admission, dates of discharge, study unit will be
recorded and used to calculate length of stay and to determine the incidence of nosocomial
infections based on microbiological data. Additional data that will be collected include birth
decade, gender, and all microbiologic data for positive surveillance or clinical cultures for
MRSA or VRE. All positive blood cultures will also be recorded. Data entry will be entered
into a password protected Access database. The Access database was developed during
previous pilot work within the CDC prevention Epicenters (2003-2006) and has been used
extensively by four centers (Johns Hopkins, McGuire, Memorial Sloan Kettering and
Washington University) during their single institution evaluation of the effectiveness of
chlorhexidine bathing. (see Appendix A). As with previous work completed within the CDC
Epicenters, patient identifiers (in this case patient names and medical record number) will
be removed from the database prior to submission to the coordinating center (McGuire).
This data and research will not be used or disclosed to any persons or entity outside of the
study institutions. All data collection files will be password protected and stored on
computers belonging to study investigators. Personal health information will be maintained
with the database during the collection of unit census data, microbiology data, and medical
record review. All patients will be assigned a study identification number that is unique to
each institution. Each participating institution will maintain a password protected code key
file at their institution that will link study identifiers to patient identifiers. This code key will
be accessible only to study investigators and study staff. Any hard copies of datasets will
be stored in a locked filing cabinet. After all data are collected, analyzed, and published,
linkage between patients and their unique identifier will be destroyed, with the exception of
data collected through Infection Control Departments as part of hospital operations.
Identified datasets related to infection control activities will be maintained at the primary
institution according to hospital operations policy.
7.3 Waiver of Documentation of Written Informed Consent

This study will involve all adult patients admitted to the proposed study units. As such there is no recruitment strategy. It is intended to encompass all patients within the participating units. This study will be seeking waiver of documentation of written informed consent in accordance with 21 CFR 56.109(c):

“An IRB shall require documentation of informed consent in accordance with Sec. 50.27 of this chapter, except as follows: (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or (2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an exception from informed consent for emergency research are met.”

1. The intended research presents no more than minimal risk to the patients. The intent is to study the potential differences between two accepted bathing products for patients and to determine if there is the potential to reduce nosocomial infections. Both products are FDA approved products and as such pose minimal risk to those patients involved. Bathing with chlorhexidine is an accepted procedure within the hospital and is often applied to selected patient populations within the hospital including pre-operative patients.

2. The activities within the proposal do not normally require informed consent. Bathing is an accepted practice within the hospital and does not require written informed consent. Surveillance cultures are normally done in the course of many hospital surveillance activities and the standard of care is to require only verbal permission prior to collection.

In accordance with 45 CFR 56.109(d), subjects in the trial will be given a written statement about the nature of the study.

“(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research. “

An example of the patient information sheet is included in Appendix I.

7.4 Waiver of HIPAA Authorization

This clinical research study will be seeking waiver of written HIPAA authorization based on the following:

1. Use or disclosure of protected health information involves no more than minimal risk to the privacy of individuals. We will keep all data in a secure Access database that is password protected and accessible only to dedicated research personnel. Data entry for individual patients will be coded and not include patient’s full name or complete social security number. All patients will be assigned a study identification number that is unique to each institution. As with previous work completed within the CDC Epicenters, patient identifiers (in this case patient names and medical record number) will be removed from the database prior to submission to the coordinating center (McGuire). Following this de-
identification, the only protected health information contained within the database that will be forwarded to the coordinating center (McGuire) are the dates of admission and discharge dates from the study units. None of the other protected health information identifiers are contained within the database. Personal health information will be maintained with the database during the collection of unit census data, microbiology data, and medical record review. Each participating institution will maintain a password protected code key file at their institution that will link study identifiers to patient identifiers. This code key will be accessible only to study investigators and study staff. Any hard copies of datasets will be stored in a locked filing cabinet. All data collection files will be password protected and stored on computers belonging to study investigators. After all data are collected, analyzed, and published, linkage between patients and their unique identifier will be destroyed, with the exception of data collected through Infection Control Departments as part of hospital operations. Identified datasets related to infection control activities will be maintained at the primary institution according to hospital operations policy. During the course of the study, information collected will not be disclosed to anyone other than the study personnel. This data and research will not be used or disclosed to any persons or entity outside of the study institutions.

2. *The research cannot practicably be conducted without the waiver.* Given the large number of subjects, the research cannot be completed easily without the waiver. Since the experimental design of the study is intending to study the effect of universal bathing on an intensive care unit, the inability to obtain patient specific data from even a small number of patients would adversely effect our ability to draw conclusions about the effect of bathing. Patients who do not receive the proposed intervention (chlorhexidine bathing) could serve as reservoirs of microorganisms that could impact transmission.

3. *The research could not practicably be conducted without access to and use of the protected health information.* Accurate determination of lengths of stays and total patient days for all involved study participants will require access to dates of admission and discharge (protected health information). Without this information the research can not be practically conducted.

7.5 Protection Against Risk.

The study site Principal Investigator is responsible for the preparation and submission of all documents and periodic reports required by the local IRB. All protocol amendments affecting the safety and welfare of study participants must be approved by the IRBs prior to implementation. All investigators and participating sites will be in full compliance with human subjects and HIPAA requirements. This study protocol will be submitted to the Centers for Disease Control for IRB approval and the CDC may defer to local center's IRB for human subject research protection oversight. The sponsoring institution and participating institutions promise that the study will be conducted to good clinical practice guidelines, applicable laws and regulations, and will report to investigators and regulatory authorities significant findings that could affect the safety and well being of research subjects. All study investigators and staff have been trained in human subjects research and HIPAA regulations.

Monitoring of any unexpected adverse effects or serious adverse events related to study procedures will be the responsibility of local investigators and are to be reported immediately to the steering committee as well as appropriate IRB. All unexpected adverse events and serious events are to be reported and sent to the steering committee at the
coordinating center (McGuire) within five working days on the adverse event form (see Appendix H.)

For the purposes of this research protocol unexpected adverse events and serious adverse events will be defined as follows:

**Unexpected adverse event**: Any adverse reaction or experience that is not listed in the current labeling for the drug product or investigators brochure. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. Known adverse reactions to chlorhexidene containing topical products include irritation, sensitization, and generalized allergic reactions especially in the genital area. Chlorhexidine should be kept out of the ears and eyes. "Unexpected," as used in this definition, refers to an adverse experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

**Serious adverse drug event.** Any adverse reaction or experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 7.6 Potential Risks

This clinical research involves minimal risk to the patients involved since it involves only the use of two FDA approved products. Chlorhexidine has been widely used as a topical agent for skin disinfection in concentrations ranging from 0.5% to 4%. It is used extensively for skin disinfection, handwashing, oral care, irrigation of surgical wounds, the urinary bladder or vagina, topical treatment of burn wounds, and treatment of peritonitis in peritoneal dialysis (47). Daily bathing with chlorhexidine has been used within the hospital environment as a means to disinfect the skin and decrease the transmission of nosocomial pathogens including MRSA and VRE (18-25, 29). Sage 2% Chlorhexidine Gluconate Cloths has been shown to reduce bacteria that can potentially cause skin infection. In addition, 2% Chlorhexidine Gluconate Cloths have been used as a daily bathing cloth in several studies and shown to be well tolerated. In the VRE transmission study (Vernon et al.), 394 patients received daily bathing with the 2% Chlorhexidine Gluconate Cloth with a lower reported rate of skin irritation in comparison to patients who received soap and water bathing (29). In the Skin Cleansing with Chlorhexidine Study (Protocol 05-006), 343 patients have undergone daily bathing with the 2% chlorhexidine cloth with no reported adverse events attributable to chlorhexidine bathing (see Investigators Brochure). No Serious Adverse events have been reported to date in any clinical trial involving 2% Chlorhexidine Gluconate Cloths. Despite the overall low rate of expected adverse events, several restrictions will be place for the use of the 2% Chlorhexidine Cloth. The 2% Chlorhexidine cloth will not be used in the following situations:
1) on patients with known allergies to chlorhexidine gluconate or any other ingredients in the product
2) on burn patients with a high percentage of disrupted body surface area.
3) for lumbar punctures or in contact with the meninges, or
4) on open skin wounds; and
5) the product should be kept out of the eyes, ears, and mouth

Potential recognized risks of bathing with chlorhexidine include local skin irritation, sensitization, allergic reaction and irritation of mucous membranes. Chlorhexidine is not to be used in children. This research only involves adult patients aged 18 years or older.

7.7 Potential Benefits Of The Proposed Research To The Subjects And Others

The intent of this study is to demonstrate that the routine use of chlorhexidine in bathing practices will lead to reduced skin colonization with resistant bacteria including MRSA and VRE. This reduction can lead to significant declines in the incidence of MRSA and VRE and nosocomial bacteremias. Such reductions could have profound effects on associated health care costs and mortality. Since the intervention that is proposed is of minimal risk to the involved patients the potential benefits far outweigh any potential risk to individual patients.

7.8 Importance Of The Knowledge To Be Gained

MRSA and VRE are serious nosocomial pathogens associated with high morbidity and mortality for involved patients. In addition, nosocomial bacteremias are the leading cause of death among intensive care unit patients. Novel interventions that reduce these complications would greatly benefit large populations within our healthcare systems. If changes in bathing practices prove to be effective in reducing these complications, this would represent a simple intervention that could be applied broadly to all hospitals.

7.9 Inclusion of Women and Minorities

The proposed clinical research will involve all adult patients admitted to participating units. There will be no exclusion of any gender, racial or ethnic minority. Racial or ethnic origin of patients in previous pilot studies completed to date was not accurately determined (this information was not collected). This does not compromise the scientific objectives of the research, since the proposed intervention it is to be applied universally and race, ethnic origin and gender have no bearing on the intended effect. Although exact demographics for the targeted study populations are not readily available, we have estimated the distribution of gender and racial and ethnic groups to be enrolled based on prior studies done in the ICU environment.

7.10 Inclusion of Children

This clinical research will involve the enrollment of children. However it will only involve children from the age of 18-20 and as dictated by local policies for admission to the participating units. All of the proposed study units currently only admit adult patients. For most of the participating units this includes patients ≥18 years of age. Since the definition of children for the purpose of this application include any patient < 21 years of age, we will be enrolling children.
8. Literature Cited.


Appendix A. Example of Access Database Data Entry Form
Appendix B. Classification of Bloodstream Infections
Appendix C. Definitions of all Entry fields in Access Database
Appendix D. Sage Comfort Bath™ Product Brochure
Appendix E. Sage, Inc. Chlorhexidine Impregnated Washcloth Product Brochure
Appendix F. MSDS – Sage Comfort Bath™
Appendix G. MSDS – SAGE 2% Chlorhexidine Gluconate Cloth
Appendix H. Unexpected Adverse Event Reporting Form
Appendix I. Example of patient Information Sheet
Appendix A. Example of Access Database Data Entry Forms

[Image of a database interface titled "MRSA and VRE Epidemiology" with fields for study ID, MRN, gender, age at first unit admit, etc., and data entry for unit name, unit admit date, cultures prior to unit admit, and cultures during unit admit.]
Enter ALL POSITIVE MRSA/VRE microbiologic tests within the study period spanning from the date of this unit admission through 2 days beyond this unit discharge [surveillance and clinical tests]

Enter ALL NEGATIVE surveillance tests sent for MRSA/VRE in the same period as above
### Appendix B. List of Microbiologic Classification of Blood Stream Infections

<table>
<thead>
<tr>
<th></th>
<th>NO GROWTH/NEGATIVE</th>
<th>37. Corynebacterium jeikeium</th>
<th>74. Other (not listed elsewhere)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acrobacter species</td>
<td>38. Corynebacterium, others</td>
<td>75. Pasteurella multocida</td>
</tr>
<tr>
<td>2.</td>
<td>Acinetobacter baumannii</td>
<td>Cryptococcus neoformans</td>
<td>76. Peptostreptococcus species</td>
</tr>
<tr>
<td>3.</td>
<td>Acinetobacter calcoaceticus</td>
<td>Diphtheroid</td>
<td>77. Porphyromonas species</td>
</tr>
<tr>
<td>4.</td>
<td>Acinetobacter lwoffii</td>
<td>Enterobacter aerogenes</td>
<td>78. Prevotella species</td>
</tr>
<tr>
<td>5.</td>
<td>Acinetobacter, others</td>
<td>Enterobacter cloacae</td>
<td>79. Propionibacterium species</td>
</tr>
<tr>
<td>6.</td>
<td>Actinomyces species</td>
<td>Enterobacter, others</td>
<td>80. Proteus mirabilis</td>
</tr>
<tr>
<td>7.</td>
<td>Aeromonas species</td>
<td>Enterococcus faecalis (vanco-sensitive)</td>
<td>81. Proteus vulgaris</td>
</tr>
<tr>
<td>8.</td>
<td>Alcaligenes species</td>
<td>Enterococcus faecalis (vanco-resistant)</td>
<td>82. Proteus, others</td>
</tr>
<tr>
<td>10.</td>
<td>Bacillus anthracis</td>
<td>Enterococcus faecium (vanco-resistant)</td>
<td>84. Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>11.</td>
<td>Bacillus cereus</td>
<td>Enterococcus gallinarum</td>
<td>85. Pseudomonas, others</td>
</tr>
<tr>
<td>12.</td>
<td>Bacillus subtilis</td>
<td>Enterococcus, others</td>
<td>86. Serratia marcescens</td>
</tr>
<tr>
<td>13.</td>
<td>Bacillus, others</td>
<td>Escherichia coli</td>
<td>87. Serratia, others</td>
</tr>
<tr>
<td>14.</td>
<td>Bacteroides fragilis</td>
<td>Flavobacterium species</td>
<td>88. Sporothrix schenckii</td>
</tr>
<tr>
<td>15.</td>
<td>Bacteroides, others</td>
<td>Fungus</td>
<td>89. Staphylococcus aureus (methicillin-sensitive)</td>
</tr>
<tr>
<td>16.</td>
<td>Blastomyces dermatitidis</td>
<td>Fusarium species</td>
<td>90. Staphylococcus aureus (methicillin-resistant)</td>
</tr>
<tr>
<td>17.</td>
<td>Branhamella catarrhalis</td>
<td>Fusobacterium species</td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Burkholderia cepacia</td>
<td>Gram-negative cocci unspecified</td>
<td>91. Staphylococcus capitis</td>
</tr>
<tr>
<td>19.</td>
<td>Campylobacter species</td>
<td>Gram-negative rod unspecified</td>
<td>92. Staphylococcus coagulase negative</td>
</tr>
<tr>
<td>20.</td>
<td>Candida albicans</td>
<td>Gram-positive cocci unspecified</td>
<td>93. Staphylococcus epidermidis</td>
</tr>
<tr>
<td>21.</td>
<td>Candida glabrata</td>
<td>Gram-positive rod unspecified</td>
<td>94. Staphylococcus haemolyticus</td>
</tr>
<tr>
<td>22.</td>
<td>Candida kruusei</td>
<td>Haemophilus species</td>
<td>95. Staphylococcus hominis</td>
</tr>
<tr>
<td>23.</td>
<td>Candida lusitaniae</td>
<td>Histoplasma capsulatum</td>
<td>96. Staphylococcus saprophiticus</td>
</tr>
<tr>
<td>24.</td>
<td>Candida parapsilosis</td>
<td>Klebsiella oxytoca</td>
<td>97. Staphylococcus warneri</td>
</tr>
<tr>
<td>25.</td>
<td>Candida tropicalis</td>
<td>Klebsiella pneumoniae</td>
<td>98. Staphylococcus, others</td>
</tr>
<tr>
<td>26.</td>
<td>Candida, others</td>
<td>Klebsiella, others</td>
<td>99. Streptothromomonas maltophilia</td>
</tr>
<tr>
<td>27.</td>
<td>Citrobacter diversus</td>
<td>Lactobacillus species</td>
<td>100. Streptococcus group A (pyogenes)</td>
</tr>
<tr>
<td>28.</td>
<td>Citrobacter freundii</td>
<td>Listeria monocytogenes</td>
<td>101. Streptococcus group B (agalactiae)</td>
</tr>
<tr>
<td>29.</td>
<td>Citrobacter koseri</td>
<td>Malassezia furfur</td>
<td>102. Streptococcus group D (bovis)</td>
</tr>
<tr>
<td>30.</td>
<td>Citrobacter, others</td>
<td>Micrococcus species</td>
<td>103. Streptococcus pneumoniae</td>
</tr>
<tr>
<td>31.</td>
<td>Clostridium difficile</td>
<td>Moraxella catarrhalis</td>
<td>104. Streptococcus viridans</td>
</tr>
<tr>
<td>32.</td>
<td>Clostridium perfringens</td>
<td>Morganella morganii</td>
<td>105. Streptococcus, alpha hem</td>
</tr>
<tr>
<td>33.</td>
<td>Clostridium, others</td>
<td>Neisseria gonorrhoiae</td>
<td>106. Streptococcus, beta hem</td>
</tr>
<tr>
<td>34.</td>
<td>Coagulase negative staph (CNS)</td>
<td>Neisseria meningitidis</td>
<td>107. Streptococcus, others</td>
</tr>
<tr>
<td>35.</td>
<td>Coccidioides immitis</td>
<td>Neisseria, others</td>
<td>108. Torulopsis glabara</td>
</tr>
</tbody>
</table>

**Note:** Underlined organisms represent common skin contaminants for the purpose of assigning a BSI classification. Organisms in **bold** represent coagulase-negative staphylococcus species.
Appendix C. Definitions of all Entry fields in Access Database

Demographics Form

1. **Epicenter**: Drop list for participating centers in study
2. **Start Date**: Starting date of study period
3. **End Date**: Last date of study period
4. **Study ID**: sequential ID number given to study patients
5. **MRN**: Medical record of study patient used during data entry for tracking and accuracy. Field is removed prior to data submission to coordinating center
6. **Last Name**: Last name of study patient used during data entry for tracking and accuracy. Field is removed prior to data submission to coordinating center
7. **First Name**: First name of study patient used during data entry for tracking and accuracy. Field is removed prior to data submission to coordinating center
8. **Gender**: Gender of study participant
9. **First MRSA Institutional Culture Date**: Date of the first recorded positive culture for MRSA at the institution for the study participant
10. **First VRE Institutional Culture Date**: Date of the first recorded positive culture for VRE at the institution for the study participant
11. **Age at First Unit Admit**: Age of the study participant at the time of unit admission. Age is chosen from drop down list that is listed in decades; 1) <18, 2) 18-35, 3) 36-45, 4) 46-55, 5) 56-65, 6) 66-75, 7) 76-85, and 8) >85.

Unit Subform

12. **Unit ID**: Numbering system for ICU admissions, each admission is given a unique unit ID number, all study ID are patient specific and thus each study ID may have multiple unit ID numbers. Autonumbered on Dataview sheet.
13. **Unit Name**: Name of study unit, up to two units in study per participating institution
14. **Unit Admit Date**: Date of admission to study unit
15. **Unit Discharge date**: Date of discharge from study unit
16. **Study ID**: Sequential ID number given to study patients
17. **Mupirocin during Admit**: Was patient placed on mupirocin during any portion of the admission, (yes or no, checkbox)
18. **Cultures Prior to Unit Admission**: Were there cultures for MRSA or VRE present prior to admission to study unit (present or none)? Present prompts entry into Pre-Admit Cultures subform.

19. **Cultures During to Unit Admission**: Were there any cultures taken during study unit admission (none or present)? Cultures include any cultures positive for MRSA, VRE and all positive blood cultures. Present prompts entry into Cultures subform.

Pre-Admit culture form

20. **Specimen Site**: Site of most recent MRSA or VRE culture prior to admission

21. **Specimen Date**: Date of most recent MRSA or VRE culture prior to admission

22. **MRSA Result**: Result of most recent MRSA culture prior to admission (yes, no, not eval)

23. **VRE Result**: Result of most recent VRE culture prior to admission (yes, no, not eval)

24. **Organism**: MRSA or VRE, on this form should only reflect results of MRSA and VRE culturing prior to admission.

25. **StudyID**: Sequential ID number given to study patients generated on demographics form.

Cultures subform

26. **Specimen Site**: Site of MRSA or VRE culture during study unit admission. Data on all blood cultures is also entered into this field by selecting blood culture as specimen site.

27. **Specimen Date**: Date of MRSA or VRE culture during study unit admission

28. **MRSA Result**: Result of MRSA culture during study unit admission (yes, no, not eval)

29. **VRE Result**: Result of VRE culture during study unit admission (yes, no, not eval)

30. **Organism**: MRSA or VRE, on this form should only reflect results of MRSA and VRE culturing during study unit admission.

31. **StudyID**: Sequential ID number given to study patients generated on demographics form.
Comfort Bath®
Cleansing Washcloths

The ultimate in rinse-free bathing!

Thick, ultra-soft washcloths are premoistened with a rinse-free, aloe and vitamin E formula. Warm and soothing, they make full-body cleansing and moisturizing easy in just one step. Just warm Comfort Bath in a microwave or warmer. No rinsing. No mess. No more time-consuming, uncomfortable basin baths!

Using Comfort Bath also provides an opportunity to observe skin condition from head to toe. It also eliminates potential contamination from dirty basins and hospital tap water during bathing.

America's number one basinless bathing brand, Comfort Personal Cleansing® products are trusted by more US hospitals than all other brands combined.

Full-body bathing made easier!
Comfort Bath's rinse-free washcloths thoroughly cleanse and nourish with aloe and vitamin E, so they leave skin feeling clean, soft and moisturized.
Comfort Bath® Cleansing Washcloths

- Our Bacloforte-heavyweight, Tencel® & polyester blend washcloths are as thick as the laundered kind. With the cleanliness of towelling, they feel good even to fragile skin, yet they have superior strength and durability.
- Maximum amount of rinse-free cleansing solution and moisturizers, balanced with oil and vitamin E, they nourish and soften skin.
- Eliminates potential contamination from dirty hospital and toilet water during bathing.
- Dermatologist-tested formula proven hypoallergenic, gentle and non-irritating.
- Can be used on all body areas including the face.
- Portable pH is closest to normal, healthy skin.
- Saves nursing time, increases patient and nursing satisfaction. Makes and more comfortable than a bottle bath.
- Replaces soap, lotion, hot water, basins, laundered washcloths and towels reduces laundry and linen replacement.
- Fully insulated, reusable packaging. Washcloths stay warm throughout the bath, when warmed in our commercial-grade microwave or microwave.
- Rinse-free product contains USP purified water.
- Ask about coupons customized with your facility’s name! Comfort Bath® Cleansing products are available to drugstores nationwide.

For customizable protocols, performance improvement plans, educational materials and more, visit www.sageproducts.com/education

ORDERING INFORMATION

FRAGRANCE FREE COMFORT BATH®
A nonbreakbulk package of 4 packages per case
Reorder #7915

FRAGRANCE FREE COMFORT BATH®
A nonbreakbulk package of 4 packages per case
Reorder #7915

COMFORT BATH®
A comfort bath® package of 4 packages per case
Reorder #7905

COMFORT BATH®
A comfort bath® package of 4 packages per case
Reorder #7900

A better way to bathe

Hygienic and cost efficient

According to a study in the American Journal of Critical Care, Comfort Bath® treated was as effective on a soap and water warm bath. It offered more opportunities to recondition the skin, reduced blood-borne pathogens, reduced contamination, Comfort Bath® was most competitive with the warm bath as well in the study. It also included some use such as lost water consumption and less replacement. Comfort Bath® is less toxic, required fewer products, and was significantly preferred by nurses.

Patient and nurse satisfaction

In a recent hospital study, 90% of patients who received a lush bath said it was much better than a warm bath. Meanwhile, 10% of patients preferred Comfort Bath® over the lush bath. Allowing Comfort Bath® 100% for the bath, 97% of their skin felt soft, and 92% said it was warm, comfortable, and easy to use.

In another study, Comfort Bath® was preferred by 100% of nurses. In fact, all nurses noted that Comfort Bath® was easy to administer and left their patients clean and satisfied.

3009 Three Oaks Road, Cary, Illinois 60013 • www.sageproducts.com • 800-323-2220
220895 02/28/2018
Introducing
an entirely new
FDA-APPROVED
alcohol-free CHG formula

SAGE® 2% CHLORHEXIDINE GLUCONATE CLOTH
PATIENT PREOPERATIVE SKIN PREPARATION

in the first and only
FDA-APPROVED
applicator cloth.
SURGICAL SITE INFECTIONS: Prevalence, Cost & Mortality

There are approximately 60 million inpatient and ambulatory surgical procedures performed in the U.S. annually. For surgery patients, SSIs are the leading hospital-acquired infection at 36% and the third most common hospital-acquired infection overall. Surgical site infections occur after 2.6% to 5% of procedures, translating to at least 1.3 million SSIs annually. Patients who develop SSIs are twice as likely to die, 60% more likely to spend time in an ICU, and more than five times more likely to be readmitted to the hospital. SSIs also increase length of stay by 7 to 10 days and account for $25,546 in average costs.

In a study of elderly patients, SSI due to S. aureus was responsible for a more than 5-fold increase in mortality, more than 12 additional hospital days, and excess costs of more than $40,000.

In a 7-year, 478-patient study, methicillin-resistant S. aureus (MRSA) in a surgical wound resulted in over a 12-fold increase in mortality compared to patients without an SSI. For patients with an SSI, mean costs were $38,770 higher than those without infection. For MRSA SSIs, mean costs were $84,020 higher. 2.6% to 5% of surgical procedures result in surgical site infections. 7 to 10-day increase in length of stay. $25,546 average increase in cost.
CHLORHEXIDINE GLUCONATE
Fast-acting, Broad-spectrum, Persistent

“One of the most important attributes of CHG is its persistence.”

“One of the most important attributes of CHG is its persistence. It has strong affinity for the skin, remaining chemically active for at least 6 hours. Indeed, it probably has the best persistent effect of any agent currently on the market.”

CHG is the only preoperative skin prep agent that the CDC recognizes as having “excellent” activity against gram-positive bacteria as well as “excellent” residual activity.
SAGE® 2% CHLORHEXIDINE GLUCONATE CLOTHS
An entirely new FDA-approved, alcohol-free CHG formula in the first and only FDA-approved applicator cloth

Addressing a known risk factor for surgical site infections: microorganisms on the skin

**UNIQUE 2% CHG FORMULA**
Sage's unique, patent-pending formulation is rinse-free, quick-drying, and proven to provide rapid bactericidal action. It contains no alcohol or harsh detergents, eliminating immobility concerns and reducing the potential to dry out skin.

- Fast-acting and broad-spectrum. Effective against a wide range of microorganisms, significantly reducing their number on intact skin.
- Extremely persistent. Demonstrates continued antimicrobial activity for up to 6 hours after application.
- Free of alcohol and harsh detergents. Contains surfactants to loosen dirt and debris. Soothes skin with moisturizers and humectants.

**UNIQUE, ONE-STEP APPLICATOR CLOTH**
Now, skin prep can truly be achieved in one step. Sage's non-abrasive, textured cloth distributes a uniform dose of CHG to the site, providing a skin-friendly yet effective scrub to remove debris and organic matter—while allowing CHG to cover the area to be prepped.

- Delivers a uniform dose of CHG. Each cloth contains 500mg.
- No drip, runs or pooling associated with other skin prep products.
- Large 7.5 in. x 7.5 in. cloth makes it easier to prep body contours and hard-to-reach areas.

### Sage 2% CHG Cloth: effective against the most prevalent SSI-causing pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Sage 2% CHG Cloth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>✔</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>✔</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>✔</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>✔</td>
</tr>
<tr>
<td>E. coli</td>
<td>✔</td>
</tr>
<tr>
<td>Group D streptococcus</td>
<td>✔</td>
</tr>
<tr>
<td>Other gram-positive cocci</td>
<td>✔</td>
</tr>
</tbody>
</table>

---

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LOG$_{10}$ REDUCTION STUDY RESULTS

In this study, the Sage 2% CHG cloths met both clinical and in vitro standards required by the FDA,
for the treatment of surgical site infections.

Sage 2% CHG Cloths to the Inguinal Site

Sage 2% CHG Cloths to the Abdominal Site

ORDERING INFORMATION

Sage® 2% Chlorhexidine Gluconate® Cloths

- 1 cloth per package, cloth size 3.5" x 3.5"
- 50 packages per case
- Reorder #9705
- Reorder #9706

Sage® 2% Chlorhexidine Gluconate® Cloths - Multi-pack

- 3 individually-wrapped packages (2 cloths per package, cloth size 3.5" x 3.5"
- 32 packages per case
- Reorder #9707

Dispenser Bracket for #9705 and #9706

- Not included
- Reorder #9708

Dispenser Tray for #9707

- Not included
- Reorder #9701

1-800-343-2220 • www.sagproducts.com
Sage Products: The Interventional Patient Hygiene Company

What is Interventional Patient hygiene?
Sage Products has a core belief in prevention—that evidence-based interventions will lead to improved outcomes. Our goals are to promote a positive patient hygiene interaction between caregivers and patients, achieve improved clinical outcomes, reduce adverse events and increase satisfaction. We are reaching these goals by focusing a return to the basics of nursing care. With our industry-leading brands and commitment, we are pioneering the drive toward Interventional Patient Hygiene.

Visit our FREE Clinical Education Website!
www.sageproducts.com/education
Sage's unique skin protection education that can help your facility improve care— including Performance Improvement Plans, Evidence-Based Protocols, Clinical Studies, Customizable Programs and more!

- Reducing VAP Risk Factors
- Preventing Skin Breakdown
- Improving Patient Hygiene

SAGE PRODUCTS INC
3809 Union City Road • Cary, NC • 27513
www.sageproducts.com • www.sageproductsinc.com
800-333-2225
Appendix F. MSDS - Comfort Bath® Wash cloth

MATERIAL SAFETY DATA SHEET

Manufactured by: Sage Products Inc.
3609 Three Oaks Road
Cary, IL 60013

Telephone: Product Info 815 453 4700
           Tech Info 815 453 4700
           Emergency 800 424 6200

1 PRODUCT IDENTIFICATION

Product Name: Comfort Bath™ PBS Wipe Solution
(Non-soap, non-lotion cleansing).

Product Numbers: 7412-X, 7800, 7800-K, 7812*-, 7813-K*, 7813-W*, 7814*, 7855, 7870,
7875, 7900, 7900-EU*, 7900M*, V7900, 7904, 7911, 7913*, 7915, 7916,
7926, 7927*, 7950*, 7955, 7960*, 7970, 7982, 7998

Sage Item Number: R86096C

Chemical Family: Aqueous mixture.

Formula: Proprietary.

DOT Hazard: Not listed.

Chemical Hazard Rating: Health 0
                         Flammability 0
                         Reactivity 0

2 INGREDIENTS / HAZARDS CLASSIFICATION

NON-HAZARDOUS SOLUTION AS PER OSHA’S HAZARD COMMUNICATIONS STANDARD (29 CFR 1910.1200)

3 PHYSICAL AND CHEMICAL DATA

Boiling Point: Not determined.

Vapor Pressure: Not determined.

pH Value: 4.0 - 6.0

Stability: Stable.

Appearance & Odor: Clear, light straw color. Clean, fresh-like, characteristics of fragrance.

Specific Gravity: 1.007-1.017 @ 25°C

Vapor Density (Air=1): Not determined.

Volatility: Negligible.

Solvability in Water: Complete.

4 FIRE AND EXPLOSION HAZARD DATA

Flash Point: Non-flammable. Ref. Setalash Closed Tester, ASTM D-3278 @ ambient. No flash up at 105°C (221°F) - limit of instrument. Will not burn or propagate flame.

Extinguishing Media: Use appropriate extinguishing media according to the class of material burning around this solution.

Sage MSDS #18

1
5 Reactivity Data

Stability: Stable

Hazardous Polymerization: Will not occur.

Incompatibilities: None known

Decomposition Products May Include: None known

6 Health Hazard Data

Emergency First Aid Procedures: Handle in accordance with good industrial hygiene and safety practices.

Ingestion: Non-toxic. Seek medical attention immediately if overdose has been taken.

Eye Contact: Non-irritating.

Skin Contact: Non-irritating. (Ref.: FMSA Primary Dermal and Eye Irritation tests).

7 Spill or Leak Procedures

Steps to Be Taken If Material is Released or Spilled: Contain all spilled material, absorb material with inert material and place in dry containers for disposal.

Waste Disposal Method: Dispose of in accordance with all local, state and federal regulations.

8 Special Protection Information

Respiratory Protection: Not usually required.

Protective Gloves: Not usually required. For unusually prolonged exposure use chemical resistant, gauntlet type or equivalent.

Eye Protection: Not usually required, but wear chemical splash goggles or face shield when condition requires.

9 Special Precautions

For Chemical Emergency Domestic North America (800) 424-9300
Spill, Leak, Fire, Exposure, or International, Call (703) 527-3667 (Collect Calls
Accident Accepted)
Call CHEMTREC Day or Night

10 Preparation of MSDS

Prepared by Safety Department on: October 22, 1996
This data was prepared from current, reliable sources, however, Sage Products Inc. makes no warranty regarding its accuracy. Because of conditions beyond our control, it is the user’s responsibility to determine safe conditions for usage.

Rev. #10: 05/26/06

Sage MSDS #18 2
Appendix G. MSDS - 2% Chlorhexidine Gluconate Cloth

MATERIAL SAFETY DATA SHEET

Manufactured by: Sage Products Inc.
3009 Three Oaks Road
Cary, IL 60013

Telephone: (815) 455-4700
Product Info (815) 455-4700
Tech Info (815) 455-4700
Emergency (800) 424-9300

1 PRODUCT IDENTIFICATION

Product Name: 2% Chlorhexidine gluconate* Cloth
* Equivalent to 500 mg Chlorhexidine gluconate per cloth
Product Number: 9601-X, 9602-X, 9605, 9606, 9705, 9706, 9707
Sage Item Number: F88426
Product Type: Topical Antimicrobial Cloth
Chemical Family: N/A

Chemical Hazard Rating:  
- Health 0
- Flammability 0
- Reactivity 0

2 HAZARDOUS INGREDIENTS

THE HAZARD COMMUNICATION STANDARD REQUIRES THAT SUCH MIXTURES BE ASSUMED TO PRESENT THE SAME HEALTH HAZARD AS DO COMPONENTS THAT CONSTITUTE AT LEAST 1% OF THE MIXTURE (0.1% FOR CARCINOGENS), ALTHOUGH OSHA HAS NOTED THAT THE HAZARDS OF INDIVIDUAL COMPONENTS MAY BE ALTERED BY INCLUDING THEM IN A MIXTURE.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>CAS Registry No.</th>
<th>PBL/TLV</th>
<th>% Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine gluconate</td>
<td>18472-51-0</td>
<td>Not established</td>
<td>2</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>57-55-6</td>
<td>Not established</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Glycerin</td>
<td>56-81-5</td>
<td>Not established</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Polyester Fiber</td>
<td>25038-59-9</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

SOME OF THE INGREDIENTS IN THIS MIXTURE ARE TRADE SECRETS (TS).


N/A - Not Applicable

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### 3 PHYSICAL DATA

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling Point</td>
<td>N/A</td>
</tr>
<tr>
<td>Vapor Pressure</td>
<td>N/A</td>
</tr>
<tr>
<td>Freezing Point</td>
<td>N/A</td>
</tr>
<tr>
<td>Auto-ignition Temp</td>
<td>Not Known</td>
</tr>
<tr>
<td>Solubility in Water</td>
<td>N/A</td>
</tr>
<tr>
<td>Appearance &amp; Odor</td>
<td>White polyester cloth with mild odor</td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>N/A</td>
</tr>
<tr>
<td>Vapor Density (Air = 1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Flash Point</td>
<td>&gt; 212 °F</td>
</tr>
<tr>
<td>Lower Explosive Limit</td>
<td>None</td>
</tr>
<tr>
<td>Upper Explosive Limit</td>
<td>None</td>
</tr>
</tbody>
</table>

### 4 FIRE AND EXPLOSION HAZARD DATA

**FLASH POINT METHOD:**
- Estimated Flammable Limits in Air: Non-Flammable
- Extinguishing Media Includes: Foam or water
- Special Fire Fighting Procedures: Use a self-contained breathing apparatus in close proximity to fire.
- Unusual Fire & Explosion Hazards: Treat as a solid that burns with low smoke density

### 5 REACTIVITY DATA

**STABILITY:** STABLE

**Hazardous Polymerization:** Will not occur.

**Incompatibilities:** None known

**Decomposition Products May Include:** CO, CO2
6 HEALTH HAZARD DATA

IMMEDIATE HEALTH HAZARD DATA:

Skin Absorption: Not likely. Product does not absorb well through skin.

Ingestion: Not likely. Considered non-toxic. If cloth is swallowed seek medical attention.

Inhalation: Not considered an inhalation hazard.

Skin: Not expected to present a skin hazard under anticipated conditions of normal use. If irritation occurs, discontinue use.

Ear: Hazardous to middle ear, with perforated eardrum. Seek medical attention.

Eyes: Keep out of eyes. If contact occurs rinse promptly and thoroughly with water and seek medical attention.

EMERGENCY FIRST AID PROCEDURES:

Ingestion (swallowing): N/A

Inhalation (breathing): N/A

Skin Contact: Flush with water, if irritation persists, get medical attention.

Eye Contact: Flush with water for fifteen minutes, get medical attention.

7 SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED.

Procedures: Wipe dry any surfaces.

Waste Disposal Method: Place in appropriate container and dispose of with all federal, state and local ordinances.

8 SPECIAL HANDLING/PROTECTION INFORMATION

Inhalation: N/A

Skin: If handling for long periods, wear protective gloves. Wash after handling product.

Eyes: Keep out of eyes. If product contacts eye(s), flush with plenty of water, if irritation persists, seek medical attention.

Storing: Store at room temperature.
9 SPECIAL PRECAUTIONS

For Chemical Emergency
Spill, Leak, Fire, Exposure, or Accident
Call CHEMTREC Day or Night

Domestic North America (800) 424-9300
International, Call (703) 527-3887 (Collect Calls Accepted)

10 PREPARATION OF MSDS

Prepared by Safety Department on: 7/6/05

This data was prepared from current, reliable sources, however, Sage Products Inc. makes no warranty regarding its accuracy. Because of conditions beyond our control, it is the user’s responsibility to determine safe conditions for usage.

Date Issued: 7/8/05
Revisions: 3rd: 5/18/06
ADVERSE EVENT SUBMISSION FORM

The Principal Investigator must promptly report to the IRB, in writing, any unanticipated side effects, hazards, or other problems involving risks to subjects or others. Promptly report all adverse events considered to be related to research procedures to the Steering Committee.

Date:
Principal Investigator, Sponsor: Climo, Michael
Protocol#: CI06-003
Protocol Title: Multicenter Evaluation of The Effectiveness of Source Control With Daily Chlorhexidine Skin Preparation in Reducing Nosocomial Infections Including MRSA and VRE

Funding: SAGE Products, Inc., and Center for Disease Control and Prevention
Research Coordinator(s):
Phone: Fax:

Report Type: Initial Follow-up
Subject Identifier # (study ID number, do not list medical record number or other personal identifier):
AE Date:
AE Description (brief):

Is the adverse event a previously described complication that is listed in the “Risk” section of the Investigator’s Brochure Yes No

This is a (an):

☐ Unanticipated/Unexpected Event
(Any untoward event that is not identified with the current investigator brochure or study protocol)

☐ Serious Adverse Event
(Any untoward medical occurrence that results in death, is life-threatening, requires patient hospitalization, prolongs existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital abnormality)

The opinion of the Principal Investigator is that the relationship of the research procedure is:

☐ Unrelated
☐ Probably not related
☐ Possibly related
☐ Probably related
☐ Related
☐ Other:

INVESTIGATOR SIGNATURE DATE
(Sub-investigator may sign if the investigator is unavailable (i.e. out of the country)
Appendix I. Example of Patient Information Sheet

XXXXXXXXX Medical Center
SUBJECT INFORMATION SHEET

“Multicenter Evaluation of the Effectiveness of Source Control with Daily Chlorhexidine Skin Preparation in Reducing Nosocomial Infections Including MRSA and VRE”

We are trying to learn whether the ways that patients are bathed can affect their risk of acquiring infections in the intensive care unit. We are especially interested in knowing if a new bath procedure will reduce the number of harmful bacteria on your skin and lower your risk of infection.

The Comfort Bath Cleansing System from Sage Products Inc. is one way that patients can be bathed. The Comfort Bath Cleansing System has been available since 1999. It is used in 20% of US hospitals. The Comfort Bath System, as shown in the picture below, contains eight disposable washcloths, premoistened with a rinse-free cleansing and moisturizing solution.

The bath procedure involves warming the packet and using one washcloth at a time to clean each separate body part. You will be bathed with this product or with a new version of the Comfort Bath System that contains 2% chlorhexidine gluconate (CHG), as shown in the picture above. CHG is an antiseptic agent that has been used for skin cleansing for many years. It is used routinely in hospitals to clean skin before surgery and is available over-the-counter at your local drugstore. The use of CHG in the Comfort Bath System for patient bathing has been studied at other hospitals under the supervision of the FDA but during this study will (1) be used in an experimental manner, as it is not currently approved as a general skin cleanser; (2) may cause potential adverse experiences, such as skin irritation, sensitization, and generalized allergic reactions; (3) that the 2% Chlorhexidine Gluconate* Cloth should not be used: (a) on patients with known allergies to chlorhexidine gluconate or any other ingredients in the product, (b) for lumbar punctures or in contact with the meninges, or (c) on open skin wounds; and (4) the product should be kept out of the eyes, ears, and mouth.

The Comfort Bath System is provided to you by the manufacturer at no charge. You will not be charged for the product.

If you have a question about this information, you may call Dr. XXXX XXXX at (XXX) XXX-XXXX or Mr. XXXX XXXX, R.N. at (XXX) XXX-XXXX.
Summary of Protocol Changes from version 1.0 to version 1.3

1. Section 6.5 (page 13) was amended to indicate that skin care moisturizers compatible with the use of chlorhexidine would be utilized by all study units as follows:

   “Many skin care moisturizers that contain anionic emulsifiers may adversely affect the residual antibacterial effect of chlorhexidine and should be avoided during routine care during periods in which chlorhexidine is in use. Skin care products that are known to be compatible with chlorhexidine include: Aquaphor® Original Formula Ointment, Lubriderm® Dry Skin Care Lotion, Eucerin® Original Lotion, Vaseline® 100% Pure Petroleum Jelly, PROVON® Moisturizing Lotion. Participating study units will be asked to utilize one of these products for skin care during the proposed study.”

2. Section 6.76 Mupirocin Use was added on page 16.

   “Each Study patient will have information about the concurrent use of mupirocin use during the admission recorded. This information is being collected to determine if concurrent mupirocin use affects the clearance of MRSA from the study population. Use of any mupirocin during the admission will be recorded in the Access Database.”

3. Section 7.3 (page 25) was changed to indicate that the trial would be conducted with waiver of documentation of written informed consent instead of waiver of informed consent.

   “This study will involve all adult patients admitted to the proposed study units. As such there is no recruitment strategy. It is intended to encompass all patients within the participating units. This study will be seeking waiver of documentation of written informed consent in accordance with 21 CFR 56.109(c):

   “An IRB shall require documentation of informed consent in accordance with Sec. 50.27 of this chapter, except as follows: (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or (2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an exception from informed consent for emergency research are met.”

   1. The intended research presents no more than minimal risk to the patients. The intent is to study the potential differences between two accepted bathing products for patients and to determine if there is the potential to reduce nosocomial infections. Both products are FDA approved products and as such pose minimal risk to those patients involved. Bathing with chlorhexidine is an accepted procedure within the hospital and is often applied to selected patient populations within the hospital including pre-operative patients.

   2. The activities within the proposal do not normally require informed consent. Bathing is an accepted practice within the hospital and does not require written informed consent. Surveillance cultures are normally done in the course of many hospital surveillance activities and the standard of care is to require only verbal permission prior to collection.
In accordance with 45 CFR 56.109(d), subjects in the trial will be given a written statement about the nature of the study.

“(d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research. “

An example of the patient information sheet is included in Appendix I. “

4. Section 7.4 (page 26) was amended to include a more detailed explanation of the rationale for a waiver of HIPAA authorization as follows:

“Since the experimental design of the study is intending to study the effect of universal bathing on an intensive care unit, the inability to obtain patient specific data from even a small number of patients would adversely effect our ability to draw conclusions about the effect of bathing. Patients who do not receive the proposed intervention (chlorhexidine bathing) could serve as reservoirs of microorganisms that could impact transmission.”

5. Section 7.6 (page 27) was amended with a more detailed description of the known adverse reactions to the topical use of chlorhexidine and exclusions to its use as follows:

“Chlorhexidine has been widely used as a topical agent for skin disinfection in concentrations ranging from 0.5% to 4%. It is used extensively for skin disinfection, handwashing, oral care, irrigation of surgical wounds, the urinary bladder or vagina, topical treatment of burn wounds, and treatment of peritonitis in peritoneal dialysis (47). Daily bathing with chlorhexidine has been used within the hospital environment as a means to disinfect the skin and decrease the transmission of nosocomial pathogens including MRSA and VRE (18-25, 29). Sage 2% Chlorhexidine Gluconate Cloths has been shown to reduce bacteria that can potentially cause skin infection. In addition, 2% Chlorhexidine Gluconate Cloths have been used as a daily bathing cloth in several studies and shown to be well tolerated. In the VRE transmission study (Vernon et al.), 394 patients received daily bathing with the 2% Chlorhexidine Gluconate Cloth with a lower reported rate of skin irritation in comparison to patients who received soap and water bathing (29). In the Skin Cleansing with Chlorhexidine Study (Protocol 05-006), 343 patients have undergone daily bathing with the 2% Chlorhexidine Gluconate Cloth with no reported adverse events attributable to chlorhexidine bathing (see Investigators Brochure). No Serious Adverse events have been reported to date in any clinical trial involving 2% Chlorhexidine Gluconate Cloths. Despite the overall low rate of expected adverse events, several restrictions will be place for the use of the 2% Chlorhexidine Cloth. The 2% Chlorhexidine cloth will not be used in the following situations:

1) on patients with known allergies to chlorhexidine gluconate or any other ingredients in the product
2) on burn patients with a high percentage of disrupted body surface area.
3) for lumbar punctures or in contact with the meninges, or
4) on open skin wounds; and
5) the product should be kept out of the eyes, ears, and mouth

Potential recognized risks of bathing with chlorhexidine include local skin irritation, sensitization... “

7. Appendix I “Example of Patient Information Sheet” was added on page 53.

8. Minor spelling and formatting changes were made throughout the protocol.
Initial Statistical Analysis Plan

The effect of daily bathing with chlorhexidine impregnated washcloths on incidence density of BSI, MRSA, and VRE incidence will be modeled by means of Generalized Estimating Equations (GEEs) under the Poisson distribution family. Since each unit is observed twice under the study’s crossover design (once under the experimental and once under the control condition) and the targeted outcome is in the form of counts (here new cases or infections related to patient days of exposure), the GEE methodology is needed to model the count outcomes while accounting for the natural clustering effects induced by repeated observation of units.

Our study design requires three separate analyses based upon the type of surveillance (MRSA only, VRE only, or both) employed by the units. The analysis of BSI rates will use data from all units and will incorporate a three level fixed effect designating surveillance type. The analyses of MRSA and VRE rates, respectively, will be based on only those units engaging in the corresponding type of surveillance. In the latter analyses, a two level fixed effect for surveillance type will be incorporated (MRSA only versus both - or VRE only versus both).

The fundamental model in these analyses will specify treatment, order of presentation, and type of surveillance fixed main effects. Offsets in each model will be unit specific total patient days during the exposure periods. Even though the study design targets minimizing order and type of surveillance effects and neither are expected to be present in any magnitude, their possible effects will be incorporated for control purposes. If either proves to be significant, their interactive effects with
treatment will also be examined. Such interactive effects are likewise not expected to be present.

All significance tests in these analyses will be conducted given two-tailed alpha of .05. In addition, 95% confidence intervals estimating treatment and control rates as well as their ratio will be constructed. It should be noted that in this study, there can be no missing data and consequently no missing data issues. Analyses are planned to be conducted using the SAS software for Windows (Version 9.1.3 or later).

Final Statistical Analysis Plan

We evaluated changes in the mean incidence of MRSA and VRE acquisition and the development of bloodstream infections using a Poisson regression model that included consideration of the prevalence of MRSA and VRE as a confounder. We tested the null hypothesis that the incidence rate during the baseline period equals the incident rate during the intervention period using PROC GENMOD in SAS (version 9.2, Cary, NC) to fit a Poisson regression model. Modeling included considerations of the monthly prevalence of MRSA and VRE in the comparison to exclude the possibility that observed reductions in incidence were associated with clustering of MRSA and or VRE. The monthly prevalence was calculated as the proportion of admitted patients with prevalent cases of MRSA or VRE on admission to study units compared to the total number of patients.

The Cox proportional-hazards regression model was used to compare the differences in the time to development of incident primary bloodstream infections
between the control group and the intervention group (chlorhexidine bathing). For the model, the survival time was calculated as 1) the interval between admission and discharge from the study unit for those patients with no diagnosis of incident primary bloodstream infection and as 2) the interval between admission and the first positive culture for patients diagnosed with primary bloodstream infections.

Characteristics of individual units examined to determine if they influenced observed reduction in primary bloodstream infection included unit size, unit type, observed length of stay, use of central venous catheters, median age of patients, gender of patients, baseline primary BSI rate, baseline incident MRSA rate, baseline incident VRE rate, prevalence of MRSA, and prevalence of VRE. We compared changes in the mean incidence of primary bloodstream infections between the control period and intervention periods. Continuous variables were examined by two sample t test and linear regression modeling. Categorical variables were examined by Fisher exact test.

Summary of Changes to Statistical Analysis Plan

1. The final Poison Regression modeling included considerations of the monthly prevalence of MRSA and VRE in the comparison to exclude the possibility that observed reductions in incidence were associated with clustering of MRSA and or VRE.

2. The final Poison Regression model did not incorporate a three level fixed effect designating surveillance type since all participating units performed surveillance for both MRSA and VRE.
3. The final statistical analysis included the Cox proportional-hazards regression model to compare the differences in the time to development of incident primary bloodstream infections.