Benefits of Enhanced Terminal Room (BETR) Disinfection Study

Study Protocol and Analysis Plan

1. INTRODUCTION

This document describes the main protocol components and statistical analysis plan (SAP) for the primary manuscript for the Phase 2 of "A Four-Arm Prospective, Multicenter Study to Assess the Clinical Efficacy, Effectiveness, and Feasibility of Enhanced Room Disinfection with Chlorine and UV Light Using Clinical and Microbiologic Outcomes," funded by the CDC Prevention Epicenters Program (U54CK000164).

2. STUDY OBJECTIVES

The primary objective of the study is to determine whether enhanced terminal room disinfection strategies will decrease the clinical risk of acquisition and infection due to multidrug-resistant organism (MDROs) in clinical practice. The specific hypotheses are:

1. *Enhanced terminal room disinfection strategies will decrease the overall risk of acquisition and infection due to the "BIG 4": MRSA, VRE, C. difficile, and MDR-Acinetobacter (MDRAB).*

2. *Enhanced terminal room disinfection strategies will decrease the risk of acquisition and infection for each of the components of the BIG 4.*

3. STUDY ENDPOINTS

a. Primary endpoints: The study includes two primary endpoints. For the purposes of power calculations and defining a primary statistical outcome, we will be analyzing the composite outcome of "first positivity" of acquisition and infection with MRSA, VRE, *C. difficile*, and MDRAB among patients considered to be "exposed" according to our inclusion criteria. This outcome will be determined by combining bed flow and microbiological data from study hospitals. In light of our a priori belief that the spore-forming organism *C. difficile* is more likely to spread through environmental means than vegetative bacteria, our second primary outcome is "first positivity" specifically of *C. difficile*.

b. Secondary endpoints:

1. First positivity – Exposed patients. These secondary outcomes will include the clinical incidence of individual pathogens among exposed patients as determined by data obtained from microbiological laboratories in study hospitals.
    a. Incidence of first positivity of MRSA among exposed patients
    b. Incidence of first positivity of VRE among exposed patients
    c. Incidence of first positivity of MDRAB among exposed patients
2. First positivity – Entire hospital. These secondary outcomes will include the clinical incidence of target pathogens (collectively and individually) among all patients admitted to the study hospitals as determined by data obtained from microbiological laboratories in study hospitals.
    a. Incidence of first positivity of BIG 4 for entire hospital
    b. Incidence of first positivity of MRSA for entire hospital
    c. Incidence of first positivity of VRE for entire hospital
    d. Incidence of first positivity of CDI for entire hospital

e. Incidence of first positivity of MDRAB for entire hospital

3. Adverse outcomes
   a. Missed opportunities – rate and description. We will summarize the number of times a UV-C device failed to be used and, if available, the reason it wasn't used.
   b. Time on diversion - days per 6-month study period, as determined using bed control administrative logs from study hospitals.
   c. Emergency room wait time - minutes per patient, as determined using bed flow data from study hospitals.
   d. Questionnaire results – HCW perception of cleaning methods
   e. Room cleaning time – minutes per room, as determined using bed flow and environmental services work flow datasets from study hospitals.

The term "first positivity" is defined as the first time (either colonization or infection) a clinical culture grows MRSA, VRE*, C difficile*, or MDRAB in an exposed patient. The terms "first positivity" and "clinical incidence" are used interchangeably (Ellingson, Jernigan ICHE 2011; Cohen ICHE 2008). Clinical incidence is the most appropriate term, as our data relied on routine clinical activities. While we use the term "patient-level" analyses, all analyses are actually at the hospital level. We changed the number of patients' data included in analyses by either including only those who met our criteria as exposed (i.e., primary outcomes and secondary outcomes b.1.) or all patients in the hospital (i.e., secondary outcomes b.2.). In both instances, patients could have had multiple admissions and, potentially, multiple exposures.

4. STUDY METHODS

a. Overall study design and plan

The study was designed as a pragmatic, prospective, multicenter, cluster-randomized, crossover trial with 2x2 factorial design to evaluate four different strategies for terminal room disinfection in nine study hospitals. The 28-month study period took place from April 2012 to July 2014. The 28-month period was separated into four 7-month study periods. Each study period consisted of a 1-month "wash in" period during which hospitals implemented and refined protocols followed by a 6-month period of data collection (Figure 1).

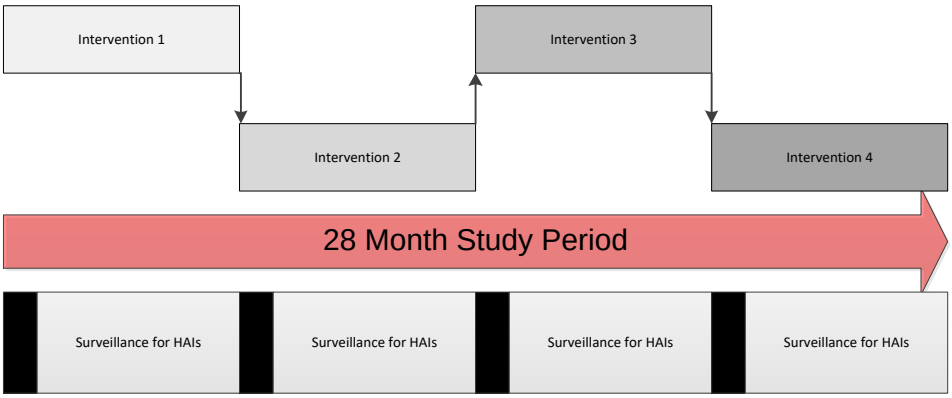


Figure 1. Schematic of crossover design. Each institution will randomly receive four interventions over the course of the 28-month study period. The first month of each intervention will be considered a "wash-out" month and surveillance data will not be counted (black boxes).

b. Intervention

Each hospital will perform cleaning and disinfection of targeted rooms using four disinfection protocols: A) standard terminal disinfection using quaternary ammonium; B) enhanced disinfection with quaternary ammonium and UV device; C) enhanced disinfection with bleach; D) enhanced disinfection with bleach and UV device (Figure 2). The intervention is performed on the room. From a practical, implementation perspective, the cleaning strategies will be applied to contact precautions. From an analysis perspective, eligible rooms will include any room from which a) a patient with infection due to MRSA, VRE, CDI, or MDRAB has been transferred or discharged or b) a patient with known colonization with MRSA, VRE, and MDRAB has been transferred or discharged and c) the patient remained in the room for >24 hours prior to transfer or discharge.

Figure 2. 2x2 Factorial Design

		UV-C emitting device	
		No	**Yes**
Chemical Disinfectant	**Quaternary ammonium-containing solution except hypochlorite (bleach)-containing solution for *C. difficile* rooms**	A	B
	Hypochlorite (bleach)-containing solution	C	D

c. Selection of study sites

Nine study hospitals participated, including two tertiary care hospitals, six community hospitals participating in the Duke Infection Control Outreach Network, and one Veteran's Affairs hospital (Table 1).

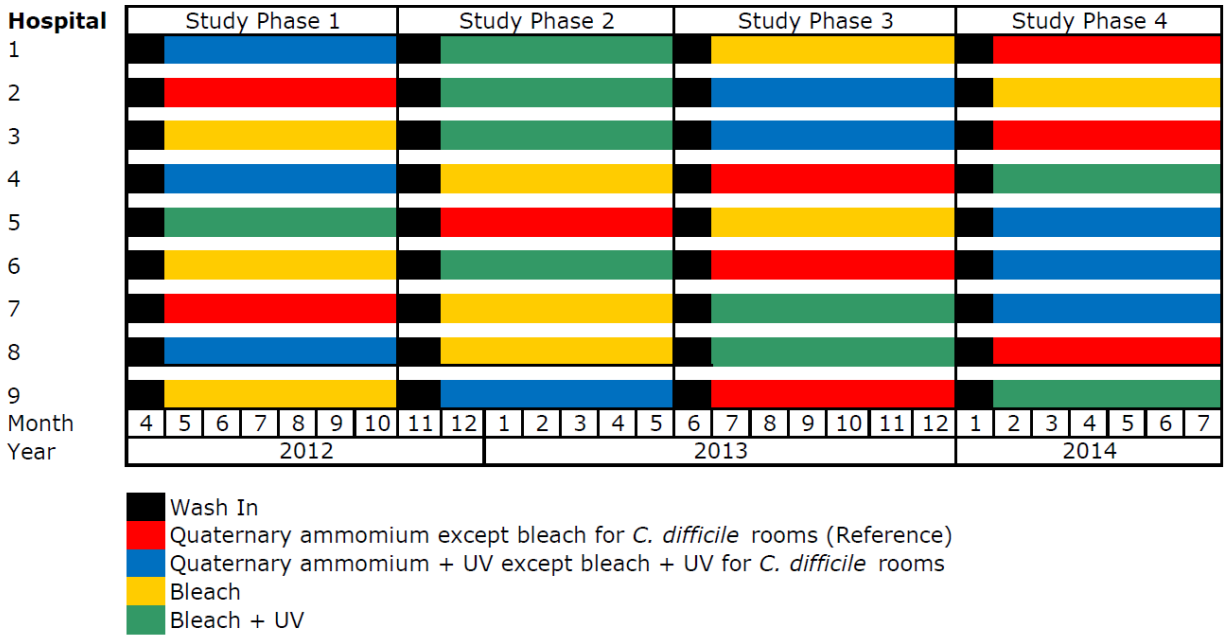
Table 1. Study Hospitals			
Hospital	Location	Bed Size	Type
Alamance Regional Medical Center	Burlington, NC	218	Community
Chesapeake Regional Medical Center	Chesapeake, VA	310	Community
Duke Raleigh Hospital	Raleigh, NC	148	Community

Duke Regional Hospital	Durham, NC	202	Community
Duke University Hospital	Durham, NC	950	Tertiary
Durham Veteran's Affairs Hospital	Durham, NC	271	Veteran's Affairs
High Point Regional Health System	High Point, NC	335	Community
Rex Hospital	Raleigh, NC	660	Community
University of North Carolina Hospitals	Chapel Hill, NC	853	Tertiary

d. Randomization

Randomization occurred at the level of the hospital. All hospitals used each of the four strategies an equal amount of time. The order in which the four protocols were utilized was randomly assigned to each study hospital (Figure 3). Randomization was performed by random number generators for each hospital.

Figure 3. Randomization scheme for 9 study hospitals



e. Blinding

Because of the nature of the strategies being evaluated in this study, blinding of the assignment of the hospital was impossible. Investigators, environmental service personnel, and infection prevention personnel were aware of the assignment in order to effectively implement and monitor the intervention.

5. ANALYSIS POPULATIONS

No hospitals dropped out of the study. Data will be obtained from all patients admitted to acute care or intensive care beds in all study hospitals. Data will not be obtained from patients admitted only to emergency room or other non-acute care locations.

a. **Inclusion** - Patient stays with duration greater or equal to 24 hours will be included in the analyses.

b. **Exclusion** - Wash-in periods will be excluded from the analyses. Patient stays where a patient had prior community-acquired infection (diagnosed within 48 hours from hospitalization) or a microbiologically proven history of infection or colonization with the same target MDRO during the 12 months prior to the admission will be excluded.

6. DERIVED AND COMPUTED VARIABLES

a. General strategy for aggregating data at the hospital level

All variables were collected and calculated during all four study phases at each study hospital. Variables were calculated and/or summarized for each of the disinfection strategies/phases individually.

b. Incident cases and exposure-days

1. A seed room was defined as a room containing a patient with microbiologically proven current or history of infection or colonization with one or more target MDROs (i.e., potentially "seeded" by the inhabitant).
2. Exposed patient - The next patient admitted to the seed room was an "exposed patient."
3. Incident case - Exposed patients qualified as a potential "incident case" of acquisition[1] if they met the following criteria:

    - In seed room for ≥24 hours ***AND***
    - A positive clinical culture with one of the target MDROs ***AND***
    - The organism identified in the clinical culture was the same target MDRO isolated from the preceding patient in the seed room ***AND***
    - The positive culture was obtained during the index admission either during or after exposure to the seed room ***OR***
    - The positive culture was obtained during hospital readmission
        - Within 90 days of discharge for MRSA, VRE, and MDR *Acinetobacter*[2] ***OR***
        - Within 28 days of discharge for *C. difficile*[3]

4. Exposure days - Exposure days were calculated as the number of days the exposed patient spent in the seed room. Patients excluded from the numerator were also excluded from the denominator.

c. Clinical incidence – Exposed Patients

1. Clinical incidence of MRSA, VRE, *C. difficile*, or MDRAB among exposed patients

    The clinical incidence of all 4 target organisms (rate/10,000 exposure days) will be calculated for each study phase individually.
    a. Numerator: qualifying incident cases of any of the target organisms
    b. Denominator: exposure days for all exposures

2. Clinical incidence of *C. difficile* among exposed patients

The clinical incidence of *C. difficile* (rate/10,000 exposure days) will be calculated for each study phase individually.

a. Numerator: qualifying incident cases of *C. difficile*
b. Denominator: exposure days among patients exposed to *C. difficile* seed rooms

3. Clinical incidence of MRSA among exposed patients

The clinical incidence of MRSA (rate/10,000 exposure days) will be calculated for each study phase individually.

a. Numerator: qualifying incident cases of MRSA
b. Denominator: exposure days among patients exposed to MRSA seed rooms

4. Clinical incidence of VRE among exposed patients

The clinical incidence of VRE (rate/10,000 exposure days) will be calculated for each study phase individually.

a. Numerator: qualifying incident cases of VRE
b. Denominator: exposure days among patients exposed to VRE seed rooms

5. Clinical incidence of MDRAB among exposed patients

The clinical incidence of MDRAB (rate/10,000 exposure days) will be calculated for each study phase individually.

c. Numerator: qualifying incident cases of MDRAB
d. Denominator: exposure days among patients exposed to MDRAB seed rooms

d. Clinical incidence – All Patients Admitted to the Hospital

Hospital-wide clinical incidence was calculated as the number of patients with hospital-acquired incidence of a target MDRO/10,000 patient days among patients who stayed in the hospital for at least 48 hours. Patients did not have to be "exposed" to a seed room to qualify for these analyses, though the same exclusion criteria were otherwise applied.

1. Hospital-wide clinical incidence of MRSA, VRE, *C. difficile*, or MDRAB

The clinical incidence of all 4 target organisms (rate/10,000 patient days) will be calculated for each study phase individually.

a. Numerator: qualifying incident cases of any of the target organisms
b. Denominator: patient days

2. Hospital-wide clinical incidence of *C. difficile*

The clinical incidence of *C. difficile* (rate/10,000 patient days) will be calculated for each study phase individually.

a. Numerator: qualifying incident cases of *C. difficile*
b. Denominator: patient days

3. Hospital-wide clinical incidence of MRSA

The clinical incidence of MRSA (rate/10,000 patient days) will be calculated for each study phase individually.

a. Numerator: qualifying incident cases of MRSA
b. Denominator: patient days

4. Hospital-wide clinical incidence of VRE

The clinical incidence of VRE (rate/10,000 patient days) will be calculated for each study phase individually.

a. Numerator: qualifying incident cases of VRE
b. Denominator: patient days

5. Hospital-wide clinical incidence of MDRAB

The clinical incidence of MDRAB (rate/10,000 patient days) will be calculated for each study phase individually.

a. Numerator: qualifying incident cases of MDRAB
b. Denominator: patient days

e. Measures for monitoring protocol fidelity

1. Use of the UV device on eligible contact precaution rooms

Compliance with use of the UV device will be calculated as a proportion:

a. Numerator: uses of the machine
b. Denominator: rooms of patients on contact precautions, as derived from infection prevention databases

2. Use of the correct chemical disinfectant

Compliance with use of the correct chemical disinfectant will be calculated as a proportion:

a. Numerator: Use of the correct chemical disinfectant
b. Denominator: Number of rooms sampled

f. Potential confounders

1. Hand hygiene compliance

Hand hygiene compliance will be calculated as a proportion:

a. Numerator: Number of times hand hygiene performed correctly
b. Denominator: Number of hand hygiene observations

2. Room cleaning compliance

Room cleaning compliance will be calculated as a proportion:

a. Numerator: Number of locations in a room from which a fluorescent marker was removed
b. Denominator: Number of fluorescent markers applied to the room

3. Colonization pressure

Colonization pressure will be calculated as a proportion.

a. Numerator: Number of patients with a current or prior (previous 12 months) infection or colonization with one of the four target MDROs during the calendar month.
b. Denominator: Number of patients admitted to the hospital during the same calendar month

g. Adverse outcomes

1. Room turnover time will be measured in minutes in two ways

    a. Total turnover time – calculated as the time from the room being declared dirty by bed control personnel to being declared clean by the environmental services personnel.
    b. Cleaning time – calculated as the time from the initiation of room cleaning to the room being declared clean by the environmental services personnel.

2. ED wait time – calculated as the amount of time (minutes) between the ED physician's decision to admit the patient and departure from the ED

3. Diversion – calculated as the number of hours the study hospital was on any form of diversion

7. STUDY CHARACTERIZATION ANALYSES

Demographic and comorbidities data will be described by study phase using mean (standard deviation) and median (IQR) for continuous variables and number (percent) for categorical variables. Comorbidity data will be obtained using enhanced ICD-9-CM code data obtained from administrative databases from study hospitals. The ICD-9 codes of interest will be used to calculate Charlson scores. Enhanced ICD-9-CM codes of interest are provided in Table 2.

Table 2. ICD-9-CM codes

Comorbidities	**Enhanced ICD-9-CM**
Myocardial infarction	410.x, 412.x
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
PVD	093, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4
Cerebrovascular disease	362.34, 430.x-438.x
Dementia	290.x, 294.1, 331.2
COPD	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8
Rheumatic disease	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725.x
Peptic ulcer disease	531.x-534.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7

Diabetes mellitus (uncomp)	250.0-250.3, 250.8, 250.9
DM complicated	250.4-250.7
Hemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0-344.6, 344.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586.x, 588, V42.0, V45.1, V56.x
Malignancy	140.x-172.x, 174.x-195.8, 200.x-208.x, 238.6
Mod/Severe liver disease	456.0-456.2, 572.2-572.8
Metastatic solid tumor	196.x-199.x
AIDS/HIV	042.x-044.x
Arrhythmias	426, 426.13, 426.7, 426.9, 426.1, 426.12, 427.0-427.4, 427.6-427.9, 785, 996.01, 996.04, V45.0, V53.3
Valvular disease	093.2, 394.x-397.x, 424.x, 746.3-746.6, V42.2, V43.3
Pulmonary circulation disease	415, 415.1, 416.x, 417, 417.8, 417.9
HTN uncomplicated	401.x
HTN complicated	402.x-405.x
Other neuro disorder	331.9, 332, 332.1, 333.4, 333.5, 333.92, 334.x-335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3
Chronic pulmonary disease	416.8, 416.9, 490.x -505.x, 506.4, 508.1, 508.8
Hypothyroid	240.9, 243.x, 244.x, 246.1, 246.8

8. EFFICACY ANALYSES

a. Analyses of clinical incidence - primary and secondary outcomes

Incidence rates will be compared between different disinfection protocols (study phases) using Poisson regression model with log of hospital-level number of “first positivity” cases as the outcome, log of hospital-level total days of exposure as an offset term and variables for intervention phase (B: quaternary ammonium + UV light, C: bleach, or D: bleach + UV light; A: standard disinfection will be used as reference), study period in the crossover sequence (1, 2, 3 or 4), and hospital as covariates. Interaction between intervention and study period will be evaluated. Generalized estimating equations (GEE) approach will be used to adjust for clustering by hospital. Individual models will be created for each primary and secondary efficacy outcome.

Each of the three enhanced terminal room disinfection strategies will be compared to the standard strategy; the null hypothesis in each case is that there is no difference in the clinical incidence rate between the enhanced strategy and the standard strategy. Each of the study phases will be compared to study phase A (reference) except for the patient-level analysis of *C. difficile*. As this comparison involved the comparison of bleach vs. bleach + UV-C for exposed patients, results from study phases B and D were compared to results from study phases A and C. Additional analyses will compare interventions using UV light vs those without UV light. In these analyses, variables for UV light (yes/no) and bleach (vs. quaternary ammonium) will replace the variable for intervention in the regression models.

The intention-to-treat (ITT) population will include all exposed patient stays, as described above. Per protocol (PP) population will exclude patient stays during study periods using UV light (phases B and D) if UV light was not documented as used before patient entered the room, or where the room was not in fact a seed room. For the purpose of the PP analysis, the UV device will only have to be turned on in the room; cycle completion will not be required for inclusion. Analyses of the outcomes for exposed patients will be conducted according to ITT and PP populations; analyses of the outcomes for the entire hospital will be conducted on ITT population only. Statistical tests will be performed at a two-sided significance level of 0.05 with no adjustment for multiple comparisons.

b. Alternative models

Poisson regression may not provide the best fit to the data in case of overdispersion. In addition to Poisson regression, overdispersed Poisson and negative binomial regression models will be evaluated for each outcome. Of the three candidate models, the model that has the smallest median squared deviation (squared difference between predicted and observed rate; median will be evaluated across hospitals and interventions) will be selected.

9. ADVERSE OUTCOMES ANALYSES

To understand if the interventions led to downstream adverse outcomes, we will analyze three potential adverse outcomes: increase in room turnover time, ER wait time, and time on diversion. In general, adverse outcomes will be described by study period using mean (standard deviation) and Median (IQR) for continuous variables and number (percent) for categorical variables. No statistical comparisons will be performed between the different study phases.

a. Room turnover time

Total turnover time and cleaning time will be calculated using the strategy described above. Data will be obtained from environmental services logs for <u>all</u> rooms during each of the study periods, and the median time during the 6-month study period will be calculated. This approach will provide information on the impact, if any, of the additional time required for using the UV devices on overall environmental services operations.

b. Emergency room (ER) wait time

ER wait time will be calculated using the strategy described above. Data will be obtained from bed flow datasets and analyzed on all patients admitted to the hospital from the ER during each 6-month study period.

c. Time on diversion

Time on diversion will be calculated using the strategy described above. Time on diversion will be obtained from hospital operations datasets. The total time on diversion per month will be calculated for each month of each 6-month study period.

10. SAMPLE SIZE AND POWER CONSIDERATIONS

We performed two power calculations prior to the initiation of the study, one for the hospital-level analysis of eligible exposed patients and one for the hospital-wide analysis of all patients admitted to the hospital. Best estimates were made based on review of 4-years of surveillance data from study hospitals and published literature. Prior to our study, the proportion of new colonization/infection that occurs in rooms from which a patient with MRSA, VRE, *C. difficile*, and/or MDR-Acinetobacter was discharged is unknown. All power calculations were performed with two-sided 0.05 significance level.

a. **Eligible exposed patients** – Our power calculation for this analysis was based on the following assumptions. First, we projected that a total of 7,000 patients would be exposed to a seed room and eligible for inclusion in our study at the 9 study hospitals. Second, all seed rooms would be contaminated. Third, 11% of exposed, eligible patients would develop the outcome of interest. Thus, we projected that the outcome would occur in 190 (11%) of 1,750 patients during the baseline period. Based on these assumptions, our study had 80% power to detect an absolute decrease in the proportion of outcomes caused by the four target organisms of 3% for any of the enhanced disinfection strategies and >99% power to detect an absolute decrease of 5% or more.

b. **Hospital-wide** – Our power calculation for this analysis was based on the following assumptions. First, we projected that 1.96 million patient days of care would be provided at the 9 study hospitals during the study period. Second, for each 6-month intervention period, we projected that approximately 491,200 patient-days of care will occur (distributed across 9 participating hospitals). Third, we projected that 959 outcomes due to the four target organisms would occur during the baseline (or reference) 6-month period, for a baseline incidence rate of 1.95/1,000 patient-days. Under these assumptions, the study had 60% power to detect a 10% decrease in incidence rate, 92% power to detect a 15% decrease and >99% power to detect a 20% decrease.

11. STATISTICAL/ANALYTICAL ISSUES

a. General rules

Unless specified otherwise, all hypothesis testing will use two-sided tests with alpha level of 0.05. No formal adjustment for multiplicity of analyses is planned; any statistically significant findings will be interpreted with caution. P-values, effect estimates and 95% confidence intervals will be reported to aid in the interpretation of the results. Underlying assumptions for parametric tests will be evaluated and transformations or nonparametric tests will be used when appropriate.

b. Adjustment for covariates

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

Important hospital- and patient-level parameters listed in Section 6f and 7 may be used as covariates in secondary analyses.

c. Handling of missing data

Missing data will not be imputed.

12. REPORTING CONVENTIONS

Statistical analyses will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

In general, order statistics including median, min, and max will be reported to the same level of precision as the original observations. Time variables with information on seconds, however, will be rounded to and reported in minutes.

No preliminary rounding will be done. 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/GRANT

Our initial protocol and grant submission focused on outcomes that specifically met CDC criteria for a healthcare-associated infection (HAI). After discussions with the CDC at the beginning of the grant cycle (prior to study initiation), we elected to change the primary focus of the study from HAIs to "clinical incidence," as described above. This change was performed to overcome potential issues related to differences in HAI surveillance techniques across hospitals and to improve the plausibility of our outcomes.

No sensitivity analyses were originally planned. During the course of the study, however, we began to wonder about the impact of the inclusion criterion requiring 24 hours of "exposure" to the seed room—an arbitrary choice by our team at the beginning of the study to ensure the patients exposed to the seed rooms had a true exposure to the environment. As a result, we repeated our primary analyses without this requirement as a post hoc sensitivity analysis.

Finally, one of our adverse outcomes, ER wait time, was modified during the course of the study. Our initial intention was to measure and report the specific time between when the decision was made to admit the patient and when the patient left the ER to go to a hospital room. These data proved too challenging to acquire for some study hospitals. As a result, we accepted "total time in the ER," defined as the time from arrival to the ER to when the patient left the ER to go to a hospital, as a proxy measure for our initial outcome.

REFERENCES

1. Huang SS, Rifas-Shiman SL, Warren DK, et al. Improving methicillin-resistant Staphylococcus aureus surveillance and reporting in intensive care units. *The Journal of infectious diseases.* 2007;195(3):330-338.
2. Avery TR, Kleinman KP, Klompas M, Aschengrau A, Huang SS. Inclusion of 30-day postdischarge detection triples the incidence of hospital-onset methicillin-resistant Staphylococcus aureus. *Infect Control Hosp Epidemiol.* 2012;33(2):114-121.
3. McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kutty PK. Recommendations for surveillance of Clostridium difficile-associated disease. *Infect Control Hosp Epidemiol.* 2007;28(2):140-145.