Nasal Iodophor Antiseptic vs Nasal Mupirocin Antibiotic in the Setting of Chlorhexidine Bathing to Prevent Infections in Adult ICUS: A Randomized Clinical Trial

NCT#: 03140423

4/28/2017

Conduct a cluster-randomized non-inferiority trial comparing mupirocin vs iodophor for nasal decolonization of ICU patients on *S. aureus* clinical cultures and all-cause bloodstream infection in the setting of routine chlorhexidine bathing (Mupirocin-Iodophor Swap Out Trial).

1.1 Significance and Innovation

Intensive care units (ICUs) have one of the highest rates of healthcare-associated infections due the patients' severity of illness and frequent use of medical devices.[1] [2] [3] We previously conducted a cluster-randomized trial of decolonization in adult ICUs (REDUCE MRSA Trial) in the Hospital Corporation of America (HCA) health system.[4] We showed that ICUs using chlorhexidine (CHG) antiseptic for routine daily bathing and mupirocin antibiotic for nasal decolonization of all admissions experienced a 37% reduction in methicillin-resistant *Staphylococcus aureus* (MRSA) clinical cultures and a 44% reduction in all-cause bloodstream infection. Nasal mupirocin has been shown to be important because CHG does not clear the nasal reservoir of *S. aureus*, one of the most common and virulent healthcare-associated pathogens.[5] [6] [7]

In response to the REDUCE MRSA Trial and other clinical trials,[4] [8] [9] ICU decolonization has been adopted throughout HCA's ICUs and broadly across the United States. However, despite evidence showing that the combination of mupirocin and CHG is effective in reducing all-pathogen ICU infection as well as *S. aureus* carriage and infection,4 [10] [11] [12] many hospitals outside HCA are omitting mupirocin due to concerns of eliciting mupirocin resistance. We found an increase in mupirocin resistance from 10% to 17% during the 18 month period of the REDUCE MRSA trial,[13] and others have reported high rates of resistance in clinical settings.[14] [15] [16] [17] [18] [19]

Alternative agents that do not readily engender resistance to mupirocin but prevent infections are thus needed. This phenomenon of resistance emerging with use has been observed for many antibiotics. In contrast, antiseptics, such as alcohol, iodophor, and CHG, have not been shown to engender clinically meaningful resistance, likely due to their small molecular size.[20] [21] [22] [23] [17] [18] [19] [20] [24] We did not identify CHG resistance in the REDUCE MRSA Trial,[14] and prior studies evaluating antiseptics versus antibiotics for prevention of urinary tract infection or otitis media have found no evidence of antiseptic resistance.[25] [26] Of specific relevance to this study, iodophor resistance has not been reported despite over 50 years of use in healthcare and households.

In this aim, we evaluate the ability of a nasal antiseptic to perform similarly to mupirocin when used in combination with CHG for universal ICU decolonization. This trial will be the first large-scale comparison of intranasal antibiotic vs. antiseptic as components of a standard decolonization regimen with CHG. It will be conducted as a pragmatic comparative effectiveness trial in over 100 community hospitals, and thus have immediate applicability to the most U.S. hospitals.

1.2 Approach

1.2.1 Study Population

This trial is based in the HCA Healthcare (formerly Hospital Corporation of America) system, which is the largest private inpatient provider in the U.S., including over 168 hospitals across 23 states in the US and areas in the United Kingdom. Hospitals are predominantly community-based, although they range in size from small facilities to large complex tertiary medical centers. HCA supports an annual volume of 2 million US admissions and 8 million emergency department visits. Overall, 1 in 20 admissions in the U.S. occurs in an HCA facility.

The Mupirocin-Iodophor Swap Out trial will focus on the study population of patients in adult intensive care units (ICUs) in HCA hospitals. All U.S. HCA hospitals with an adult ICU will be eligible to participate. Exclusion criteria include ICUs with an average length of stay of less than 2 days, and HCA hospitals that are not able to transfer or merge data into the centralized data warehouse for the baseline and intervention periods of the study (e.g. newly-acquired hospital that lack baseline data or hospitals not using MEDITECH as an electronic health system platform). The latter exclusion only applies to a small number of facilities, mostly those who were newly-acquired.

1.2.2 Study Design

As mentioned above, the HCA health system adopted universal ICU decolonization for adult ICUs in response to the results of the REDUCE MRSA Trial. HCA corporate guidance to their hospitals espouses use

of twice daily nasal mupirocin for the first 5 days of an ICU stay and daily chlorhexidine bathing for the duration of the ICU stay. The corporate campaign launched in Spring of 2013 with high compliance adoption by July 2013. Subsequent HCA evaluations demonstrated a 24% reduction in health system ICU central line associated bloodstream infections attributable to universal ICU decolonization.[27]

In this context, we will conduct a two-arm 18-month non-inferiority cluster randomized controlled trial of HCA hospitals, evaluating two regimens. Hospitals randomized to Arm 1 will be assigned to the mupirocin-based usual care regimen for adult ICUs in the HCA health system. This will involve universal decolonization for all admitted patients using ICU-wide daily bathing with 2% chlorhexidine cloths for the duration of the ICU stay plus topical intranasal mupirocin ointment (bilateral nares) for the first five days of the ICU stay. Hospitals will be provided with re-training of HCA's corporate guidance for this regimen and adherence will be tracked. Half of participating hospitals (minimum sample size of 60 hospitals) will be assigned this arm. We anticipate an average of 1.75 adult ICUs per hospital, or at least 105 ICUs in this arm.

Hospitals randomized to Arm 2 will be assigned to the iodophor-based regimen for adult ICUs in the HCA health system. This will involve universal decolonization for all admitted patients using ICU-wide daily bathing with 2% chlorhexidine cloths for the duration of the ICU stay plus topical intranasal iodophor (10% povidone-iodine to bilateral nares) for the first five days of the ICU stay. Hospitals will be provided with re-training of HCA's corporate guidance for CHG bathing plus new training for the use of nasal iodophor. Adherence will be tracked. Half of participating hospitals (minimum sample size of 60 hospitals) will be assigned this arm. We anticipate an average of 1.75 adult ICUs per hospital, or at least 105 ICUs in this arm.

Thus, both arms will implement some form of universal decolonization during the ICU stay. The protocol will involve discontinuation of the regimen upon ICU discharge, regardless of whether the full intervention therapy had been applied during the ICU stay.

Table 1. Mupirocin-Iodophor Swap Out Trial Design Characteristics and Outcomes

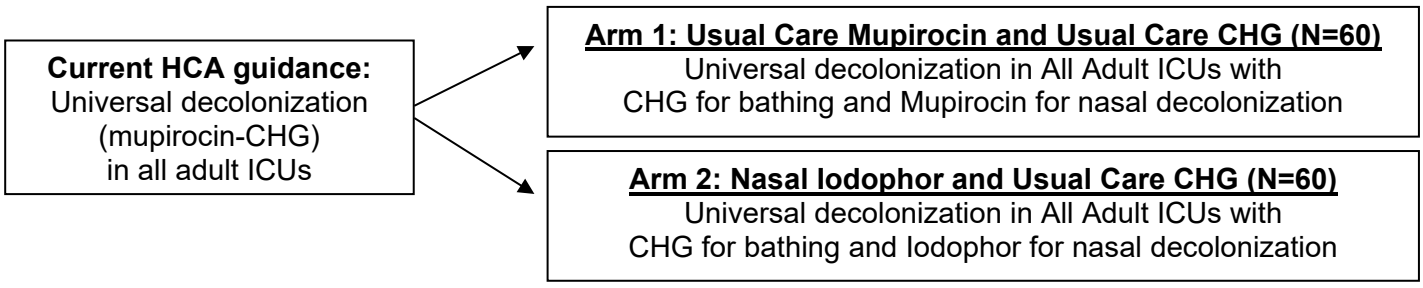
Study Design	Cluster-randomized non-inferiority clinical trial
Unit of Randomization	Hospitals (all ICUs in a hospital will be assigned to the same regimen*)
Study Population	Adult ICU patients in participating HCA hospitals
Inclusion Criteria	Hospitals with at least 1 adult ICU, stable infection prevention initiatives and products during baseline period, agreement to refrain from new initiatives conflicting with the trial
Exclusion Criteria	ICUs with mean length-of-stay of less than 2 days. HCA hospitals having an electronic health record other than MEDITECH.
Group Assignments **Arm 1 (N=60 hospitals)** **Arm 2 (N=60 hospitals)**	 Routine care: ICU decolonization with daily CHG baths and mupirocin for 5 days, twice daily Intervention: ICU decolonization with daily CHG baths and iodophor for 5 days, twice daily
Study Period	**24-Month Baseline Period** (Retrospective Data): May 2015 – Apr 2017 **4-Month Training and Phase In Period**: May – Oct 2017 (not included in analysis) **18-Month Intervention Period:** Nov 2017 – Apr 2019
Primary Outcome	ICU-attributable *S. aureus* clinical cultures (MRSA + MSSA)
Secondary Outcomes	ICU attributable MRSA clinical cultures; ICU-attributable all-cause bloodstream infection;

* patient-level data will be analyzed by hospital

This trial will be registered with Clinicaltrials.gov, following approval by the Harvard Pilgrim Health Care Institutional Review Board, but prior to intervention launch.

Randomization will occur on the hospital level. All adult ICUs in a given hospital will be assigned to the same regimen (Figure 1).

Figure 1: Study Arms of Mupirocin-Iodophor Swap Out Trial



1.2.3 Steering Committee

This trial will be governed by a Steering Committee that is composed of the following representatives (Table 2). This steering committee will be responsible for the design and conduct of this trial.

Table 2. Steering Committee Members

Institution	Member	Title/Expertise
Hospital Corporation of America		
	Kenneth Sands, MD, MPH	Chief Epidemiologist and Chief Patient Safety Officer
	Russell Poland, PhD	Assistant Vice President Research and Scientific Communications
	Julia Moody, MS	Director, Infection Prevention
CDC Prevention Epicenters		
Harvard Pilgrim Health Care	Richard Platt, MD MS (PI)	Senior Investigator, Professor and Chair, Dept of Population Medicine
	Ed Septimus, MD	Lecturer, Harvard Medical School Professor, Texas A&M Medical School Former Medical Director of Infection Prevention and Epidemiology Clinical Services Group, Hospital Corporation of America
UC Irvine	Susan Huang, MD MPH (Co-PI)	Lead Investigator; Professor and Hospital Epidemiologist
U Mass Amherst	Ken Kleinman, PhD	Statistician, Professor, Biostatistics
Stroger Hospital Cook County/ Rush Medical School	Robert Weinstein, MD (PI)	Professor of Medicine, Infectious Diseases; Expertise in chlorhexidine and HAI
	Mary Hayden, MD	Professor of Medicine (Infectious Diseases) and Pathology; Expertise in microbiology
Centers for Disease Control and Prevention (CDC)	John Jernigan, MD MPH	Division of Healthcare Quality Promotion; Program lead for CDC Prevention Epicenters

1.2.4 Recruitment

HCA hospitals will be recruited by HCA staff using their usual infrastructure for seeking participants for system-wide quality improvement projects. In particular, recruitment will be performed under the direction of Ed Septimus, MD (Medical Director, Infection Prevention), Julia Moody, MS (Director, Infection Prevention and Control), and Jason Hickok, MBA RN (Asst Vice President, Laboratory, Infection Prevention, and Research), with the support of Jonathan Perlin MD PhD, Chief Medical Officer of HCA. HCA health system is divided into two Groups (National and American), which in turn are divided into geographic divisions. Recruitment will be encouraged by HCA Group Presidents and HCA Division leadership.

Hospitals recruited as participants will be provided with the trial design and a description of both arms of the study. They will agree to be randomized and to implement their assigned protocol. An attestation letter confirming commitment to the trial will be signed by the Chief Executive Officer of each participating hospital. We will use a centralized IRB structure with each participating hospital ceding to the Harvard Pilgrim Health Care IRB.

1.2.5 Randomization

Randomization will occur during Spring 2017 and participating hospitals will be notified. This will be done because of the requisite 3-5 month period to submit and schedule the approval of intervention protocols by relevant hospital committees which often meet monthly or quarterly. As per routine policy in all hospitals, no training or implementation activities may occur prior to obtaining requisite hospital committee approvals. This will allow approval to occur and appropriate training of staff to occur prior to the phase in period which will involve acquisition and introduction of intervention product.

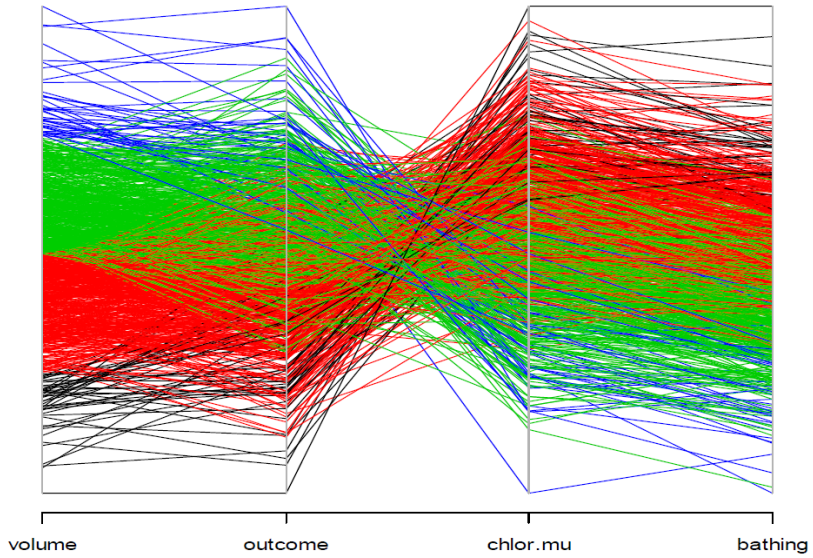
While this study is one of the largest cluster-randomized trials of hospitals, simple randomization of 120 hospitals will not ensure balance of key variables by chance alone, and without care could even result in very unequal numbers of hospitals in each arm. Achieving balance on key features of the randomization units (in this case, hospitals) is a critical task in cluster-randomized trials, but little literature on it exists. Unlike individually-randomized trials, information about the clusters is often known in advance, but the number of clusters to be randomized can be relatively small. The existence of a priori data can mitigate the small numbers and help to obtain adequate balance through stratification or other methods. One attractive approach is to establish tuplets—matched sets (pairs, for a two-arm trial) – in which one member of each tuplet is

assigned to each arm. Schemes for constructing tuplets need not be guided by theory. A formal approach would be to calculate the Mahalanobis distance between hospitals across all key variables and choose the set of tuplets with the minimum average distance. In this approach, we could standardize the variables, and then multiply by values calibrated to reflect any difference in the importance of balancing them. Other approaches are more ad hoc, such as prioritizing broad classes of balance on a key variable and making pairs within these strata based on lower-priority variables. However, there is no “best” method of tuplet construction, only sets that come closer to meeting the varied needs of each trial.

We will use methods to inform the choice of tuplet-construction scheme which we previously developed in the REDUCE MRSA trial. We will establish the pairs under several plausible tuplet-construction schemes, and use graphical methods to compare all possible realizations for balance between the arms under each scheme. For example, if two variables were to be balanced, we would tentatively divide the sample into two groups under a tuplet construction scheme and then generate a scatterplot showing the between-arm absolute value of the mean difference for one variable on the x-axis and the second on the y-axis for each possible result of the randomization. We would then divide the groups again under the same scheme, and find another point on the scatterplot. Repeating many times would show the typical and distribution of balance under a scheme. Comparing the resulting scatterplots from each tuplet-construction scheme can reveal the relative risks of imbalance and benefits for balance accruing to each randomization scheme, in a practical sense. One tuplet construction method may result in generally close balance on one key characteristic and very variable balance on the other, while a competing scheme has good median balance on both characteristics, but where each has a long tail implying a few bad-luck assignments with poor balance.

We hope to consider balance on more than two factors, and for assessing the impact on balance in this case, we will use a parallel coordinates plot, a multivariate plot method. A simulated example is shown in Figure 2. There we show a potential result of a single tuplet construction method. The variables shown are volume, baseline rate of an outcome, the baseline rate of chlorhexidine use, and baseline rate of bathing. Each blue, red, green, or black line shows the mean difference between arms for all four variables for one potential realized randomization. The results show that a few randomizations, in blue, are relatively imbalanced on volume and outcome but balanced on chlorhexidine use and bathing, while a few others, in black, have the reverse pattern. The green and red realizations are approximately equally balanced across these variables. If we considered it more important to balance on volume and outcome, this would probably not be an ideal scheme.

Figure 2.



As a final note, we could consider the relative costs and benefits of strata of four, rather than tuplets, which are strata of two. There are sound statistical reasons to expect power to be slightly better with strata of four, although there is some debate on this point. However, the balance between the arms may be worse. The balance is of central importance, since balance ensures that the observed effect is not confounded—confounding requires that the confounder be out of balance between the arms. We will examine whether the

gain in power is strong enough, and the loss of balance slight enough, to pursue strata of four in place of tuplets.

We will focus on balancing the baseline outcome values in participating hospitals, baseline adherence to the HCA guidance for universal decolonization with chlorhexidine and mupirocin, measures of case severity index, and ICU patient day volume. We will additionally consider accounting for demographics, and ICU length of stay.

1.2.6 Phase In Timeline

Trial implementation timeline is shown in Table 3.

Table 3. Implementation Timeline

Process	Timeline
Collect Baseline Data	Data collection, cleaning, and derivation of randomization variables and confirmation of power occurs Summer 2016-Spring 2017
Randomization	Randomization will occur in Spring 2017
Notification	Hospitals notified of randomization status to schedule the relevant hospital committees for approval
Committee Approvals	Jan-Mar 2017
Training	Prior to phase-in, coaching calls, training materials and computer-based training will be launched
Phase In Launch	May-October 2017: Implementation of nasal iodophor in intervention arm. Both arms: pharmacy tracking of nasal decolonization product and feedback reports
Intervention Period	November 2017 – April 2019

Both arms will be provided with training and coaching conference calls and study campaign materials (Table 4). All training and coaching scripts as well as intervention materials will be designed by the Steering Committee, which will meet weekly during the trial. Strategies will heavily favor mechanisms that utilize HCA's current infrastructure for performance improvement and quality improvement projects.

Table 4. Intervention Elements

Type of Element	Leader	Frequency/Comments
Coaching Conference Calls	Investigators	Monthly during intervention
Intervention Tool Kit		
Campaign flyers	Developed by Investigators/study staff	
Powerpoint materials	Developed by Investigators/study staff	
Instructional materials	Developed by Investigators/study staff	
Help line	HCA leaders, study staff	

All training calls will be led by study investigators, Dr. Susan Huang (lead investigator) and Dr. Edward Septimus (site PI for HCA). Campaign materials will be disseminated at the start of the phase-in period, and will include an information packet as well as flyers and web-based information.

1.2.7 Implementation

Intranasal iodophor will be implemented in the intervention arm using an admission order set similar to the current HCA process for universal mupirocin. This arm will receive iodophor product and training during the Phase-In Period (Table 5). The routine care arm will receive refresher training for mupirocin and support for admission order processes during that period to ensure that differential compliance is not a driver of trial results. Both arms will receive refresher training in CHG bathing and processes.

Table 5. Mupirocin-Iodophor Swap Out Trial Protocol Training Materials

Protocol Training	Description
1. Computer Based Training	Arm-specific protocol training module required of all staff in participating units
2. Nursing Protocol	Nursing protocol for use of mupirocin vs. iodophor
3. Dos and Don'ts	Quick reference protocol guide
4. Patient Talking Points	Talking points for common patient questions about the assigned protocol
5. Frequently Asked Questions	Staff answers to common patient questions about the protocol
6. Huddle Training	Periodic refresher training on key protocol points
7. Just in Time Training	On-the-spot training and reference guide for temporary/float nurses
8. Study Related Events	Forms for reporting study related events (iodophor) and side effects (mupirocin)

Toolkit binders with trial instructions and protocols will be provided to each unit nursing and medical director, infection prevention program lead, nurse education team, and Chief Nursing Officer for each participating hospital in each arm.

Feedback on compliance will be provided to each hospital. Usual care hospitals will receive at least monthly compliance data on daily chlorhexidine bathing and use of nasal mupirocin. Iodophor-CHG hospitals will receive at least monthly compliance feedback on daily chlorhexidine bathing and use of nasal iodophor.

Staff skills assessment forms (bathing observation checklist) will be used by peer nurses or the unit nursing director to ensure adherence to the assigned protocol. Nurses in HCA hospitals currently document bathing activities each shift. We will use this electronic documentation for compliance tracking of whether a CHG bath or shower was given. Compliance with nasal decolonization will be tracked through patient and unit-specific automated pharmacy reports for administration of either product. Compliance will be assessed and fed back to unit champions during twice-monthly coaching calls with a goal of 85% compliance, a level we have previously achieved in this population. Periodic maintenance reminders will be provided in both arms and will reflect common lapses identified by ongoing compliance assessments.

Study investigators will perform site visits as needed to various participating hospitals based upon requests for assistance, concerns about application of intervention protocols, or evidence of low compliance. These procedures are comparable to those used by HCA when implementing other Quality Improvement protocols. Oversight for the design and conduct of this trial will be provided by the Steering Committee (see above), which will meet weekly.

1.2.8 Nasal Iodophor

Nasal iodophor will be used for the nasal decolonization regimen for hospitals randomized to Arm 2 (Iodophor arm), using Clorox Nasal Antiseptic Swabs, a 10% povidone-iodine product. This product is FDA cleared for use in the nose and the manufacturer has released guidance for routine use for decolonization. Thus, the use of povidone-iodine swabs in the Swap Out Trial is to apply one swab in a circular motion to each nostril for 30 seconds, twice daily for 5 days.

Clorox Nasal Antiseptic Swabs has a separate set of directions for pre-operative nasal decolonization, which continues to use double the dose for a one-time application. Participating sites will be trained to ensure that they are aware of the differences in manufacturer guidance for routine ICU decolonization vs pre-operative indications which requires application of two swabs per nostril.

1.2.9 Likelihood of Study-Related Events

Regarding safety, we note that 10% iodophor has been the national standard of care for pre-surgical preparation for surgery for decades, including on mucous membranes of the nose and throat. It is also used for nasal decolonization prior to joint surgery, where it has been shown to be better tolerated than mupirocin.[28]

The evidence for anaphylaxis for iodophor has been specifically related to contrast dye where an iodine-containing substance is injected directly into the bloodstream. This type of adverse event carries a 1% risk for direct injection into the bloodstream and is exceedingly rare in the use of iodophor for mucous membranes (so rare that estimates of frequency are not available).

In addition, as part of a pilot decolonization intervention study, povidone-iodine nasal antiseptic swabs were applied to residents in three southern California nursing homes for 6 months. Two swabs were applied in a circular motion to each nostril, twice daily for 5 days every other week (total of 13 weeks of application to residents). Accounting for facility census and protocol adherence, a total of 22,020 applications were administered across all three facilities without any adverse events reported.[29-30] We note that this pilot involved a contributed product from 3M, which was 5% povidone iodine swabs (also FDA cleared for nasal use).

After the above pilot, as part of routine quality improvement, one of the nursing homes continued the use of nasal iodophor, but changed to a 10% povidone-iodine product (Clorox) and used one swab per nostril per application instead of 2 swabs per nostril per application. This was due to the fact that nursing staff felt that the two-swab-per-nostril regimen was redundant in application. Accounting for facility census and protocol adherence, a total of 1,987 applications were administered without any report of adverse events. Given the interest in a simpler regimen, we asked to evaluate whether the effect on nasal decolonization of S. aureus was similar between the prior 5% povidone-iodine two-swab regimen and the 10% one-swab povidone-iodine swab regimen. Nasal and skin cultures were taken from residents confirmed nearly identical reductions in MRSA with the 5% povidone-iodine two-swab regimen and the 10% one-swab povidone-iodine swab regimen.

1.2.10 Monitoring Study-Related Events

To monitor the occurrence of study-related events, a Study-Related Events Submission Form will be provided to Arm 2 facilities to document all events possibly related to use of iodophor, as part of study procedures. Clinical staff will be required to provide specific details regarding the event such as the body parts affected, the agent related to the event, a description of the reaction, and the corrective action that was taken to resolve the event. Clinical staff will be instructed to report all events to their designated nurse manager or director who will securely fax Study-Related Event Forms (iodophor). All clinical decision-making related to study related events will be at the discretion of the treating physician, not trial investigators or study staff, as is routine for quality improvement protocols.

Facilities will be asked to submit Study-Related Event Submission Forms as events are found. We will use our regular trial coaching calls to prompt facilities to report on schedule. Call attendance will be tracked. In the event that a facility is unable to attend, study staff will follow up to obtain a status update. A database will be used to document reported study-related events that take place in participating facilities. This tool will enable the project staff to closely track and assess any events deemed to be associated with the trial. The user will be able to document specific details regarding the event, and it will allow the user to keep a case open if the event is ongoing or close a case if the event is resolved.

Additionally, a Side-Effects Form for mupirocin-related events will be provided to Arm 1 facilities. Clinical staff at Arm 1 facilities will be asked to document and report all events possibly related to use of mupirocin, providing the same type of information as requested in the iodophor form. While nasal mupirocin is not part of the intervention, this information is requested so that the frequency and severity of mupirocin-related events can be compared to that of iodophor.

1.2.11 Outcomes

Individual level data from patients in all participating ICUs will be obtained from the HCA corporate data warehouse, including demographics, census (including ICU patient days), bathing queries, pharmacy (nasal decolonization product administration), diagnostic and procedure codes (enabling comorbidity score assessment), and microbiology testing results.

The primary outcome will be *S. aureus* clinical cultures (MRSA and MSSA) attributed to the participating ICU (>2 days into the ICU stay until 2 days after ICU discharge). Secondary outcomes intended for primary manuscript, include: 1) ICU-attributable MRSA clinical cultures, 2) ICU-attributable all-cause bloodstream infection.

Table 6. Mupirocin-Iodophor Swap Out Trial Outcomes

Outcome	Metric
Primary Trial Outcome	ICU-attributable *S. aureus* clinical cultures (MRSA + MSSA)
Secondary Trial Outcomes	ICU-attributable MRSA clinical cultures ICU-attributable all-cause bloodstream infection

1.2.12 Data Collection

Descriptive data, outcome data and variables for addressing confounding will be derived from microbiology, census, pharmacy, and claims data from participating hospitals. The following data elements will be collected (Table 6) using encrypted study IDs.

Table 6. Data Elements

Source Data	Result Types	Elements
Microbiology: Finalized Results	All positive and negative cultures	Pathogen name (if culture is positive), patient identifier, date of collection, body site of collection, antimicrobial susceptibility
Census Data	Line item per admission	Patient identifier, hospital admission date, hospital discharge date, ICU vs. non-ICU charge code by calendar date, age in years, gender
Claims Data	Line item per admission	For case mix adjustment: Diagnosis codes (ICD9-ICD10) Procedure codes (ICD9/ICD10/CPT codes)
Pharmacy	Mupirocin and iodophor dispensing	Patient identifier, date range dispensed, ICU location

Nursing Queries	Bathing responses	Data on whether a bath was given, and if yes, with a CHG or non-CHG bathing soap product.

We will use claims data to collect diagnostic and procedure codes that will be used for case mix adjustment for both hospital-wide, ICU-specific, and post-ICU outcomes. Case mix will be assessed using a comorbidity score (e.g. Elixhauser score) as well as evaluating the individual components of that score (e.g. diabetes, renal disease) and evidence of major surgery.

1.2.13 Statistical Analysis and Power

The primary analysis will be an as-randomized proportional hazards model to evaluate for noninferiority at a margin of 10% (difference in relative hazard). Model terms will include arm, period (baseline vs. intervention) and an arm by period interaction term to assess whether the difference in relative hazard between the baseline and intervention period differs significantly between the two arms. Clustering within hospital will be accounted for using shared frailties, i.e., a random intercept for each hospital, and, if it should become technologically feasible, an additional random intercept for each ICU within hospital and for repeated hospital stays for each person.

- Null hypothesis (H_0): the change in relative hazard of clinical culture of *S. aureus* in the Iodophor-CHG arm is higher than (inferior to) the change in the Mupirocin-CHG arm by more than 10%
- Alternative hypothesis (H_1): the change in relative hazard of clinical culture of *S. aureus* in the Iodophor-CHG arm is higher than (inferior to) the Mupirocin-CHG arm by 10% or less

Phase-in period data will not be included in the analysis.

To be explicit, the primary analysis will take the form of $\lambda_{ij}(t) = \lambda_0(t)e^{\beta_1 Arm_{ij}+\beta_2 Per_{ij}+\beta_3 Arm_{ij}*Per_{ij}+\gamma_i}$ where $\lambda_{ij}(t)$ is the time t of the *S. aureus* clinical culture for person j at hospital i. The baseline hazard function for time t, $\lambda_0(t)$, is shared by all people; $\gamma_i$is the frailty shared by patients at hospital i. The linear predictor in the exponent functions as in a linear model, where Arm_{ij} indicates the treatment arm of person j in hospital i is the iodophor arm, and Per_{ij} indicates that person j in hospital i was seen in the intervention period. Thus β_3 is the estimated differential effect of iodophor relative to mupirocin in the intervention period compared to baseline. While software is currently not able to include frailties for multiple visits per person or for multiple ICUs per hospital on the scale of the data, we will include them if this should become possible by the time the trial is analyzed.

The primary outcome of the trial is ICU-attributable *S. aureus* clinical cultures (MRSA + MSSA) where ICU-attributable is defined as *S. aureus* cultures occurring in specimens collected from study cohort patients from the 3rd day of an ICU stay through 2 days after ICU discharge. This outcome will be assessed using an as-randomized unadjusted proportional hazards model as described above with two-sided significance set at alpha = 0.05, consistent with FDA standards of non-inferiority (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials). The pre-specified non-inferiority margin, we repeat, is 10%.

There is reason to suspect that nasal iodophor may be inferior to mupirocin due to FDA clearance based upon suppression versus cidal kill for *S. aureus*, which is the reason for the non-inferiority trial. However, conversely, if iodophor is found to be non-inferior, we are declaring the a priori intent to assess for superiority because of evidence of mupirocin-resistant *S. aureus* strains where none is expected to exist for iodophor. For this reason, if iodophor is found to be non-inferior in the primary outcome of the trial, we will also report the pre-specified assessment of superiority which is already performed in the primary analysis.

Secondary non-inferiority outcomes include 1) ICU-attributable MRSA clinical cultures and 2) ICU-attributable all-cause bloodstream infection. These will be assessed using an as-randomized unadjusted proportional hazards model as described above. We will use two-sided significance tests set at alpha = 0.05 for each outcome to determine possible inferiority with greatest possible sensitivity, again with a non-inferiority margin of 10%. Due to the above antibiotic-resistance rationale to suspect possible superiority, if non-inferiority is met for these secondary outcomes, we will perform a pre-specified assessment of superiority at a two-tailed significance set at alpha = 0.025, which accounts for the multiple comparisons of two outcomes. To be clear, the non-inferiority tests are not adjusted for multiple testing, while the superiority tests, if they are performed, will be adjusted for multiple testing, for conservatism.

Additional analyses will include as-treated and adjusted models, which will be reported as point estimates with confidence intervals without p-values. The reason for including these analyses is to provide additional information related to the trial outcomes for reader assessment of potential confounders. The reason to not include them in a formal multiple comparisons adjustment is because these analyses are non-independent evaluations related to the as-randomized unadjusted analyses.

While 140 HCA hospitals are eligible for recruitment, we have HCA corporate commitment to assure the participation of at least 120 hospitals. Power was assessed using simulation methods. We simulated hospitals using information from HCA regarding ICU size and from a prior trial (REDUCE MRSA Trial) regarding likely rates of *S. aureus* in the baseline period. With 120 hospitals, we will have 82% power to detect non-inferiority within a hazard ratio of 1.1, based upon 2014 HCA ICU-attributable *S. aureus* clinical cultures of 4.8 cases per 1,000 ICU-days. While the intent is to confirm non-inferiority, we assume that iodophor will eradicate 5% more *S. aureus* than mupirocin due to existing mupirocin resistance. We estimate that total ICU patients in the intervention period will be ~171,500 patients who stay >2 ICU days.

References

1 Fagan RP, Edwards JR, Park BJ, Fridkin SK, Magill SS. Incidence trends in pathogen-specific central line-associated bloodstream infections in US intensive care units, 1990-2010. Infect Control Hosp Epidemiol. 2013 Sep;34(9):893-9.

2 Burton DC, Edwards JR, Srinivasan A, Fridkin SK, Gould CV. Trends in catheter-associated urinary tract infections in adult intensive care units-United States, 1990-2007. Infect Control Hosp Epidemiol. 2011 Aug;32(8):748-56.

3 Burton DC, Edwards JR, Horan TC, Jernigan JA, Fridkin SK. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997-2007. JAMA. 2009 Feb 18;301(7):727-36.

4 Huang SS, Septimus E, Kleinman K, Moody J, Hickok J, Avery TR, Lankiewicz J, Gombosev A, Terpstra L, Hartford F, Hayden MK, Jernigan JA, Weinstein RA, Fraser VJ, Haffenreffer K, Cui E, Kaganov RE, Lolans K, Perlin JB, Platt R; CDC Prevention Epicenters Program; AHRQ DECIDE Network and Healthcare-Associated Infections Program. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med. 2013;368(24):2255-65.

5 van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing *Staphylococcus aureus* infections in nasal carriers. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD006216.

6 Watanakunakorn C, Axelson C, Bota B, Stahl C. Mupirocin ointment with and without chlorhexidine baths in the eradication of *Staphylococcus aureus* nasal carriage in nursing home residents. Am J Infect Control. 1995 Oct;23(5):306-9.

7 Harbarth S, Dharan S, Liassine N, Herrault P, Auckenthaler R, Pittet D. Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother. 1999 Jun;43(6):1412-6.

8 Climo MW, Yokoe DS, Warren DK, Perl TM, Bolon M, Herwaldt LA, Weinstein RA, Sepkowitz KA, Jernigan JA, Sanogo K, Wong ES. Effect of daily chlorhexidine bathing on hospital-acquired infection. N Engl J Med. 2013;368(6):533-42.

9 Milstone AM, Elward A, Song X, Zerr DM, Orscheln R, Speck K, Obeng D, Reich NG, Coffin SE, Perl TM; Pediatric SCRUB Trial Study Group. Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: a multicentre, cluster-randomised, crossover trial. Lancet. 2013 Mar 30;381(9872):1099-106.

10 Schweizer ML, Chiang HY, Septimus E, Moody J, Braun B, Hafner J, Ward MA, Hickok J, Perencevich EN, Diekema DJ, Richards CL, Cavanaugh JE, Perlin JB, Herwaldt LA. Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip, or knee surgery. JAMA. 2015 Jun 2;313(21):2162-71.

11 O'Grady S, Hirji Z, Pejcic-Karapetrovic B, Fung S, Dedier H, Takata-Shewchuk J, Zhang K, Conly J. A double-blind, randomized, controlled trial of topical polysporin triple compound versus topical mupirocin for the eradication of colonization with methicillin-resistant *Staphylococcus aureus* in a complex continuing care population. Can J Infect Dis Med Microbiol. 2009 Fall;20(3):e49-55.

12 Bode LG, Kluytmans JA, Wertheim HF, Bogaers D, Vandenbroucke-Grauls CM, Roosendaal R, Troelstra A, Box AT, Voss A, van der Tweel I, van Belkum A,Verbrugh HA, Vos MC. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. N Engl J Med. 2010 Jan 7;362(1):9-17.

13 Lolans K, Haffenreffer K, Avery TR, Kleinman K, Li H, Kaganov RE, Lankiewicz J, Moody J, Septimus E, Weinstein RA, Hickok J, Jernigan J, Perlin JB, Huang SS, Platt R, Hayden MK. Chlorhexidine (CHG) and mupirocin susceptibility of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in the REDUCE-MRSA trial. IDWeek: A Joint Meeting of the Infectious Disease Society of America, Society for Healthcare Epidemiology of America, HIV Medicine Association, and the Pediatric Infectious Disease Society. Philadelphia, PA. October 8-12, 2014.

14 Patel JB, Gorwitz RJ, Jernigan JA. Mupirocin resistance. Clin Infect Dis. 2009;49(6):935-41.

15 Robicsek A, Beaumont JL, Thomson RB, Govindarajan G, Peterson LR. Topical therapy for methicillin-resistant *Staphylococcus aureus* colonization: impact on infection risk. Infect Control Hosp Epidemiol 2009;30:623-32.

16 Upton A, Lang S, Heffernan H. Mupirocin and *Staphylococcus aureus:* a recent paradigm of emerging antibiotic resistance. J Antimicrob Chemother 2003;51: 613-7.

17 Vivoni AM, Santos KR, de-Oliveira MP, Giambiagi-deMarval M, Ferreira AL, Riley LW, Moreira BM. Mupirocin for controlling methicillin-resistant *Staphylococcus aureus*: lessons from a decade of use at a university hospital. Infect Control Hosp Epidemiol. 2005 Jul;26(7):662-7.

[18] Harbarth S, Dharan S, Liassine N, Herrault P, Auckenthaler R, Pittet D. Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant *Staphylococcus aureus.* Antimicrob Agents Chemother 1999;43:1412-6.
[19] Simor AE, Stuart TL, Louie L, et al. Mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* strains in Canadian hospitals. Antimicrob Agents Chemother 2007;51:3880-6.
[20] Fleischer W, Reimer K. Povidone-iodine in antisepsis--state of the art. Dermatology.1997;195 Suppl 2:3-9.
[21] Sheldon AT Jr. Antiseptic "resistance": real or perceived threat? Clin Infect Dis. 2005 Jun 1;40(11):1650-6.
[22] van Meurs SJ, Gawlitta D, Heemstra KA, Poolman RW, Vogely HC, Kruyt MC. Selection of an optimal antiseptic solution for intraoperative irrigation: an in vitro study. J Bone Joint Surg Am. 2014;96(4):285-91.
[23] Reimer K, Wichelhaus TA, Schäfer V, Rudolph P, Kramer A, Wutzler P, Ganzer D, Fleischer W. Antimicrobial effectiveness of povidone-iodine and consequences for new application areas. Dermatology. 2002;204 Suppl 1:114-20.
[24] Capriotti K, Capriotti JA. Topical iodophor preparations: chemistry, microbiology, and clinical utility. Dermatol Online J. 2012;18(11):1.
[25] Clayton MI, Osborne JE, Rutherford D, Rivron RP. A double-blind, randomized, prospective trial of a topical antiseptic versus a topical antibiotic in the treatment of otorrhoea. Clin Otolaryngol Allied Sci. 1990 Feb;15(1):7-10.
[26] Freeman RB, Smith WM, Richardson JA, Hennelly PJ, Thurm RH, Urner C, Vaillancourt JA, Griep RJ, Bromer L. Long-term therapy for chronic bacteriuria in men. U.S. Public Health Service cooperative study. Ann Intern Med. 1975 Aug;83(2):133-47.
[27] Septimus E, Hickok J, Moody J, Kleinman K, Avery TR, Huang SS, Platt R, Perlin J. Closing the Translation Gap: Toolkit Based Implementation of Universal Decolonization in Adult Intensive Care Units Reduces Central Line Associated Bloodstream Infections in 95 Community Hospitals. Clin Infect Dis. 2016 May; 63(2):172-7.
[28] Maslow J, Hutzler L, Cuff G, Rosenberg A, Phillips M, Bosco J. Patient experience with mupirocin or povidone-iodine nasal decolonization. Orthopedics. 2014 Jun;37(6):e576-81.
[29] McKinnell JA,* Miller LG,* Singh R, Kleinman K, Peterson E, Evans KD, Dutciuc TD, Heim L, Gombosev A, Estevez M, Launer B, Tjoa T, Tam S, Bolaris MA, Huang SS. Prevalence and Factors Associated with Multidrug Resistant Organism (MDRO) Colonization in Three Nursing Homes. Infect Control Hosp Epidemiol. 2016. In press.
[30] Miller LG, McKinnell JA, Singh R, Kleinman K, Gombosev A, Dutciuc T, Evans K, Tjoa T, Heim L, Launer B, Bolaris M, Ramsay K, Kim D, Estevez M, Peterson E, Huang SS. Reduction of MDRO Colonization in Nursing Home Residents with Routine Use of Chlorhexidine Bathing and Nasal Iodophor (Project PROTECT). IDWeek (5th Annual Joint Meeting of IDSA, SHEA, HIVMA, and PIDS), October 26-30, 2016 (New Orleans, LA).