

Ethics/Regulatory Call with Dr. Huang’s Demonstration Project - ABATE
Date: June 17, 2013
MINUTES

Attendees:

<input checked="" type="checkbox"/>	Jeremy Sugarman (Johns Hopkins)	<input checked="" type="checkbox"/>	Laurie Kunches (Harvard Pilgrim)	<input checked="" type="checkbox"/>	Clayton Huntley (NIH)	<input checked="" type="checkbox"/>	Tammy Reece (Coord Center)
<input checked="" type="checkbox"/>	Rob Califf (Duke)	<input checked="" type="checkbox"/>	Julie Kaneshiro (OHRP)	<input checked="" type="checkbox"/>	Catherine Meyers (NIH)	<input type="checkbox"/>	
<input checked="" type="checkbox"/>	Susan Huang (UC Irvine)	<input checked="" type="checkbox"/>	Jerry Menikoff (OHRP)	<input checked="" type="checkbox"/>	Wendy Weber (NIH)	<input type="checkbox"/>	
<input checked="" type="checkbox"/>	Sheila Fireman (Harvard, IRB)	<input checked="" type="checkbox"/>	Irene Stith-Coleman (OHRP)	<input checked="" type="checkbox"/>	Sarah Carr (NIH)	<input type="checkbox"/>	
<input checked="" type="checkbox"/>	Julie Lankiewicz (Harvard)	<input checked="" type="checkbox"/>	Ivor Pritchard (OHRP)	<input checked="" type="checkbox"/>	Carla James (NIH)	<input type="checkbox"/>	
<input checked="" type="checkbox"/>	Paula Tebeau (Harvard)	<input checked="" type="checkbox"/>	Dave Wendler (NIH)	<input checked="" type="checkbox"/>	Josephine Briggs (NIH)	<input type="checkbox"/>	

These minutes were circulated to all participants on the call for two rounds of review and they reflect all corrections that were received.

AGENDA ITEMS	DISCUSSION	ACTION ITEM
Review of Demonstration Project	<ul style="list-style-type: none"> • Dr. Huang gave an overview of the ABATE (Addressing Bioburden while Admitted To Eliminate) Infection Trial. ABATE will efficiently evaluate the impact of decolonization on multi-drug resistant organisms and hospital-associated infections (HAIs) in the general patient population outside ICUs. This cluster-randomized trial will randomize ~50 hospitals treating nearly 400,000 patients to evaluate 1) universal daily chlorhexidine bathing, combined with 2) nasal decolonization with mupirocin for known carriers of methicillin-resistant <i>Staphylococcus aureus</i> (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. • Lead centers involved include: UC Irvine, Harvard Pilgrim Health Care Institute (Lead IRB), Rush University, Stroger 	

	<p>Hospital of Cook County, CDC, and Hospital Corporation of America</p> <ul style="list-style-type: none"> • Trial Design: 2-arm cluster randomized trial, ~50 hospitals and their adult non critical care units, includes: adult medical, surgical, step down, oncology, excludes: pediatrics, rehab, psych, peri-partum, BMT. • Arm 1: Routine Care. Routine product and policy for showering/bathing. • Arm 2: Decolonization. Daily shower/bathing with chlorhexidine routine for all patients, mupirocin nasal ointment x 5 days if known to be MRSA+ (carriers). • Primary outcome: Clinical cultures with multi-drug resistant organisms. Secondary outcomes: 1) bloodstream infections: all pathogens, 2) urinary tract infections: all pathogens, 3) infectious readmissions: all pathogens, 4) emergence of resistance among key pathogens. • No questions of protocol design voiced. 	
<p>Minimal Risk</p>	<ul style="list-style-type: none"> • Sheila Fireman from the Harvard IRB reviewed the minimal risk documentation that was provided to the group (appended). They reviewed the proposed use of the products and considered that the probability of harm was low and that there were no known risks of using these products beyond usual care. They felt that this was consistent with quality improvement measures, since they are using FDA approved products in accordance with current product labeling. They concluded that the intervention and the data/evaluation met the criteria for minimal risk. • Special conditions that have been addressed or under review: 1) Children over 12 yrs. old - minimal risk as the products are labeled for use over age 12, 2) Pregnant Women – Under review but believed to be minimal risk, 3) Prisoners – no more than minimal risk. Mupirocin is FDA regulated product, but still minimal risk. • There was consensus that the study met criteria for a “minimal risk” determination. 	

<p>Consent (Patient and Physician)</p>	<ul style="list-style-type: none"> • IRB is requiring subjects be provided with written information about the research in admission materials and on posted flyer in room. Nurses are trained to discuss the intervention within the context of a hospital wide initiative. • Clarified that the plan is to have a waiver of consent in that notices about the project will be posted but there will be no need for an affirmative agreement participate. That is, no verbal individual consent will be obtained. • Written consent it not usually required for hospital bathing or choice of soap/antibacterial. The choice of the product is at the hospital-level for both arms. Patients can ask for a bath at any time and they can refuse a bath as well. Close monitoring routinely in place with hospital infection control staff to monitor changes in outbreaks or hospital-associated infections. • Posting of the flyers will occur in both Arms of the project. • The group considered whether the study was exempt from FDA/IND regulations, as such regulations may impact on the informed consent process. As published FDA guidances relate that studies of regulated products that use products in accordance with product labeling are exempt from IND regulations, the consensus was that FDA would therefore not have jurisdiction for this trial. As there have been similar discussions about other projects within the Collaboratory, NIH staff indicated that further discussion with FDA staff about this issue would be worthwhile. 	<ul style="list-style-type: none"> • NIH will follow up with staff at FDA to verify that studies of regulated products that are used in accordance with labeling are exempt from IND regulations.
<p>HIPAA</p>	<ul style="list-style-type: none"> • The consensus of the group was that the criteria for U.S. Health and Human Services Regulation 45 CFR 164.512 were satisfied and waiver of HIPAA was acceptable and no concerns mentioned. • Patient identifiers will remain at the individual hospitals and not disclosed externally. Coded data will be shared for research and the code key will be accessible only to Infection Control and Prevention staff at HCA. 	
<p>Monitoring and oversight</p>	<ul style="list-style-type: none"> • The study will require a Data and Safety Monitoring Plan, which will be approved by NIAID, the primary NIH IC, prior to study initiation. 	

ABATE Minutes

	<ul style="list-style-type: none"> • Currently there is no plan to formally appoint an external DSMB for study oversight. NIAID has reviewed the project and in accordance with their policies, does not require that a DSMB be constituted for this project. 	
Issues beyond the ABATE Trial	<ul style="list-style-type: none"> • None voiced. 	
Conclusion of meeting	<ul style="list-style-type: none"> • Follow-up needed as noted in action items. 	<ul style="list-style-type: none"> • Case study will be written up to provide guidance for others planning similar trials to facilitate navigation of the ethics and regulatory issues.

***Supplementary Material
for ABATE Trial***

Supplementary Material

ABATE Infection Project: REGULATORY AND ETHICS ISSUES:

- I. Intervention: Cluster randomized trial of QI initiative in general medical and surgical units in 50+ HCA hospitals; excludes pediatric & specialty units including obstetrics, bone marrow transplants and rehab units.
 - a. Randomization: at hospital level rather than individual in order to evaluate the intervention as a hospital quality improvement campaign using usual hospital improvement infrastructure. Population based research, must be applied universally
 - i. Arm I: Routine daily bathing with chlorhexidine cloths for all non-critical care patients plus routine nasal decolonization with mupirocin for patients with MRSA.
 - ii. Arm II: Routine daily bathing with soap and water (usual care)
- II. Risk Determination: Minimal Risk
 - a. The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered during routine clinical practice. The probability of harm or injury occurring as a result of participation in the intervention or use of chlorhexidine or mupirocin is low. No additional risk to being randomly assigned to either treatment option, both fall within variation in current hospital practice regarding infection prevention.
 - b. Assessment of Risk:
 - i. Daily bathing with chlorhexidine: No more than minimal risk
 - i. Risks: skin irritation (low incidence); No adverse effects in long term ICU patients or outpatient bathing for 9 months. Evidence suggesting improved skin condition compared to soap and water.
 - ii. Increased microbial resistance? (rare, case report level).No studies supporting likely increase in chlorhexidine resistance, which is rare.
 - iii. Antiseptic soap, sold over counter without restriction.
 - iv. Not invasive procedure
 - v. Products and methods are in use in normal course of hospital prevention practice for decolonization & pre_operative_bathing without known harm to patients.
 - i. Chlorhexidine bath as current standard has been implemented by hospitals both inside and outside of HCA. Endorsed for preoperative bathing by CDC guidelines;
 - ii. Used routinely for ICU mouth care
 - iii. Gold standard for preparing skin prior to placement of central line devices
 - iv. 20 year usage outside of US for wound care: shows no tissue injury, no delay to healing;
 - ii. Mupirocin: No more than minimal risk
 - a. FDA Regulated product

- b. Risks: Hypersensitivity to ingredients (low incidence); Burning, stinging, itching of nose (low incidence);
- c. Increased microbial resistance? (low incidence). Mupirocin resistance is uncommon and not routinely measured despite broad use in surgical settings. Studies are conflicting on potential for emergence of resistance. No studies suggesting extensive resistance. Currently already widely used prior to certain surgeries per national guidelines.
 - i. Routinely used by some hospitals as quality improvement campaigns pre-operatively or in ICUs.
 - i. used in hospitals and in published QI initiatives for decolonization without known harm to patients;
 - ii. used for staph decolonization prior to surgery;
 - iii. used for decolonization by public health agencies in Europe.
 - d. Not invasive procedure; Systemic absorption is minimal.
- iii. Special populations :
 - a. Children (over 12 yr) if admitted to adult units, Minimal risk
 - i. Subpart A review: no more than minimal risk
 - ii. Products labeled for use over age 12; no additional risks than those associated with general population
 - iii. Alteration of consent and waiver of documentation of consent permitted under 45 CFR 46.46.116(d)
 - b. Pregnant Women – under review but believe minimal risk
 - c. Prisoners– No more than minimal risk
 - i. Subpart C Review: 45 CFR 46.303 Probability and magnitude of physical or psychological harm normally encountered in daily lives or in routine medical, dental, or psychological exams of healthy persons.
 - ii. Prisoner epidemiology waiver

III. CONSENT: Alteration and Waiver of Documentation of Consent

- a. Use of FDA regulated product. Could not waive consent in its entirety if using FDA regulated product in research. FDA Project is research/quality improvement initiative. Opted to modify consent requirements and documentation of consent for consistency with the FDA regulations. 21 CFR 56.109(c)
 - i. Minimal risk and involves no procedures for which consent would normally be required (see below)
- b. Waiver of Documentation of consent 45 CFR 46.117(c)
Research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.
 - i. Written consent is not usually required for hospital bathing or choice of soap/antibacterial.

ABATE: SUPPLEMENTARY MATERIAL

- ii. Hospital committees and leadership normally determine infection prevention policies, standardized nursing procedures, as well as the selection of drugs on hospital formularies rather than individual patients or practitioners. Patients can always refuse bath; protocol requires discontinuation if subjects show sensitivity to chlorhexidine.
 - iii. Close monitoring routinely in place with hospital infection control staff to monitor changes in outbreaks or hospital-associated infections.
 - iv. IRB is requiring subjects be provided with written information about the research in admission materials and on posted flyer in room. Nurses are trained to discuss the intervention within the context of a hospital wide initiative.
 - c. Alteration of elements of consent 45 CFR 46.116 :
 - i. Alteration of some of the IC elements in the patient information sheet that were confusing when describing a hospital wide initiative for infection control.
 - ii. The research involves no more than minimal risk to the subjects
 - iii. The waiver or alteration will not adversely affect the rights and welfare of the subjects; (patients can still refuse bath or decolonization)
 - iv. The research could not practicably be carried out without the waiver or alteration: Formal consent is impracticable; infection prevention requires a unified population based approach which would be compromised if the intervention were substantially limited. Both the intervention and validity of results are dependent on the application system wide. Comparative effectiveness research requires system to be functioning similar to usual operations; IC may create bias due to lack of representative sample. Notably, outcomes are infectious and population-based approaches can yield different results than non-population based approaches.
 - v. The subjects will be provided with additional pertinent information after participation. IRB is requiring that written information be provided to patients in admission materials and on posted wall notices.
 - d. HIPAA: Waiver of authorization for collection of MRSA and bacterial isolates from patients at participating hospitals. Direct patient identifiers will remain at the individual hospitals and not disclosed externally. Coded data will be shared for research and the code key will be accessible only to Infection Control and Prevention staff at HCA.
- IV. Local Context issues as Reviewing IRB: HCA providing IRB with relevant legal, regulatory and community norms on issues relating to this study for each state in which there is a participating hospital relevant to special practices/populations.

ABATE Infection Project

Active Bathing to Eliminate Infection

Susan Huang, MD MPH

Associate Professor and Hospital Epidemiologist

Division of Infectious Diseases & Health Policy Research Institute

University of California Irvine School of Medicine



HCA



RUSH



UCIRVINE



Trial Rationale

- National priority to reduce hospital infections
- Includes focus on multi-drug resistant pathogens (e.g. MRSA)
- Quality improvement/patient safety initiatives
 - Determined at hospital leadership/policy level
 - Required by The Joint Commission for accreditation
 - Applied to hospital population as usual care protocols
 - Patient are not involved or informed
 - Often precedes science
 - Examples: hospital drug formularies, bathing products

Pragmatic Trial of Hospitals

Purpose

- Compare 2 currently employed quality improvement (QI) strategies to reduce hospital infections
 - Both in current use today in hospitals
 - Unknown which is better

General Intervention

- Change in bathing soap for all patients
- Use of ointment for nose in select patients

Study Population & Design

Trial Design

- 2-arm cluster randomized trial
- 56 hospitals and their adult non critical care units
- Includes: adult medical, surgical, step down, oncology
- Excludes: pediatrics, rehab, psych, peri-partum, BMT

Arm 1: Routine Care

- Routine product and policy for showering/bathing

Arm 2: Decolonization

- Daily shower/bathing with chlorhexidine routine for all patients
- Mupirocin nasal ointment x 5 days if known to be MRSA+ (carriers)

Soap and Ointment Products

Chlorhexidine

- Over the counter antiseptic soap
- Used in healthcare for over 50 years: dental, skin, wounds
- Not systemically absorbed
- Routinely used for pre-operative bathing, skin cleansing before inserting devices, oral mouth wash in ICUs
- Recent cluster randomized trials showing benefit in ICUs when used universally for daily bathing as QI projects

Soap and Ointment Products

Mupirocin

- Topical antibiotic ointment (prescription)
- Not absorbed
- FDA approved for removing MRSA from the nose (the main reservoir for MRSA carriage)
- Common usage
 - Hospitals decolonizing MRSA carriers
 - National guidance prior to cardiac/joint surgery
 - Recent cluster randomize trial favoring use in ICUs
- In this study, used in the small subset of patients who have MRSA

Potential for Resistance

Chlorhexidine

- Resistance is rare despite use in healthcare for 50 years
- Wide use in ICUs
- Not used for therapy for infection
- Resistance unmonitored except research

Mupirocin

- Resistance unmonitored except in research
- Wide use to decolonize MRSA carriers in hospitals/pre-op
- Not used for therapy for infection
- Estimated relevance in <1% of hospital patients
 - <10% of patients known to harbor MRSA
 - <10% of those with resistant strain (10% of 10% = 1%)

Study Conduct

- Uses usual hospital infrastructure for quality improvement
- No on-site investigators
- Supported by health system infrastructure
(Hospital Corporation of America)
- Twice monthly arm-specific conference calls
- Distributed tool kits, FAQs
- Site visits for training, as needed
- Reliance on central IRB

Outcomes

Obtained from central health system data warehouse

Primary Outcomes

- Clinical cultures with multi-drug resistant organisms

Secondary Outcomes

- Bloodstream infections: all pathogens
- Urinary tract infections: all pathogens
- Infectious readmissions: all pathogens
- Emergence of resistance among key pathogens



Pragmatic Clinical Trials Demonstration Project NIH Collaboratory

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

ABATE (Addressing Bioburden while Admitted To Eliminate) Infection Trial

PI: Susan Huang, MD MPH (UC Irvine)

Partners: UC Irvine, Harvard Pilgrim Health Care Institute, Rush University, Stroger Hospital of Cook County, CDC, and Hospital Corporation of America

Lead IRB: Harvard Pilgrim Health Care

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 50 hospitals treating nearly 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.
- 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 of this proposal 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 sterile site healthcare-associated infection. Secondary outcomes will include readmission caused by infection.
- 2) Assess whether universal chlorhexidine bathing and selective MRSA decolonization result in increased resistance to chlorhexidine or mupirocin.
- 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