Supplementary Online Content

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eAppendix . BUGG Statistical Analysis Plan

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

BUGG Statistical Analysis Plan (1/11/13)

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LIST OF ABBREVIATIONS

CAUTI	Catheter-Associated Urinary Tract Infection
CLABSI	Central Line Associated Blood Stream Infection
HCW	Healthcare Worker
HH	Hand Hygiene
HIPAA	Health Insurance Portability and Accountability Act
MRSA	Methicillin-resistant *Staphylococcus aureus*
NHSN	National Healthcare Safety Network
VAP	Ventilator-Associated Pneumonia
VRE	Vancomycin-resistant *enterococci*

1. BACKGROUND AND PROTOCOL HISTORY

This statistical analysis plan is designed to augment the BUGG manual of operations and protocol. Please see manual of operations and protocol for details of this study.

2. PURPOSE OF THE ANALYSIS

The purpose of this analysis plan is to specify details for the principal set of analyses to be performed at the completion of the intervention period following closure of the clinical database.

3. STUDY AIMS AND ENDPOINTS

a. Primary Endpoint

The outcome of interest is the acquisition of an antibiotic-resistant pathogen. In the protocol this was defined as VRE or MRSA as determined by perianal surveillance cultures for VRE and by nasal surveillance cultures for MRSA. For the purposes of power calculations and defining a primary statistical outcome, we will be analyzing the composite outcome of acquisition of VRE or MRSA. Key secondary endpoints will be VRE and MRSA analyzed as individual outcomes.

b. Secondary Endpoints

1. Acquisition of VRE or MRSA analyzed as individual outcomes as described above.

2. Hospital-acquired infections (HAIs), including catheter-associated bloodstream infection, catheter-associated urinary tract infection and ventilator-associated pneumonia as a composite HAI outcome and individually. HAIs will be defined using the standard definitions of the National Healthcare Safety Network (NHSN) of hospitals.[1]

3. Overall bacteremia rates and overall *C. difficile* rates as determined by administrative data pulls.

4. Care-related factors such as healthcare worker visits, healthcare worker hand-hygiene compliance, and non-infectious adverse events. Non-infectious adverse

events will be measured by a modified Institute for Healthcare Improvement (IHI) trigger tool.[2]

5. Length of ICU stay as determined by ICU admission and discharge (or ICU death)

6. Length of hospital stay as determined in aggregate by hospital administrative data.

7. Death from any cause during the ICU stay and death from any cause during the hospital stay.

4. STUDY METHODS

a. Overall study design and plan

The study was designed as a cluster randomized trial that took place during the period from September 2010 to September 2012. This time frame incorporated a planned baseline matching period from 9/11/2011-11/10/2011. Each of the ICUs was randomized using a matched-pairs design based on baseline transmission rates. The randomization process was completed in December 2011. ICUs were randomized either to implement universal glove and gowning procedures or to continue with the standard of care. ICUs could not perform active surveillance. During the intervention phase of the study, all healthcare workers (nurses, physicians, nurse extenders, respiratory therapists, social workers etc.) in the intervention group were required to wear gloves and gowns for patient contact and when entering any patient room. Compliance with gown and glove use, hand hygiene and frequency of healthcare worker entry were monitored by observers. The intervention period began on January 4, 2012 and continued for 9 months until October 4, 2012.

References are made to patient-level data or analyses throughout this analysis plan. In fact these are actually at the ICU visit level. That is, it was possible for a subject to have data collected for multiple ICU admissions. For the purpose of these analyses, ICU admissions will be treated independently.

b. Selection of study sites

i. Inclusion Criteria

ICUs that were included were: adult medical, surgical or combined medical surgical ICU defined as:

- Medical ICU (MICU) ≥ 80% of patients have a medical condition and have not undergone a surgical procedure during the current hospital stay
- Surgical ICU (SICU) ≥ 80% of the patients have undergone a surgical procedure during the current hospital stay
- Combined Medical/Surgical ICU (MICU/SICU) – a roughly equivalent mixture of patients with medical conditions who have not undergone surgical procedures and patients who have undergone surgical

procedures during the current hospital stay. Each group makes up > 20% and less than 80% of the total number of patients
- Written approval of the study from the institution's IRB. The institution had the ability to rely on the IRB approval provided by the central IRB at the University of Maryland, School of Medicine
- Agreement to not perform active surveillance for MRSA or VRE that will be fed back to patients during the study period

ii. Exclusion Criteria

Pediatric ICUs and other non-medical or non-surgical ICUs were excluded.

c. Randomization

In December 2011, after the baseline period was complete, randomization occurred at the ICU level. ICUs were matched by the rate of colonization acquisition with MRSA or VRE (primary outcome of study) during the baseline period. All 20 ICUs were randomized. Sites were ranked according to their baseline colonization acquisition incidence rate. ICUs were grouped together to form blocks of size 2 (i.e., matched pairs). Within each block, ICUs were randomly assigned to standard control strategy or universal glove and gown in a 1:1 ratio so that all sites had a 50% probability of being assigned to either study arm.

d. Blinding

Because of the nature of the strategies being evaluated in this study, blinding of the assignment of the ICU to the universal glove and gown or standard control strategy was impossible. The investigators were aware of the assignment of each ICU in order to monitor implementation of each strategy (although all adverse event attribution was conducted without knowledge of assignment on the part of the two physician review).

5. ANALYSIS POPULATIONS

None of the 20 ICUs dropped out of the study. All 20 ICUs are the analysis population. All patients in the ICU were part of the analysis population except for pregnant women, prisoners and minors who did not have nasal or perianal cultures obtained.

6. DERIVED AND COMPUTED VARIABLES

a. General strategy for aggregating data at the month and period level

The following sections on derived and computed variables reference several derived variables that are defined for the baseline and intervention period as well as for each month of the baseline period and the intervention period.

i. Baseline

Sites initiated data collection by September 7, 2011.

ii. Randomization/implementation

There will be no estimates (monthly or period) based on patient-level data for the randomization/implementation period for the month of December 2011 in which baseline was complete and the intervention had not yet begun.

iii. Intervention

For the intervention period (January 4, 2012 – October 4, 2012), estimates for January 2012 will be based on data starting January 4, 2012, and data for the first 4 days of October 2012 will be incorporated into September.

b. General strategy for weighting data

For the purpose of describing the ICU populations under study and for adjusting efficacy analyses for characteristics aggregated at the ICU level, efforts will be taken to weight estimates to reflect the entire population of ICU admissions at each site within a study period.

c. Length of stay

ICU LOS will be calculated for all ICU admissions and therefore weighting is not necessary. ICU LOS will be computed by allowing ½ day for the day of ICU admission, ½ day for the day of ICU discharge, and 1 day for each ICU day between admission and discharge. For ICU admissions where the admission and discharge dates differ (i.e., discharge does not occur on the same date as admission), this calculation is algebraically equivalent to calculating discharge date – admission date. For ICU admissions where the dates of admission and discharge are the same, this approach is algebraically equivalent to assigning 0.5 days for LOS.

For each ICU and for both the baseline and intervention period separately (but not for individual months), we will calculate the average LOS.

For total hospital length of stay, data is obtained from each hospital on a monthly basis. This is calculated as the date between admission to the hospital and date of discharge from the hospital for patients who were admitted to the study ICU. These data are available only in aggregate.

d. Swab collection and microbiology

All swabs were collected at each individual ICU and on an individual patient level and then cultured in the central microbiology lab as described in the MOP and protocol. All positive cultures for potential MRSA or VRE were confirmed with polymerase chain reaction (PCR). VRE isolates obtained during the baseline period were confirmed by PCR prior to randomization. MRSA isolates obtained during the baseline period were *not* confirmed by PCR prior to randomization due to time constraints required by the intervention sites to plan intervention implementation. All isolates were confirmed by PCR by the end of the study.

e. Colonization/infection and patient-days at risk

i. Colonization with MRSA at time of ICU admission:

A patient is considered to have been colonized (positive) with MRSA if a positive MRSA resulted from a nasal surveillance culture collected upon admission to the ICU.

ii. Colonization with VRE at time of ICU admission:

A patient is considered to have been colonized (positive) with VRE if a positive VRE resulted from a perianal surveillance culture collected upon admission to the ICU.

iii. Outcome:

The outcome of interest is the acquisition of an antibiotic-resistant pathogen consisting of VRE or MRSA as determined by perianal surveillance cultures for VRE and by nasal surveillance cultures for MRSA. The outcomes will be analyzed primarily as a composite outcome (VRE or MRSA) and as a key secondary outcome secondarily as two separate, individual outcomes.

A patient with acquisition will be defined as:

1. A patient who has an initial ICU surveillance culture that is negative for an antibiotic-resistant pathogen.
2. A patient with subsequent discharge surveillance culture within the same ICU admission that is positive for an antibiotic-resistant pathogen.

iv. New colonization event for either MRSA or VRE (Primary Endpoint):

A subject is eligible for a new colonization event with MRSA or VRE for a given ICU visit if eligibility criteria for either MRSA or VRE events are satisfied as described above e.g. a patient colonized with VRE on admission surveillance culture but not colonized with MRSA on admission surveillance culture is eligible to acquire MRSA on ICU discharge surveillance culture. Both MRSA and VRE events are assessed at the same time, at the time of ICU discharge when surveillance discharge cultures are obtained. It may be possible for the subject to have a second colonization event at a subsequent ICU admission.

Patient-days at risk for colonization with MRSA or VRE

For both endpoints, the patient days at risk for each ICU stay eligible for new colonization event will be calculated as the length of ICU stay, described above.

f. Incidence rate of colonization

i. Incidence rate of colonization with MRSA

Incidence rate of colonization with MRSA (number of new colonization events per 1000 patient ICU days at risk) will be calculated separately for the baseline and intervention period and for each month during these periods using the following formula:

$$IR = \frac{\#\text{ ICU admissions with new MRSA colonization event}}{\#\text{ patient-days at risk}} \times 1000$$

Only ICU admissions eligible for a new colonization event with MRSA will contribute data to the incidence rate calculation. For each ICU, the number of patient-days at risk and the number of new colonization events for MRSA will also be summed across the study period.

ii. Incidence rate of colonization with VRE

Incidence rate of colonization with VRE (number of new colonization events per 1000 patient ICU days at risk) will be calculated separately for the baseline and intervention period and for each month during these periods using the following formula:

$$IR = \frac{\#\text{ ICU admissions with new VRE colonization event}}{\#\text{ patient-days at risk}} \times 1000$$

Only ICU admissions eligible for a new colonization event with VRE will contribute data to the incidence rate calculation. For each ICU, the number of patient-days at risk and the number of new colonization events for VRE will be summed across the study period.

iii. Incidence rate of colonization with MRSA or VRE

Incidence rate of colonization with MRSA or VRE (number of new colonization events per 1000 patient ICU days at risk) will be calculated separately for the baseline and intervention period and for each month during these periods using the following formula:

$$IR = \frac{\#\text{ ICU admissions with new MRSA or VRE colonization event}}{\#\text{ patient-days at risk}} \times 1000$$

Only ICU admissions eligible for a new colonization event with MRSA or VRE will contribute data to the incidence rate calculation. For each ICU, the number of patient-days at risk and the number of new colonization events for MRSA or VRE will be summed across the study period. Events will contribute to the period in which they occurred.

g. Subgroup estimates

We will also estimate MRSA, VRE, and MRSA or VRE incidence rates in subgroups defined by type of facility (MICU vs. SICU vs. MICU/SICU) and ICU size (ICU-level factors).

h. Hospital-acquired infections

We will calculate the following hospital-acquired infection rates: central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), and ventilator-associated pneumonia (VAP). Consistent with the CDC National Hospital Safety Network, we will use the following formulas:

$$\text{CLABSI rate} = \frac{\#\text{ICU admissions with new CLABSI event}}{\#\text{central-line days at risk}} \times 1000$$

$$\text{CAUTI rate} = \frac{\#\text{ICU admissions with new CAUTI event}}{\#\text{catheter-days at risk}} \times 1000$$

$$\text{VAP rate} = \frac{\#\text{ICU admissions with new VAP event}}{\#\text{ventilator-days at risk}} \times 1000$$

The above rates will be calculated for both the baseline and intervention periods.

i. Hospital bacteremias

We will measure the rate of positive blood cultures or bacteremias per 1000 patient days. These data will be obtained from laboratory records from each hospital ICU. These data will be analyzed as a single outcome and also by type of organism (e.g. MRSA, VRE etc.) The organisms will also be categorized into groups including Gram-positive bacteria, Gram negative bacteria, contaminants and non-contaminants and the data will be analyzed using these categories. These data will initially be analyzed comparing sites on the intervention to control, that will adjust for other factors. The rate of bacteremia will be calculated using the following formula:

$$\text{Bacteremia rate} = \frac{\#\text{ICU admissions with new bacteremia event}}{\#\text{patient-days at risk}} \times 1000$$

We will also calculate the following:

$$\text{Bacteremia rate} = \frac{\#\text{positive blood cultures while in the ICU}}{\#\text{patient-days at risk}} \times 1000$$

j. Hospital *Clostridium difficile* infections

We will measure the rate of *C. difficile* positive tests per 1000 patient days. These data will be obtained from laboratory records from each hospital ICU. These data will be analyzed as a single outcome. These data will initially be analyzed comparing sites on the intervention to control, that will be adjusted for other factors. The rate of *C. difficile* will be calculated using the following formula:

$$\text{C difficile rate} = \frac{\#\text{ICU admissions with new C difficile event}}{\#\text{patient-days at risk}} \times 1000$$

k. Mortality

i. ICU mortality

We will measure the mortality rate in the ICU. The number of deaths will be the number of patients admitted to the study ICU who died <u>while in the study ICU</u> during the same admission. This is the number of patients among those who

were admitted during the month who ended up dying in the ICU. Time at risk is defined as the ICU lengths of stay

ii. Hospital mortality

We will also measure the mortality rate in the hospital. The number of deaths will be the number of patients who were admitted to the study ICU who died while in the hospital during the same admission. This is the number of patients among those who were admitted during the month who ended up dying in the hospital. Time at risk is defined from admission to the ICU to discharge (or death) in the hospital.

We will flag deaths that occur within ICU and hospital admission. The mortality rate in the ICU and hospital will be calculated for the baseline and intervention periods using the following formulas:

$$\text{ICU Mortality Rate} = \frac{\#\text{ ICU admissions who die in the ICU}}{\#\text{ ICU patient-days at risk}} \times 1000$$

$$\text{Hospital Mortality Rate} = \frac{\#\text{ ICU admissions who die in the hospital}}{\#\text{ hospital patient-days at risk}} \times 1000$$

Note that for the initial analyses, ICU admissions will be treated independently. Therefore, a single subject with multiple ICU admissions during a period may contribute to the denominator of cumulative incidence more than once, but obviously at most once to the numerator.

Censoring on a monthly basis was necessary as mortality data was obtained in aggregate through a data pull from hospital data.

l. Healthcare worker visits

The average number of healthcare worker (HCW) visits per half-hour observation period will be calculated using the following formula:

$$\text{Mean} = \frac{\#\text{ HCW visits}}{\#\text{ half-hour observation periods}}$$

This calculation will be performed separately for the intervention and standard control sites. The calculation for standard control sites will additionally be stratified for patients on contact precautions and patients not on contact precautions at the time of observation.

We requested that sites perform 16 30-minute observations per month for a total of 480 minutes of observations per site.

m. Glove and gown compliance

The proportion of healthcare worker visits that are gown compliant will be calculated used the formula:

$$\text{Gown} = \frac{\#\text{HCW visits with gown compliance}}{\#\text{HCW visits}}$$

The proportion of healthcare worker visits that are glove compliant will be calculated using the formula:

$$\text{Glove} = \frac{\#\text{HCW visits with glove compliance}}{\#\text{HCW visits}}$$

We requested that sites perform 16 30-minute observations per month for a total of 480 minutes of observations per site.

Both calculations will be made separately for control and intervention sites, but the visits for control sites compliance will be reported for patients on contact precautions.

n. Hand-hygiene compliance

The proportion of healthcare worker visits that are hand-hygiene (HH) compliant upon room entry and exit will be calculated using the formula:

$$\text{HH room entry} = \frac{\#\text{HCW visits with HH entry compliance}}{\#\text{HCW visits}}$$

The proportion of healthcare worker visits that HH exit compliant upon room exit will be calculated using the formula:

$$\text{HH room exit} = \frac{\#\text{HCW visits with HH exit compliance}}{\#\text{HCW visits}}$$

We requested that sites perform 16 30-minute observations per month.

Both calculations will be made separately for standard control and intervention sites. Additional calculations for control sites will also be stratified by whether the patient was on contact precautions.

o. Other ICU characteristics and patient characteristics at the ICU level

i. Enrollment

$$\#\text{ ICU admissions per 30 days} = \frac{\#\text{ICU admissions}}{\#\text{days in period}} \times 30$$

$$\#\text{ patient-days per 30 days} = \frac{\#\text{sum LOS}}{\#\text{days in period}} \times 30$$

ii. Demographics

- Sex: % male; % female
- Age: Mean age (yr)

- Primary ICD-9 codes for admission: % in the 5 most common ICD-9 codes encountered in the study at admission and "other."
  These 3 variables have been requested as part of a data pull submitted in aggregate for each participating intensive care unit from administrative data that is available on a monthly basis.

7. STUDY CHARACTERIZATION ANALYSES

Because the primary unit of analysis is the ICU, all study characterization data will be focused on the ICU level.

a. ICU and patient characteristics

Using the ICU as the unit of analyses, 3 types of ICU-level comparisons will be made on characteristics of the ICU and the patient population within the ICU. These are as follows:

1. Baseline period – compare sites assigned to standard control with those assigned to intensive control. ICU level variables will be compared using weighted paired t-tests to account for the pair-matched design. The weighting accounts for differences in the number of patients or number of patient-days (LOS) where applicable.

2. Intervention period – compare sites assigned to standard control with those assigned to intensive control. The analysis approach will be similar to #1.

3. Across period – Weighted paired t-tests will assess within-site changes across period, separately for standard control and intervention sites. Next, within-site changes will be compared between standard control and intervention sites using weighted paired t-tests and weighted paired Wilcoxon rank-sum tests.

   Following is a list of population characteristics:

   - Enrollment (ICU admission rate) per month
   - Patient-days in ICU per month
   - ICU LOS and total hospital LOS
   - Gender
   - Central-line days
   - Catheter-days
   - Ventilator-days
   - Age

   In addition to the 3 comparisons listed above (within baseline period, within intervention period, and across periods), ICU-level data aggregated at the monthly level (rather than study period) will also be examined by regressing within-pair differences on time using weighted linear regression and a with a random matched-pair effect to see if there are changes over time.

   To be consistent with CONSORT Statement recommendations[3], findings from this analysis will not be used to determine covariates for adjustment in secondary

efficacy analyses (section 8). Rather, this analysis will be used to assess randomization in the baseline period, determine consistency of case-mix within site across periods, and aid in interpretation of results of efficacy analysis.

b. Compliance with protocol specified assessments and assigned intervention

i. Swab collection

For all visits, admission perianal and nasal swabs were to be collected within one day of ICU admission. Rates for on-time swab collection will be summarized by site as well as across all sites separately for nasal and perianal swabs, and separately for the baseline and intervention period as well as for the 2 periods combined.

Discharge swabs were to be collected within 2 days before or after discharge. For all ICU admissions, rates for on-time discharge swab collection will be summarized by site as well as across all sites separately for nasal and perianal swabs, and separately for the baseline and intervention period as well as for the 2 periods combined.

ii. ICU-Level data

For hand-hygiene compliance and gown and glove compliance, mean and standard deviation for number of observation sessions, days and hours per week of study participation will be presented for each site separately for the baseline and intervention period.

8. EFFICACY ANALYSES

a. Primary efficacy analyses

The primary analysis will use the ICU as the unit of analysis and will compare the change in incidence rate of new colonization events with MRSA or VRE in ICUs implementing the intensive control strategy compared to those using the standard control strategy during the intervention period relative to the incident rate in the baseline period.

The primary hypothesis, that the incidence rate of acquired MRSA and VRE as a composite outcome (MRSA or VRE; primary endpoint) and individual antibiotic-resistant outcomes (key secondary endpoints) will drop more in ICUs implementing the intervention compared to those implementing the standard control strategy will be tested using a weighted paired t-test. The weighting accounts for potential differences in cluster sizes (i.e., patient-time at risk) between ICUs. The test will be performed by calculating matched-pair differences (intervention – control) of within-site changes (intervention period – baseline period).[4] The hypotheses of differences in changes in the outcome between the 2 control strategies will be tested formally with $\alpha=0.05$ with no adjustment for multiple comparisons.

i. Subgroup analysis by type of facility

These evaluations will be assessed by a weighted regression of intervention-period MRSA or VRE rates on intervention assignment after adjusting for baseline rates, facility type, and intervention assignment-by-facility interaction terms with a random effect for matching group.

Descriptive p-values of 0.05 or less based on a test that the interaction terms are 0 will be used as evidence of differences in control strategy effect across facility types. For instances in which differences are found, stratified analyses will be used to describe the control strategy effects for the associated facility types.

b. Secondary efficacy analyses

i. Hospital-Acquired Infections: CAUTI, CLABSI, VAP

Rates of HAI will be compared between intervention and control sites using a strategy similar to that for the primary efficacy analysis. Thus, the ICU will be the unit of analysis.

A secondary site-level analysis will be performed using quasi-Poisson linear mixed effects models with a random effect to account for site. This approach will compare intervention-period HAI rates between intervention and standard control sites while controlling for site-level baseline rates as a covariate, log of site-level catheter-days, log of site-level central-line days, and log of site-level ventilator days as offsets for CAUTI, CLABSI, and VAP, respectively. The use of quasi-Poisson distributions allows over- or under-dispersion relative to the Poisson distribution.

ii. Length of ICU stay

Length of stay will be operationalized as time until ICU discharge to compare discharge rates between intervention and control sites. The same methods for the primary efficacy analysis can be used (in this case, weighted t-tests to compare differences in changes in discharge rates).

A patient-level time-to-discharge analysis will also be performed. Time to discharge during the intervention period will be analyzed to compare discharge rates between intervention and standard control sites using the Cox proportional hazards frailty model (to account for within-ICU correlation).[5]

iii. Mortality

Mortality will be operationalized as rate of death in the ICU and hospital as described above. The same methods for the primary efficacy analysis can be used (in this case, weighted t-tests to compare differences in changes in mortality rate).

iv. Healthcare worker visits

Rates of healthcare-worker visits will be compared between intervention and control sites using a weighted t-test of within matching-group differences. In

this case, weighting will account for the differences in number of observation periods between the sites. A secondary analysis will compare patients in intervention sites to patients in control sites on contact proportions using a weighted t-test.

v. Glove and gown compliance

Rates of gown compliance and glove compliance will be compared between patients in intervention sites and patients on contact precautions in control sites using a weighted t-test of within matching-group differences. In this case, weighting will account for the differences in number of healthcare worker visits between the sites.

vi. Hand-hygiene compliance

Rates of hand-hygiene room entry and room exit compliance will be compared between patients in intervention sites and patients in control sites using a weighted t-test of within matching-group differences. In this case, weighting will account for the differences in number of healthcare worker visits between the sites. A secondary analysis will be done comparing hand hygiene between intervention sites and control sites for only patients on contact precautions in control sites.

9. SAFETY ANALYSES

To understand if the intervention is associated with more adverse events, random patient chart reviews are being conducted. Adverse events are defined as "harm related to medical care and not the patient's underlying condition."[2] Chart review will be accomplished using the guided Institute for Healthcare Improvement Trigger Tool Chart review.[2,6] After a training session and review of sample cases, reviewers at each site receive monthly lists of randomly identified patients to review. Sites confirm that patients do not have MRSA or VRE while in the ICU (and would not be on precautions in the control arm). Then reviewers complete review addressing standardized "trigger items." Each site will complete reviews for 90 patients over the 9 month study intervention.

For each patient, the number of events that occurred in the ICU and the number of events that occurred in the hospital will be calculated.

The rate of ICU events per patient will be calculated using the following formula:

$$\text{ICU Event Rate} = \frac{\#\text{ICU Events}}{\#\text{Patients ICU days}}$$

The rate of all events during the hospital stay will be calculated using the following formula:

$$\text{All Event Rate} = \frac{\#\text{In-hospital events}}{\text{Average hospital LOS}}$$

Rates of preventable adverse events and severe adverse events will also be calculated in the same fashion as above. If a difference in event rates is observed, secondary analyses

will include types of adverse events in intervention and control groups (neurological, cardiac, healthcare-associated infections, surgical etc.).

Comparison and agreement of site reviewers to each primary physician reviewer and between physician reviewers will be completed.

Rates will be compared between intervention and control sites using a Poisson exact test.

10. SAMPLE SIZE ADEQUACY

Data from the baseline period were used to assess sample size adequacy. Using admissions from the whole baseline period, the mean rate of MRSA or VRE was 30 new colonizations per 1000 person-days. Using two months of admission data (month 1: admissions 9/11/11 to 10/10/11; month 2: admissions 10/11/11 to 11/10/11), we calculated the monthly standard deviation to be 15 new colonizations per 1000 person-days and the longitudinal intraclass correlation coefficient (correlation between adjacent monthly colonization rates in the same site). This calculation was important for determining the expected standard deviation for a longer follow-up period. Assuming no drop in colonization in sites assigned to standard control, a 25% rate reduction in sites assigned to the intervention, an autoregressive correlation, nine months of follow-up in the intervention period, and a 25% gain in efficiency due to matching, the 20 ICUs (10 per group) were sufficient to reach 80% power to reject the null hypothesis of no difference in changes in MRSA or VRE colonization rates between sites assigned to the standard control group and sites assigned to the intervention group using a two-sided weighted t-test with 5% type I error.

11. STATISTICAL / ANALYTICAL ISSUES

a. General rules

All hypothesis testing will use two-sided tests. The p-value for the primary efficacy analysis will be considered statistically significant if the value is <=0.05. For secondary analyses listed in the protocol for which specific hypotheses are given, the hypothesis tests will assume to represent descriptive weight of evidence measures rather than formal tests for statistical inference with p-values <=0.05 considered to provide reasonable evidence in favor of the research hypothesis.

b. Adjustment for covariates

For the primary efficacy analysis, no covariates will be included for adjustment.

Because the primary efficacy analysis will have limited degrees of freedom, adjustment using additional ICU-level covariates is not possible.

Important patient-level and ICU-level parameters listed in Section 8.b may be used as covariates in secondary analyses.

c. Handling of dropouts and missing data

i. Patient-level data collection

Missing admission or discharge cultures
Significant study resources were invested to ensure that swabs were collected on-time and received at the lab in condition suitable for analysis. All inferential analyses will be based on available data.

Exploratory sensitivity analyses may be performed examining the percent of ICU admissions in each arm that contributed to the primary outcome but that did not have both swabs collected at admission or discharge. If there are differences in the percents in the 2 groups, we will determine the 95% CI for the average LOS for these patients with missing swabs and investigate event rates among the larger group with LOS in this interval to see if there are differences between the groups. If necessary, a revised definition of IR will be computed.

ii. ICU-level data collection

Missing data
Required data missing from administrative records is validated upon arrival and any missing values should be minimal and will be considered to be missing at random.

All available data will be analyzed without weighting or imputation.

d. Multicenter studies

For the primary analysis, the ICU will be the unit of analysis, allowing each ICU to be treated as an independent unit. In secondary analyses that involve patient-level assignments, procedures will be used that will adjust for site.

12. REPORTING CONVENTIONS

Analyses will be performed using R version 2.15.0 software.

Derived variables such as IR will be formatted to 1 more significant digit than the precision of the data used in the calculation.

Moment statistics including mean and standard deviation will be reported at 1 more significant digit than the precision of the data.

Order statistics including median, min and max will be reported to the same level of precision as the original observations. Following R rules, the median will be reported as the average of the two middle numbers if the dataset contains even numbers.

P-value will be reported to 3 decimal places if > 0.001. If the value is less than 0.001 then we will report '<0.001'. We will report p-values as 0.05 rather than .05. No preliminary rounding will be performed, rounding will only occur after analysis. To round, consider digit to right of last significant digit: if < 5 round down, if >=5 round up.

13. CHANGES TO ANALYSES PLANNED IN THE PROTOCOL

The following paragraphs summarize general strategic shifts in the analysis approach between the protocol and this analysis plan document. These modifications were prompted by a better understanding of the study data realized during trial conduct, a refined perspective afforded by the time to assimilate various perspectives, and a more sensitive prioritization and realistic use of resources.

Sample size adequacy was initially performed, prior to site recruitment, assuming baseline rates of VRE and MRSA of 5% each. We performed power calculations based on assumptions of number of beds, length of stay, and percent positive on admission with VRE and MRSA. We also presumed a 12-month intervention and performed calculations for 18 sites. We refined this calculation in Section 10 using monthly information collected during the baseline period as planned prior to the baseline period.

In the protocol, 30-day mortality was described as an outcome. However, administrative databases for hospitals did not contain 30-day mortality but rather unit-level ICU mortality and hospital mortality, which are being used for this outcome.

14. REFERENCES

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