Active Bathing to Eliminate Infection (ABATE Infection) Trial

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Study Protocol

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Pragmatic Clinical Trials Demonstration Project

Title: Decreasing Bioburden to Reduce Healthcare-Associated Infections and Readmissions

ABATE (Addressing **B**ioburden while **A**dmitted **T**o **E**liminate) **Infection Trial**

Project Narrative

Healthcare-associated infections are one of the 10 most frequent causes of death in the United States and incur over $6.5 billion dollars of healthcare costs each year. Although most prevention trials have focused on intensive care unit (ICUs), where the daily risk for infection is the highest, the majority of healthcare-associated infections occur outside of ICUs. This cluster-randomized controlled trial will evaluate whether bathing non-ICU patients with antimicrobial soap prevents healthcare-associated infections and the readmissions they cause.

Abstract

Healthcare-associated infections (HAIs) are a leading cause of preventable morbidity and mortality. Prevention of HAIs is a national priority for patient safety and best practice because of their high morbidity, mortality, and cost, incurring over $6.5 billion dollars of healthcare costs each year. Most infections result from common bacteria that normally live on the skin or in the nose and which overcome the body's normal defenses because of invasive medical devices, surgical incisions, or the physiologic effects of hospitalization. Studies in intensive care units (ICUs) indicate that decolonization of patients' skin with chlorhexidine, and nares with mupirocin can prevent many HAIs. However, evidence is lacking about the effectiveness of decolonization in non-ICU settings, where the majority of HAIs occur, and where medical care, risk of infection, patient-to-patient interactions, pathogen transmission, and bathing practices differ considerably from ICU settings. Decolonization is thus rarely used in these settings, despite its potential to meaningfully decrease the HAI rate.

The ABATE Infection Trial (**A**ddressing **B**ioburden while **A**dmitted **T**o **E**liminate Infection) will efficiently evaluate the impact of decolonization on HAIs in the general patient population outside ICUs. This cluster-randomized trial will randomize 54 hospitals treating over 400,000 patients to evaluate 1) universal daily chlorhexidine bathing to prevent infections from all pathogens, combined with 2) nasal decolonization with mupirocin for known carriers of methicillin-resistant *Staphylococcus aureus* (MRSA), one of the most common causes of HAIs. While decolonization has been successful in short-stay high risk areas, such as ICUs, this trial will address the much larger problem of HAIs in non-ICU medical and surgical wards. This patient population has typically not been evaluated because the complexity and cost of sufficiently large randomized trials to demonstrate effectiveness have been beyond the reach of conventional hospital-based trials.

This trial will provide a critically needed evaluation of decolonization to reduce hospital infection risk and infectious readmissions in nearly all hospitalized patients. It will provide essential information to determine whether routine decolonization through daily bathing with chlorhexidine should become standard practice for 40 million patients hospitalized each year in the United States alone. Alternatively, it will suggest that tailored strategies distinct from those effective in ICU settings are needed for these patients outside ICUs.

This trial will also illustrate the strengths of a new model of clinical effectiveness research that quickly and efficiently addresses critical management questions by embedding research into the usual delivery of health care, and using the organizational and informatics strengths of a large hospital system.

Specific Aims – UH2
Pragmatic Clinical Trial – Planning Phase

It is a national priority to reduce the morbidity, mortality, and cost of healthcare-associated infections (HAIs) and their associated readmissions to their lowest practicable level. There have been notable successes in preventing HAIs in intensive care units, where the risk per patient is highest. The focus now needs to address the larger fraction of HAIs that occur in general medical, surgical, and oncology units, where medical care, risk of infection, patient-to-patient interactions, pathogen transmission, and bathing practices differ considerably from ICU settings. To that end, we propose the ABATE Infection Trial (**A**ddressing **B**ioburden while **A**dmitted **T**o **E**liminate Infection) to reduce the reservoirs of bacteria on the skin and in the nose that are the major causes of these infections. This cluster-randomized trial will assess whether the strategy of body decolonization with chlorhexidine plus nasal mupirocin will significantly reduce the rate of HAIs and readmissions among patients in general hospital units when compared to routine bathing care.

We recently completed a successful ICU based cluster-randomized trial involving 43 hospitals, 72 ICUs, and 75,000 patients using interventions similar to those proposed here. We propose to use our experience and collective knowledge to conduct the ABATE Infection Trial in general hospital units. In the planning phase of this trial, we will:

1) Recruit hospitals for a cluster-randomized trial of 1) routine daily bathing with chlorhexidine for all patients plus 2) routine nasal decolonization with mupirocin for patients harboring methicillin-resistant *Staphylococcus aureus* (MRSA) in general medical and surgical units to reduce infection and readmissions.

2) Obtain Institutional Review Board (IRB) approval for the cluster-randomized trial and maximize efficiency by having most hospitals cede to a central IRB.

3) Develop trial educational materials and routine electronic nursing queries for daily bathing and decolonization in general medical and surgical inpatient areas. Additionally, begin baseline strain collection activity to assess resistance.

4) Obtain baseline data on HAI infection rates for participating hospitals to lay the foundation for trial outcomes. These will be obtained using corporate data warehouse capabilities of Hospital Corporation of America (HCA).

Specific Aims – UH3
Pragmatic Clinical Trial – Trial Intervention Phase

The majority of healthcare-associated infections (HAIs) occur outside of ICUs, in general medical, surgical, and oncology units. The ABATE Infection Trial (**A**ddressing **B**ioburden while **A**dmitted **T**o **E**liminate Infection) seeks to reduce these HAIs and the readmissions they cause to their lowest practicable level by reducing the reservoirs of the pathogens that cause most HAIs. This cluster-randomized trial will target all pathogens through bathing with chlorhexidine and additionally target carriers of methicillin-resistant *Staphylococcus aureus* (MRSA) through nasal decolonization with mupirocin. This intervention strategy will be compared to routine care in non-ICU medical, surgical, and oncology units.

This trial will assess a high yield strategy that is relevant to the large majority of hospitalized patients. If successful, this decolonization strategy would become best practice for preventing infection among 40 million patients hospitalized each year in the United States alone.

Specific aims for the Trial Intervention Phase are as follows:

1) Conduct a 50+-hospital cluster-randomized controlled trial of routine chlorhexidine bathing and selective MRSA decolonization versus standard-of-care practices for all hospitalized patients in non-critical care adult medical, surgical, and oncology units. The primary outcome will be clinical burden of gram-positive multi-drug resistant organisms. Secondary outcomes will include clinical burden of gram-negative multi-drug resistant organisms, bloodstream infections, and readmissions caused by infection.

2) Assess whether universal chlorhexidine bathing and selective MRSA decolonization result in increased resistance to chlorhexidine or mupirocin among bacterial strains collected during the trial.

3) Estimate the costs associated with the intervention (chlorhexidine + selective MRSA decolonization) and the attributable medical costs of healthcare associated infections in adult general inpatient units and infectious readmissions, in order to evaluate the potential for cost savings associated with the strategy of reducing bioburden to prevent infection

1.0 Significance - Overall

1.1 The Problem of Healthcare-Associated Infections: Burden and Trends

Healthcare-associated infections (HAI) are one of the top 10 causes of death in the United States. Each year in the U.S., over 1.7 million HAIs occur, resulting in 100,000 annual deaths at a cost of over 6.5 billion dollars.[1] In Europe, over 4.5 million HAIs occur each year and are responsible for 16 million additional hospital days and 37,000 attributable deaths at a cost of over 7 billion Euros.[2] Among developed nations, the World Health Organization (WHO) has reported that 1.4 million people have an HAI at any given time. [3] Thus, 5-10% of hospitalized patients experience an HAI, a risk that is estimated to be 20-fold higher in developing nations.

The recognition of HAIs as a leading cause of death has led to numerous state and national responses. In 1999, the Institute of Medicine (IOM) report "*To err is human: building a safer health system"* galvanized efforts to prevent healthcare associated adverse events, including HAIs.[4] In 2003, the IOM identified HAI prevention as a top 20 priority area for national action.[5] In 2008, the U.S. Government Accountability Office issued a report on HAIs in Hospitals calling for national efforts by the Department of Health and Human Services to prioritize prevention practices and standardize HAI surveillance.[6] In the meantime, The Joint Commission continued to increase its requirements for routine HAI surveillance for hospital accreditation,[7] and the Centers for Medicare & Medicaid Services (CMS) outlined and implemented a multi-year plan requiring hospitals to publicly report HAIs and to ultimately perform well on HAI rankings or face reductions in reimbursement.[8] Furthermore, state legislative mandates have been passed in 29 states which require hospitals to report HAI events, generally through the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) system.[9] In addition to providing gold-standard criteria for identifying HAIs, NHSN has become the national repository for hospitals to report HAI surveillance data; nearly 5,000 hospitals report detailed data on HAI events through this system. Through use of NHSN data, numerous state health departments are generating public reports of hospital-specific HAI performance.

1.2 Major Types of Healthcare-Associated Infections and Their Consequences

The most frequent HAIs are urinary tract infections, pneumonia, bloodstream infections, and surgical site infections. Each carries significant morbidity and mortality both in and out of ICUs. CDC estimates 530,000 healthcare-associated urinary tract infections, 275,000 surgical site infections, 220,000 bloodstream infections, 235,000 pneumonias, and 350,000 other infections annually.1 These HAIs account for 100,000 estimated deaths. HAIs also prolong hospitalizations and cause readmissions.[4-6] Finally, HAIs incur large costs, with average direct medical costs of approximately $500-1,000 per urinary tract infection and $10,000-20,000 per surgical site infection, central line-associated bloodstream infection, or pneumonia.[10]

1.3 Pathogenesis and Preventability of Healthcare Associated Infections

The largest fraction of HAIs are caused by bacteria that reside on the skin and in the nose and gain access to the bloodstream, lungs, and bladder by way of devices and incisions that breach normal host defenses. These bacteria may be the patient's normal flora, or they may be new, often antimicrobial resistant, organisms acquired during hospitalization. Current evidence and expert opinion suggests that 65-70% of catheter-related bloodstream and urinary tract infections may be preventable.[11] We discuss below a prevention strategy, decolonization of the skin and nasal reservoirs, that should positively impact these types of infections.

1.4 Rationale for Testing Strategies for HAI Reduction Beyond Intensive Care Units

For over 30 years, the major focus of HAI prevention has centered on ICUs because the combination of high complexity medical care and severity of illness result in ICU patients having the highest risks for HAIs.[12 13 14 15 16 17 18 19] Numerous studies have described the morbidity and mortality attributable to this setting and demonstrated gains in reducing catheter-related bloodstream infections,[14-17 20] catheter-related urinary tract infections,[21 22 23 24 25] and pneumonia[26 27 28 29] in ICU settings.

In recent years, the substantial gains in reducing HAIs in ICUs have caused national attention to turn to the much larger number of HAIs occurring outside of ICUs. Non-ICU settings most commonly consist of step-down units which represent an intermediate level of care between the ICU and a routine non-ICU area, as well as medical, surgical, mixed medical/surgical, and oncology units. It is estimated that 75% of HAIs occur outside of ICU settings.1 Nevertheless, there have been no large scale trials to reduce HAIs in the non-ICU general inpatient units. For this reason, we will adapt our successful decolonization strategy for HAI reduction in ICUs to target the majority of healthcare-associated infections in non-critical care units.

In addition, the effect of the decolonization regimen we will study should persist beyond discharge. Chlorhexidine bathing reduces skin bioburden for several days after use, and mupirocin reduces MRSA nasal

reservoirs for several weeks. Thus, inpatient decolonization may prevent HAIs that manifest in the highly vulnerable period immediately following discharge. We have shown that a large number of HAIs occur shortly after discharge and cause readmissions.[30 31 32 33 34 35 36 37] This post-discharge period is a time of high risk for subsequent infection due to medical devices such as central venous catheters and surgical drains, surgical wounds, decubitus ulcers, fragile pulmonary status, and poor clearance of secretions. For example, we have shown that 24% of inpatients who acquire methicillin-resistant *Staphylococcus aureus* (MRSA) during a hospital stay develop post-discharge MRSA infection. Half of these infections occur within one month of discharge.[30 33] We have similarly shown that over one third of HAIs due to vancomycin-resistant enterococci occur shortly after discharge.[32] The importance of HAIs as a cause of 30-day readmissions is also been highlighted by the Pennsylvania Health Care Cost Containment Council, which reported that patients with HAIs were five times more likely to be readmitted within 30 days due to a new HAI or complication of HAI.[38]

It is important that we not simply assume that approaches that work in ICUs will also work in non-ICU settings or have a beneficial effect on HAIs that manifest after discharge. There are several reasons for this. First, the decolonization regimen cannot be delivered in an identical fashion in the non-ICU setting. Patients are awake and some may refuse a daily bath. In contrast to the ICU, where bed baths are uniformly performed, patients may choose to perform their own bed bath. Others may choose to shower, where rinsing of the chlorhexidine leaves less residual effect on the skin compared to patients who receive a no-rinse bed bath. Thus, in the current delivery model, it will be more difficult to standardize the intervention or ensure that it is applied uniformly and effectively. Nevertheless, this is an important aspect of pragmatic clinical trials in non-ICU settings. Second, the level and intensity of contact differs between patients and nursing staff, and between patients themselves, especially those sharing a room. Since these interactions are important determinants of transmission of pathogens to patients, the results of an ICU intervention are not necessarily predictable in the non-ICU setting. Third, because the use of invasive devices is lower in non-ICU settings, reducing the density of bacterial reservoirs on the skin and in the nose may convey a smaller benefit. Finally, when applied to all patients in general hospital units, widespread use can incur meaningful incremental cost, small risks of skin rashes, the unpleasantness of intranasal application of ointment, and a risk of eliciting antimicrobial resistance. There are also potential opportunity costs of widespread adoption, since hospitals will need to be alert to concomitant use of other products that are not compatible with chlorhexidine bathing. Thus, it is important to test the effectiveness of a decolonization regimen under conditions of actual use, and to assess both its impact on infections, but also to monitor adverse effects on individuals and microbial resistance patterns.

1.5 Importance of Methicillin Resistant *Staphylococcus aureus* (MRSA) Subset of HAIs

Any strategy for preventing a large fraction of all HAIs must be effective against MRSA, which is arguably the most important single pathogen in healthcare-associated infection when accounting for virulence, prevalence, diversity of disease spectrum, and propensity for widespread transmission.[30 33 39 40 41] MRSA is highly antibiotic resistant and causes a wide spectrum of disease, including skin infection, deep organ abscesses, pneumonia, surgical site infections, bone and joint infections, blood and urine infections, and sepsis.[39 40] MRSA causes or complicates 278,000 U.S. hospitalizations annually, resulting in 56,000 septic events and 19,000 deaths. [39] Prevention efforts have focused on healthcare facilities since critically and chronically ill patients experience the majority of MRSA morbidity and mortality.

Among HAIs in 2009-10, *S. aureus* (two-thirds of which is MRSA) has become the most common pathogen**.** It is the most common cause of ventilator associated pneumonia and surgical site infection, and has recently become the most common cause of central-line associated bloodstream infections.[42 43] It is also the 8th most common cause of catheter-associated urinary tract infections.[39] Increasing MRSA morbidity and mortality have fueled a national call for action. The IOM ranked prevention of MRSA infection in the quartile of highest importance when asked to provide a “top 100” list of health issues for comparative effectiveness research and rank them into quartiles.[44] Over 15 states have mandated reporting of MRSA infections through CDC’s NHSN surveillance system, and 10 states require screening of high risk patients in hospitals to ensure detection, promote contact precautions (i.e. single room, use of gowns and gloves), and prevent transmission.[9] Furthermore, CMS will reduce reimbursement to hospitals that fail to report MRSA bloodstream infections by 2013. This widespread concerted and legislated response toward MRSA is unprecedented in US healthcare.

1.6 MRSA Strategies for Disease Prevention – Screening and Isolation

We first describe MRSA prevention strategies as a prelude to describing strategies that target all pathogens. Two main strategies have emerged as successful in reducing MRSA infection in hospitals. The first involves “active screening” to find MRSA carriers and isolate them to prevent the spread of MRSA to other

patients. Active screening involves culturing patient's nostrils (nares), the major reservoir for MRSA in humans. The goal of this strategy is to implement contact precautions for all MRSA carriers to prevent transmission of MRSA to patients who are not colonized.[45 46] Preventing transmission prevents many infections since 33% of patients who become colonized in the hospital develop infection within 1 year.[30 33] We and others have shown that active screening can reduce hospital-associated transmission and MRSA infection by 35-70%.[47 48 49 50 51]

Although active screening for high risk patients is mandated by 10 states,[9] screening and isolation do not benefit the large and growing population of 1.8 million inpatients who already harbor MRSA.[41] Between 5-12% of hospitalized patients are MRSA carriers at discharge,[41 48 52] and we have shown that many develop invasive disease within one month of discharge.[30 33] Thus, interventions to reduce post-acquisition morbidity could have the highest benefit and meet the greatest need by targeting existing carriers of MRSA.

1.7 MRSA Strategies for Disease Prevention –Decolonization

The second major strategy for preventing MRSA infection involves the use of various topical,[17 53 54] and sometimes systemic,[55] antimicrobial agents to "decolonize" MRSA carriers and prevent subsequent MRSA infection. Systemic regimens are not favored in the US due to side effects and the theoretical risk of accelerated emergence of antibiotic resistance. Most commonly, a combination of chlorhexidine body washes and mupirocin ointment applied to the nares is used for a period of 5-7 days. This strategy can be applied to carriers identified through routine clinical cultures, or coupled to active screening programs. We will test the combination of decolonizing the skin with chlorhexidine, which targets MRSA and other bacteria, plus decolonizing the nose with mupirocin, which targets the main reservoir for MRSA carriers.

1.8 Universal Strategies Affecting All Pathogens

In contrast to the above strategies that specifically target MRSA, it is possible that universal strategies that impact all pathogens may be more effective than strategies that target a specific pathogen like MRSA. This is particularly relevant due to rising numbers of other highly antibiotic resistant pathogens such as vancomycin-resistant enterococcus and multi-drug resistant gram negative bacilli, including extended spectrum beta-lactamase producers and carbapenemase-resistant enterobacteriaceae, for which therapeutic options are limited. Such strategies may also require fewer resources, and thus be "dominant" in terms of coupling greater benefits with lower costs. For example, a successful universal strategy could obviate the need for routine screening for MRSA and applying targeted isolation or decolonization. We describe here the evidence in support of universal chlorhexidine bathing and universal application of mupirocin to high risk patients to prevent infections due both to *S. aureus* and also to other pathogens.

One increasingly well evaluated universal strategy for pathogen control in ICUs is the routine use of chlorhexidine bathing in place of usual soap and water baths for all patients. This strategy stems from the strong evidence that chlorhexidine is the most effective skin preparation for central line placement when outcomes of central line infections are measured, and from other studies showing marked reductions in skin bacterial colony counts for several days following serial bathing.[54-58] In fact, national recommendations for prevention of surgical site infections (SSI) from the CDC's Hospital Infection Control Practices Advisory Committee (HICPAC) call for bathing or showering with chlorhexidine at least twice before the operation. The CDC ranks this recommendation as a category IB: "Strongly recommended for implementation and supported by some experimental, clinical or epidemiologic studies and strong theoretical rationale."[56]

In addition, the Society of Thoracic Surgeons has recommended universal mupirocin for all cardiac surgery patients unless screening nares cultures show lack of *S. aureus* carriage.[57] This strategy is supported by evidence of reduction in *S. aureus* surgical site infections in excess of 20%.[58 59]

1.9 Effectiveness of Decolonization with Mupirocin and Chlorhexidine

The use of decolonization to prevent HAI has biological plausibility. It reduces bacterial carriage, which commonly precedes infection. This reduction in bioburden reduces the likelihood of infection from a patient's own flora and also reduces the spread of pathogens from one patient to another. Nevertheless, definitive trials are needed to develop best practice guidance on when decolonization should be used, and, as with any antimicrobial agent, use must be balanced by the risk of engendering antibiotic resistance.

Mupirocin is a prescription drug that was FDA approved in 2002 for topical treatment of mild wounds due to *S. aureus* and *Streptococcus pyogenes*. A nasal formulation is also approved for eradicating nasal carriage of *S. aureus*. Mupirocin is highly effective in eradicating *S. aureus* in the short term. Several studies have shown 90% efficacy within two weeks of a 5-day regimen.[60 61 62 63 64] It also significantly reduces short-term hospital-associated MRSA transmission and infections by over 50% in observational and cross-over

intervention studies.[16 17 53 54 65 66] Long term efficacy over weeks to months drops substantially after a single treatment regimen to approximately 60% after 6-8 weeks, largely due to re-colonization with the patient's original strain.[17 57-59 61-64 67] Increased failure to decolonize was noted if additional cultures were taken from body sites other than the anterior nares, suggesting that both serial treatment as well as additional decolonization of sites other than the nose are necessary for prolonged eradication of MRSA.[17 65 68 69]

To improve body surface decolonization, chlorhexidine body washes are now routinely given with mupirocin for MRSA decolonization. Chlorhexidine gluconate (CHG) has been safely used for bathing, showering and dental hygiene for over 50 years. It is an over-the-counter product that is 4% solution intended for direct application to skin as an antimicrobial skin cleanser. Numerous studies have shown marked reductions in skin bacteria following serial CHG bathing or showering,[70-76] and it is widely used as a pre-operative showering agent based upon CDC guidelines that recommend its use.[56] It is also the gold standard in periodontal hygiene, including oral care in ventilated patients.[70 71 72] Evidence exists to support the need for repeated application for sufficient skin decontamination,[74 73 74 75] as well as for low bacterial counts to persist for one to two weeks following use.[76 77] In addition, the concept of a universal strategy for decolonization has gained favor since evidence is mounting that CHG can reduce colonization and infection from a variety of healthcare associated pathogens.[15 16 84] Studies by members our investigative group and others have demonstrated a 52-87% reduction in bloodstream infection in ICU patients.[15-17 78] There is also growing evidence that CHG skin bathing may reduce MRSA acquisition and infection by 50% in high risk settings such as ICUs.[16 17 55 66] This approach and others led to our recent definitive cluster-randomized trial of 43 hospitals demonstrating the success of routine chlorhexidine bathing and mupirocin decolonization in ICUs to significantly reduce HAIs (see Preliminary Data Section 6.10.2, (confidential trial results).

The definitive success of decolonization with chlorhexidine and mupirocin in reducing HAIs in ICUs provides the foundation for a trial evaluating whether these successes can be translated to non-critical care units. Since most HAIs occur outside the ICU and after hospital discharge, targeting the larger general patient population has the potential to make a much greater impact on HAIs by reducing the skin and nasal carriage of important pathogens during a time when patients are highly vulnerable to infection.

1.10 Safety of Mupirocin and Chlorhexidine

Both mupirocin and CHG have excellent safety profiles. Systemic absorption of both drugs is minimal.[79 80 81 82 83] Of the minimal amount of mupirocin that is absorbed, nearly all is rapidly converted to monic acid, an inactive metabolite.[79 80] Furthermore, systemic absorption remains negligible following single or repeated intranasal applications over consecutive days in adults.[84] Multiple observational studies and randomized controlled trials have also shown no systemic absorption of mupirocin following intranasal application.[82 83 85 86 87] Safety data for mupirocin from the manufacturer states that <1% of patients in clinical trials withdrew due to adverse events. The most frequently reported adverse events were as follows: rhinitis (1.0%), taste perversion (0.8%), and pharyngitis (0.5%). Post-marketing surveillance has not resulted in any additional concerns.

As an over-the-counter skin cleanser used in healthcare for over 50 years, CHG has an even more extensive safety record.[15 17 53 54 88 89 90 91 92 93 94] Several groups have confirmed the absence of systemic absorption following topical use or oral rinsing with CHG.[95 96 97 98] Moreover, even if ingested, CHG is known to have negligible absorption with undetectable blood levels.[99 100 101] Side effects are largely limited to skin irritation, which is rare, and anaphylaxis has only been reported as case reports.[102 103] Estimates for these effects are expected to be very small given the large numbers of people using an unregulated over-the-counter product. No deleterious effects have been reported with daily use in either long-term ICU patients[16 78 85] (Sage Inc, personal communication regarding routine use in >400 ICUs) or outpatient daily bathing for 9 months.[74] The major manufacturer of over-the-counter CHG states that CHG "can be used many times a day without causing irritation, dryness, or discomfort."[74] It is also safe on superficial wounds.[104]

1.11 Emergence of Resistance to Mupirocin and Chlorhexidine

The use of mupirocin and chlorhexidine for decolonization appropriately raises the issue of whether these agents will engender antimicrobial resistance. Small proportions of mupirocin resistance have been reported in some,[48 105] but not all studies.[17 106 107] As an example, Robicsek et al. reported that mupirocin resistance remained relatively low during a 3-year period of widespread use, but did increase from 4.1% to 7.2% among MRSA isolates.[48] Other studies have reported declines in mupirocin resistance under continued use for high risk patients.[108 109 110] Finally, one ICU study has reported evidence of clinically meaningful levels of mupirocin resistance at 8.6% despite lack of use,[111] suggesting variability in regional susceptibility may exist.

Chlorhexidine resistance in MRSA has not been reported in the United States. A chlorhexidine

resistance gene in MRSA has been newly reported in Europe, but the clinical significance is not fully known.[112] Regardless of whether or not significant resistance has emerged, any trial evaluating the use of these products for decolonization purposes needs to perform careful monitoring for the development of antibiotic resistance.

1.12 Need for a Cluster-Randomized Controlled Trial in General Inpatient Units to Achieve Significant Reduction in Healthcare-Associated Infections

Cluster randomization is the preferred experimental method for evaluating decolonization approaches to prevent all-cause HAIs. There are several reasons for this. Foremost is the fact that there is considerable transfer of pathogens from one patient to another, for instance on the hands of healthcare workers and sometimes via inanimate objects (medical equipment, furniture, etc). Thus, interventions that affect all patients in a location are more likely to succeed, and also much more likely to predict the performance in actual practice. Cluster randomization also has advantage of studying interventions under conditions of actual use, of minimizing the disruption to normal practice, and of allowing the use of health system resources for ensuring compliance with the intended treatment. We discuss these issues in more detail in Sections 2.1-2.3 below.

1.13 Summary of Overall Significance

The well publicized focus on HAI prevention by all major agencies and stakeholder groups, including the CDC, CMS the Joint Commission, the Institute of Healthcare Improvement, the IOM, the National Quality Forum, the newly formed national Partnership for Patients of the Department of Health and Human Services (dedicated to patient safety and HAI prevention across the continuum of healthcare), and numerous national societies including the American Medical Association, the Infectious Diseases Society of America, and the Society for Healthcare Epidemiology of America, provide the impetus to perform a definitive high impact trial on HAI prevention in non-ICU inpatient populations.

Large cluster randomized trials for HAI prevention (our own) in ICUs have demonstrated that it is possible to prevent many HAIs. There is a great need to focus on broader patient populations in whom the majority of HAIs occur and in whom medical care, risk of infection, patient-to-patient interactions, pathogen transmission, and bathing practices differ considerably from ICU settings. A randomized trial sufficiently generalizable to assess HAI reduction in broad patient populations has not previously been undertaken because the scope of such a study is not possible under usual funding mechanisms. A head-to-head trial of decolonization versus standard of care bathing will enable us to determine whether this potentially important strategy has a role in all patient populations.

2.0 Significance – UH2 Planning Year

The topic for this proposal is thus a critically needed area of comparative effectiveness study. It addresses the following two top quartile (the highest rating) priority topics from the Institute of Medicine's top 100 national priority areas across all domains of medicine released in 2009:[44]

- Compare the effectiveness of strategies for reducing healthcare-associated infections (HAI), including catheter-associated bloodstream infection, ventilator associated pneumonia, and surgical site infections
- Compare the effectiveness of various screening, prophylaxis, and treatment interventions in eradicating methicillin resistant *Staphylococcus aureus* (MRSA) in communities, institutions, and hospitals.

The ability to conduct a well designed pragmatic trial requires careful thought as to the best study design to fit the question to be answered – in this case, how best to ascertain whether routine decolonization can reduce HAIs, including MRSA infection, in the general hospitalized patient population.

2.1 Design Elements of Pragmatic Design in Comparative Effectiveness Trials

In designing this proposal, we will provide a practical roadmap of a well-designed trial that showcases the six defining characteristics of comparative effectiveness research (CER) highlighted by the Institute of Medicine in their 2009 report "Initial National Priorities for Comparative Effectiveness Research."[44] In so doing, it will enable other trials to adopt and mirror strategies for effective research. We are well suited to provide this roadmap as an investigative team that has previously worked together to conduct a related cluster-randomized trial on decolonization in ICUs (see Section 5.0.1-5.0.2 Investigative Team and Sections 5.30.1, 6.10.1-6.10.2, Preliminary Data). In this proposal, we will highlight the ability of the ABATE Infection Trial to address the six defining characteristics of comparative effectiveness research (CER) (see Section 4.3). These six characteristics are:

- #1: CER has the objective of directly informing a specific clinical decision from the patient perspective or a health policy decision from the population perspective.

- #2: CER compares at least two alternative interventions, each with the potential to be "best practice."
- #3: CER describes results at the population and subgroup levels.
- #4: CER measures outcomes—both benefits and harms—that are important to patients.
- #5: CER employs methods and data sources appropriate for the decision of interest.
- #6: CER is conducted in settings that are similar to those in which the intervention will be used in practice.

2.2 Usual Processes for Quality Improvement in Hospitals

Most quality improvement activities in hospitals focus on process measures rather than outcomes. To the extent they do address outcomes, they are often unable to determine with confidence that an intervention improves (or harms) patients. We highlight two important reasons for the inability to learn as much as possible from quality improvement initiatives. First, the improvements are implemented without a robust comparator. It is very common, for instance, to perform a before-after comparison. These comparisons provide the least persuasive evidence,[113] and are well documented to lead to incorrect conclusions.[114] Second, evaluations of interventions in routine care settings often include too few patients to provide a robust estimate of their effect.

Through this trial, we will create new tools and approaches to conducting robust, reliable, generalizable research that incorporates the best quality improvement methods. This will be a key step in the creation of a learning health system – one that generates evidence in the course of delivering best quality clinical care. We will share methods and materials for implementation as well as programs for trial processes and outcomes.

2.3 Cluster-Randomized Trial Design for Quality Improvement Research for HAI

Despite their strengths, conventional randomized clinical trials (RCTs) have important limitations. Although they are excellent tools for judging *efficacy* (performance under ideal conditions), they often fail to judge *effectiveness* (performance under conditions of actual use). This is because most RCTs require more standardization and a higher level of medical care than occurs in practice. In addition, generalizability may be lost because participants in RCTs are often not representative of the eventual target group. Furthermore, RCTs are often very costly and time-consuming to implement. For example, the ALLHAT study of initial treatment of hypertension, often cited as a pragmatic clinical trial,[115] cost over $80 million and took 8 years to complete.[116]

Cluster-randomized trials are RCTs which randomize groups (clusters) rather than individuals. Cluster randomization is the only feasible method for randomization when an intervention must be applied or is usually applied to an entire group, such as a community-based health promotion campaign or a hospital quality improvement initiative applied to hospital units or clinical services. They are also the only method for evaluating interventions for which the status of individuals is linked, for instance when shared exposure to contagious illness is an important consideration, as commonly occurs in hospital settings.

Cluster-randomized trials have several advantages in comparative effectiveness studies. First, by applying interventions at the hospital, practice, or health plan level, cluster-randomized trials can more readily study interventions under conditions of actual use. For instance, a cluster-randomized trial that uses existing clinical and administrative mechanisms incorporates the impact of group dynamics (advocacy, peer pressure, reminders) among healthcare providers. Second, cluster-randomized trials are often intended to be applied to an entire hospital, Intensive Care Unit (ICU) or clinic population without exclusion, which enhances generalizability. Third, cluster-randomized trials are able to harness the healthcare delivery system's existing administrative capacities, including quality improvement programs and data collection systems, simplifying the logistics of implementation and reducing study costs.[19]

The increasing availability of electronic health information facilitates the implementation of cluster-randomized trials, as routinely collected electronic health information can be used to assess baseline status, monitor implementation, and measure outcomes. This proposal will provide a seminal trial that demonstrates several of the design strengths of cluster-randomized trials. It will generate comparative effectiveness evidence in an efficient and timely manner, thus enabling swift policy action and impacting best practice guidance.

2.4 Critical IRB Considerations for Cluster-Randomized Trials

For the US healthcare system to adopt cluster randomization as a common method for studying comparative effectiveness, several conditions will need to be satisfied.[19] First, the concept of group randomization, often without individual consent, raises important ethical issues about individual choice and participation in research.[117] There will need to be agreement that it is ethical to perform cluster randomization. Importantly, these concerns must be balanced by the fact that quality improvement decisions are routinely made on behalf of patients every day in U.S. hospitals, often without sufficient evidence to guide the choice of protocol or product. In addition, without cluster-randomized trials, it would not otherwise be possible to study

quality improvement initiatives in the manner in which they are actually applied in healthcare.

In general, cluster-randomized trials require waiver of individual informed consent to compare group-level effects in response to interventions such as a formulary change, a new hospital policy or campaign, or an insurer change in policy. Requirement of individual consent would preclude the ability to test population response because the intervention would not be uniformly adopted across all patients. The IRB governing such trials must be familiar with the national guidance related to waiver of documented individual informed consent and also familiar with the intersection of research inquiry and routine healthcare improvement processes.[117 118] Additional experience and familiarity is needed related to minimal risk criteria, the issues related to randomizing groups (hospitals, clinics, communities) rather than individual patients, whether the activity is being performed under standard quality improvement methods, and whether the activity under study is already commonly used in healthcare despite lack of a definitive trial. Finally, the IRB needs to understand the full range of options, including delegation of the consent decision to a designated representative of the cluster.

In this proposal, we will share and publish our ethical considerations and approach to IRB issues that are highly relevant to this and other cluster-randomized trials. This shared experience will help the medical community use rigorous research methods to develop evidence for best practice as part of usual medical care.

3.0 Significance – UH3 Trial Implementation Years

As mentioned above, our topic addresses two of the top 100 national priority areas –HAI elimination and MRSA eradication - identified by the Institute of Medicine for medical comparative effectiveness research.[44] If successful, routine decolonization through daily bathing with chlorhexidine would become best practice for preventing infection among 40 million patients hospitalized each year in the United States alone.

3.1 Context and Conduct of Hospital-based Cluster-Randomized Trials for Disease Prevention

Although the cluster-randomized trial design is well described in public health settings, there are relatively few successful examples in modern clinical care environments that demonstrate the power of this design, its advantages for conducting research embedded in usual medical care, and the relative practicality of implementation. This is particularly important for the fields of infectious diseases and infection prevention since assumptions of independence are violated among individual participants due to contagiousness. In these situations, identifying large numbers of randomizable groups for study is critically important to determining realistic intervention effects. Since the usual method of improving care in medical facilities and clinics is to adopt or test improvement strategies for all patients or for a selected subset of hospital units or clinics, the study of interventions in this setting should apply to all patients in a medical area and be highly generalizable.

The methodology and learning experiences needed to successfully conduct large cluster-randomized trials that randomize entire hospitals is not well described due to lack of experience. This proposal will provide guidance as to the conduct of such trials, including approach, materials, and use of technology to expedite and standardize trial activities, to assess compliance during usual care, and to efficiently obtain results. This trial will expand our understanding of simplified large scale research among numerous hospitals in many states.

3.2 Secular Trends and Best Practice Foundation

Secular trends in medical care are well described phenomena that can negatively impact proper assessment of clinical trials. Without control groups, trialists may conclude that an intervention has had an effect when they are actually only observing concurrent changes occurring in the population-at-large. This is partly because hospitals frequently introduce new practices and launch multiple initiatives that overlap in time and place. Thus, cluster-randomized trials should employ a control arm. In addition, control arms should reflect current best practice in order to understand whether the intervention advances science by producing benefit over the current gold standard. Thus, it is vital to ensure that best practice is achieved in participating groups before the start of the trial. Finally, it is imperative that medical approaches and processes be monitored during the course of the trial to prevent additional quality improvement initiatives from confounding results.

3.3 Implementation of Cluster-Randomized Trials in Hospitals

Effectiveness research should maximize use of usual care and care improvement processes. Trials targeting infectious disease prevention should therefore engage existing hospital infection prevention programs and use their methods to effect change in clinical practice and ensure compliance for patient safety. It is well known in the field of hospital epidemiology that practice change succeeds best when there is a unit champion or leader to serve to promulgate new initiatives and influence peers.[119 120 121] Thus, engaging existing unit champions such as nurse managers or medical directors for trial initiatives is a usual and customary approach

to effect change. In addition, it is uncommon for hospitals to implement divergent processes across similar units. To mirror actual practice, prevent confusion and avoid trial contamination due to shared patients and staff across units, cluster-randomized trials of inpatient processes should ideally randomize hospitals, not units.

In addition, pragmatic clinical trials should utilize routine and recognizable hospital processes such as standardized nursing protocols, computer-based training, and routinely scheduled events (e.g. nursing acuity assessments, bathing, central line dressing changes) and be cognizant of the impact of the trial on necessary and expected activities such as nursing shift change, and cleaning and product restocking schedules.

3.4 Maximizing the Use of Electronic Health Records to Support Research

In order to effectively and efficiently conduct trials in care settings, all segments of the healthcare and lay communities need to understand the importance of acquiring information during the routine delivery of care.[122] [123] The advent of robust electronic health record (EHR) systems and the impetus provided by the meaningful use incentive programs by CMS allow trials to be conducted in highly efficient and technologically advanced ways. In this trial, we will showcase how robust EHR systems across large health systems can be leveraged to implement standardized protocols, easily query compliance, and obtain key data elements such as the presence of devices during customary nursing documentation routines, employ usual hospital surveillance and infection reports, and ensure rapid data capture and cleaning for trial analyses. In this way, robust EHR systems can close the gap between effectiveness and efficacy across hospital populations.

3.5 Analysis of Cluster-Randomized Trials

Finally, cluster-randomized clinical trials need to employ different statistical methods that account for the relatedness of outcomes within groups. For example, increasing numbers of patients with infectious outcomes will increase the contagiousness level in a group setting. Thus, accounting for intra-cluster correlation is imperative to obtaining credible results for trials that use this methodology.

3.6 Trial Significance – Overall Summary

Healthcare-associated infections are a top 10 cause of death in the U.S. and a focus of intense national attention by numerous federal agencies. Although most prevention trials have focused on ICUs, where the daily risk for infection is the highest, the majority of healthcare-associated infections occur outside of ICUs. This cluster-randomized controlled trial will evaluate whether decreasing the bacterial bioburden of non-ICU patients through bathing with chlorhexidine and eradicating MRSA with nasal mupirocin prevents healthcare-associated infections and the readmissions they cause. Importantly, the conduct of this trial by a highly experienced team will provide a critical roadmap to the design, conduct, and analysis of large scale cluster-randomized trials, and will produce generalizable toolkits and programs for future trials.

4.0 Innovation

This proposal to conduct a large scale cluster-randomized trial will be one of the most innovative and important trials for prevention of HAIs. It has direct applicability to all hospitalized patients and it will generate guidance, materials, resources, and software products that will improve the design and conduct of future cluster-randomized trials.

4.1 Innovation – Overall Project

We will conduct a trial whose result can influence the care of the majority of hospital patients while demonstrating all key elements of comparative effectiveness research as follows:

- **Element #1: CER directly informs a specific clinical decision from the patient perspective or a health policy decision from the population perspective.**
  The ABATE Infection Trial will evaluate whether chlorhexidine bathing should be routinely used for essentially all hospitalized patients to prevent hospital and post-discharge infections. This is relevant for both patients and policy.
- **Element #2: CER compares at least two alternative "best practice" interventions.**
  The ABATE Infection Trial is a head-to-head comparison of routine bathing of non-critical care patients with soap and water (current best practice) versus daily chlorhexidine bathing (improvement strategy) for all patients plus nasal mupirocin for decolonization of MRSA carriers.
- **Element #3: CER describes results at the population and subgroup levels.**
  The ABATE Infection Trial will analyze its results across the overall hospital population and also among critical subgroups of patients who may be at higher risk for outcomes, such as those harboring multi-

drug resistant pathogens, and those with significant comorbidities (e.g. diabetes, renal failure, cancer) This is important since it is well documented that these patient subsets are at higher risk[13 30-35 40 45-46] of healthcare-associated infections and may benefit disproportionately from decolonization.

- **Element #4: CER measures outcomes—both benefits and harms—that are important to patients.** The ABATE Infection Trial will evaluate not only beneficial outcomes of reducing HAI and the readmissions they cause, but also potential harms including whether resistance to the decolonization agents (chlorhexidine and mupirocin) is differentially engendered in the two arms of the trial.
- **Element #5: CER employs methods and data sources appropriate for the decision of interest.** The ABATE Infection Trial uses a cluster-randomized trial and a corporate data warehouse to evaluate this question across a large number of hospitals. In addition, it uses routinely available data sources that are commonly used to assess HAIs by infection prevention programs in the U.S. and applies them in such a way so as to maximize and showcase the use of electronic medical records.
- **Element #6: CER is conducted in settings that are similar to those used in practice.** The ABATE Infection Trial uses a cluster-randomized trial to mimic the way bathing care is usually delivered in hospitals, and the method by which quality improvement is performed in hospitals. In addition, this trial will be implemented in a large number of community hospitals, the most common type of hospital providing care in the U.S..

The focus on prevention of HAIs in non-ICU settings is an important area of innovation. Trials to reduce infection in non-critical care areas are largely lacking because of the large number of hospitals and patients that are needed to address events that occur with low frequency, but affect very large numbers of patients in the aggregate. Collectively, patients in non-ICU settings are responsible for the majority of healthcare-associated infections and any hope for elimination must invest in these critically needed trials to determine the best strategy for adoption. This trial will be a first-in-class effort in this important patient safety realm.

This trial will also make an important contribution to the active debate about when to focus HAI prevention strategies on those that target specific pathogens, like MRSA, vs strategies intended to impact many pathogens.[124] This is an important issue that has both scientific and practical ramifications. The scientific issues concern the impact of decolonization on patients' normal bacterial flora and on the ecology of the healthcare systems that employ it. The practical consequences have much to do with the organization and cost of medical care. Our recent trial, the REDUCE MRSA trial[125] (see Preliminary Data Sections 5.30.1, 6.10.1-6.10.2) has definitively opened the door to testing all pathogen approaches in the general patient population.

4.2 Innovation – UH2 Planning Year

In contrast to most trials, the ABATE Infection Trial will recruit community hospitals which provide the majority of inpatient care in the U.S.. Thus, our trial will take place in generalizable contexts and produce generalizable solutions. Our Health Care System (HCS) collaborator, Hospital Corporation of America (HCA), consists of over 160 community hospitals nationwide, structured into 3 regional groups across 20 states.

Another unique feature is that this trial will demonstrate high efficiency in startup time for a large scale cluster-randomized trial. Our previous trial recruited 45 hospitals in 6 weeks. We will again utilize an infrastructure that enables rapid recruitment and encourages hospitals to cede ethical review to a lead IRB for oversight. This will streamline the approval process and serve as an example for future trials.

An additional significant innovation includes the development of statistical graphics for cluster-randomized trials that allow improved strata construction to improve balance among covariates. This is important since the number of clusters in such trials is often small enough that imbalance in covariates is more likely to occur by chance when compared to large individual randomized trials. Thus, measures to reduce the chance of imbalance will be a substantial contribution to the field.

Finally, our proposal capitalizes on an excellent data warehouse infrastructure to efficiently track patient outcomes. We will include not only outcomes of infections occurring during the hospital stay, but also extended outcome assessment to the immediate post-discharge period. This design feature is particularly important to assess impact across the continuum of healthcare delivery and will be a valuable consideration for other trials.

4.3 Innovation – UH3 Trial Intervention Years

This pragmatic clinical trial will advance the nation's progress toward what the IOM calls a "learning healthcare system" - one that both generates and uses evidence to guide clinical decision-making. It will

accomplish this in several ways. First, it will call upon the usual quality improvement infrastructure at each intervention hospital to implement our decolonization strategy in a manner familiar to their medical staff. We will engage Infection Prevention program managers at each participating hospitals and secure representative unit champions. Second, it will create a recognizable electronic module within standard nursing documentation that will enable nurses to enter answers to a small number of process and compliance questions. Third, these answers will be beneficial not only to the trial, but will also serve to capture essential device utilization data that assists with publicly reported metrics. Reports generated from these results will be retrievable by users at the participating hospitals. This provides a key example of the use of electronic medical records for research.

Beyond the innovative intervention of using chlorhexidine bathing in non-critical care units to reduce HAIs, this trial will be one of the first to ensure that other quality improvement projects adopted by the hospital during the baseline and trial period do not interfere with the interpretation of the trial's effect. The first trial to do this was our previous cluster-randomized trial of chlorhexidine bathing in ICU areas. The ABATE Infection Trial will assess potential new initiatives on a frequent basis and will proactively request that all participants report any new initiatives under consideration so that investigators may determine if a conflict exists.

We will also generate sharable computer programs related to both trial process and analysis. This programming code, employing parallel commercial and open-source code, will be made publicly available.

5.0 Approach – UH2 Planning Year

5.0.1 Investigative Team – Expertise

We have assembled an impressive multidisciplinary team with expertise in infectious diseases, infection prevention and healthcare epidemiology, microbiology, individual and cluster-randomized clinical trials, survey design, statistics, and cost analysis.

Susan Huang, MD MPH (Co-Principal Investigator) is an Associate Professor of Medicine and the Medical Director of Epidemiology & Infection Prevention at the University of California Irvine (UCI) Medical Center. She has over a decade of research experience addressing healthcare associated infections (HAIs), including multi-drug resistant pathogens, surgical site infections, bloodstream infections, and outbreaks. This is coupled with practical experience in leading quality improvement initiatives as a hospital epidemiologist. With longstanding expertise in MRSA, Dr. Huang is the lead investigator of two federally-funded randomized clinical trials on decolonization strategies. She is the lead investigator for a recently completed 43-hospital cluster-randomized trial (REDUCE MRSA Trial)[125] evaluating ICU decolonization with chlorhexidine and mupirocin. She is also the lead investigator for a large individual randomized trial on post-discharge decolonization for MRSA carriers (Project CLEAR).[126] The ABATE Infection Trial provides the important bridge to study the value of decolonization in non-ICU settings. currently co-leads a CDC Prevention Epicenters grant, a research consortium for preventing HAI.

Dr. Huang is joined by several experts (**Table 1**) with combined extensive expertise in HAI research, including comparative effectiveness research, clinical trials, and decolonization studies (**Table 2**).

Table 1. Co-Investigators for the ABATE MRSA Infection Trial

Co-Investigator	Institution	Relevant Expertise
Ed Septimus, MD	Hospital Corporation of America	Medical Director, Infection Prevention program for national corporation of >160 US hospitals; proactive quality improvement programs for MRSA, rapid dissemination of best practice
Mary Hayden, MD	Rush University Medical School	Associate Professor of Medicine (Infectious Diseases) and Pathology/Laboratory Medicine; Expertise in infectious diseases and microbiology; use of mupirocin and chlorhexidine for decolonization, antimicrobial susceptibility testing
John Jernigan, MD MS	Centers for Disease Control and Prevention (CDC)	Deputy Director, Division of Healthcare Quality Promotion at CDC, Epidemiologist and infectious diseases physician; expertise in MRSA, national HAI surveillance, definitions, reporting, outcomes
Robert Weinstein, MD	Stroger Hospital of Cook County	Professor and Chair of Medicine, renown expertise in infectious diseases, healthcare epidemiology; pioneered chlorhexidine for decolonization
Ken Kleinman, ScD	Harvard Medical School/ Harvard Pilgrim Health Care Inst.	Associate Professor and biostatistician with longstanding expertise in longitudinal and clustered data methods related to infectious diseases, and statistical software. Involved with numerous HAI projects, including lead statistician for the REDUCE MRSA Trial (ICU decolonization)
Daniel L. Gillen, PhD	UC Irvine	Associate Professor in Statistics; biostatistician and trialist. Lead statistician for multiple randomized trials.

Table 2. Investigative Team Expertise in Healthcare Associated Infections

	RANDOMIZED CONTROL TRIAL	COHORT STUDY	TIME SERIES	MODELING SIMULATION	ECONOMIC ANALYSIS
MRSA					
Detection / surveillance Hospitals, [127] [128] nursing homes, [129] metrics [35, 130] [131] [132]		X			
Risk factors: adults, [30, 133] [134] children [135]		X			
Sequelae: pre- and post-discharge [30, 31, 33]		X			
Prevention Assessing vaccine targets by antibody response [136] Active surveillance, isolation on bacteremia, **RCT** [18, 47, 137] [138] [139] [140] [141] [142] Environmental cleaning on transmission [143] [144] ICU Decolonization: 3 arm cluster **RCT** [19, 125] Post-Discharge Decolonization **RCT** [126]	X	X	X		
Dynamic modeling: inter-facility transmission [145] [146] [147] [148]				X	
Cost-effectiveness [149]					X
Guidelines [150] [151]					
Resistant Gram Negative Pathogens					
Klebsiella pneumoniae carbapenemase [152] [153] **Prevention** [154] [155]		X			
Blood Stream Infection (BSI)					
Detection / surveillance Adults, [156] [157] Neonatal ICU [158] [159]		X		X	
Risk factors: ICU [160] [161]		X			
Sequelae: ICU [158]		X			
Prevention Decolonization [15, 16, 78, 162] Transducer cleaning **RCT** [163]	X	X			
Surgical Site Infection (SSI)					
Develop/validate automated detection algorithms: Inpatient algorithms [164] [165] [166] [167] [168] Post-discharge algorithms [169] [170] [171] [172] [173] [174]		X			
Risk factors [175] [176] [177] [178] [179]		X			
Sequelae: [180] [181]		X			
Prevention [182] [183] [184] Choice of antimicrobial [176] Intraoperative antibiotic redosing **RCT** [185] Antibiotic prophylaxis **RCTs** [186] [187]	X	X			
Cost-effectiveness [177, 188]					X
Ventilator Associated Pneumonia (VAP)					
Detection / surveillance [189] [190] [191] [192] [193]		X			
Guidelines [194]					
Catheter Associated UTI (CA-UTI)					
Detection / surveillance [195]		X			
Risk factors [196]		X			
Sequelae: Increased mortality [25]		X			
Prevention Antimicrobial irrigation **RCT** [197] Tamper-evident seals **RCT** [24]	X				
Cost-effectiveness [198]					X
Guidelines [199]					
Hospital Outbreak Detection					
Automated algorithms [200] [201]		X		X	

5.0.2 Investigative Team – Experience in Randomized Controlled Trials

Our seasoned investigative team are experts in decolonization with relevant experience working together in two major clinical trials – the REDUCE MRSA Trial: a 43-hospital cluster-randomized trial of an

critical care MRSA decolonization quality improvement strategy,[19 125] and Project CLEAR: a post-discharge randomized clinical trial on education vs decolonization for MRSA carriers.[126]

The recently completed REDUCE MRSA Trial was a three-way cluster-randomized trial of 43 hospitals (74 ICUs) in the Hospital Corporation of America healthsystem - the same healthcare system partner in this proposal. The three arms included: 1) ***screening and isolation (standard of care)***: nasal screening for MRSA followed by isolation if positive, 2) ***targeted decolonization***: screening, followed, if positive, by isolation and decolonization with chlorhexidine baths and nasal mupirocin for 5 days, and 3) ***universal decolonization***: cessation of screening, universal application of mupirocin for 5 days, and daily chlorhexidine baths. Its primary outcome was MRSA clinical cultures with a secondary outcome of all pathogen ICU-associated infection (see Section 6.10.2).

The REDUCE MRSA recruitment, design, implementation tools, data capture methods, and analytic processes are highly relevant for this trial of decolonization in non-critical care settings. In addition, the genesis of the REDUCE-MRSA trial was based upon extensive, long-term collaboration between the CDC public health experts, academic investigators, and HCA clinical leaders.

Project CLEAR is an ongoing chlorhexidine and mupirocin decolonization trial that enrolls MRSA+ patients upon hospital discharge to either education or serial decolonization. Its primary outcomes are MRSA infection and readmission and its implementation tools will also be translatable to the ABATE Infection Trial.

5.0.3 Health Care System (HCS) Partners

Our healthcare system partner is Hospital Corporation of America (HCA) and its three regional U.S. Groups. As one of the largest providers of healthcare in the U.S., HCA provides 5% of all major acute care services in the U.S. though its 160+ hospitals. HCA has conducted several successful infection prevention campaigns at the Group and Corporate level, including MRSA screening of high risk patients, antibiotic stewardship, and prevention bundles for central line associated infections. HCA has also actively engaged in several research studies, especially those in the arena of HAI. They have been the healthcare system partner for multi-center studies on reducing central line-associated bloodstream infections and surgical site infections, in addition to the REDUCE MRSA Trial. Key highlights of the HCA system include:

- ***Corporate Structure for Infection Prevention/Quality***
  Our HCA co-investigators are the corporate leaders of Quality, Performance Improvement, and Infection Prevention who lead all regional and system-wide initiatives in this arena. HCA will contribute the highly experienced services of Dr. Edward Septimus (HCA site principal investigator, Medical Director of Infection Prevention and Epidemiology), Jason Hickok, MBA RN (Associate Vice President, Patient Safety and Infection Prevention), and Julia Moody, MS (Clinical Director of Infection Prevention and Epidemiology) to pursue this second major cluster-randomized trial with study investigators. This group has previously provided key collaborative coordination and implementation support for the REDUCE MRSA Trial.
- ***Corporate/Group/Divisional Structure for Recruitment***
  HCA hospitals are divided into the National Group, Central Group, and the Southwest Group. The Groups consist of 50+ hospitals and are governed by a Group President and Chief Financial Officer. New quality improvement initiatives are determined and implemented at the Group level. In the ABATE Infection Trial, we will leverage the leadership from all three Groups to ensure adequate and rapid recruitment.
- ***Corporate Data Warehouse***
  HCA has established a corporate data warehouse that includes highly standardized hospital and unit census information, patient demographic data, admission and discharge information, billable charges, including coded diagnostic and procedure codes from each admission, and supply chain data. In addition, laboratory and microbiology data are also stored in the HCA data warehouse. Data flow continuously from each hospital to the central database where HCA Information Technology teams can access, retrieve, standardize, and analyze clinical data as needed for this proposal and other needs.
- ***Corporate Information Technology and Services (IT&S)***
  HCA's IT&S sector consists of 3,605 employees nationwide. Corporate IT&S is located in Nashville, TN where decision support programmer and analytic teams build and maintain HCA's clinical documentation system and data warehouse. HCA's IT&S sector has previously provided key elements for research trial needs, including computer based training modules, pharmacy logic to target products to participating units, nursing queries for daily documentation of trial protocols, and patient-level data for analysis.

- ***Corporate Supply Chain***
  HCA Supply Chain Services (SCS) coordinates products and supplies to its facilities. For trial purposes, HCA's SCS is able to channel products and divert products that may be incompatible with trial products. They also assess product volume needs in real time and ensure proper garnering of necessary supplies.
- ***Corporate Regulatory/Compliance for Trial Assistance***
  HCA's corporate regulatory affairs and risk management office (David Vulcano MBA, Associate Vice President for Clinical Research) will work closely with a lead investigator IRB to provide coordinated central IRB approval for participating hospitals. This office is familiar with the regulatory process of clinical trials and has facilitated FWA, IRB, and required research training necessary for hospitals to either submit their own IRB or cede to an investigator IRB in order to participate in cluster-randomized trials.
- **Corporate Financial Services Group**
  HCA's Financial Services Group handles conducts value analyses and cost-effectiveness analyses on the Group and corporate level and will be a valuable resource for this proposal.

HCA provides an ideal test bed for a cluster-randomized trial of hospitals to reduce HAI. Its community hospital base provides generalizability to U.S. hospitals and its centralized infrastructure allows efficient implementation and data collection across participating hospitals. Importantly, HCA has pursued initiatives to ensure best practice standards so that this trial would evaluate improvement strategies over current gold standard care.

5.10.0 Aim 1: Recruit hospitals for a cluster-randomized trial of 1) routine daily bathing with chlorhexidine for all patients plus 2) routine nasal decolonization with mupirocin for patients harboring methicillin-resistant *Staphylococcus aureus* (MRSA) in general medical and surgical units to reduce infection and readmissions.

It is important to improve the speed and efficiency of clinical trials to address urgent needs for evidence-based practice. The ABATE Infection trial will use a novel, efficient process to recruit hospitals to participate in this cluster-randomized trial. We will focus on recruiting community hospitals, to increase the relevance of our research to the U.S. healthcare system.

5.10.1 Preliminary Data

As mentioned above, we recently completed a 43-hospital 16-state cluster-randomized trial of decolonization in ICUs. Recruitment for that study was accomplished within 6 weeks. Recruitment activities leveraged HCA's managerial leadership and communications systems to inform hospital decision makers (chief executive officers, chief medical officers, chief nursing officers, ICU directors) about the trial and to advocate for participation. The trial also used corporate survey systems to assess eligibility.

Specifically, HCA's 3 regional Groups supported recruitment. Each Group governs quality improvement initiatives for its 50+ hospitals. Requests for participation were endorsed by the President of each Group. Each respondent was given a survey to confirm inclusion criteria were met, including minimal use of decolonization products. Participation was confirmed by a signed letter of participation from hospital administration.

5.10.2 Recruitment Infrastructure and Process

We will leverage similar systems to recruit 54 hospitals for the ABATE Infection Trial. First, we will use email and provide webinars through HCA's webhosting system to introduce the trial and the process for participation. Second, solicitations for hospital participation will be extended to all 160 HCA hospitals through the three regional Group Presidents with corporate HCA support (see letter of support). Third, our HCA co-investigators, who are the system-wide leaders of quality, performance improvement, and infection prevention, will provide direct-to-hospital endorsement for the trial. Finally, we will directly reach out to hospital participants of our previous trial. Recruitment announcements will utilize usual corporate and regional HCA communication channels and will be directed at hospital leadership (Chief Executive Officer, Chief Medical Officer, Chief Nursing Officer) and infection prevention program directors.

5.10.3 Criteria and Survey for Eligibility

Enrollment criteria for hospitals include a) being a licensed acute care U.S. hospital belonging to Hospital Corporation of America, and b) willingness to be randomized at the hospital-level to either usual bathing care or decolonization. Within hospitals, units that were eligible for participation included a) participating adult units of the following types: adult step-down (transitional care after leaving an ICU), medical, surgical, medical/surgical, and oncology non-critical care units, b) minimal current use of routine daily chlorhexidine bathing in these units (<30% of patients), c) less than 30% of unit patients undergoing cardiac or

arthroplastic surgery, and d) average length of stay of at least 2 days. Among eligible units, we will allow for national standards for pre-operative bathing with chlorhexidine and pre-operative *S. aureus* decolonization for cardiac and arthroplastic surgery. In addition, hospitals must confirm that they will avoid other discretionary infection prevention and quality initiatives for the duration of the trial, both the 1-year baseline and 18-month intervention period, (NOTE: intervention was extended to a 21-month trial in June 2015). The baseline period begins in the planning year and extends into the first half of the UH3 trial phase. Further details of the trial design, including rationale for the baseline observation period and timeline are found in UH3 Aim 3, Section 6.10.4.

We will exclude pediatric and specialty units, including psychiatry, obstetrics/post-partum, bone marrow transplant, and rehabilitation/skilled nursing units. Adult units that occasionally have children <12 are permissible, but children <12 admitted to participating units will not be included in the mupirocin protocol.

For each potential hospital participant, enrollment criteria will be assessed by administering an electronic survey to each eligible unit's champion as well as through the evaluation of baseline administrative data from the HCA data warehouse. The survey will additionally request contact information and details about infection prevention practices, bathing practices, and use of chlorhexidine and mupirocin. As done previously, surveys will be administered through HCA's usual survey channels and results will be compiled and returned to investigators in a database format. An example survey from our previous REDUCE MRSA trial is provided in **Appendix A**.

5.10.4 Limitations and Planned Solutions

The main limitation of this recruitment aim is the potential failure to recruit 50 hospitals. While we believe this is unlikely due to our previous trial of 43 HCA hospitals, should enrollment be less than 50, we will pursue an elongation of the 18-month trial, (NOTE: intervention was extended to a 21-month trial in June 2015).

5.10.5 Milestones and Timeline

Recruitment will occur in the first quarter of the UH2 planning year. A full description of UH2 milestones and timeline is found below in Section 5.60.0.

5.20.0 Aim 2: Obtain Institutional Review Board (IRB) approval for the cluster-randomized trial and maximize efficiency by having most hospitals cede to a central IRB.

The current standard of engaging institutional review board (IRB) processes at each participating hospital is a substantial hurdle for multi-center studies, particularly those involving dozens of sites, as this proposed study does. In fact, even minor modifications required by different IRBs may substantially delay or even prevent standardization across a trial, without measurable improvements to patient safety.[202] [203] In addition, requiring institution-specific IRB review for multi-center trials has been associated with lower participation rates and highly redundant effort.[204] Additionally, smaller and community-based hospitals often lack the resources, expertise and infrastructure to maintain local IRB committees. Outsourcing to commercial IRBs is a costly option that may deter facilities from participating in worthwhile research opportunities. These factors contribute to slower, smaller, less representative trials.

5.20.1 Preliminary Data – Experience with Centralized IRB Coordination

We have relevant experience of IRB coordination from our REDUCE MRSA cluster-randomized trial. The Harvard Pilgrim Health Care (HPHC) IRB, in conjunction with HCA's corporate regulatory affairs liaison, coordinated the IRB approval of 43 hospitals. Efficient approval was realized by having 38 of 43 IRBs cede to the HPHC IRB, a process that also included helping hospitals with no Federal Wide Assurance number obtain one. Human protection training requirements were set by HPHC for all ceded sites. Changes to the study protocol received streamlined review by the HPHC IRB and the other 4 IRBs that governed the remaining 5 hospitals. In addition, HCA corporate and the CDC, which co-funded the trial with the Agency for Healthcare Research and Quality, both delegated IRB oversight to the HPHC IRB through IRB Authorization Agreements.

The HPHC IRB has 16-years of experience governing a breadth of research studies, including cluster-randomized trials, multi-site intervention and observational cohort studies, genetic typing studies, studies involving the collection of bacterial strains, and studies involving large administrative databases. Many of its research studies have included quality improvement innovations, a critical expertise for this trial. As mentioned above in Section 2.4, IRBs that govern trials of quality improvement strategies must be familiar with the

intersection of research inquiry and routine healthcare improvement processes, and with the national guidance related to a waiver of documented informed consent.[117 118]

For the REDUCE MRSA trial, the HPHC IRB determined that a decolonization initiative for ICU patients was minimal risk. It further waived documentation of informed consent based upon regulatory criteria under 45 CFR 46.116(d), 117(c) (2) and 56.109(c) (1).(38). Posted notices describing the trial and arm-specific details were required in all patient rooms (see **Appendix B**). The HPHC IRB also required hospital infection prevention programs to attest to performing surveillance for healthcare associated infections during the trial and to inform the study team of unusual rates or types of ICU infections.

5.20.2 Centralized IRB Coordination for the ABATE Infection Trial

We will employ a similar centralized IRB process for the ABATE Infection Trial. The HPHC IRB, in conjunction with HCA's corporate regulatory affairs and risk management office (David Vulcano MBA, Associate Vice President for Clinical Research), will provide central oversight for this trial and will facilitate delegation of IRB governance from participating hospitals and assurance of human subjects training through a custom-tailored "Human Subjects Protection Training for ABATE Site Research Liaisons" that was co-developed by HCA and HPHC. This training will be offered via the centralized HCA HealthStream training module, which allows for real-time facility/individual completion tracking. Since the ABATE Infection Trial involves a similar decolonization intervention to the REDUCE MRSA Trial, except in a lower risk non-critical care population, we anticipate that this trial will also have documentation of informed consent waived based upon regulatory criteria under 45 CFR 46.116(d), 117(c) (2) and 56.109(c) (1).(38) since 1) trial activities meet minimal risk criteria, 2) the trial randomizes hospitals, not patients, 3) all assigned activities will be performed under standard hospital quality improvement procedures, and 4) some US hospitals have implemented similar quality improvement protocols despite lack of definitive evidence on best practice. We will collect attestations from hospital infection prevention programs stating that they will continue to conduct routine surveillance for HAIs in all participating units and will inform the trial team of any unusual trends or occurrences.

While we have optimized ceding and delegation procedures for this study, we believe the foundational work that we and our IRB have done has general utility.[117] We would be very willing to share our experience and materials with other UH2/UH3 programs and with Collaboratory leadership.

5.20.3 Limitations and Planned Solutions

Despite our structured approach and HCA corporate support of ceding IRB oversight to the HPHC IRB, it will be the prerogative of participating hospitals to use their own IRBs. For hospitals that choose to do so, we will coordinate standardized IRB protocols and all subsequent modifications during the trial.

5.20.4 Milestones and Timeline

IRB approval for all participating hospitals will occur in the second quarter of the UH2 planning year. A full description of UH2 milestones and timeline is found below in Section 5.60.0.

5.30 Aim 3: Develop trial educational materials and routine electronic nursing queries for daily bathing and decolonization in general medical and surgical inpatient areas.

In the planning year, we will develop all trial materials for hospital staff and patients, as well as compliance assessment tools and processes for the phase-in and intervention periods.

5.30.1 Preliminary Data

We have previously developed materials for two chlorhexidine and mupirocin decolonization trials (see description in Section 5.0.2). The REDUCE MRSA Trial produced materials for ICU staff and Project CLEAR produced materials for patients following hospital discharge. These materials contribute to the proposed protocol since our ICU materials involved educating staff for decolonizing sedated patients, and our post-discharge materials involved direct-to-patient education for decolonization at home. The ABATE Infection Trial will need materials for staff whose patients are awake, and often ambulatory.

Relevant materials from the REDUCE MRSA Trial are found in **Appendix C**, and include a 1) PowerPoint presentation introducing the trial to participating hospital leadership and unit champions, 2) computer based training modules for frontline staff, 3) a nursing decolonization protocol, 4) "Just in Time" training materials for registry (temporary/float) nurses, 5) frequently asked questions by staff, 6) talking points for staff to patients, 7) adverse event forms and training documents, and 8) a brief daily electronic nursing documentation module for assessing chlorhexidine and mupirocin compliance in ICU patients, as well as documenting reasons for non-use (**Appendix C**); this was incorporated into HCA's centralized system for daily

documentation of nursing care. Relevant materials from the Project CLEAR Trial include 1) bathing and showering instructions for patients, 2) frequently asked questions by patients, 3) adverse events information, and 4) a quick reference guide (**Appendix D**).

In addition, during the REDUCE MRSA trial, we collected MRSA isolates from all participating hospitals. To do this, we created laboratory toolkits (**Appendix E**), which included 1) detailed instructions, 2) a Frequently Asked Questions (FAQ) sheet, 3) collection log sheets, 4) deidentified study ID labels, and 5) a quick reference wall chart (**Appendix F**) providing a streamlined diagram of the key elements for collection. Details were reviewed in laboratory-specific coaching calls (**Appendix G**).

5.30.2 Development of Hospital Trial Materials for Participating Units

The ABATE Infection Trial materials will be modeled after those developed for the REDUCE MRSA and Project CLEAR Trials. Here, we describe the materials that will be created in the planning year. The manner in which these materials will be used is described in detail in UH3 Aim 1 (see Section 6.10.8 and 6.10.9).

Study arm-specific binders will be developed for distribution after randomization (see Section 6.10.5). These will be distributed to each hospital's leadership, infection prevention program liaisons, and the nurse educator, nurse manager, and medical director of participating units. We anticipate 50 hospitals with an average of 4 participating units each, for a total of 14 binders per hospital, or 700 total binders (350 per arm). Binder contents are detailed in **Table 3**. In addition to distributing paper copies of this binder by mail, we will also use HCA's intranet (Atlas) to post these trial-specific materials. Similar to our prior trial, study arm-specific intranet sites will be created; each site will have access only to material about its assigned treatment regimen.

Table 3. Contents of ABATE Infection Trial Toolkit Binders

Educational Material	Description
1. Welcome and Summary of Goals	Introductory information on the trial
2. Study Investigators	Lists all investigators and collaborators involved in the trial
3. Table of Contents	Summary of documents included
4. Phone Matrix	Contact information for lead investigators, HCA co-investigators, and study staff
5. Frequently Asked Questions*	Answers to common staff questions about the trial or protocol
6. Patient Talking Points*	Talking points for common patient questions about the trial or protocol
7. Dos and Don'ts*	Quick reference guide on protocol
8. Kick-Off Protocol PowerPoint*	PowerPoint slides used in the kick-off webinar
9. Computer Based Training*	Printout of protocol training module
10. Just in Time Training*	On-the-spot training and reference guide for temporary/float nurses
11. Patient Instructions	Patient instruction sheets for self-bathing/showering with chlorhexidine
12. Nursing Protocol**	Nursing protocol for use of chlorhexidine and mupirocin
13. Study Related Events Form**	Forms for reporting study related adverse events
14. Technical Document*	Instructions on setting up nursing protocol and pharmacy orders

*Indicates arm specific information (control vs. intervention arm) ** Decolonization arm only

HCA routinely uses computer based training (CBT) modules to ensure completion of required health learning activities. The system (HealthStream) allows selective assignment to specific hospitals, units, and job types throughout HCA hospitals. We will develop arm-specific CBT modules to be completed by all frontline staff who work in participating units. The CBTs will focus on the rationale behind the trial, review protocol details related to the assigned treatment arm, and make clear that the assigned treatment is routine practice for the hospital for the duration of the trial. Compliance will be tracked locally and centrally by HCA's Director of Clinical Education Development, who will provide detailed reports to HCA co-investigators.

5.30.3 Development of Electronic Nursing Documentation Modules

HCA uses a centralized system (MEDITECH) for documentation of nursing care. We will create arm-specific electronic MEDITECH documentation screens that will require nurses to answer questions each daytime and evening shift about whether each of their patients was bathed with chlorhexidine and whether nasal mupirocin was administered. In the Usual Care Arm, if a chlorhexidine bath or shower was provided (non-compliance with protocol), it will require one of the following reasons (e.g. pre-operative bathing, physician order, or free-text response). In contrast, in the Decolonization Arm, if chlorhexidine is not given (non-compliance with protocol), it will similarly require one of a different set of reasons (e.g. patient allergic, patient refused, physician refused, or free-text response). An example from our prior trial is found in **Appendix C**. These responses will be tracked for monthly compliance assessments in both arms.

5.30.4 Development of Laboratory Materials for Collecting Bacterial Isolates and Launch of Baseline Strain Collection

In the planning year, we will also develop materials for the microbiology laboratories of participating hospitals to begin to collect bacterial strains throughout the trial. The reason for collection is to assess whether universal decolonization engenders resistance to decolonizing agents. Requested strains will include MRSA as well as select gram negative bacteria in which resistance to chlorhexidine has been reported. Laboratories will collect, batch, and send bacterial isolates on a monthly basis using the same protocol regardless of arm. Full details are provided in UH3 Aim 2, but the development of materials is described here.

We will create a PowerPoint presentation for an introductory webinar to participating laboratories at the beginning of strain collection. This presentation will introduce laboratory staff to study staff and detail the entire process for de-identified strain collection. This will be followed by mailed laboratory toolkits (see example from prior trial, **Appendix E**), which will include 1) a Step-by-Step instruction sheet, 2) a Frequently Asked Questions (FAQ) sheet, 3) collection log sheets with a clipboard, 4) de-identified study ID labels, 5) FedEx mailing instruction sheets, 6) a shipment packing list, 7) a shipping schedule, and 8) a quick reference wall chart with a streamlined diagram of key elements for collection (see example from prior trial, **Appendix F**).

In order to ensure that the volume of MRSA+ and gram-negative rod (GNR) isolates that are collected during the baseline period are sufficient to support analysis around whether or not study agents engendered resistance, it will be crucial to obtain a full 12-months worth of isolates. It is anticipated that participating ABATE Infection Study hospital laboratories will begin collecting and banking isolates that fit study criteria beginning 3/01/2013 and continue collection through 2/28/2014 in order to support this activity. Collected isolates will include MRSA+ and the following eight select GNR organisms. Isolates will have already been collected as part of a patient's routine medical care.

E. coli	*P. aeruginosa*
K. pneumoniae, K. oxytoca	*A. baumannii*
P. mirabilis	*S. maltophilia*
S. marcescens	*Burkholderia spp.*

Once full IRB approval is obtained (either via ceding to the HPHC IRB or pursuing individual review) at each participating hospital during the baseline year (see Section 5.20.0), isolates may then be shipped to the central study laboratory at Rush University, Chicago for analysis and storage.

5.30.5 Limitations and Planned Solutions

The main limitation to this aim would be insufficient development and preparation time. Since similar materials exist from our prior trials, we anticipate rapid development and assembly.

5.30.6 Milestones and Timeline

All laboratory trial materials will be developed during the first half of the planning year, prior to initiating baseline collection of isolates. Hospital trial materials will be developed in the latter half of the planning year. A full description of UH2 milestones and timeline is found below in Section 5.60.0.

5.40.0 Aim 4: Obtain baseline data on HAI infection rates for participating hospitals to lay the foundation for trial outcomes. These will be obtained using corporate data warehouse capabilities of Hospital Corporation of America (HCA).

During the planning year, we will work with the NIH Collaboratory to develop and validate our electronic methods and tools for data sampling. We will extract data from the centralized data warehouses of HCA and develop adequate control measures to ensure high quality data extraction and cleaning methods.

5.40.1 Preliminary Data

We have had extensive experience with data from HCA's centralized data warehouse through our previous trial. The REDUCE MRSA Trial evaluated similar outcomes (clinical cultures and all-cause bloodstream events) in ICU locations. Data streams familiar to this investigative group include hospital census, microbiology, pharmacy, supply chain, MEDITECH documentation, and administrative data.

5.40.2 Hospital Corporation of America Centralized Data Warehouse

The following data elements (Table 4) will be requested from HCA's Information Technology team to sample patient descriptors and baseline primary outcomes and ensure adequate processes for high quality data pulls. For details about trial design, outcomes, and analysis, see UH3 Aim 1 (Section 6.10).

Table 4. Data Elements Requested from HCA's Centralized Data Warehouse

Source Data	Desired Results	Elements
Primary Outcome		
Census Data	Adult patient days by unit Readmissions within 30 days	Patient identifier (coded), hospital, unit location, hospital and unit admission date, hospital and unit discharge date, age in years, gender
Microbiology Finalized Results	Sterile site cultures, all pathogens	Pathogen name (if culture is positive), patient identifier (coded), date of collection, body site of collection, antimicrobial susceptibility, quantification of urine culture count (e.g. ≥50,000 colonies)
Claims data	Identification of infectious readmissions	Diagnosis codes (ICD9) Procedure codes (ICD9/CPT codes)
Descriptors		
Claims data	Identification of comorbidities Use as case mix adjustors	Diagnosis codes (ICD9)
Pharmacy	Mupirocin dispensing	Patient identifier (coded), date range dispensed, unit location
Supply Chain	Chlorhexidine use	Patient identifier (coded), date used, unit location

5.40.3 Data Access – Virtual Machine

To maximally protect the large volume of protected health information required for the ABATE Infection Trial, HCA will establish a mechanism similar to our previous trial where our programmer analysts gain access to HCA data behind the HCA firewall. Programmer analysts will receive remote access to a virtual machine where requested data will be placed after extraction by HCA's information technologists. This extraction process will involve replacement of names and medical record numbers with coded identifiers. Programmers will access this virtual machine to clean and analyze data, and to generate summary level output for review with our statistician. All data cleaning and analysis will be performed using SAS 9.3 (SAS, Cary, NC).

5.40.4 Data Validation, Cleaning and Calculation of Baseline Outcome Data

We will use data from March 1, 2013-Feb 28, 2014 as the baseline data for our study cohort. This requires exclusion of the first two days in a hospital unit (CDC criteria).[206] We will describe their age, gender, and comorbidity characteristics based upon ICD-9 diagnostic codes. We will compare these characteristics across units and across hospitals and identify any outliers in the data by looking for unexpected month to month variation or substantial missing data across hospitals and units. Data discrepancies will result in discussions with HCA co-investigators and information technologists for repeat data pulls and examination of data for errors in coding or variations in data storage.

We will evaluate primary outcomes in the baseline period by identifying isolation of a gram-positive multi-drug resistant organism (MRSA or VRE) from a clinical culture among the patients who meet eligibility criteria. Secondary outcomes derived from the HCA data warehouse will include isolation of a gram-negative multi-drug resistant organism from a clinical culture, all-cause bloodstream infection, blood culture contaminants, urinary tract infection (with an a priori expectation of greater impact in men than women due to endogenous infection), *C. difficile* infection, 30-day infectious readmissions and all-cause readmissions, and emergence of chlorhexidine and mupirocin resistance in bacteria isolated from participating units.

Using CDC criteria, blood cultures due to skin commensals will require at least two cultures within 2 calendar days to quality as a sterile site event.[206] Urine cultures will be required to have at last 50,000 colony counts. Outcomes will be calculated as events per 10,000 patient days, and similar evaluations for data discrepancies or missing data will be performed.

5.40.41 Data Standardization

Currently, microbiology data from HCA facilities is found in a single system (Meditech). However, Meditech allows for four methods of reporting microbiology results, including a form of free text. In response to excessive data cleaning requirements to standardize across facilities, the investigative team and the HCA corporate laboratory services leadership instituted the standardization of reported microbiology results across the ABATE facilities. This decision was driven in large part by the perceived value of this direction for corporate HCA. ABATE Trial facilities are considered a pilot roll out of what will ultimately be a corporate-wide microbiology laboratory standardization campaign.

Microbiology laboratories serving facilities in the ABATE Infection Trial were notified of the requirement to report microbiology results via a single acceptable reporting mechanism in March 2013, one month prior to the start of baseline data collection. The selected mechanism allows for maximal electronic parsing of data into required elements for determining microbiologic outcomes. As of March 2013, only 30% of participating hospitals were using this desired mechanism for reporting culture results. By June 2013, half of participating hospitals had fully converted to this mechanism, and by early September 2013, 91% (50/54) of facilities had converted. Previously used methods of robust data cleaning and standardization will be required from the start of the baseline period until complete adoption for all hospitals and we are well-versed in this process.

5.40.42 Data Creation

Since tracking of patient bathing is not routinely done in U.S. hospitals, a single nursing query was created to be completed once daily asking if a bath/shower was completed in the past 24 hours and whether the bath/shower involved chlorhexidine. If a bath/shower was not provided (regardless of use of chlorhexidine), the prompt requires a reason by providing common drop down options or free text entry. This bathing query was activated in March 2013 and is in use at all participating hospitals.

5.40.5 Limitations and Planned Solutions

Should data barriers fail to be resolved for specific hospitals, we will evaluate the possibility of obtaining needed data variables directly from the facility rather than the data warehouse. If missing or insufficient data cannot be resolved, we will note the time period and exclude the hospital from analysis for that period of time. We note that this has not been the case for previous trial evaluations using HCA data.

5.40.6 Milestones and Timeline

During the planning year, HCA data will be extracted for 4-months of the baseline period. A full description of UH2 milestones and timeline is found below in Section 5.60.0.

5.50.0 Collaboratory Work Groups

Throughout the planning and intervention phases, we will work closely with the NIH Collaboratory Coordinating Center to align study design, implementation processes, data extraction and quality control plans, and confirmation of study outcomes. Our lead investigators will actively participate in the HCS Research Collaboratory Steering Committee, and members of our investigative team will actively participate in HCS Research Collaboratory Work Groups established by the Collaboratory Coordinating Center as follows:

Table 5. Collaboratory Work Group Members

Collaboratory Work Group	Investigative Team Member(s)
Electronic Health Records (EHR)	Adrijana Gombosev (Project Coordinator)
Regulatory/Ethics	Julie Lankiewicz, MPH (Project Coordinator), Sheila Fireman, JD (IRB Administrator, HPHC), and David Vulcano MBA, (Associate Vice President for Clinical Research, HCA)
Biostatistics/Study Design	Ken Kleinman, ScD (Lead biostatistician), Daniel Gillen, PhD (biostatistician). Extensive experience in clinical trials, including HAI and cluster-randomized trial experience.
Provider-Health Systems Interactions	Adrijana Gombosev (Project Coordinator), Susan Huang, MD MPH (PI)
Stakeholder Engagement	Edward Septimus, MD (Site PI, HCA)
Collaboratory Work Group	Investigative Team Member(s)

5.60.0 UH2 Planning Phase Milestones and Timeline

We summarize our milestones for this 1-year planning phase (**Table 6**). Each is described with concrete deliverables and its contribution to the UH3 intervention phase.

Table 6. Planning Year Milestones and Timeline

UH2 Milestone	Details / Purpose	Timeline			
		Q1	Q2	Q3	Q4
Aim 1: Recruitment					
1. Call for Participation	Identify interested hospitals for ABATE Infection Trial	x			
2. Deliver Survey for Unit Eligibility	Tool to assess 1) stable infection control practices and 2) sufficiently low use of trial intervention products	x			
3. Administer Survey for Eligibility	Exclusion of ineligible units within hospitals	x			
4. Finalize Letters of Participation	Final set of hospital and unit participants identified for trial	x			
Aim 2: IRB					
1. Lead Institution IRB Approval	Central IRB application and approval obtained	x			
2. Active IRB Ceding of Participants	Streamlined process for transferring primary IRB responsibility		x	x	

3. Deliver Adverse Events Forms	Reporting forms for monitoring study related events				x
Aim 3: Develop Study Materials					
1. Finalize Trial Timeline w CCC	Confirm plans for baseline and intervention periods, launch dates				
2. Host Kick-Off Webinar	Develop and host PowerPoint to introduce process and protocol		x		
3. Launch Bathing e-Documentation	Develop (Q2) and activate (Q3 start) MEDITECH e-documentation nursing for all participating units to assess bathing frequency and products			x	x
4. Deliver Complete Trial Toolkit	Develop nursing protocol, FAQs, patient talking points, computer based training module, bathing/showering instruction sheets				x
5. Host Lab Introductory Webinar	Develop and host PowerPoint to introduce collection protocol		x		
6. Deliver Complete Microbiology Collection Toolkit	Develop strain collection instruction sheet, inventory sheet, FAQs, packing instructions, log sheets		x		
7. Launch Strain Collection	Begin baseline strain collection to assess resistance			x	
Aim 4: Data Sampling					x
1. Establish remote access to HCA virtual machine	Set up structure for analytic access to HCA data behind their firewall for all trial analysis				x
2. Extract sample census and outcome variables	Demonstration of data extraction and cleaning process to CCC related to accessibility, process, quality control, programming				x
3. Sample baseline outcomes	Calculate baseline outcomes using a sample of data from baseline time period. This will enable confirmation of projected baseline outcomes and confirmation of adequate power for trial				x
4. Finalize trial outcomes with CCC	Based upon baseline sample, finalize all trial outcomes				x

Together, these milestones will perform five critical functions to enable the launch of the trial in the UH3 intervention phase. First, we will identify and finalize the 54 participating hospitals and their intervention units. Second, we will achieve IRB approval at all sites for trial launch. Third, we will initiate the baseline period, which will include collection of baseline bacterial strains from all participating hospitals and will assess baseline bathing/showering frequencies in all units. Fourth, we will develop all main trial materials and toolkits in preparation for intervention launch. Fifth, we will demonstrate the ability to pull a sample of baseline data and outcomes. This will enable us to demonstrate the feasibility and efficiency of our data processes, identify data cleaning and quality control routines, and confirm power estimates for the study using actual baseline data. The achievement of these milestones will enable a smooth transition into the UC3 trial phase, which includes the second part of the baseline period plus the phase-in and intervention periods.

5.70.0 UH2 Planning Phase Summary

This UH2 proposal provides the foundation for a critically needed trial to reduce the majority of healthcare-associated infections which are occurring outside of ICU settings. Despite large successes in the ICU arena in reducing healthcare associated infections (HAIs), these gains have not translated to reductions in the greater number of non-critical care units in hospitals. This trial will enable the testing of a decolonization protocol that can be applied during routine bathing and showering processes to assess its ability to reduce HAIs for the vast majority of hospitalized patients.

6.0 Approach – UH3 Trial Intervention Phase

6.0.1 Estimated US Impact

HAIs remain a top 10 cause of death in the U.S. despite marked reductions in ICU infections. The ABATE Infection Trial (**A**ddressing **B**ioburden while **A**dmitted **T**o **E**liminate Infection) seeks to further national gains by targeting the majority of HAIs which occur in non-ICU medical, surgical, and oncology units each year, including readmissions due to HAI occurring shortly after discharge.[1] Our goal is to reduce a large part of the 1.7 million HAIs that occur each year by testing decolonization strategies that reduce the risk for all patients. If successful, routine decolonization through daily bathing with chlorhexidine would become best practice for preventing infection among 40 million patients hospitalized each year, and would substantially reduce the $6.5 billion dollars of direct healthcare costs associated with HAIs in the U.S. alone.

6.0.2 Hypothesis

We hypothesize that daily bathing and showering of non-critical care hospitalized patients with chlorhexidine will meaningfully reduce healthcare-associated gram positive multi-drug resistant bacteria (MRSA and VRE). We further hypothesize that it will also reduce other healthcare associated events such as gram negative multi-drug resistant pathogens, all cause bloodstream infection, urinary tract infection, C difficile infection, blood culture contamination, and readmissions. This intervention strategy will be compared to routine bathing and showering care in 50 community hospitals.

6.10 Aim 1: Conduct a 50+-hospital cluster-randomized controlled trial of routine chlorhexidine bathing and selective MRSA decolonization versus standard-of-care practices for all hospitalized patients in non-critical care adult medical, surgical, and oncology units. The primary outcome will be clinical burden of gram-positive multi-drug resistant organisms. Secondary outcomes will include clinical burden of gram-negative multi-drug resistant organisms, bloodstream infections, and readmissions caused by infection.

This aim describes the study design, implementation, and analysis of a large cluster-randomized trial to assess whether universal chlorhexidine bathing plus selective MRSA decolonization will significantly reduce sterile site infections and infectious readmissions in patients on non-critical care units. This study will illustrate the efficiency of cluster randomization in a network environment for evaluating the effectiveness of decreasing bioburden for HAI reduction. Salient features include minimizing the burden of implementation and evaluation, ensuring advocacy by system leaders, streamlining multi-site policy implementation, using existing quality improvement personnel and methods, using information about processes of care and outcomes obtained as part of routine medical care, and leveraging informatics capabilities that allow centralized access to these data. The use of an existing infrastructure is maximized by randomizing entire hospitals, so that all participating units in each hospital use the same intervention protocol, supply chain, and compliance and reporting procedures.

6.10.1 Preliminary Data – A Multi-center Cluster-Randomized Trial of Decolonization in ICU Patients

We highlight additional features of the REDUCE (**R**andomized **E**valuation of **D**ecolonization vs **U**niversal **C**learance to **E**liminate) MRSA Trial (see initial description in Section 5.0.2),[19 125] a recently completed 43-hospital cluster-randomized trial by this investigative group. Use of similar features will enable efficient implementation of the ABATE Infection Trial. Features include:

- **Robust health system infrastructure** for corporate communications, decision-making and coordination of activities at the regional and corporate levels, and information technology support.
- **Efficient recruitment and IRB clearance** have already been described in UH2 Aims 1 and 2.
- **Easy accessibility** to trial staff in multiple sites through a real-time collaborative e-mail platform – enabling multi-user simultaneous editing for categorizing and prioritizing email inquiries, assigning them to specific responders, and streamlining workflow processing – and toll-free number enabling excellent coverage across time zones. Over 5,000 distinct email inquiries were fielded, as well as over 200 phone calls originating from unit champions or infection prevention programs at participating hospitals.
- **Division of labor** by trial staff enabled collection of 5,000+ specimens by 44 microbiology laboratories which were coordinated by east coast staff due to the fact that laboratories generally work early shifts from 6am-2pm. Conversely, since bathing of ICU patients was generally performed on the evening/ night shift, the west coast trial staff fielded all coordination questions related to protocol implementation.
- **Readily available training and trial materials** were provided to unit champions and infection prevention programs, including study binders (see Preliminary Data section 5.30.1), computer-based training modules posted to participating unit staff, 55 site visits for chlorhexidine cloth bathing instruction and training as well as ad hoc requests for additional site visits.
- **Centralized product distribution** by HCA's corporate central supply and pharmacy systems enabled tracking of usage to ensure adequate supply. It also allowed diversion of product when demands exceeded planned supply. Importantly, central supply chain prevented distribution of incompatible products and facilitated substitutions. Specialized pharmacy routines were also used to ensure trial product delivery to participating units.
- **Routine mechanisms for compliance** were leveraged, including electronic nursing queries inserted in the usual framework of nursing documentation, and associated electronic reports of these queries which were retrievable by unit champions. In addition, periodic observed bathing events (3 per quarter per unit) were performed by the unit champion and reported to study staff.
- **Arm-specific coaching calls** were used to build camaraderie and engagement. They occurred weekly in intervention arms and every other week for standard-of-care arms for the first several months of the initial trial period before converting to monthly calls. A total of 48 coaching calls were provided during the REDUCE MRSA Trial. They were used to allow same-arm hospitals to discuss issues and share solutions about protocol implementation. In addition, coaching calls enabled investigators to review compliance performance across participating hospitals, and inquire about the presence of new initiatives and adverse events. Roll call was taken at all calls. Special topic coaching calls and podcasts

were also provided to give expert review of the literature and allow expanded question and answer sessions for common questions from frontline staff (e.g. safe use of chlorhexidine on wounds).

- **Trial-specific coordinating calls** were held regularly, including weekly investigator group calls and monthly steering committee calls during the intervention period, followed by weekly data analyst meetings and bimonthly statistical meetings during the end-intervention and post-intervention period. The investigator and steering committees played the important role of adjudicating whether new or upcoming hospital initiatives were in conflict with the trial. In the REDUCE MRSA Trial, a total of 70 new initiatives were brought before the investigative team with 35 of them not initiated because of a real or perceived conflict with the trial. One hospital dropped out of the trial in favor of a conflicting initiative.
- **Detailed logs** were maintained related to contact information on unit champions and infection prevention liaisons, adverse event logs, new initiative requests, and the determination of whether they conflicted with the trial. All calls and emails were cataloged into major groups and documented with various study staff in charge of specific types of inquiries.

6.10.2 Preliminary Data – Results of REDUCE MRSA Trial of Decolonization in ICUs

The REDUCE MRSA Trial was an 18-month 3-arm cluster-randomized trial involving 74 adult ICUs in 43 community hospitals,[205] with the goals of reducing clinical isolates of MRSA and bloodstream infections due to all pathogens. All ICUs in a hospital were assigned to the same arm. Study arms were: 1) ***screening and isolation (pre-trial standard of care)***: nasal screening for MRSA followed by isolation if positive, 2) ***targeted decolonization***: screening, followed, if positive, by isolation and decolonization with chlorhexidine baths and nasal mupirocin for 5 days, and 3) ***universal decolonization***: cessation of screening, universal application of mupirocin for 5 days, and daily chlorhexidine baths. Proportional hazards models with shared frailty were used to assess differences in infection reductions across the arms while accounting for clustering by hospital.

We randomized 43 hospitals in 16 states. There were 74 adult ICUs with 48,390 admissions in the baseline period and 74,256 in the intervention period. There were significant differences between arms in the relative hazards for intervention vs. baseline for both clinical isolates of MRSA and bloodstream infections caused by all pathogens (Table). In each case, universal decolonization produced a significantly greater reduction than screening and isolation. Targeted decolonization was not significantly different from screening and isolation alone. Adjusted analyses yielded similar results (Table).

Table. Primary Outcome Event Rates and Proportional Hazard Model Results for REDUCE MRSA Trial

Strategy	ICU-Attributed MRSA Clinical Cultures				ICU-Attributed Bloodstream Infections (all pathogens)			
	Baseline*	Intervention*	HR^	HR_{adj}+	Baseline*	Intervention*	HR^	HR_{adj}+
Screening and Isolation	13.7	11.9	0.92	1.0	16.8	15.3	0.99	0.98
Targeted Decolonization	16.1	12.2	0.75	0.83	17.9	13.8	0.78	0.77
Universal Decolonization	13.8	8.3	0.63	0.69	23.7	13.7	0.56	0.55
P-value$	--	--	**0.01**	**0.02**			**<0.0001**	**<0.0001**

* Events per 1,000 patients

^ HR = Hazard Ratio from primary unadjusted analysis; model estimates are not equal to ratio of raw risk due to differential length-of-stay and effect of clustering within hospital

+ HR_{adj} = Hazard Ratio from secondary adjusted analysis

$ P-value from proportional hazards model

Universal decolonization with chlorhexidine and mupirocin in adult ICUs resulted in a 37% reduction in MRSA clinical cultures and a 44% reduction in bloodstream infections due to all pathogens. The targeted decolonization arm was not significantly different from screening and isolation alone. Universal decolonization also eliminates the need to obtain surveillance cultures and reduces need for isolation.

6.10.3 Preliminary Data - HAI Rates in Non-Critical Care Units in Health Care System Partner Hospitals

Using non-ICU data from hospitals participating in the REDUCE MRSA Trial, we estimated the baseline rates of bacteremia due to all pathogens as well as due to MRSA alone (**Table 7**). These data reflect non-ICU data from only the 13 hospitals (104,852 admissions) in the universal decolonization arm of the REDUCE MRSA Trial. We use this arm to provide conservative estimates since this arm had non-significant reductions in post-ICU sterile site infections due to all pathogens.

Table 7. Estimates of HAI Rates in Non-ICU Areas Targeted by the ABATE Infection Trial

	Non-ICU Estimate	Events/10,000 Patients
MRSA Bloodstream Infection	62/104,852	5.9
All Pathogen Bloodstream Infection	894/104,852	85.3

These data include all patients in non-ICU areas excepting areas that would be excluded in this trial (pediatrics, psychiatry, obstetrics, rehabilitation/skilled nursing, bone marrow transplant units).

Readmission Rates due to Infections in Health Care System Partner Hospitals

Using the same cohort above, but restricting to those discharged during the study period (N=103,874), we calculated a 0.038 rate of readmission due to infectious diagnoses within 30 days of discharge. Admissions were deemed to be due to infections if ICD-9 infectious diagnoses were found in the primary or secondary diagnosis position. Infectious diagnoses were limited to those likely to be hospital associated (mainly bacterial). These data will be used for power calculations for the ABATE Infection Trial (Section 6.10.12).

6.10.4 Trial Design and Study Population

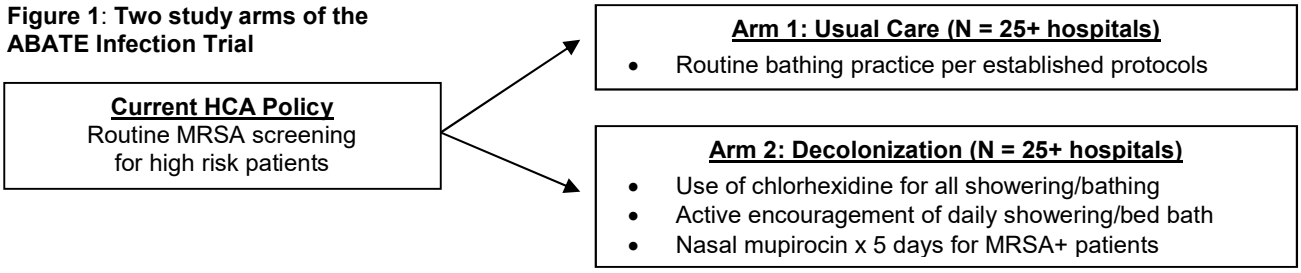
The ABATE Infection Trial will be a cluster-randomized controlled trial of 54 HCA hospitals, evaluating 2 regimens to reduce HAIs in general hospital adult units (**Figure 1**).

Our intent is to move forward with 54 hospitals to allow for unanticipated withdrawal where a hospital might drop from the trial. For example, early withdrawal from the trial may be required due to a conflicting intervention. Hospitals generally have multiple simultaneous campaigns ongoing to improve patient care. For the ABATE Trial, we require monthly confirmation of either no interventions/ new campaigns at their hospital or a reporting to the Steering Committee of what campaigns or interventions are in consideration or being launched. Should the Steering Committee identify a conflict, the hospital must decide to either withdraw from the trial or not pursue the proposed campaign or intervention. Given that conflicts are likely to arise and hospitals have the option to drop out of the trial despite CEO commitment to the trial, we will proceed with the 54 hospitals with the intent that at least 50 will remain in the trial for the full duration.

The ABATE Infection Trial will employ a 12-month baseline period from March 1, 2013 to February 28, 2014, a 2-month phase in period from April 1 to May 31, 2014and an 18-month intervention period from June 1, 2014 to November 30, 2015, (NOTE: intervention was extended to a 21-month trial in June 2015, ending February 29, 2016). The unit of randomization will be the hospital, with all participating units within a hospital assigned to the same arm. This preserves the usual structure for quality improvement and avoids confusion of having similar units, often with shared patients and staff, assigned to different protocols.

Since 2007, current practice across all HCA hospitals involves high compliance nasal MRSA screening for the following high risk patients: patients transferred from other facilities (including other acute care hospitals, rehabilitation centers, skilled nursing facilities, assisted living centers), ICU patients, hemodialysis patients, and patients undergoing cardiac, orthopedic, and open spine surgery. Screening compliance has been >90% on serial HCA internal surveys. MRSA+ patients are placed into isolation precautions, which involve assignment to a single room plus gown and glove use by medical staff.

Figure 1: **Two study arms of the ABATE Infection Trial**



HCA hospitals will be randomized into two study arms. Both arms will continue to conduct routine MRSA screening for high risk patients and will place MRSA+ patients in isolation precautions. The first arm will continue the routine policy of offering assisted or unassisted daily showers/bed baths with regular soap, and will agree not to institute components of the other arm for the duration of the study. In the second arm, all patients will be encouraged to shower or have a bed bath daily with chlorhexidine products. In addition, patients known to be MRSA+ will receive nasal mupirocin ointment twice a day for 5 days. We anticipate an average of 4 adult non-critical care units per hospital, for a total of 200+ units across the 54 hospitals.

For full recruitment details, see UH2 Aim 1. Participating hospitals will commit to having all eligible general adult non-critical care units participate in the trial. These are defined as step-down, medical, surgical, medical/surgical, and oncology units. Children <12 admitted to participating units will not receive the mupirocin protocol.

Hospital leadership will identify a trial champion for each unit as well as a liaison from their Infection Prevention Program and their Microbiology Laboratory. Participants agree to report all new initiatives slated to occur during the trial and to defer them if study investigators determine that they conflict with the trial. In addition, participating hospitals agree to collect bacterial isolates as specified in UH3 Aim 2 (Section 6.20).

A summary of the overall study design is found in **Table 8**. Despite the large-scale nature of this cluster-randomized trial, The ABATE Infection Trial will take precautions to adjust for imbalance in confounders or outcomes across the 54 participating hospitals. As described further below, imbalance in the numbers of patients and baseline outcomes will be minimized by a randomization strategy that stratifies by admission volume and baseline multi-drug resistant organisms from a clinical or screening culture (primary outcome) across participating populations in trial hospitals. Residual imbalance in baseline outcomes will be further addressed by including a 1-year baseline period and comparing the changes between intervention and baseline periods between the two arms of the trial (see Analysis Section 6.10.11). As mentioned in UH2 Aim 4, complete data for the baseline period will be obtained from electronic health records and can be obtained after recruitment and after the trial is completed.

Table 8. Key Design Elements of the ABATE Infection Trial

Study Design	Cluster-randomized trial
Unit of Randomization	Hospitals
Study Population	Adults (≥12 years old) in one of the following non-critical care units: step-down, medical, surgical, medical/surgical, oncology units
Exclusions	Children (<12 years old), specialty units, including pediatrics, psychiatry, obstetric/post-partum, rehabilitation/skilled nursing, bone marrow transplant. Units with high utilization of chlorhexidine and mupirocin, including units with >30% cardiac/orthopedic surgery patients. Units with mean length-of-stay < 2 days.
Study Period	**Baseline Year:** March 1, 2013-February 28, 2014 **2-Month Phase In Period**: April 1, 2014-May 30, 2014 (not included in analysis) **21-Month Intervention:** June 1, 2014-February 29, 2016 (NOTE: intervention was extended from an 18-month to 21-month trial, in June 2015)

6.10.5 Operational Plan for Implementation

We describe several elements of our operational plan and infrastructure for conducting the trial, including protocols for governance and communication. In addition, we provide details regarding randomization and intervention implementation.

6.10.51 Governance

The ABATE Infection Trial is governed by a Steering Committee of trial investigators that convenes weekly to discuss plans, track progress, ensure timelines, address problems and concerns, and oversee actions of trial subcommittees. The Steering Committee reviews all trial protocols, surveys, training and educational materials, and communications to trial participants. A critical function of the Steering Committee includes soliciting and reviewing hospital-based interventions and campaigns to assess if a trial conflict exists. Site visits are also conducted by Steering Committee members.

Subcommittees that report to the Steering Committee include project coordination, data cleaning and analysis, information technology, and products. Each of these teams meets weekly to ensure trial progress. Each team includes at least one member of the steering committee. All troubleshooting issues are raised with the Steering Committee. Project coordination teams include east coast (Harvard) and west coast (UCI) teams which cover trial communications across all time zones. East coast project coordination includes oversight of IRB activities, laboratory strain collection, study-related events, and product compatibility issues. West coast project coordination includes all help line (phone and email) communication with trial hospitals about implementation and conduct, creation and deployment of all trial materials including surveys, and toolkits (e.g. protocols, computer-based training, staff and patient education materials, frequently asked questions, coaching call presentations and notifications, and on-site training).

The data cleaning and analysis subcommittee meets weekly and consists of programmer analysts, the lead statistician, and lead investigator. This team defines required data pulls, reports on monthly quality control checks and preparing for stratified randomization of participating hospitals. The information technology team involves trial programmer analysts interfacing with HCA data warehouse experts and HCA project managers to

identify and pull multiple data streams corresponding to needed variables. Finally, the products team includes HCA supply chain and ABATE project coordinators to plan the roll out of trial product, including cloth warmers, and decolonization products.

Lastly, the ABATE Infection Team attends weekly Collaboratory Grand Rounds and interfaces closely with several NIH Collaboratory Working Groups.

6.10.52 Communication Infrastructure to Hospitals and Laboratories

We have a robust communication infrastructure to participating hospitals and laboratories (**Table 9**).

Table 9. ABATE Infection Trial Communication Infrastructure

Communication Component	Purpose
Toll-Free Number	ABATE Help Line for participating hospitals and units
Email Account	ABATE email for participating hospitals and units
Electronic Surveys	Method for obtaining standardized information from participants. To date, 4 surveys have been conducted (enrollment, facility details, unit details, unit engagement)
Coaching Calls	Webinar-based power point presentations detailing progress, upcoming activities, and timeline. Also used to feedback compliance to participants. Occasionally used for relevant special expert presentations (cutting edge science). System logs user and time on/off call. During intervention phase, coaching calls will be arm-specific and occur once monthly for the routine care arm and twice monthly for the intervention arm.
Polling Questions	Electronic webinar-based polling questions that detail respondent and answer for rapid, real-time inquiries during coaching calls
Toolkits	Binders distributed to each unit and hospital trial leaders with introduction, trial phone numbers/contacts, protocols, staff training materials, patient education materials, frequently asked questions, wall posters/clings.
Podcasts	Brief audio files (~3 min) recorded by trial investigators covering topics raised by participating hospitals. Intended for use by hospital educators for front line staff to address concerns, misconceptions, and important processes.
Video	Brief video for bathing training intended for front line staff by educators, managers
Observation Forms	Standardized assessment forms for direct observation of adequacy of bathing process; used as one method for determining compliance which is feedback to participants
Study-Related Event Form	Form to report potential study-related events
On-Site Training	In-person train-the-trainer sessions on application of bathing cloths

6.10.53 Randomization

Randomization will occur at approximately the 8th month of the baseline period. Each participating hospital will be notified of their placement at that time. This will be done because of the requisite 1-3 month period to submit and schedule intervention protocols for approval 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 54 hospitals will not ensure balance of key variables by chance alone, and without blocking could even result in unequal numbers of hospitals in each arm. For example, with a naïve randomization, there would be a 9% chance of a 22-33 split, or worse. Thus, randomization will be stratified, with strata constructed to maximize the chance of balance for both baseline admission volume and the primary outcome, MRSA and VRE clinical cultures attributable to participating units. In addition, we will evaluate the possibility of constructing strata that balance additional variables, such as the mean comorbidity index (Romano score) of all patients in a hospital's participating units, the percent of patients bathing daily, and the baseline use of chlorhexidine and mupirocin.

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. 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 enhance methods to inform the choice of tuplet-construction scheme which we developed in the REDUCE MRSA trial,[125 205] and share them (see software sharing plan). One example method is to 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 must be balanced, we could 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 presented an early version of this work at the April 2013 coordinating center meeting.

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 to the right 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.

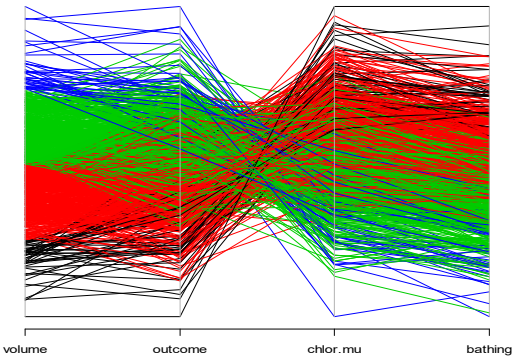


Figure 2. Parallel Coordinates Plot Showing Simulated Balance Across Multiple Variables

As a final note, the statistical core advised us to 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.[206 207] 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 the strata of four in place of tuplets.

6.10.6 Finalized Outcomes

Study outcomes were finalized following deliberation of the Steering Committee during the UH2 planning year. Deliberations included response to recent published literature, including the REDUCE MRSA Trial which was conducted by our investigative team.[125 205] The primary outcome will be the presence of at least one clinical culture with gram-positive multi-drug resistant bacteria (MRSA and VRE) attributable to a participating unit. This outcome was solidified following recent clinical trial evidence of the success of chlorhexidine (with and without mupirocin) in reducing these pathogens in ICUs.[125 205] An *a priori* secondary outcome intended for the primary manuscript is all-cause bloodstream infection attributable to a participating unit. Additional *a priori* secondary study outcomes intended for secondary manuscripts are provided in **Table 10.**

Table 10. Study Outcomes

Primary Outcome
MRSA and VRE clinical cultures [a]
Secondary Outcomes (Primary Manuscript)

All-cause bloodstream infection [a b]
Secondary Outcomes (Secondary Manuscripts)
Gram-negative multi-drug resistant organisms [a]
Urinary tract infections [a]
C difficile clinical tests [a]
Blood culture contamination
30-day infectious readmissions
Emergence of resistance to chlorhexidine or mupirocin [a]
Cost effectiveness

[a] Attributable to participating units. Defined as occurring >2 days into a participating unit stay through 2 days following unit discharge

[b] Includes subsets of GP and GN MDROs as well as key pathogens such as *S. aureus*

These outcomes are designed to maximize the evaluation of the impact of decolonization in non-critical care settings. They will address major concerns in healthcare related to reduction of antibiotic-resistant pathogens, and impact on a range of hospital-associated infections. They will also assess the likelihood that bacterial strains will develop resistance to chlorhexidine and mupirocin following broad use among inpatients.

6.10.7 Baseline Period Activities

The 1 year trial baseline period begins in the UH2 Planning Phase and ends in the UH3 Trial Intervention Phase. It serves two major purposes. Its primary function is to provide baseline outcome data for both arms (see Analysis Section 6.10.11). Second, it enables the collection of baseline bacterial strains which will be used to assess if antibiotic resistance is differentially engendered between the study arms (see strain collection details in UH3 Aim 2, Section 6.20. These activities will occur during the Planning Phase, when we will perform recruitment, develop educational materials and computer based training modules, and program electronic nursing prompts and compliance reports for the intervention protocol (UH2 Aim 3, Section 5.30).

6.10.8 Phase-In Period Activities

There will be a 2-month phase-in period after the baseline period. During this period, which will not contribute to either the baseline or intervention periods, we will disseminate campaign products and materials to the Decolonization Arm. Since our intervention utilizes usual care processes, including standardized nursing protocols (for chlorhexidine, a non-prescription product) and standardized order sets (for mupirocin, a prescription drug FDA approved for this use), these processes need to undergo usual hospital approval by nursing standards committees, and medical executive or quality standards boards. All hospitals will schedule protocol approval for the committee meetings immediately following the randomization date. After randomization, hospital champions will submit trial decolonization protocols to requisite committees to ensure timely approval for implementation in the phase-in period. This was achieved in <30 days in our prior trial.

Following randomization, frontline staff will be required to complete trial-specific and arm-specific computer based training modules (see Trial Materials, Section 5.30.2). CBTs will be assigned to specific units and frontline staff and, for the decolonization arm, will include a bathing video on bathing technique. CBT training can and will begin prior to hospital committee approval and staff will be given 21-days to complete it.

In addition, hospitals will participate in arm-specific coaching calls. Calls will occur every other week during the phase-in period. All coaching calls will be webinars and led by trial investigators, including active attendance and support by HCA leadership. A PowerPoint slide set will be reviewed with a question and answer session, and a set of key questions will be posed to each hospital via automated webinar poll. All coaching calls will be recorded and placed on arm-specific ABATE Infection Trial sites on the HCA intranet for continued access by designated participants in each arm. Common questions posed to Decolonization Arm participants during this phase will include hospital committee approval status, CBT training status, product stocking, removal/replacement of products incompatible with chlorhexidine and posting of wall clings providing bathing instruction, (see description of trial materials in Section 5.30.2, and wall cling examples from a prior trial in **Appendix B, H**). Participants will be highly encouraged to share concerns and solutions with one another.

In both Decolonization and Usual Care Arm coaching calls, hospital participants will be required to confirm that no new hospital initiatives have been planned (or report the initiative to trial investigators for determination of trial conflict). Hospitals that are not represented on coaching calls will receive an email from core staff and a phone call from HCA trial liaisons. In our previous trial, we found that sharing hospital-specific status reports in PowerPoint presentations, and rapid follow-up for non-response resulted in very high rates of

participation from all hospitals in all arms. Between calls, core staff will follow up on any ongoing issues and document resolution.

As described in UH2 Aim 2, IRB approval will be obtained for each hospital during the Planning Year; we most hospitals to cede authority to a central IRB for approval. In the phase-in period, once trial protocols are further approved by required hospital committees, intervention activities will be put into place (**Table 11**). Decolonization Arm hospitals will replace usual soap with 4% liquid chlorhexidine solution in all showers in participating units. Mesh sponges will be provided for shower use since they substantially enhance product lathering. In addition, 2% no-rinse chlorhexidine cloths for bed baths (contributed by Sage, Inc – see letter of support) will be stocked for routine bed baths by patients and nursing assistants. Unit nurse educators will be engaged and all nurses and bathing staff will be trained to encourage daily bathing or showering. In addition, the phase-in period will include compliance assessments that routinely accompany HCA quality improvement initiatives. A summary of activities is found in **Table 11** and is detailed in UH2 Aim 3 (Section 5.30.2).

Table 11. Phase-In Activities for Decolonization Arm

Phase-In Protocol Activities	Details	Activated
1. Arm-Specific Binder and Talking Points Materials Disseminated	Sent to all hospital liaisons, including hospital Nurse Educators for dissemination via usual infrastructure. Reviewed on coaching calls for train-the-trainer assistance.	Just prior to Phase In
2. Arm-Specific Coaching Calls	Weekly for Decolonization Arm during Phase-In period and early part of Intervention period, then transitions to twice per month when processes stably underway. (Of note, twice monthly for Usual Care Arm)	Just prior to Phase In
3. Computer Based Training and Bathing Video	Investigator prepared modules will be posted to participating unit staff and tracked through usual corporate assignment infrastructure	Just prior to Phase In; 21-day required completion time.
4. Just-In Time Training and Buddy Process	Materials created for registry nurses readily available with assigned buddy process for new nurses. Common registry services notified.	Just prior to Phase In
5. Chlorhexidine Product and Warmer Stocked	Stocking and par levels initiated. Warmers delivered and plugged in.	Immediately prior to Phase In
6. Compatibility Verification	Bathing and prophylactic (non-treatment) wound products incompatible with chlorhexidine removed from stocks and replaced with compatible products. Alternative products available for those with allergies.	Prior to Phase In
7. Pharmacy Module for Mupirocin Ordering	Electronic standardized order sets will be developed to enable automatic prescribing of mupirocin for MRSA+ patients.	Testing at Start of Phase In, Activated at Go Live Date
8. Bathing Training Site Visit	Site visits jointly by trial investigators and Sage Inc Medical Science Liaisons (MSLs) for usual training on 2% chlorhexidine cloths and proper warmer use. MSLs will ensure training is consistent with trial scripts and talking points.	Month Prior to Phase In
9. Daily Nursing Queries	Programmed nursing queries (standard for HCA hospitals) will be posted to units for daily e-documentation of whether bathing/showering occurred and with what product.	Already activated in Baseline period, in both Arms
10. Wall Clings Posted	Decolonization bathing instructions will be posted in all rooms in participating units	Go Live date during Phase In
11. Compliance Reports	Compliance e-reports added to routine e-reports run by unit managers/champions and assessed daily until reasonable compliance achieved (determined by investigator team). Once achieved, compliance assessment changed to weekly.	Go Live date during Phase In
12. Bathing Observations	Unit managers will observe 3 assisted bed baths per quarter per unit and to query nursing assistant about comfort level with bathing wounds and other common occurrences (see prior trial example, **Appendix I** and explanation of skills assessment forms, **Appendix J**)	Go Live date during Phase In

During the phase-in period, core staff will work with participating units in Decolonization Arm hospitals to ensure all bathing and prophylactic (non-treatment) wound products in participating units are compatible with chlorhexidine. Study staff will use previously established spreadsheets from our recent ICU decolonization trial (see REDUCE MRSA Trial in preliminary data Section 5.30.1) to collect data on products not previously

assessed. Detailed information for the active and inactive ingredients of all additional products, including soaps, lotions, and skin barrier products will be collected. Manufacturers of these products will be contacted to obtain any known information regarding chlorhexidine compatibility. In the absence of data, a PhD Ingredient Scientist (Dr. Frederick Siegel) will be consulted to adjudicate additional ingredients.

Hospitals will set a Go Live date no later than the start of the second month of the phase-in period. All interventions will be discontinued upon discharge from a participating unit. Patients readmitted to a participating unit will have the protocol applied anew. Timeline for Phase In is provided in Table 12.

Table 12. Timeline for Phase In Processes

Randomization	Randomization will occur in November 2013
Notification	Hospitals will be notified of their randomization status in Nov-Dec 2013 to schedule the decolonization protocol into their relevant hospital committees for approval
Committee Approvals	Jan-Feb 2014
Supply Chain	Assessing facility requirements for cloth warmers (space, voltage) will occur Feb-Mar 2014; Stocking of warmers will occur Mar 2014; Products to hospital units the week before launch.
Training	Coaching calls, training materials distributed Feb-Mar 2014. Computer-based training requirement completed by all relevant staff Feb-Mar 2014. On site bathing training Mar-Apr 2014 by ABATE trial investigators/study staff in conjunction with Medical Science Liaisons from Sage Inc (supplier of 2% chlorhexidine cloths)
Launch – Phase In	April 1, 2014 for 2 months, rapid feedback for compliance using daily bathing queries, direct observation by nurse managers using standardized assessment tools
Intervention – Go Live	June 1, 2014 for 18 months (NOTE: intervention was extended to a 21-month trial in June 2015)

6.10.9 Intervention Period Activities

Intervention period activities will be identical to phase-in period activities. As mentioned in **Table 11**, compliance feedback will be shared monthly during coaching calls based upon nursing queries embedded in usual e-documentation (see UH2 Aim 3 and **Table 11** above) that will require a response each shift about whether a bath or shower had occurred and, if so, with what product. For the Decolonization Arm, a negative response will require a reason from a drop down menu. E-reports will be used for chlorhexidine since it is not a prescription drug. Pharmacy records will be used to track dispensing of mupirocin.

In addition to on-site bathing training provided to all intervention hospitals in the phase-in period, we will perform site visits to participating hospitals in either arm based upon requests for assistance, concerns about intervention protocols, or evidence of low compliance. For the usual care arm, evidence of decolonization would constitute “low compliance.” Site visits would be comparable to those used by HCA when implementing other Quality Improvement protocols. In addition, HCA leadership (specifically, the quality performance and infection prevention team that are co-investigators on this proposal) performs routine site visits to all hospitals on a rotating basis and will incorporate encouragement, inquiries, and process assessments related to trial activities and microbiology laboratory submission of isolates (see UH3 Aim 2) during visits to trial hospitals.

Special coaching calls and podcasts on trial rationale will be provided to both arms. As in our previous trial, wound care nurses from HCA hospitals will provide expertise to the Decolonization Arm hospitals during coaching calls and will be reachable for questions throughout the phase in and intervention period.

Investigators will continue to have weekly calls during the intervention phase, as well as active participation in the NIH HCS Research Collaboratory Steering Committee and Collaboratory Work Groups. All activities will be conducted in concert with the HCS Research Collaboratory Coordinating Center (CCC).

6.10.10 Data Acquisition

The Data and Analytics Team will include lead investigators, HCA co-investigators, trial programmer analysts, statisticians, and HCA information technologists. Data pulls will be based upon detailed specifications and will be accompanied by data dictionaries. Data will be pulled from census, microbiology, pharmacy, supply chain, nursing query reports, and administrative data from HCA corporate data warehouses as described in UH2 Aim 4 (Section 5.40). Numerators for most outcome data will be derived from microbiology final result files limited to sterile site specimens from participating hospitals. Denominators will be derived from unit-specific census data. We will also provide descriptive data including demographic and comorbidity data from administrative claims data, compliance data from nursing queries, and product use from pharmacy and supply chain data, and data on use of hand hygiene products, glove, and gown use across arms.

6.10.11 Statistical Analysis

All outcomes will be assessed similarly. Here, we use the example of the primary outcome: clinical cultures with MRSA or VRE (first per patient). MRSA and VRE clinical cultures will be attributed to participating units if the collection date occurred >2 days after admission to that unit through two days after discharge from that unit. This attribution is consistent with CDC guidance for surveillance of nosocomial infections.[208]

Main trial results will be based upon as-randomized, unadjusted analyses using proportional hazards models to account for patients' variable tenure in the unit. This is necessary for the usual reasons: dichotomizing patients into those with vs. without infections would require us to define a fixed time-frame (within first x days of eligibility, ignoring some infections and omitting patients with shorter stays) or to ignore exposed time (counting infection during unit stay regardless of different length of stay). In addition, power is greater for proportional hazards models than for logistic regression models.[209] [210] [211] [212]

As discussed with the Statistical Core Working Group of the Collaboratory, clustering within hospital will be accounted for using shared frailties. The frailties are added model terms that allow unique hazards ratios for each hospital, and are necessary to account for clustered randomization.[213] Model terms will include individual-level data on arm, hospital, outcome events, trial period (baseline vs. intervention) and an interaction term between trial period and arm. The assessment of trial success will be determined by the significance of the interaction term, which assesses whether the difference in hazard between the baseline and intervention period differs significantly between the two arms. We can write a simple version of the model symbolically as:

$$\lambda_{ij}(t) = \lambda_0(t)e^{\beta_1 Arm_{ij}+\beta_2 Period_{ij}+\beta_3 Arm_{ij}*Period_{ij}+\gamma_i}$$

where i is a hospital, j is a person within the hospital, Arm and $Period$ are indicator variables and are = 0 for patients in a hospital in the control arm or baseline period and 1 if in the intervention arm or period. The overall hazard rate over time for person ij is defined as $\lambda_{ij}(t)$, a function of the baseline hazard $\lambda_0(t)$, which is similar to the intercept in a linear model, times the proportionality for that subject, which is defined by the covariates Arm_{ij} and $Period_{ij}$ and the associated parameters, as well as the frailty, γ_i. The frailties are closely analogous to the random effect in generalized linear mixed models, and account for the clustering (similarity of hazard) within a given hospital. The ultimate effect of the intervention is assessed through β_3: as parameterized, if it is negative and has p-value < .05 (or 95% CI excluding 0) then the intervention reduces the risk of infection. We plan to assess the need for different frailties by hospital by period (instead of just by hospital), as well as additional clustering by unit within hospital. In addition, we will investigate the need to adjust for the stratified randomization scheme described above in **Section *6.10.53***

Subsequent analyses will include as-treated and covariate-adjusted models. Adjusted models will account for individual characteristics such as age, gender, comorbidities based upon ICD-9 codes, and receipt of intervention products. We will also account for unit type (step down, medical, surgical, etc.) and baseline bathing frequency if this is not balanced after randomization. All analyses will be performed using current versions of SAS (9.4, as of writing, SAS Institute, Cary NC) and/or R (3.0.2, as of writing).[214]

In addressing considerations of interim analyses to determine whether early stopping might be possible, the decision has been made not to pursue an interim analysis for several reasons. First, this trial meets the requirements of a minimal risk study. The study of topical bathing/decolonization therapy necessitates neither interim analyses nor stopping rules since reasonably anticipated adverse events are considered minor. Second, the collection time plus the lag in obtaining data and the relatively sparse power suggest that it is highly unlikely that an early look would result in a stoppage of the trial for either futility or success. Third, the addition of an interim analysis would affect power estimates in such a way to create an elongation of the trial beyond the time period that is acceptable to our health system partner. As described in detail above, participation in the trial requires a continuous assertion that other hospital interventions and campaigns that may conflict with the trial will not be pursued. This restriction to the usual tendency of hospitals to pursue multiple simultaneous interventions for prolonged periods of time was a critical consideration in designing the length and size of this trial. With regard to assessment of adverse events, we have built in a reporting system for both mild and severe side effects, defining study-related events that show no signs of improvement within 7 days of stopping product as serious events. The study-related events monitoring and reporting system is described in detail in our Data Safety Monitoring Plan and in our Decolonization Educational Materials.

6.10.12 Power (Updated June 2015, following reassessment of power)

In many settings, an analytic approach to power is possible: given the assumptions of the model (e.g., logistic regression) are met, a relatively simple closed-form solution exists. However, generating the expected values to plug in may be difficult. In addition, some settings are complex enough that closed-form solutions may be difficult to generate. Many cluster-randomized designs fall into this class. In cluster-randomized problems, it is also difficult to obtain reliable estimates of the additional parameters that are required, most notably the between-cluster variance or, equivalently, the intra-class correlation coefficient. Further additional complications are introduced for time-to-event outcomes such as those needed in the ABATE Infection Trial.

In a previous trial, we used the logistic regression analogue to proportional hazards regression models and simulation to estimate power.[210] Now, however, we propose an interesting and, to our knowledge, novel approach to power calculation, which we dub "bootstrap power calculation." This method is described below and in an article published since the trial was planned.[215] Briefly, the bootstrap is a powerful technique that uses the observed sample to approximate the underlying population, rather than a convenient analytic distribution.[216] The bootstrap power approach relies on the fact that we possess a large quantity of baseline data already. Loosely put, we (1) bootstrap a sample of observations from our observed baseline data to serve as the baseline sample in the power calculations. Then we (2) bootstrap another sample from the baseline data to serve as the intervention period data. Next, (3) we implement the randomization scheme in the bootstrapped sample. Then (4), for a randomly selected subset of the outcomes (e.g., bloodstream infections) observed in the bootstrapped intervention period sample in the hospitals randomized to intervention, we artificially change the outcome from infection to no infection. This represents the effect of the intervention, which we control by changing the size of the subset selected for this change. Simultaneously (5), for this subset we change the date of the event from the date of infection to the date of discharge, transfer to a non-eligible unit, or death—i.e., the date of censoring, had no infection been observed. Finally (6), we fit the planned frailty model described in **Section 6.10.11** above and record whether the null hypothesis of no association was rejected or not. This process is repeated many times, and the proportion of rejections is an estimate of the power under the given effect size. A confidence limit on this estimated power can be generated. In the table below, we show the power for removing the outcome from 0, 10, 20, and 30% of the subjects in the intervention arm in the intervention period. Removing 0% of the outcomes is a test of the technique: since we are not reducing the infection rate, the null is true, and rejections should occur only about 5% of the time.

In the initial planning of the trial, we used the available 4-month baseline sample of patients from our participating trial hospitals and used three bootstrap samples to represent each 12-month baseline and 4.5 bootstrap samples to represent the 18-month intervention period. This resulted in the power shown in **Table 13**.

Table 13: Power and Exact 95% CI for Primary and Select Secondary Outcomes*

Intervention Effect	Primary Outcome MRSA, VRE Clinical Cultures	Gram Negative MDRO** Clinical Cultures	All Pathogen Bacteremia
*0%	5.6% (4.3-7.2%)	4.1% (3.0 – 5.5%)	5.2% (3.9 – 6.8%)
10%	33% (28-37%)	15% (12 – 18%)	23% (19 - 27%)
20%	92% (90-94%)	44% (40 – 49%)	68% (63 - 72%)
30%	100% (99-100%)	82% (79 – 86%)	98% (96 – 99%)

*Based on 500 bootstrap samples for each effect size, except for the 0% estimate, for which we did 1000 simulations to increase confidence that the alpha level is maintained when the null is true.

** Gram-negative multi-drug resistant organism clinical cultures

The above power estimates (**Table 13**) show that the technique has the desirable characteristic of rejecting the null only 5% of the time when it is true. We also see that power for MRSA or VRE clinical culture is ample, even if we prevent only 20% of the infections. For both selected secondary outcomes, the power is less, but still quite acceptable if the intervention prevents 30% of the infections. The primary strengths of the bootstrap power approach are that it allows us to avoid using literature estimates for the parameters when such estimates may not apply to the trial population, and it also avoids unrealistic assumptions about regularity (equal cluster sizes) or distribution (logistic instead of frailty models). The main weakness in this case is that correlation within hospital is generated to be the same in the baseline and intervention periods. In addition, we have not received all desired randomization stratification data by the time of this submission. Thus, stratification in the bootstrap process is limited to hospital size and the baseline rate of the outcomes. We believe that these are relatively benign issues: the correlation structure is unlikely to change importantly from

period to period during the actual study, and the stratification is mainly to promote balance. It may affect the power, but mainly by reducing the variability in the outcome.

After the baseline period, we were able to re-estimate the power, using the data collected in the full baseline period. We used the bootstrap process outlined above, except that we used the observed 12-month data for the baseline. We assessed the power for the original proposal of an 18-month intervention and for a slightly extended 21-month intervention period, oversampling the observed 12-month baseline data as needed in each case (**see Table 14**). This updated power assessment was considered to be more accurate in that it used approximately three times as much real data—12 months vs. four months—compared to the original estimate. Furthermore, additional cleaning steps were applied to the 12 months of baseline data. In these new assessments we focused on an intervention effect of 20%. The power for the primary outcome was 99.9% (95% CI: 99.4-99.99%) with 18 or 21 months of follow-up. For all pathogen bacteremia, the power was 85% (95% CI: 83-87%) with 18 months follow-up and 89% (87-90%) with 21 months follow-up. The steering committee decided to use 21 months of follow up to ensure greater power with less common secondary outcomes and account for lessened effects at sites that may drop out of the trial.

Table 14: Revised Power and Exact 95% CI for Primary and Select Secondary Outcomes*

Analysis	Effect	Primary Outcome MRSA, VRE Clinical Cultures	All Pathogen Bacteremia
As-randomized, 18-mo	20%	99.9% (99.4% – 99.99%)	85% (83% – 87%)
As-randomized, 21-mo	20%	99.9% (99.4% – 99.99%)	89% (87% – 90%)

6.10.13 Limitations and Planned Solutions

This study has limitations. First, we require the enrollment of at least 50 HCA hospitals. While we believe this is possible due to our previous trial of 43 HCA hospitals, should enrollment drop unexpectedly to less than 50, we will pursue an elongation of the 18-month trial, (NOTE: intervention was extended to a 21-month trial in June 2015). Secondly, if hospital committee approvals for trial protocols are delayed, we will expand the phase-in period to a total of 3 months. We note that our prior trial completed phase-in within 30 days. Third, if decolonization is significantly better at preventing infection, we appreciate that we are unlikely to be able to distinguish between effects of chlorhexidine and the effects of active encouragement to bathe or shower. Nevertheless, the results of this study would reflect a real world intervention which would likely entail both processes.

Cluster randomization does not allow every question of interest to be addressed. It typically results in more misclassification of exposure than individual randomized controlled trials do, either because individual providers choose to use a non-recommended regimen for some patients, or they fail to adhere fully to the assigned regimen. To the extent that the frequency of failure is consistent with the level that occurs in usual clinical practice, these failures are part of the overall effectiveness measure. Thus, cluster randomization in inpatient systems may offer a relatively low-cost and broadly generalizable means to examine many of the priority topics for comparative effectiveness research. In addition, this study design does not allow for blinded assignment or implementation. Nevertheless, this reflects the pragmatic nature of our intervention and directly mirrors the design and implementation of hospital quality improvement initiatives.

6.10.14 Dissemination Plan

We will disseminate trial results through presentations at national meetings, and publication in peer-reviewed journals, and press releases. We will also use our contacts at the CDC, membership on the national advisory committee that recommends infection prevention strategies (HICPAC – the Healthcare Infection Control Practices Advisory Committee), membership on the Institute of Medicine Roundtable on Value & Science-Driven Health's Innovation Collaborative on Clinical Effectiveness, participation in national societies such as the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA), and contacts with state departments of public health to disseminate trial results.

Through the Collaboratory's website and dissemination mechanisms, we will also make our decolonization toolkit publicly available. This toolkit includes information about healthcare-associated infections, mupirocin protocols, chlorhexidine bathing protocols (for showering and bed bathing), extensive product compatibility guidance, frequently asked questions guides, wall charts for patient bathing instruction, audio podcasts and special coaching calls.

6.20 Aim 2: Assess whether universal chlorhexidine bathing and selective MRSA decolonization result in increased resistance to chlorhexidine or mupirocin among bacterial strains collected during the trial.

In order to assess whether routine use of chlorhexidine for bathing and selective use of mupirocin for MRSA decolonization engenders increased resistance to these agents over the course of the trial, we will collect bacterial strains from participating units during the baseline and intervention periods in each study arm.

6.20.1 Preliminary Data (Confidential, do not cite or distribute)

We collected 4,321 MRSA isolates during the REDUCE MRSA trial, a trial of decolonization with chlorhexidine and mupirocin in ICUs to reduce MRSA carriage and infection. 993 strains in the baseline period and 3,328 in the 18-month intervention period were collected from microbiology laboratories in 43 HCA hospitals across 3 arms. Strains were assessed for the presence of chlorhexidine resistance and high-level mupirocin resistance, which has been associated with decolonization failure.[55 68 217]

Chlorhexidine resistance was essentially non-existent: there was a single chlorhexidine resistant isolate which occurred in the usual care arm during the intervention period. No formal analyses were pursued.

At baseline, high-level mupirocin resistance was present at 6.7% (67/993). There were no significantly different increases across the arms between baseline and intervention periods. In the targeted decolonization arm of the REDUCE MRSA Trial, which most resembles the proposed intervention in the ABATE Infection Trial, high-level mupirocin resistance was 5.9% in the baseline period and 5.4% in the intervention period.

Processes and materials used in the collection of bacterial isolates during the REDUCE MRSA trial will be replicated by trial investigators for the ABATE Infection Trial as described below.

6.20.2 Strain Collection

Strain collection will include MRSA and other pathogens since chlorhexidine targets a broad range of microbes and rare cases of resistance have been reported in select gram-negative bacteria, namely acinetobacter, burkholderia, E coli, klebsiella, proteus, pseudomonas, serratia, and stenotrophomonas.[218 219 220] Study staff will coordinate with each clinical microbiology laboratory director for the collection of MRSA and these gram negative bacteria for a 9-month period toward the end of both the baseline and intervention periods for each arm. A total of 2,400 MRSA and 2,800 gram negative bacteria will be collected.

Trial staff will provide each microbiology laboratory with a toolkit with detailed instructions about strain collection, including the list of pathogens, participating units, and time window for collection. Microbiology technologists will be instructed to target strains with a collection date at least 2 days after admission based upon unit location and admission date, which are available during usual specimen processing. Similar to our prior trial, the toolkit will include a Step-by-Step instruction guide, a Frequently Asked Questions (FAQ) sheet, FedEx mailing instruction sheet, deidentified study ID labels, collection log sheets with clipboard, shipment packing list, and shipping schedule (see example from prior trial, **Appendix E, G**). In addition, a quick reference wall cling will be sent that provides a streamlined diagram of the key elements for collection (see example from prior trial, **Appendix F**). Details will be reviewed in laboratory-specific coaching calls.

Chocolate agar slants and shipping kits (STP-250MD, Saf-T-Pak Inc.) will be sent to each laboratory on a regular basis for monthly batch shipment of strains. Initially, trial staff will contact laboratory liaisons once weekly until processes are in place. Trial staff will contact each laboratory prior to each anticipated shipment.

Trial staff will receive faxed log sheets that include the hospital, unit, collection date, specimen source, and coded ID. A separate fully-identified log sheet will be sent internally to HCA co-investigators who will use identifiers to subsequently link coded specimen study IDs to coded individual-level trial data during the analysis phase. In the event that resistance is found to be engendered by decolonization, this linkage will allow further exploration regarding patient exposure to study products prior to specimen collection.

6.20.3 Strain Processing

For the collection of MRSA and gram negative bacterial isolates (performed by HCA staff) at participating HCA hospitals from their microbiology laboratories, log sheets that identify the patients from whom the isolates arise will be provided to HCA corporate study investigators and retained for the duration of the study period. Direct patient identifiers will not be shared external to HCA. All information transferred to Rush University, the isolate colletion core and the research analytic core at the Department of Population Medicine (DPM) at Harvard Pilgrim Health Care, will be stripped of direct identifiers and replaced by a coded identifier. Isolates will be shipped to Dr. Mary Hayden in the Division of Clinical Microbiology, our Co-Investigator at the

Rush University Medical Center in Chicago, IL. Bacterial identification will be confirmed by standard microbiologic methods. For MRSA isolates, resistance to methicillin will be verified by cefoxitin disk testing[221] and mupirocin susceptibility will be assessed by the E-test method (bioMérieux, Durham, NC). Mupirocin resistance will be determined according to Eltringham.[222]

All bacterial isolates will have susceptibility to chlorhexidine determined by a microtiter method using 20% aqueous chlorhexidine digluconate (Sigma-Aldrich LLC, St. Louis, MO) diluted in broth medium appropriate for the microbe tested.[218] Since national standards do not yet exist for chlorhexidine resistance, we will define resistance as a minimum inhibitory concentration (MIC) of chlorhexidine that is outside of the reported wildtype distribution for each microbial species. Based upon recent literature, we will use a resistance breakpoint of ≥8mcg/ml for MRSA,[17] ≥32 mcg/ml for klebsiella, pseudomonas, and serratia,[216-217] and ≥64 mcg/ml for burkholderia, proteus, and stenotrophomonas.[215-217] These species were chosen because of their relatively high chlorhexidine MICs compared to other bacterial species and/or their association with outbreaks linked to contaminated commercial chlorhexidine products (burkholderia). In addition to assessing MIC breakpoints, we will evaluate the proportion of strains with a high MIC within the susceptible range between baseline and intervention strains. Decreased susceptibility to chlorhexidine has been associated with the presence of various multidrug efflux pumps.[223 224 225] If chlorhexidine resistant (or nearly resistant) isolates are identified, we will use polymerase chain reaction methods to evaluate isolates for the presence of efflux pump genes. If efflux pump genes are found, additional characterization of resistance may be done including assays to quantify expression of efflux pumps and to measure the effect of inhibition of efflux on chlorhexidine MICs.

6.20.4 Analysis

For mupirocin and chlorhexidine separately, we will report the proportion of resistant isolates in each arm in the baseline and intervention periods. We will test differences between arms in resistance by fitting a generalized linear mixed logistic regression model with arm, baseline vs. intervention period, and their interaction as predictors. The interaction term assesses whether the difference in the probability of resistance between the baseline and intervention periods is significantly different between arms.

6.20.5 Power and Sample Size

Based upon our recent trial data, we assume high level mupirocin resistance in 0.07 of MRSA isolates at baseline. We estimate collection of 2,400 isolates (600 per arm in the each of the intervention and baseline periods). As in UH3 Aim 1, power is based on a post-only comparison of 1200 subjects, 24 per hospital. Assuming intracluster correlation of 0.001, we will have 80% power to detect 0.12 high level mupirocin resistance in the decolonization arm, assuming that resistance remains at 0.07 in the usual care arm.

For both MRSA and gram negative bacteria, we will calculate the proportion of isolates resistant to chlorhexidine. If the proportion of MRSA that is resistant is truly as large as 0.1%, we will have at least a 90% probability of detecting ≥1 resistant strain among 2400 isolates, 70% among the 1200 post-period isolates, and 45% among 600 isolates in the post period in the intervention arm. If the resistance rate increases to 0.5%, we have a 95% chance of observing at least one case in the 600 intervention isolates from the follow-up period.

6.20.6 Limitations and Planned Solutions

If decolonization is successful, it is conceivable that isolation of MRSA and other bacterial pathogens may be substantially reduced, resulting in inadequate collection. In the event that this occurs, we will broaden the time window for isolate collection. Since our baseline period is 12-months and our intervention period is 18-months, (NOTE: intervention was extended to a 21-month trial in June 2015), the current plans to collect isolates for 9-months in each period still allows for additional collection time should it be necessary. We will monitor collection progress continually so that the collection period can be extended seamlessly, if this is needed.

6.30 Aim 3: Estimate the costs associated with the intervention (chlorhexidine + selective MRSA decolonization) and the attributable medical costs of healthcare associated infections in adult general inpatient units and infectious readmissions, in order to evaluate the potential for cost savings associated with the strategy of reducing bioburden to prevent infection.

Costs of healthcare associated infections (HAIs) have been studied mainly in academic medical centers.[10 226 227 228 229 230] Estimates of HAI costs in community hospitals are needed since community hospitals represent the majority of inpatient care in the U.S., and costs may differ from academic hospitals.[231 232 233] In addition, the cluster-randomized design affords an important and unique opportunity to assess the economic value of decolonization across a large number of hospitals. In particular, case mix differences between

hospitals can be closely adjusted for due to combination of several factors: 1) control group of hospitals with stratified randomization, 2) baseline data from each hospital, and 3) availability of individual patient adjustors from electronic health records and administrative data. In this aim, we will estimate the incremental hospital costs associated with the intervention and evaluate differences in total medical costs among patients with and without HAIs in the intervention and control arms. We will then estimate the net cost of medical care for the intervention and the control groups, adjusting for key health factors.

6.30.1 Cost Analysis Study Design

A cost analysis will be pursued with HCA health economist, Kate Nolte, Ph.D., if the ABATE Infection Trial demonstrates a significant beneficial effect in its primary outcome. If this occurs, we hypothesize that decolonization will be associated with reduced costs associated with hospitalization and readmission. We will take advantage of the cluster randomized trial design to test the hypothesis that the Decolonization Arm is associated with a significantly greater reduction in total medical costs between the intervention vs. baseline period when compared to the Usual Care Arm. Our study population will include adult patients in the trial who have spent time on a participating unit. In this population, we will assess the costs of the initial hospitalization and any subsequent infectious admission within 30 days following discharge.

6.30.2 Data Sources

For overall hospitalization costs, we will obtain complete hospitalization charges from HCA financial data, which do not include intervention costs. HCA has highly standardized financial records where charges for hospital beds, procedures, and various drugs and supplies are aggregated to produce a total hospitalization charge. Since hospital charges do not reflect true costs that hospitals incur, we will apply hospital cost-to-charge ratios obtained from HCA to obtain total hospitalization costs per admission.

Intervention costs, which will not be included in HCA charge data, will be determined as follows. We will measure the volume of supplies used multiplied by a standard unit cost. For all participating hospitals, we will collect unit-specific dispensed daily doses of mupirocin and chlorhexidine product. Mupirocin dispensing will be obtained from pharmacy data and chlorhexidine usage will be obtained from daily bathing compliance data obtained during the trial. Standard unit costs for each of these will be obtained from the manufacturer, publicly available data, or published sources. Chlorhexidine costs will be calculated as the incremental costs over the unit costs of common non-chlorhexidine bathing supplies. This will be done in two ways to account for the two most common chlorhexidine products on the market. First, we will calculate the incremental cost of disposable chlorhexidine-impregnated bathing cloths (as used in this trial) compared to disposable bathing cloths. Second, we will assume all bed baths are performed using basin baths and will calculate the incremental costs of adding generic liquid chlorhexidine to basins compared to routine soap and water basin baths. Finally, we will assess differences in the amount of unit-specific gown and glove use based upon supply chain data between arms and between baseline and intervention periods. This will account for potential cost-savings due to decreased transmission from the intervention.

6.30.3 Analysis

We will use an analytic approach similar to our primary outcome of MDRO organism from a clinical or screening culture attributed to a participating non-ICU unit, with the exception that we will model will the outcome of hospitalization cost. Rather than proportional hazard models with shared frailties, we will use generalized linear mixed models to evaluate whether the Decolonization Arm is associated with significant cost-savings when accounting for clustering by hospital. Since cost data are typically quite skewed, data transformation may be required to assure adequate fit of the outcome distribution. Models will be chosen to fit the distribution: negative binomial models, or possibly, normal distributions after log transformation, for example. Either approach reduces the impact of large outliers typical in cost data. Model terms will include arm, trial period (baseline vs intervention), their interaction, unit type (step down, medical, surgical, etc.), and demographic and comorbidity variables. The assessment of whether outcomes in one arm are significantly different from the other will be determined by the significance of this interaction term, which assesses whether the mean cost difference between the baseline and intervention period differs significantly between the two arms. If significant, we will calculate the mean cost savings per case averted.

We will additionally perform a sensitivity analysis to account for potential mortality effects on total hospitalization costs. To do this, we will assign a large fixed hospitalization cost to all deaths and assess if the model still predicts cost savings.

6.30.5 Limitations and Planned Solutions

This analysis is limited by the inability to account for all potential confounders that may put one individual at higher risk for hospitalization cost. However, cluster randomization is a major asset for distributing both known and unknown confounders. The availability of data from the baseline period is an additional strength, since each hospital's patient population additionally serves as its own control.

6.40 Overall ABATE Infection Trial Summary

Healthcare-associated infections (HAI) continue to produce high morbidity, mortality, and over $6 billion dollars of annual healthcare costs in the U.S.. Most infections arise from bacterial flora, which overcome host defenses during vulnerable times such as hospitalization. Gains in HAI reduction due to decolonization regimens have been demonstrated for ICU settings, but evidence is lacking about the effectiveness of such strategies in non-ICU settings, where the majority of HAIs occur, and where medical care, risk of infection, patient-to-patient interactions, pathogen transmission, and bathing practices differ considerably from ICU settings. This 50-hospital cluster-randomized trial will critically assess whether daily bathing with chlorhexidine and intranasal mupirocin for MRSA carriers should become standard practice for 40 million patients hospitalized each year in the United States alone. Alternatively, it will suggest that tailored strategies distinct from those effective in ICU settings are needed to reduce the >1 million HAIs that occur each year in non-critical care settings.

This trial will also illustrate the strengths of an underused model of clinical effectiveness research that quickly and efficiently allows robust randomized clinical trials to be embedded into the normal delivery of health care, using the organizational and informatics strengths of a large hospital system.

6.50 UH3 Trial Intervention Phase Milestones and Timeline

We summarize our milestones and timeline for the trial intervention phase in **Table 15**. We will work closely with the NIH Collaboratory Coordinating Center during all aspects of the trial, including study design, implementation, data extraction, quality control processes, and confirmation of study outcomes. Our lead investigators will actively participate in the HCS Research Collaboratory Steering Committee, and members of our investigative team will actively participate in HCS Research Collaboratory Work Groups to align goals, activities, and deliverables to improve the conduct of pragmatic clinical trials during usual medical care.

Table 15. UH 3 Trial Intervention Phase - Annual Milestones and Timeline

UH3 Milestone	Details / Purpose	Trial Phase Timeline			
		Y1	Y2	Y3	Y4
Aim 1: Decolonization Trial					
1. Clinical Trial Registration	Registration with Clinicaltrials.gov	x			
2. Randomization of Hospitals	Cluster randomization using hospitals as the cluster	x			
3. Standardized Nursing Protocol	Approval of assigned protocol through requisite hospital committees	x			
4. Computer Based Training	All frontline staff with confirmed training on trial protocol, by arm	x			
5. Product Compatibility	Substitution of skin products incompatible with chlorhexidine	x			
6. Stocking Product	Supply chain infrastructure ensures product availability	x			
7. On Site Bathing Training	All hospitals randomized to decolonization receive on site training	x			
8. Coaching Calls	Monthly arm-specific coaching calls*	x			
9. Compliance Reports	Routine capture and reporting of protocol compliance	x	x		
10.Bathing Observations	Quarterly bathing observations to confirm process	x	x		
11.Data from Central Warehouse	Routine data pulls for needed trial data elements	x	x	x	
12.Data Cleaning Routines	Establish cleaning routines for serial data pulls	x	x	x	
13.Final Data Pull	Complete final data pulls from centralized data warehouse			x	
14.Analytic Data Set (Primary)	Establish final analytic dataset (Primary Manuscript)			x	
15.Statistical Analysis (Primary	Statistical analysis of trial outcomes (Primary Manuscript)			x	
16.Analytic Data Set (Secondary)	Establish final analytic dataset (Secondary Manuscripts)				x
17.Statistical Analysis (Secondary)	Statistical analysis of trial outcomes (Secondary Manuscripts)				x
18.Dissemination of Results	Presentations, manuscript preparation and submission			x	x
Aim 2: Resistance					
1. Strain Collection	Strain collection occurs during baseline and intervention periods	x	x		
2. Resistance Testing	Testing strains for mupirocin and chlorhexidine resistance			x	
3. Analytic Data Set	Establish final analytic dataset after cleaning, quality checks			x	x
4. Statistical Analysis	Statistical analysis of resistance outcomes				x
5. Dissemination of Results	Presentations, manuscript preparation and submission				x
Aim 3: Cost Effectiveness					

1. Data Pull for Charges	Total hospitalization charges and intervention costs acquired			x	
2. Literature Review	Common cost-to-charge ratios and usual product costs assessed			x	
3. Analytic Data Set	Establish final analytic dataset after cleaning, quality checks				x
4. Statistical Analysis	Statistical analysis of cost outcomes				x
5. Dissemination of Results	Presentations, manuscript preparation and submission				x
Resource/Software Products					
1. Decolonization Toolkit	Trial related materials to implement decolonization in hospitals	x			
2. Computer Training Modules	Computer-based training module for decolonization	x			
3. E-Documentation Modules	MEDITECH programs for nursing bathing documentation	x			
4. Product Compatibility Charts	Chlorhexidine compatibility charts for skin care products	x			
5. Podcasts and Webinar Content	Podcasts and PowerPoint presentations for decolonization	x			
6. Strain Collection Toolkit	Detailed directions for trial strain collection	x			
7. Randomization Software	SAS/R software for stratified cluster randomization		x		
8. Microbiology Mining Programs	SAS programs for parsing and analyzing microbiology results		x	x	
9. Bacterial Strain Bank	Large strain bank of MRSA and gram negative bacterial pathogens			x	x
10. Analytic Programs	SAS programs for analysis of cluster-randomized trials				x
11. Publications	Publication of all trial, resistance, and cost outcomes				x

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