Effect of Expanding (Gloving) Barrier Precautions for Reducing *Clostridium difficile* Acquisition (and Infection) in VA: The GLORI Study

Funding Agency: VA HSR&D

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Abstract

Clostridium difficile infection (CDI) has become the most common healthcare-associated infection (HAI) in U.S. hospitals, causing half a million infections and 30,000 deaths annually. CDI ranges from asymptomatic colonization, mild to severe diarrhea, pseudomembranous colitis, toxic megacolon, colonic perforation, and death. Risk factors for CDI include older age, comorbidity, hospitalization, exposure to others with CDI, and antibiotic use. Prevention of healthcare-onset (HO)-CDI has become a priority for hospitals. Hospital prevention measures are limited to modifiable risk factors (i.e., prudent antibiotic use and limiting exposure to *C. difficile*). Hospital exposure to *C. difficile* can occur directly (i.e., hands or clothing of healthcare workers) or indirectly (i.e., environmental surfaces or shared equipment) so infection prevention measures focus on healthcare worker hand hygiene and barrier precautions (i.e., use of gowns and gloves) and cleaning and disinfection of the hospital environment. However, these interventions are limited to symptomatic patients who test positive for CDI. Asymptomatic patients serve as a reservoir for cross-contamination, but microbiological screening for asymptomatic carriage of *C. difficile* is not routinely performed in healthcare. Gloving for all patient contacts may interrupt transmission from asymptomatic patients colonized with *C. difficile*.

The overall purpose of the study is to determine the effectiveness of healthcare worker use of gloves for all patient contact for reducing acquisition of *C. difficile* and HO-CDI in inpatient hospital units. The main objective of the study is to compare the effects of universal gloving for all patient contact to the current standard of care (i.e., glove and gown use only for known CDI cases). The aims of the study are:

1) Compare the effects of universal gloving for all patient contact to the current standard of care on *C. difficile* acquisition rates in hospitalized patients;

2) Compare the effects of universal gloving compared to standard of care gloving on CDI rates, other HAIs, 30-day mortality, and unit length of stay; and

3) Describe intervention fidelity, cost, and stakeholder (patients' and healthcare workers') experiences with universal gloving.

The study will be a cluster randomized trial (CRT) in ten inpatient VA hospital units. Units will be randomized either to implement barrier precautions for all patient contacts (universal gloving intervention) or continue standard of care (barrier precautions for patients with known CDI and other antibiotic-resistant organisms). The intervention will consist of all healthcare workers (nurses, providers, respiratory therapists, radiology/laboratory technicians, etc.) utilizing gloves for all patient contacts in the units randomized to receive the intervention. Unit-level data, including *C. difficile* acquisition and infection rates, mortality, length of stay, and barrier precaution compliance, will be collected monthly from all participating sites.

If universal gloving is found to be effective in reducing *C. difficile* acquisition and subsequent infection (and its associated morbidity, mortality, and costs), the results will change the paradigm for CDI prevention in healthcare settings.

List of Abbreviations

AE	Adverse Event
CAUTI	Catheter-associated Urinary Tract Infection
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CLABSI	Central Line-associated Bloodstream Infection
CP	Contact Precautions
CRT	Cluster Randomized Trial
CTSP	Centralized Transcription Services Program
HAI	Healthcare-associated Infection
HIPAA	Health Information Portability and Accountability Act
HO-CDI	Hospital Onset-*Clostridium difficile* Infection
ICU	Intensive Care Unit
IPEC	Inpatient Evaluation Center
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LSI	Local Site Investigator
MDRO	Multidrug-Resistant Organism
MRSA	Methicillin-Resistant *Staphylococcus aureus*
PCR	Polymerase Chain Reaction
PHI	Personal Health Information
PI	Principal Investigator
PII	Personally Identifying Information
RA	Research Assistant
SAE	Serious Adverse Event
VA	Department of Veterans Affairs

Contents

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2.0 Introduction

Clostridium difficile is the major infectious cause of healthcare-associated diarrhea, causing as many as 25% of cases. [1-3] *C. difficile* infection (CDI) affects 500,000 Americans each year, is responsible for 29,000 deaths annually, and has an estimated annual cost of $ 1.1 billion in the US. [4,5] Prevention of CDI is essential, and is a critical patient safety issue. [4,6-8] Transmission of highly antimicrobial-resistant *C. difficile* occurs primarily in healthcare facilities, where studies have found *C. difficile* acquisition in 1–13% of patients hospitalized for less than a week and in 50% of patients hospitalized for more than 4 weeks. [9,10] Containment of CDI has been designated a public health priority by several federal agencies, including the VA. [11,12]

Based on evidence-based guidelines from the Infectious Diseases Society of America, the VA Multidrug Resistant Organism (MDRO) Program Office developed and mandated a multifaceted national bundle for prevention of CDI at VA facilities in 2012 which includes: [13] 1) rapid, appropriate diagnostic testing for *C. difficile*, 2) empiric isolation for patients with diarrhea and suspected CDI, 3) contact isolation for patients with confirmed CDI, 4) environmental decontamination of rooms of patients with CDI, and 5) strategies for improving healthcare worker hand hygiene. However, decreases in CDI rates have been modest, variable and inconsistent.[14] A major reason for this finding is that these interventions are limited to symptomatic patients who test positive for CDI. This is a gap because asymptomatic patients are a major reservoir of C. difficile, colonization greatly increases the risk of infection and

importation of CDI from the community to the hospital is increasing.[15,16] Yet, there is a paucity of evidence on how to reduce transmission from asymptomatic patients.

The two main potential approaches to tackling transmission from the reservoir of colonized patients are to undertake regular microbiological screening or to implement universal contact precautions. The efficacy of these approaches is yet unknown. Microbiological screening at admission to detect asymptomatic carriage of *C. difficile* and place colonized patients in contact precautions is not favored by front-line healthcare workers because it is costly, labor-intensive and requires microbiology resources at each site. Universal gloving where healthcare workers don gloves upon each entry to a patient room regardless of disease state may be promising in reducing the acquisition of CDI because gloves are the most effective means of preventing hand contamination with *C. difficile* spores. Data on universal gowning and gloving is limited to organisms other than *C. difficile* and in ICU settings which cannot be extrapolated to *C. difficile* because *C. difficile* is a spore-forming organism allowing it to remain viable in adverse conditions in the environment for long periods of time and diarrhea leads to heavy, persistent environmental contamination.[17-20] We hypothesize that current standard of practice that targets glove use for only patients with known CDI does not interrupt *C. difficile* transmission from patients with asymptomatic colonization resulting in *C. difficile* acquisition and subsequent infection. The rationale for the hypothesis is that both patients with active infections and those with asymptomatic colonization serve as reservoirs for patient-to-patient transmission of *C. difficile* either through contaminated healthcare workers hands or contaminated healthcare environment (i.e., patient equipment and/or environmental surfaces). Hand and environmental contamination with *C. difficile* spores are well established and these spores are resistant to both hand hygiene and environmental antisepsis methods[21-23].

Hand hygiene is generally accepted to be the most effective means of infection prevention, and current guidance recommends the use of the preferential use of alcohol based hand rubs (ABHR) over soap and water in all clinical situations except 1) when hands are visibly soiled (e.g., blood, body fluids) and 2) after caring for a patient with known or suspected *C. difficile* or norovirus during an outbreak or if endemic rates are high.[24] *C. difficile* spores are not killed by ABHR and may be difficult to remove even with thorough hand washing with soap and water.[21,22] Strict adherence to gloving is the most effective means of preventing hand contamination with *C. difficile* spores.[25] One study prospectively studied the use of gloves in interrupting *C. difficile* transmission[26] and universal gloving has been proposed as a novel approach to prevent CDI.[27]

Of the two possible approaches to target colonization, screening patients for asymptomatic carriage has increased costs, need for microbiology resources and training, and increased use of contact precautions for those colonized. Universal gloving also results in increased use of contact precautions by gowning and gloving, but the microbiology resources are not necessary. In discussions with VA facilities, there has been much enthusiasm for universal gloving and none for screening and isolation.

3.0 Objectives

The overall goal of our research is to reduce CDI. This proposed study will study the effectiveness of healthcare workers' use of universal gloving for all patient contact in reducing the acquisition of *C. difficile* in hospitalized patients compared with current VA standard care (i.e., healthcare worker glove use when caring for patients in CP isolation) using a pragmatic cluster randomized trial (CRT) in ten inpatient VA hospital units.

We hypothesize that patients with asymptomatic carriage of *C. difficile* can shed the pathogen and therefore are an important reservoir for transmission of *C. difficile*. There are two approaches to target this colonization: microbiological screening of patients to identify those patients who are carriers of *C. difficile* and increased barrier precautions. Microbiological screening for asymptomatic carriage of *C. difficile* is not routinely performed in healthcare because data is limited regarding the use of a detection and isolation intervention to decrease transmission of *C. difficile* and therefore not recommended at present.[28] Here, we propose to implement the use of gloves for all patient contact (i.e., universal gloving) in non-ICU acute care units to prevent transmission of *C. difficile* from both patients with known infections and those patients who are asymptomatic carriers.

We have proposed three objectives:

- To compare the effects of universal gloving for all patient contact to the current standard of care on *C. difficile* acquisition rates in hospitalized patients
- To compare the effects of universal gloving compared to standard of care on CDI rates, other healthcare-associated infections (CLABSI, CAUTI, MRSA), 30-day mortality and unit length of stay.
- To evaluate intervention fidelity (hand hygiene and barrier precaution compliance; glove use for all patients and glove plus gown use for patients in contact precautions (CP) isolation), the cost and stakeholder experiences (interviews and provider-patient contact survey).

This study will be the first to evaluate whether universal gloving will prevent transmission from patients who are asymptomatically colonized with *C. difficile* in non-ICU units in an RCT. The study will also investigate the impacts of universal gloving on associated factors, including CDI, other healthcare-associated infections, and their effects on a unit's morbidity, mortality, costs and patients and healthcare workers experience. If the results of the study support universal gloving, it will change the paradigm for prevention of CDI nationwide.

4.1 Resources and Personnel

4.2 Participating Sites

The coordinating study site and personnel (including the PI) will be based at the Madison VA. The Madison VA-based team will be responsible for overall study execution, including protocol refinement, comprehensive site training, medical monitoring, handling of patient-related issues that may arise, coordination of clinical event ascertainment efforts, and interfacing with study committees and local site teams.

Five sites (Milwaukee, Hines, Bronx, Washington DC, Portland) will enroll ten inpatient units (i.e., acute medical, medical/surgical, surgical or specialty units) to participate in the study; 2 inpatient units at each site. A Local Site Investigator (LSI; see above list of names under personnel) and a Research Assistant (RA) will be assigned to each participating site to assist in completing study procedures and ensuring compliance with the study protocol at this site.

Local site responsibilities will be discussed in detail with the LSI and RA prior to beginning study procedures. These responsibilities may include:

- Maintain site documentation (e.g. study binder, study information sheets, sample code key)
- Obtain local approvals as required

- Ensure adherence to study protocol and procedures
- Provide education/training on study procedures for local staff and on-site resource for staff and patient questions
- Recruit patients and consent for swab/stool sample collection
- Specimen collection
    - Stool samples – collect swab/stool specimens,
    - provide supplies and instructions to patients performing self-collected specimen collection,
    - specimen label, store, ship
- Collect data
    - intervention fidelity
    - Clinical outcomes
- Upload data to Madison
- Recruit patients and healthcare workers for interviews/focus groups
- Facilitate and/or Conduct patient interviews
- Facilitate and/or Conduct healthcare worker focus groups
- Conduct observations of hand hygiene, contact precaution, and universal gloving practice compliance
- Recruit patients and healthcare workers for surveys
- Organize survey collection process
- Participate in meetings/check-ins with coordinating site; maintain communication
- Follow all VA privacy/information security regulations

Clinical staff (such as nursing staff) will also assist with study conduct. Clinical staff's responsibilities may include:

- Inform patients that the unit is participating in a research study and that staff will be wearing gloves during all patient care activities.
- Specimen collection
    - Stool samples – collect swab/stool specimens,
    - provide supplies and instructions to patients performing self-collected specimen collection,
    - Collect patient self-collected samples, label and store according to sample collection guidelines for RA processing

4.3 Personnel

The Madison-based study team includes the PI, Co-Investigators, Project Manager/Study Coordinator, laboratory staff, and Research Scientists.

Each participating site will name an LSI and RA to handle local procedures as described above. Additional personnel at each site (e.g. unit leadership) will be engaged as needed to ensure buy-in and adherence to study procedures.

4.4 Resources

Multiple entities will support the successful progress and completion of the study:

Executive Committee (EC): The EC will consist of the PI, the site investigators, and the research assistants. The EC will review study contact, recruitment and troubleshooting, IRB, and other regulatory issues.

Steering Committee (SC): The SC will be composed of the PI and co-investigators as well as the lead biostatistician. The SC will discuss progress, recruitment goals, review quality of the data, and troubleshoot.

Coordinating Site Committee (CSC): The CSC will be physically located at the Madison VA and led by Dr. Nasia Safdar (PI). The CSC will be responsible for overall study execution, including protocol refinement, comprehensive site training, medical monitoring, handling of patient-related issues that may arise, coordination of clinical event ascertainment efforts, and coordinating with other Committees and with VA HSR&D. The CSC will also coordinate with statistical and qualitative data experts to ensure appropriate data management, quality control and quality assurance, information technology for communication and trial conduct monitoring, statistical methods (ex. randomization, interim monitoring), analyses, interpretation of findings, preparation of results, and publication of findings from the trial.

We will work with the VA Centralized Transcription Services Program, located at the Salt Lake City VA and led by Dr. Susan Zickmund, for the transcription of qualitative interviews.

5.1 Study Procedures

5.2 Study Design

5.2.1 Experimental Design

We will conduct this study using a pragmatic stratified-cluster randomized trial (CRT) in ten inpatient VA hospital units (acute medical, medical/surgical, or surgical inpatient acute care units). Hospital units will be randomly assigned in a 1:1 ratio: 5 units will be randomized to enact universal gloving practices (intervention) and 5 units will continue standard of care (control).
Due to resource and personnel feasibility, randomization will be stratified by location to allow for the selection of one intervention and one control unit at each site.

A 6-12-month pre-intervention period will be used to conduct preliminary work at sites including training research assistants, identifying current practices, finalizing monitoring and observation plans. Each participating unit will collect data for up to 24 months – a 24-month intervention period. During the intervention period, we will collect data on a monthly basis, including C. difficile acquisition and infection rates, other infections (CLABSI, CAUTI, MRSA), mortality, length of stay, and intervention fidelity (hand hygiene compliance and barrier precaution compliance; glove use for all patients and glove plus gown use for patients in CP isolation). These unit-level data will be obtained from aggregate reports prepared by the infection control department at each site from data they have entered into the VA Inpatient Evaluation Center (IPEC) data management system and/or from VA administrative records. Patient-level data on relevant clinical characteristics such as comorbidities, prior treatments and healthcare usage, and outcomes such as HAIs will be obtained from VA administrative records for patients who consent to stool specimen collections. We will conduct interviews/focus groups with healthcare workers throughout the intervention period and individual interviews with patients throughout the intervention period. These interviews and focus groups will explore healthcare workers' and patients' experiences with the intervention. We will also conduct patient and healthcare worker survey on provider-patient contact using a Likert scale to assess the amount of contact patients have with their healthcare workers in both the intervention and control groups.

5.2.2 Intervention

In the units randomized to receive the intervention, all healthcare workers (nurses, providers, respiratory therapist, radiology and laboratory technicians, etc.) will utilize universal gloving (non- sterile gloves) for all patient contacts. If a patient in the intervention unit is known to have CDI or an MDRO, both gowns and gloves will be used as is current standard of care practice for patients in CP isolation. Signage denoting what type of precautions are needed will be placed on the door of each patient's room.

The non-intervention units will follow standard of care which consists of healthcare workers following barrier contact precautions (i.e., gloves plus gowns) only for patients with known CDI and other MDROs (e.g., MRSA).

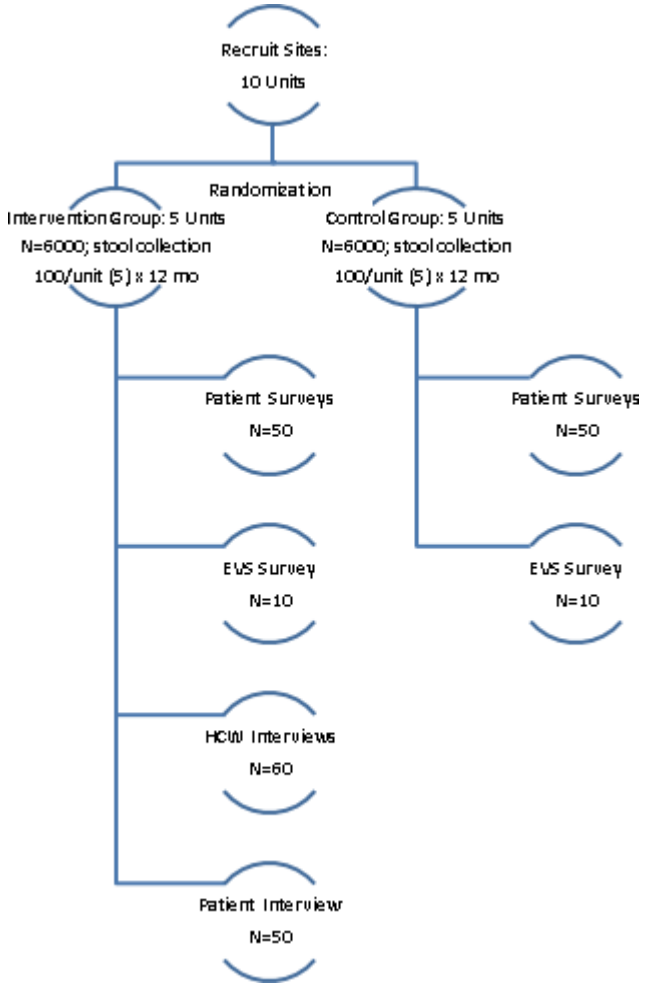
5.2.3 Study Population

The study population will be ten participating units. All patients aged 18 and above within these units will be included in the intervention and clinical data collection.

Within the units assigned to the intervention, we will conduct interviews with healthcare workers and patients about their experiences with the intervention. We will conduct focus groups with up to 60 healthcare workers (up to 12 individuals for each of the 5 sites enacting the intervention) who are aged 18 and above, are employed by the participating facility and have performed employment duties within the participating unit during the intervention period, and who agree to participate in the interview. We will interview 50 patients (10 per site enacting the intervention) who are aged 18 and above, are admitted as an inpatient to the participating unit during the intervention period, and who agree to participate in the interview.

We will also conduct surveys with patients and environmental services staff. We will aim to survey 10 patients per site at all 10 participating sites, for a total of 100 patients (50 from intervention group and 50 from control group). Given the small expected number of environmental service staff on each unit, we will aim to survey at least 1 worker per site at all 10 participating sites, for a total of 10 workers.

Focus groups and patient interviews will be conducted via face-to-face or phone/Teams call. All interviews will be audio -recorded to be transcribed later for analysis of themes and concepts unless patients decline to be recorded, in which case field notes will be taken and analyzed instead. Please see section 7.0 for specific detailed procedures for handling interview recording and transcript information.



5.2.4 Risk Analysis

5.2.4.1 Known Potential Risks

This is a minimal risk study to participating units and to the healthcare workers and patients within these units.

Physical Risks. No physical risks are anticipated from this study. Use of barrier contact precautions (gloving plus gowning) is currently the standard of care for patients with certain communicable diseases including antibiotic-resistant organisms (e.g., MRSA), so the expansion of universal gloving for care of all patients (intervention) does not present additional risk to healthcare workers or patients.

There are no physical risks associated with collection of stool samples for *C. difficile* lab testing. However, if we are unable to obtain a stool specimen, we will obtain a stool sample using a perirectal swab which may present minimal discomfort or embarrassment to patients. The perirectal swabs will be obtained using a CDC standardized methodology and standardized specimen collection technique which involves swabbing the perirectal area. Perirectal swabs

have been found to be equivalent to rectal swab specimens for detection of asymptomatic carriers of *C. difficile*.[29] The swab will be taken from the skin surrounding the anus and will not be inserted into the anus. The patient will feel a sensation similar to wiping their bottom with toilet paper during the perirectal swab. The swab collection may be associated with embarrassment but will be collected using standard of care privacy practices including the use of a privacy curtain or closing the door to the patient room. If subject reports embarrassments post procedure an assessment of the procedure and review of protocol will be conducted with staff.

If any patient desires to decline perirectal swabs, we will not collect swabs from that individual. In these cases, stool samples may be used to measure *C. difficile* acquisition rather than perirectal swabs if the patient agrees. Stool samples will be collected using standard procedures and pose no risk to the patient.

Patients may become tired during interviews and study team members will frequently elicit feedback from patients about their ability to continue during the interview.

Psychological Risks. No psychological risks are expected to result from participating in the study, including via interviews, observations, or surveys. Healthcare workers may fear repercussions from interviews, observation or survey, but potential participants will verbally agree or decline to participate in private without the knowledge of their supervisors to avoid potential feelings of coercion or fear of repercussion. Additionally, participating healthcare workers will not be subordinate in any way to study team members. There will not be any identifiable data collected; anonymity will avoid any possible repercussion and data will not be used to assess individual performance at study sites, nor will our data in any way affect participant standing at the institution. As part of the interview process, a statement will be read prior to audio recording asking the interviewee not to share personal information. Although there is no intention to collect identifiable healthcare worker data that would link interview responses to a healthcare worker, if identifiable data was inadvertently shared during audio recording, this data will be deleted from the transcripts. Participants may experience social or psychological discomfort during interviews. Study team members will frequently elicit feedback from participants about their comfort level and remind them they do not have to answer questions they are not comfortable with and that the entire interview is voluntary. Study participation will be entirely voluntary.

Social, Legal, or Other Risks. There is a minimal risk of loss of privacy or confidentiality. Only the minimum necessary identifiers will be collected and maintained for study conduct; any unintentional identifiers will be removed from the data. A unique code will be generated for each aggregate and patient-level data variable and linked to a unique code representing the hospital unit and (for patient-level data) the patient. This identifier will be for purposes of the study only and will not include individually identifiable private information; it will be used to replace all individual identifiers in the data prior to analysis. De-identified patient-level data for which participants gave HIPAA authorization to share with the University of Wisconsin and deidentified aggregate data may be shared with the University of Wisconsin (the university affiliate) as specified in a valid Data Use Agreement. Otherwise, data will be saved to the Madison VA secure server behind the VA firewall. The shared data file will only be accessible via VA computers that are password protected and accessed only by research personnel. Logs of VCS gift cards given to participants containing participants' study names and forms signed by participants (required in order to use the gift cards) will only be accessible by the minimum necessary study staff and staff from Fiscal/Budget offices at participating sites who may need to audit the logs. Computers will be maintained in locked offices with access only by research personnel. Interviews will be recorded on encrypted digital recorders or using Microsoft Teams and directly saved to the Madison VA secure server behind the VA firewall. When using Microsoft Teams access to the channel/meeting on which it is recorded will be restricted to study staff with permissions to access this data. The shared data file will only be accessible to study team members via VA computers that are password protected and automatically logged off when not in use. A unique number will be generated for each interview and this identifier will

be for purposes of the study only. Information linking identifier to audio recording or field notes will be maintained in a secure location; shared data file on the VA server behind the VA firewall accessed. The shared data file will only be accessible to study team members via VA computers that are password-protected and automatically logged off when not in use. Hard copies of field notes will be kept in locked file cabinets in locked offices accessed only by authorized research personnel.

5.2.4.2 Known Potential Benefits

No direct benefits to patients and healthcare workers are anticipated, but patients may potentially benefit if the use of gloves by healthcare workers for all patient contact prevents the spread of organisms such as *C. difficile* within the hospital setting. Others may benefit in the future from what we learn as a result of the study, as our study will address critical gaps regarding effectiveness of universal gloving for CDI prevention.

We hypothesize that the use of the universal gloving intervention will reduce *C. difficile* acquisition and infection within the units assigned to the intervention.

If this study shows a decrease in the carriage of *C. difficile*, the community at large would benefit by eliminating a potential reservoir for disease transmission. Regardless of study results, important knowledge will be gained from the study guiding future research in the prevention of healthcare-associated CDI.

5.2.4.3 Assessment of Potential Risks and Benefits

The risks to subjects in this study are minimal. In order to reduce risk and discomfort to subjects, we propose to collect stool samples when possible and then perirectal swabs f for measuring C. *difficile*. When perirectal swabs are collected, subjects can choose to have the RA/healthcare worker perform the perirectal swab or self-collect the perirectal swab. The intervention – universal gloving – is a non-invasive barrier precaution that has been a source of enthusiasm for VA healthcare facilities. As part of the study, we will also ask about stakeholders' (patients and healthcare workers) experiences with universal gloving for all patient contacts versus standard of care. In addition, a sample of patients and healthcare workers will be asked to complete a survey regarding their perception of provider-patient contact using a 5-point Likert scale. This information will help us to understand if the intervention causes a burden or unintended consequences with study participants.

The use of barrier contact precautions in both the intervention and control units will follow all standard of care procedures. It is expected of hospital accrediting standards and professional standards that equal; high quality care will be provided to all patients regardless of diagnosis. Patients on units that are in the intervention arm of the study where expanded barrier precautions (i.e., universal gloving) are used for all patient contacts will receive the same high-quality care as a patient in in the control arm of the study following standard of care procedures. Patients on units that are in the control arm of the study will have no change in their care. Educational materials used in the study will remind healthcare workers in the participating sites that patient care practices must conform to local facility standards regardless of whether expanded barrier precautions (i.e., universal gloving) are implemented for patient care.

C. difficile is an important and increasing cause of morbidity and mortality in Veterans in VA hospitals and communities. As 1) there is the potential for both short- and long-term benefits in the reduction of *C. difficile*-associated morbidity and mortality based on the findings of this study and 2) the Veterans' health, safety, and comfort has been maximized in our study design, we believe that the benefits of this study outweigh its minimal risks.

5.3 Recruitment Methods

INTERVENTION

Ten inpatient units (two each from five participating VA facilities) will be included in the study, and the intervention will be conducted at the unit level. Multiple sites have previously expressed

interest in participating in an investigation of universal gloving as well as in healthcare-

associated infection prevention research in general. Communication describing the study and the study team's/PI's contact information will be distributed to facilities. Informational teleconferences will be offered for interested facilities to provide additional study requirements and eligibility criteria. Interested facilities will be sent a screening questionnaire to assess eligibility and facility support.

This study is a cluster randomized trial: because all patients in a unit can contribute to transmission of *C. difficile*, the intervention needs to apply to all patients in the unit. As only VA facilities will be included, all patients in the unit will be aged 18 or greater.

SPECIMEN COLLECTION
Research staff will check with patient's nurse or other healthcare team member (e.g., the nursing station) prior to approaching patients for specimen collection consent to determine if it is appropriate to approach a patient based on his/her health needs and other contextual factors, for example, whether there are any patients who should not be approached because they are in quarantine or not feeling well. We will work with unit staff to refine the process for identifying patients who may be approached as needed based on unit staff's preferences; for example, members of the healthcare team may wish to make first contact with a patient by asking if they may introduce the RA to discuss a research opportunity or by distributing flyers describing the study prior to the RA visit to the unit. Research staff will approach those patients deemed appropriate on the participating units on the first study day and then subsequently newly admitted patients to ask if they are willing to speak about a voluntary research opportunity. If so, the RA will review study details and ascertain the patient's interest in providing a stool or swab specimen. The RA will assess whether it is a good time to approach the patient (e.g., by checking with the patient's nurse or other healthcare team member) prior to approaching the patient. The healthcare team members will not screen for eligibility or directly recruit patients to participate in specimen collection. Rather, the healthcare team member's role is to facilitate patient care by being an advocate for the patient. Admitted patients will be identified from VA administrative records (e.g., from the CDW) and the admission and discharge tracking system used by the participating unit (e.g., the gains and loss report).

Patient participants will be offered a $15 Veterans Canteen Service (VCS) gift card (Patriot Bucks) in exchange for their participation in the study at local sites where and when VCS gift cards are made available to the local study team. The gift card will be given to the patient by the RA after the patient provides their first specimen, regardless of whether the patient provides a second specimen prior to discharge (i.e., even if the subject later withdraws from the study). Versions of recruitment flyers referencing the gift cards will be used whenever and wherever VCS gift cards are available.

INTERVIEWS
We will recruit individual healthcare workers and patients for interviews about their experience with the intervention.

Healthcare Workers
We will conduct focus groups/interviews with up to 12 healthcare workers at each participating unit assigned to the intervention, for a total of up to 60 healthcare workers involved in focus groups. Prior to beginning the focus groups/interviews, which may take place throughout the intervention period, the Local Site Investigator and Research Assistant will discuss recruitment options with unit leadership. Recruitment strategies may include presentations at staff meetings (using verbal script) or email to unit staff. The LSI or local RA will lead these recruitment strategies, for example by presenting at staff meetings or sending emails.
Recruitment for these focus groups may also include emails to unit staff. We will discuss with unit leadership/supervisors if email is appropriate to use for their staff and, if so, how to access these email addresses. We will discuss with site staff, including unit leadership/supervisors and

local research staff, who should send the email – it will come from either the LSI, the local RA, or a member of the central research team. The email will include contact information so recipients can reply to the appropriate research team member to agree to participate, decline participation, or ask questions. Staff receiving study information sheets will be able to contact the study team to participate or select opt-in option on the study information sheet whereby the study team will contact them. Staff who select the opt-out option of the study information sheet will not be contacted and removed from the potential list of participants. If we do not hear a response (either agreement/dedination to participate or request to not be contacted again), we will follow-up a maximum of two additional times via email and/or phone.

During the recruitment process, regardless of outreach method, each potential participant will receive the interview information sheet. The healthcare worker will have time to review the sheet, and research staff will answer any questions they have before asking if they would like to participate. Healthcare workers who agree to participate in interviews will be given a brief, voluntary, anonymous demographics survey by the local RA (e.g., with the interview information sheet) to complete before or after the interview. Healthcare workers may participate in interviews even if they decline to complete the demographics survey.

Healthcare worker interview guides will be submitted to the appropriate unions for review prior to launching procedures. Interviews will take place during non-work time (e.g. lunch hour) or during supervisor-approved work time (e.g. during regularly scheduled staff meetings where patients have coverage and supervisors can leave the area). Supervisors will be notified prior to beginning any interview recruitment procedures.

Patients

We will interview 10 patients at each participating unit assigned to the intervention for a total of 50 patient interviews. During the intervention period, the site Research Assistant will work with unit staff to identify and approach patients. The RA will discuss with unit staff to determine if it is appropriate to approach a patient based on his/her health needs and other contextual factors; for example, patients will not be approached who are receiving end-of- life care, are cognitively impaired, or are unable to understand English. Patients who are under contact precaution isolation above and beyond the intervention (for example, use of gowns and gloves for all patient contact) will not be approached for interviews. We will work with unit staff to refine the process for identifying patients who may be approached as needed based on unit staff's preferences; for example, members of the healthcare team may wish to make first contact with a patient –by asking if they may introduce the RA to discuss a research opportunity or by distributing flyers describing the interviews prior to the RA visit to the unit. The healthcare team member will not screen for eligibility or directly recruit patients to participate in interviews. Rather, the healthcare team member's role is to facilitate patient care by being an advocate for the patient.

The RA will check with the patient's nurse or other healthcare team member before approaching the patient to ask him/her to participate and will not approach any patient without the nurse's or other healthcare team member's agreement that it is a good time to do so. The RA will not approach patients who have indicated they do not want to be contacted, receiving end-of-life care, cognitively impaired, non- English speakers, in contact isolation precautions or when he/she is undergoing any medical procedures. The RA will ask the patient in his/her room if he/she is willing to speak about a voluntary research opportunity. If so, the RA will meet face-to- face with the patient to assess eligibility and to provide basic information regarding the study and the voluntary nature of participation. A liberal amount of time will be allotted for discussion of the study and the patient's role in the study, and to answer any questions posed by the patient. The written information sheet will also be provided to the patient. The RA will offer the potential subject time for private contemplation and review of the documents provided or time to discuss the study with important support persons not currently with the patient. If the patient decides to participate, he/she can tell the RA in person or via the provided contact information in order to set up an interview. The RA will ask for the patient's phone number so that the

patients can be contacted regarding the interviews. In addition, the RA will ask the patient if the RA may return to the patient at a later time to check in about their decision. The RA may return to the patient one additional time to follow-up, and only with the patient's approval to do so based on the recruitment script. Patients who agree to participate in interviews will be given a brief, voluntary, anonymous demographics survey by the local RA (e.g., with the interview information sheet) to complete before or after the interview. Patients may participate in interviews even if they decline to complete the demographics survey.

SURVEYS
Patients

We will work with unit staff to refine the process for identifying patients who may be approached as needed based on unit staff's preferences; for example, the healthcare team member may wish to make first contact with a patient –by asking if they may introduce the RA to discuss a research opportunity or by distributing flyers describing the survey prior to the RA visit to the unit. The healthcare team member will not directly recruit patients to participate in the surveys. The RA will check with the patient's nurse before approaching the patient to ask him/her to participate and will not approach any patient without the nurse's agreement that it is a good time to do so. We will recruit patients to complete a Patient-Provider Contact Survey to understand perceptions of whether contact with patients is impacted due to the intervention. No PII or PHI will be included on these surveys. We will aim to obtain 10 patient surveys per site.
We will work with unit staff to determine how to share the survey with patients; options may include leaving the survey on bedside table, including survey in admission/discharge paperwork, and/or having research staff explain the survey and ask patient if they are willing to participate. A pen/pencil will be provided to patients who wish to complete the survey. We will collect completed surveys through a discreet, anonymous receptacle and/or the RA picking up surveys from patients who have agreed to complete the survey.

Environmental Services Workers
We will also recruit environmental services workers to complete a survey of their experiences with the intervention (e.g. to determine if the increased gloving impacts their workload). No PII or PHI will be included on these surveys. We will aim to obtain 1 survey per site.

We will discuss with supervisors prior to beginning any recruitment or survey procedures in order to determine the appropriate recruitment strategies for the local team and its workflow. Recruitment options include leaving an introductory flyer as well as the information sheet and survey itself in staff mailboxes. In addition, we may present the project and information sheet at regularly scheduled staff meetings where the supervisor is not present. We will provide time to answer questions as well as information for how to complete and return surveys. A discreet, anonymous receptacle will be placed for completed surveys. The survey completion should take no more than 5 minutes and thus should not interfere with work duties.

5.4 Informed Consent Procedures

Verbal Informed consent and signed HIPAA authorization will be obtained for stool sample collection from the participant.

We are requesting a waiver of informed consent for the intervention (use of universal gloving) and access to unit records (patient admission and discharge; gains and loss report, VA administrative records on unit admissions and discharges) to track compliance with study procedures and measure unit-level clinical outcomes and observe healthcare worker compliance with gloving procedures. We will work with each facility to determine how they normally track admission and discharge. We anticipate that most, if not all, sites will utilize the standard gain and loss report or admission, discharge, transfer (ADT) report available on VISTA; thus, we plan to use this report to

track admission and discharge. To track unit-level clinical outcomes, we will either ask units to provide this information to us using standard reporting parameters for each site, or we will access this information via CPRS, VISTA, and/or the VA administrative records (e.g., the CDW).

We are requesting a waiver of documentation of informed consent for patient specimen collection and healthcare worker/ patient interviews, focus groups, and surveys.

We are requesting waivers of consent because:

It is not possible to carry out the study using written individual informed consent. In this study, we are performing a cluster randomized trial. Cluster randomized trials such as these most often are granted waived consent due to the inability to carry out the research without waiver of consent. As is the case for many infection control or behavioral interventions, this intervention cannot be studied using a traditional patient-level randomization because: a) the intervention is difficult if not nearly impossible to randomize to individual patients in the unit and not other patients; b) there are group-level variables in patient units (patient-specific variables and healthcare worker-specific variables) that make the CRT the most valid study design; and c) bacteria transmission does not occur on the individual level but on a group level within a patient unit. An example of a group level variable is colonization pressure. Colonization pressure, defined as the percent of patients in a given patient unit with an infectious agent such as an antibiotic-resistant organism (MRSA), affects the probability of other patients acquiring the bacteria and developing an infection (primary and secondary outcomes of the study). Since wearing gloves and gowns to care for a particular patient (e.g., patient A) would protect that patient from acquiring an infection, but would also prevent other patients (e.g., patient B, patient C, patient D) in the same unit from acquiring bacteria from patient A. Another reason is that if the study was randomized to individual patients, it is likely that healthcare workers would be influenced by the intervention of wearing gloves and gowns and potentially being more adherent to other infection control practices. A patient-level randomized trial is inadequate to study interventions that reduce transmission of infections. CRT is the preferred design in many infectious disease and infection control studies when the investigator is worried about contamination of intervention to control patients.

(1) The research involves no more than minimal risk to the participant. Use of barrier contact precautions (gloving plus gowning) is currently the standard of care for patients with certain communicable diseases including antibiotic-resistant organisms (e.g., MRSA), so the expansion of universal gloving for care of all patients (intervention) does not present additional risk to healthcare workers or patients.

(2) The waiver will not adversely affect rights and welfare of participants. Use of barrier precautions are currently the standard of care for patients with certain communicable diseases including antibiotic-resistant organisms (e.g., MRSA). It is expected of hospital accrediting standards and professional standards that equal; high quality care will be provided to all patients regardless of diagnosis. Patients on units that are in the intervention arm of the study where barrier precautions are used for all patient contacts will receive the same high-quality care as a patient in which barrier precautions are either being used for other purposes or not being used at all. Patients on units that are in the control arm of the study will have no change in their care. Educational materials used in the study will remind healthcare workers in the participating sites that patient care practices must conform to local facility standards regardless of whether barrier precautions are implemented for patient care.

(3) Whenever appropriate, additional pertinent information will be provided to participants after participation. In the event that patients or healthcare workers request study information, each site will have readily available copies of the study information sheet which describes the purpose of the trial, the procedures involved in the trial, and who to contact for further information. No individual patient information will be provided.

5.4.1 Consent Procedures and Documentation

SPECIMEN COLLECTION (STOOL SAMPLE)

Research staff will provide study details and obtain verbal informed consent and signed HIPAA authorization from all subjects prior to swab/stool specimen and data collection. The study team will provide time to answer questions and clarify consent procedures. Interested subjects will be provided with an information sheet. A version of the information sheet detailing subject payment details will be used by local sites when VCS gift cards are available to them. An information sheet without reference to subject payments will be used whenever and wherever VCS gift cards are available for them to use. Where required by local policy, consent will be documented in the electronic medical record.

If the subject is unable to consent (incompetent, impaired decision-making capacity), the subject's legally authorized representative will be asked to provide verbal informed consent, and the subject's Personal Representative will be asked to provide written HIPAA authorization. No subjects who are unable to consent will be enrolled in the study unless verbal consent has been obtained from a legally authorized representative and written HIPAA authorization has been obtained from a Personal Representative. Local research personnel will follow all applicable laws and regulations. VHA Directive 1605.01 defines a personal representative as a person who, under applicable law, has authority to act on behalf of the individual to include privacy- related matters. The authority may include a power of attorney, legal guardianship of the individual, appointment as executor of the estate of a deceased individual, or a Federal, State, local or tribal law that establishes such authority (e.g., parent of a minor)." Competency of the subject will be determined by previous clinical assessment as documented in the medical record. If competency has not been documented in prior notes and we determine that the subject cannot consent, then discussion with the treating team regarding capacity to consent will ensue. In case of patients deemed incompetent or with impaired decision-making capacity, the legal representative would be contacted first and then a relative asked to consent for them. The legally authorized representative for the subject will be documented in the medical record (progress note or copy of legally recognized document). If the subject is later deemed to be competent, they will be re-consented as soon as possible. The plan for re-consenting subjects with fluctuating decision-making capacity or those who regain consent capacity is to review the study and consent materials and provide information on their previous participation and surrogate consent. Subject dissent would overrule surrogate consent. The subject or their representative (legally authorized representative or Personal Representative) will be first approached by the clinical care team to assess their interest in the trial. The following persons will be contacted in the following order of priority: a. health care agent (individual named as a power of attorney), b. legal guardian or c. next of kin in this order (spouse, child, parent, sibling, grandparent or grandchild) or d. close friend. The subject's medical record will be examined to determine whether a Personal Representative is documented. If a Personal Representative is not identified from the medical record, research personnel will ask the legally authorized representative whether the subject has a Personal Representative, and if so, who the Personal Representative is. The Personal Representative will be provided with the study information sheet and HIPAA authorization form. If the subject's legally authorized representative is also a subject's Personal Representative, they will be asked to provide both verbal consent and written HIPAA authorization. If no Personal Representative is identified, or the Personal Representative does not provide written HIPAA authorization, the subject will not be enrolled in the study unless they later gain capacity to

provide consent and HIPAA authorization for themselves, even if a separate legally authorized representative has provided verbal consent for the subject's participation.
Documentation by a qualified practitioner in the individual's medical record in a signed and dated progress note that the individual lacks capacity to make the decision to participate in the proposed study. NOTE: the qualified practitioner may be a member of the research team OR the individual has been ruled incompetent by a court of law. Disclosures required by the VA to be made to the subject by the investigator (the informed consent process) must be made to the subject's surrogate(s) (legally authorized representative and Personal Representative).

Discussion of the major aspects of the study with the surrogate(s) may take place either in person or over the phone. The surrogate(s) will be informed that their decision should be based upon that which the surrogate believes is, or would be, desired by the subject. If a subject's wishes cannot be determined, surrogate decisions should be based upon that which the surrogate believes to be in the subject's best interest. If feasible, the practitioner will explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances will the subject be forced or coerced to participate in a research study. Local site study personnel will be required to complete VA human subject protections training requirements prior to the start of the intervention phase of the study. In addition, local research staff will attend a virtual training session on how to obtain and document informed consent that will be conducted by the coordinating site (Madison VA) research staff.

INTERVENTION (UNIVERSAL GLOVING)

As this is a cluster randomized trial, all healthcare workers/patients within a unit will need to participate in the intervention/comparator (as assigned) and data collection in order to ensure meaningful data.

If the patient lacks decision-making capacity, the research staff will provide information to the caregiver(s)/Legally Authorized Representative (LAR). The information will be given to caregiver(s)/LAR when the subject is unconscious or clearly lacking capacity. When a caregiver/ LAR is not present in the unit, the study information sheet will be mailed. The mailing will be determined in the following order of priority: a. health care agent (individual named as a power of attorney), b. legal guardian or c. next of kin in this order (spouse, child, parent, sibling, grandparent or grandchild) or d. close friend. This information will be determined by unit staff using established procedures.

SURVEYS/INTERVIEWS

Patients and healthcare workers who are participating in surveys and/or interviews/focus groups will be informed that participation is voluntary and that they may withdraw from participation at any time, without prejudice. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. They will receive information sheets describing the purpose of the study, the procedures involved, and who to contact for further information.

5.5 Inclusion/Exclusion Criteria

VA inpatient units meeting the following criteria are eligible to participate in the study:

1. Ability to identify one of the following inpatient units as defined by CDC National Healthcare Safety Network[30] by reviewing prior 12-month patient mix data (at least 80% of patients meet patient type):

a. Adult Acute Medical Ward: Hospital area for the evaluation and treatment of patients with medical conditions or disorders.
b. Adult Acute Medical/Surgical Ward: Hospital area for the evaluation of patients with medical and/or surgical conditions.
c. Adult Acute Surgical Ward: Hospital area for evaluation and treatment of patients who have undergone a surgical procedure.

2. Ability to store collected admission and discharge stool samples from patients prior to batch mailing
3. Ability to collect and upload data (HAIs, mortality, length of stay, hand hygiene and barrier precaution compliance; glove use and glove plus gown use for CP) required for analysis
4. Local R&D Committee approval
5. Letter of support from the Hospital Director or Chief of Staff.

Intensive care units, long term care units, and mixed-acuity will be excluded. To participate

in interviews or focus groups, the individual must be:

1. 18 years of age or older
2. A patient admitted to the participating unit OR a healthcare worker who has regular work duties on the participating unit.

To participate in specimen and clinical data collection, the individual must be:

1. 18 years of age or older
2. A patient admitted to the participating unit.

5.6 Study Evaluations

Patient-level data

***C. difficile* Acquisition:** In both the intervention and control groups, we will obtain one swab or stool sample upon admission and one swab or stool sample upon discharge to test for the presence of *C. difficile.* This outcome data will be collected on an individual patient level, but de-identified prior to reporting. These test results will not be available to healthcare workers or patients at participating sites. Acquisition will be defined as a patient who has an initial test (via stool or perirectal swab) upon unit admission that is negative for *C. difficile* and a subsequent discharge test within the same unit that is positive for *C. difficile*.

Specimen collection

Research staff and/or clinical staff in both the intervention and control arms of the study will implement a standard protocol for obtaining stool or perirectal swab (depending on patient preference) samples for *C. difficile* test using standardized clinical methodology. Samples will be collected within 72 hours of patient admission and within 72 hours of anticipated discharge of all patients in participating units. *C. difficile* testing via stool sample will be obtained by using a toilet hat to collect stool and storing a sample of the stool in a sterile contained. *C. difficile* testing via perirectal swab sample will be obtained by swabbing the perianal area (a swab from the anal verge, without rectal insertion) in a circular motion, ideally until visible stool is noted on swab. The swab samples will be obtained in a private room or the privacy curtain will be drawn in semi-private rooms to protect patient privacy. The discharge sample may be collected within 72 hours prior to estimated discharge date or, if the patient is transferred to another unit within the participating facility, within 48 hours after discharge from the unit. Samples collected by research staff will be labeled with unique identifier. Samples collected by clinical staff or patient self-collected samples will be labeled in the unit by clinical staff with standard clinical pre-printed patient labels and collected on site by Research Assistants who will relabel specimens with unique identifiers, These collected samples will be refrigerated according to procedures defined by laboratory staff to ensure sample quality and then ship in batches to the Madison VA research laboratory.

The specimens will be shipped to a central microbiological research laboratory at the Wm. S.

Middleton Memorial VA Hospital in accordance with mandated U.S. regulations governing the shipment of Diagnostic Samples, Dangerous Goods and dry ice.[31] No patient identifiers will be received by the central laboratory. Microbiological work-up for *C. difficile* will follow Clinical and Laboratory Standards Institute procedures[32] and the use of a central microbiological laboratory to process these specimens will assure standardized microbiological (or molecular) methods and processing of the samples. Specimens will be tested for *C. difficile*, and *C. difficile* isolates will be tested for *in vitro* cytotoxin production using previously described procedures.[29] Shipments will be tracked using a shared database stored on the VA server.

Participants (patients and staff) will not be informed of the results of the cultures. The cultures are measuring *C. difficile* colonization, not infection. There is currently no treatment for *C. difficile* colonization, and many patients who are colonized with *C. difficile* are and remain asymptomatic. Thus, informing participants of a positive *C. difficile* culture could result in undue stress and unnecessary treatments to the patient given the possibility that the colonization will remain asymptomatic. In addition, it remains unknown whether altering behaviors of healthcare workers could impact the spread of *C. difficile* from asymptomatically colonized patients and thus there is no standard for how to care for a patient that is found to be asymptomatically colonized. So, it is not currently useful to inform healthcare workers simply of positive cultures. However, patients that develop symptoms of *C. difficile* infection, such as diarrhea, will be cultured and treated according to the standard of care in all intervention and control units. Specimen results will be stored on a database on the VA server, unless otherwise specified in a valid DUA.

Demographics: In both the intervention and control groups, for patients who consented to clinical data collection, we will obtain data on demographic characteristics (age, gender, race, weight, height) from VA administrative records (e.g., Corporate Data Warehouse [CDW] files). These data will be linked to patient specimen results (e.g., C. difficile colonization) and stored on a shared database on the VA server, unless otherwise specified in a valid DUA.

Past medical history/other hospitalization characteristics: In both the intervention and control groups, for patients who consented to clinical data collection, we will obtain data on the following characteristics from VA administrative records (e.g., using healthcare utilization dates, prescriptions, and diagnostic/treatment codes from CDW files): hospitalization characteristics (dates of admission to and discharge from the healthcare facility and participating unit, disposition [to acute care, home, home services, or skilled nursing facility/nursing home/long-term care facility], and source [i.e., where the patient was admitted from], treatments and healthcare utilization within the 90 days prior to admission and CDI occurring during their admission (antibiotic use, proton-pump inhibitor use, visits to healthcare facilities [emergency department, infusion services such as chemotherapy, hemodialysis]), CDI-related surgical intervention prior to admission, and comorbidities (acute renal failure, asthma, cancer, congestive heart failure, chronic obstructive pulmonary disease, cardiovascular disease, dementia, diabetes, inflammatory bowel disease, liver disease, paralysis, peripheral vascular disease, renal disease, rheumatic disease, peptic ulcer disease). These data will be linked to patient specimen results and stored on a shared database on the VA server, unless otherwise specified in a valid DUA.

***C. difficile* infection:** In both the intervention and control groups, we will determine the development of *C. difficile* infection during admission among patients who consented to clinical data collection by obtaining data from VA administrative records (e.g., using diagnostic codes from CDW files). These data will be linked to patient specimen results and stored on a shared database on the VA server, unless otherwise specified in a valid DUA.

Other Healthcare-Associated Infections: The incidence of other HAIs including: 1) catheter-associated bloodstream infection (CLABSI), 2) catheter-associated urinary tract infection (CAUTI), and 3) MRSA HAIs during admission among patients who consented to clinical data collection will be obtained from VA administrative records (e.g., using diagnostic codes from CDW files) for both the intervention and control groups. These data will be linked to patient specimen results and stored on a shared database on the VA server, unless otherwise

specified in a valid DUA.

Mortality: In both the intervention and control groups, mortality among patients who consented to clinical data collection will be obtained from VA administrative records (e.g., using date of death from the CDW files). These data will be linked to patient specimen results and stored on a shared database on the VA server, unless otherwise specified in a valid DUA.

Other clinical outcomes: In both the intervention and control groups, for patients who consented to clinical data collection, whether the patient had toxic megacolon or a colectomy will be obtained from VA administrative records (e.g. using diagnostic/treatment codes from CDW files). These data will be linked to patient specimen results and stored on a shared database on the VA server, unless otherwise specified in a valid DUA.

Unit-level data

***C. difficile* Infection**: The development of *C. difficile* infection will be determined by standard clinical care which is the presence of clinical symptoms and positive laboratory results. In both the intervention and control groups, hospital-onset (HO)-CDI will be collected monthly as a unit aggregate rate. In this case, hospital refers to the study unit. Research personnel will collect these data from site personnel (i.e., infection control) at participating sites which are collected as usual standard of care. The CDC definition of HO-CDI, used by the VA,[33] is defined as: 1) LabID Event specimen collected >3 days after admission to the facility (i.e., on or after day 4) and 2) CDI-positive laboratory assay: A positive laboratory test result for *C. difficile* toxin A and/or B, (includes molecular assays [PCR] and/or toxin assays) tested on an unformed stool specimen (must conform to the container) OR A toxin-producing *C. difficile* organism detected by culture or other laboratory means performed on an unformed stool sample (must conform to the container). The data will be uploaded to a shared database on the VA server, unless otherwise specified in a valid DUA.

Other Healthcare-Associated Infections: The incidence of other HAIs including: 1) catheter-associated bloodstream infection (CLABSI), 2) catheter-associated urinary tract infection (CAUTI), and 3) MRSA HAIs will be measured. HAI data will be collected monthly for both the intervention and control groups using standard CDC/VA definitions. Research staff will collect monthly aggregate data from site personnel (i.e., infection control) at participating sites which are collected as standard of care reporting to VA IPEC (inpatient evaluation center) and/or from VA administrative records. The rate will be calculated by the number of CAUTI or CLABSI per number of device days (i.e., Foley catheters or central lines) 1,000 and the number of MRSA infections per number of patient days x 1000. The data will be uploaded to a shared database on the VA server, unless otherwise specified in a valid DUA.

Mortality: In both the intervention and control groups, research staff will collect monthly aggregate 30-day mortality ratio data from site personnel (i.e., nurse manager) at participating sites which are collected as standard of care reporting to VA IPEC and/or from VA administrative records. The data will be uploaded to a shared database on the VA server, unless otherwise specified in a valid DUA.

Length of Stay: In both the intervention and control groups, research staff will collect monthly aggregate length of stay (i.e., the number of days spent in the participating unit based on unit admission and unit discharge) data from site personnel (i.e., nurse manager) at participating sites which are collected as standard of care reporting to VA IPEC and/or from VA administrative records. The data will be uploaded to a shared database on the VA server, unless otherwise specified in a valid DUA.

Intervention Fidelity Data:

Hand Hygiene Compliance: In both the intervention and control groups, hand hygiene compliance will be measured on a random sample of healthcare workers caring for patients. Research staff will perform monthly observations that will be recorded on a standard observation tool; participating site research staff will be trained by study coordinating site research staff. WHO manual for observers recommends observing a minimum of 200 hand

hygiene opportunities during each measurement period in each unit.[34] We estimate the number of hand hygiene opportunities as 10 opportunities per patient per hour.[35] The average unit will have 20 patients, therefore each month research personnel will observe hand hygiene opportunities for one hour to generate the minimum observation of 200 hand hygiene opportunities per unit per month. The data will be uploaded to a shared database on the VA server, unless otherwise specified in a valid DUA.

Contact Precaution Compliance: In both the intervention and control groups, barrier precaution compliance (i.e., healthcare worker glove plus gown use during care of patients in CP isolation) will be measured on a random sample healthcare worker contacts during care of patients in CP isolation. Research staff will perform monthly observations that will be recorded on a standard observation tool; participating site research staff will be trained by study coordinating site research staff. We estimate the average number of patient contacts by healthcare workers using barrier precautions to be 60 contacts per day.[36] The average unit will have 2-6 patients (10-30%) in CP isolation; each month research personnel will observe for one hour to generate 10% sample of 12 healthcare worker contacts using minimum estimate of patients in isolation. The data will be uploaded to a shared database on the VA server, unless otherwise specified in a valid DUA.

Universal Gloving Compliance: In the intervention group, universal gloving compliance will be measured on a random sample of healthcare workers caring for patients. Research staff will perform monthly observations that will be recorded on a standard observation tool; participating site research staff will be trained by study coordinating site research staff. We will use hand hygiene opportunity estimates[34,35] as surrogate for patient contact opportunities requiring gloving. The average unit will have 20 patients, therefore each month research personnel will observe gloving opportunities for one hour to generate the minimum observation of 200 patient contact opportunities per unit per month in the intervention unit only. The data will be uploaded to a shared database on the VA server, unless otherwise specified in a valid DUA.

Isolation Days of Care: Contact precautions can be used for reasons other than CDI such as antibiotic resistant organisms (e.g., MRSA). If a large proportion of barrier precautions are being used in the control group for these types of patients, it could confound the study endpoints. To account for this, we will collect and estimate isolation days of care. In both the intervention and control groups, research staff will collect monthly aggregate data on isolation patients from site personnel (i.e., infection control) at participating sites which are collected as standard of care reporting. We will estimate the isolation days of care by multiplying the number of patients on CP isolation by the average length of stay for the participating unit. The data will be uploaded to a shared database on the VA server, unless otherwise specified in a valid DUA.

Interviews

Healthcare Worker Experience: The study team plans to explore healthcare workers experience using barrier precautions for all patient contacts vs standard of care using qualitative methodology. Questions will address five main areas: 1) understanding of the rationale for universal gloving to reduce and prevent CDI; 2) barriers and facilitators to implementing universal gloving; 3) perceptions around how the intervention influenced healthcare workers' care of and interactions with patients and other aspects of their jobs; 4) how the healthcare workers integrated universal glove donning into their regular workflow; and 5) any other issues or areas of concern around the intervention.

Qualitative focus groups of healthcare workers (physicians, registered nurses, and health technicians who have regular and direct patient contact) will be conducted at each participating unit assigned to the intervention throughout the study period. Each focus group will include up to 12 individuals. They will last about 45 minutes with moderators following a structured interview guide, adding additional probing questions to facilitate discussion. One

moderator (either the trained LSI or local RA, or a member of the Madison-based study team) will facilitate each group discussion while another trained professional will record field notes during the group to track the flow of conversation and document nonverbal behaviors. Interviews may take place either in-person, led by trained local research staff, or virtually (telephone or webinar), led by central research staff. The central research team has previous experience with virtual focus groups. Group discussions will be audio recorded (unless participants decline to be recorded, in which case field notes will be taken instead), and tapes transcribed. Qualitative analysis will be used to identify codes, categories, and themes. Participants will be asked to complete a brief, voluntary, anonymous demographics survey that the local RA will give to the participant to complete before or after the interview (e.g., along with the interview information sheet or form 10-2303). The RA will collect the surveys from the participants once the surveys are complete. Demographic characteristics will not be linked to individual participants, and only aggregate demographic information will be obtained during analysis and shared during manuscript preparation.

Patient Experience: The study team plans to explore patient experience with healthcare workers use of universal gloving for all patient contacts vs standard of care using qualitative methodology. Questions will address three main areas: 1) patients' perceptions of the staff's practice of universal glove donning, including positive and negative perceptions; 2) any changes in care or interactions that patients perceive were related to universal glove donning; and 3) patients' understanding of the potential benefits of the intervention.

Individual interviews with 10 patients will be conducted at each participating unit assigned to the intervention during the intervention period. Patient interviews will be conducted either by trained Madison VA staff via Microsoft Teams and/or telephone or by the trained local RA in a private setting. For patients in private rooms, the door will be closed. For patients in semi-private rooms, they will be asked if drawing the privacy curtain is adequate to meet their privacy needs, and for those granting permission the privacy curtain will be drawn. Each session will be 15-30 minutes with moderators following an interview guide, adding additional probing questions to facilitate discussion. Interviews will be audio recorded (unless participants decline to be recorded, in which case field notes will be taken instead), and tapes transcribed. Qualitative analysis will be used to identify codes, categories, and themes. Participants will be asked to complete a brief, voluntary, anonymous demographics survey before or after the interview. The RA will collect the surveys from the participants once the surveys are complete. Demographic characteristics will not be linked to individual participants, and only aggregate demographic information will be obtained during analysis and shared during manuscript preparation.

Cost Analysis

Cost: We will conduct a cost-identification analysis to assess cost of providing the intervention. To estimate costs of the intervention of universal gloving, we will obtain cost data direct observation, estimates and consultation with the study facility. To estimate the cost of the intervention, we will calculate the cost of implementing universal gloving and the usual care barrier approach. The cost of glove supply costs will be obtained from the research team and facility. We will also estimate the supply costs associated with the usual care gloving. We will estimate supply costs by collecting glove use data. We will obtain a monthly list of supplies (i.e., gloves) issued to each participating unit in both groups from their distribution departments. To estimate the return on investment of using universal gloving, we will also estimate the potential savings that result from a decrease in C. difficile infections and colonization. We will compare estimated HAI costs obtained from the literature before and after the intervention. We will estimate HAI costs based on published reports.[37]

Survey

Provider-Patient Contact: Surveys of patients will be used to assess perception of provider-patient contact and patient satisfaction with this contact. Survey results will be compared between the control or intervention group to determine if the intervention may be impacting patient satisfaction with their care. Surveys will be conducted during the patient's stay in the unit and may be returned to any member of their care team or left at the nurse's station upon

discharge. The local research assistant will collect all surveys for analysis.

Environmental Services Experience: Healthcare workers in environmental services will be surveyed to determine if the additional use of gloves in the unit may be impacting workflow/workload (for example, by increasing the frequency of trash disposal required on the unit). Surveys may be returned to a secure location (e.g. a drop box) and the local research assistant will collect all surveys from this location for analysis.

5.7 Safety Monitoring

This study poses minimal risk to participants. To ensure the safety of healthcare workers and patients in participating units we will use regularly collected VA quality and safety metrics. Metrics that are regularly collected by VA that will be monitored here may include information on falls, hand hygiene compliance, contact precaution/personal protective equipment use compliance, and patient satisfaction (e.g. SHEP scores). Hand hygiene and contact precaution/ personal protective equipment use compliance data from observations conducted as part of our research will be complemented with standard data collected by infection control to monitor for changes in adherence to infection control practices.

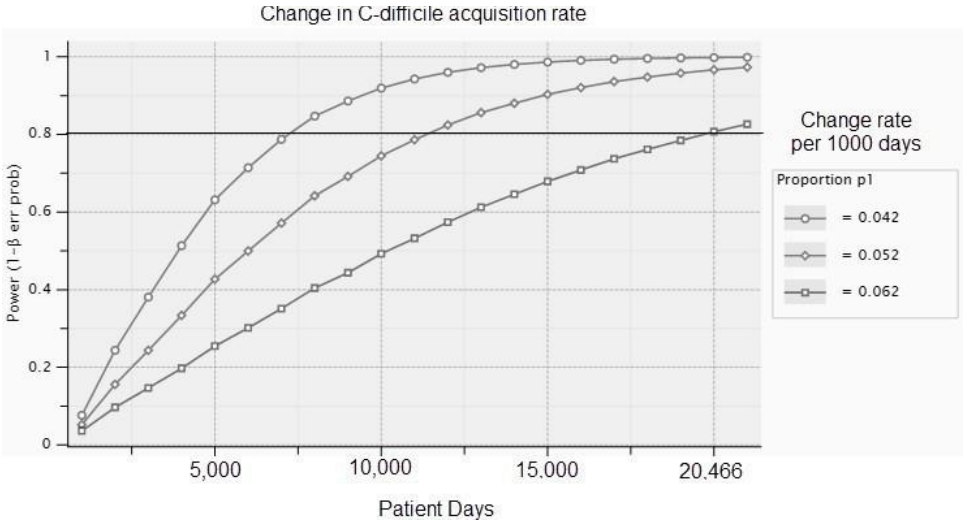
We will work with the LSI and RA at each site to develop a site-specific plan for transmitting these metrics, i.e., whether the Madison study team will download these aggregate data from the Corporate Data Warehouse or whether the local study team will upload these data to the Madison study team using VA-secure methods behind the VA firewall. The Provider-Patient Contact survey will also be used to monitor patient responses to the intervention and ensure that the universal gloving practices are not causing a negative impact on patient experience.

Given the minimal risks posed by this study, we do not anticipate that any safety conditions will trigger suspension of the study. If we find significant negative impacts, we will notify the site LSI to communicate issues with unit leadership and develop a response plan. For example, if hand hygiene compliance data show a significant negative impact upon introducing the intervention, we will work with the LSI and unit leadership to educate unit staff on the importance and workflow of hand hygiene in combination with gloving practices.

5.8 Data Analysis

5.7.1 Sample Size Determination

Initial power calculation determined that 10 patient units are necessary to detect a 36% relative reduction (6.2%) in acquisition of *C. difficile* in the intervention vs. no reduction in the control group based on a presumed rate of 9.7 acquisitions per 1,000 patient days; recent literature report an average C difficile acquisition rate of 9.7 per 1,000 patient-days [38] and expected reduction of C. difficile acquisition of 36%. [39] Each arm of the study will require 9,879 patient days of care. On average, it is estimated that each patient unit will have a 25-bed capacity with an estimated 100 admissions per month and 5-day length of stay. We will plan to enroll 10 units, 5 for each arm. These power calculations will be revised based on actual baseline-period data. The statistical power calculation was conducted using G*Power.[40] We have incorporated an intracluster coefficient of 0.40 for this study.



5.7.2 Statistical Analyses

Analyses will be conducted by the lead biostatistician in collaboration with resources from the Coordinating Site Committee (see above).

Demographics: All unit level and patient level categorical demographic information will be summarized on table 1 as proportions and frequencies. We will output all continuous data using mean plus standard deviation or median plus range.

C. difficile acquisition Rate: Acquisition rates will be obtained from each unit and comparisons for differences between control and intervention units using a chi-squared test. We will conduct a crude and adjusted linear and logistic regression model to determine predictors of C.diff acquisition in patients. Additionally, we will model the incidence of C.diff acquisition for intervention and control patients using Poison regression models and to determine the gloving impact.

CDI Infection Rate: For unit-level data, we will compare changes in CDI infection rates between the intervention and control units using the chi-squares test or Fisher's exact test with post-hoc pairwise comparisons. For patient-level data, infection rates will be modelled for specific time periods (during 3, 6, 9 and 12 months; or every 3 months of the study period [up to 24 months]) using incidence split modeling to determine the point of highest infection within each unit, with appropriate covariate adjustment. We will use the Royston's trend test to conduct a time-trend analysis for CDI infection rates for specific time periods (during 3, 6, 9 and 12 months; or every 3 months of the study period).

Other HAI Rates: All other rates between intervention and control units will be compared using chi-squared test or Fisher's exact test, with post-hoc pairwise comparisons. All incidence and risk analysis will be conducted using Poisson regression models with covariate adjustment. For specific time periods (during 3, 6, 9 and 12 months; or every 3 months of the study period), we will use incidence split modeling to determine the point of highest infection within each unit, with appropriate covariate adjustment. We will use the Royston's trend test to conduct a time-trend analysis on the monthly HAI (CAUTI and CLABSI).

Length of Stay: A weighted two-sample and paired t-test will be used to compare mean length of stay between the intervention and control units.

30-Day Mortality: Using patient level data, we will conduct a 30-day survival analysis to determine the hazard of mortality for control and intervention units using a cox proportional hazards model with Kaplan Meier curves. Within each unit, a risk analysis will be conducted to

determine the predictors of 30-day mortality. Additionally, we will examine survival percentages at specific periods of the intervention period (i.e. 3, 6, 9 and 12 months; or every 3 months of the intervention period) using life tables and log-rank tests to determine at which points mortality was highest for each unit.

Other clinical outcomes: Rates of toxic megacolon and colectomy will be compared between intervention and control units using chi-squared test or Fisher's exact test, with post-hoc pairwise comparisons. All incidence and risk analysis will be conducted using Poisson regression models with covariate adjustment. For specific time periods (during 3, 6, 9 and 12 months), we will use incidence split model to determine the point of highest infection within each unit, with appropriate covariate adjustment. We will use the Royston's trend test to conduct a time-trend analysis on the monthly outcomes.

Intervention Fidelity: We will calculate the compliance rates for both the intervention and control units and compare them using a chi-squared test. We will conduct a univariate logistical regression model to determine the odds of compliance with respect to additional unit characteristics such as number of beds and location. Monthly compliance will be modeled using a time series graphing technique with trend analysis estimates.

Isolation Days of Care: Monthly aggregate data of isolation patients will be collected from infection control at participating sites which are collected as standard of care and we will estimate the days of care by multiplying this number by the average length of stay for the participating unit. We will make comparisons between the intervention and control groups using the analysis of variance (ANOVA).

Healthcare Worker Experience: After verification of transcription accuracy, team members will use VA-approved software to facilitate data organization, coding, and retrieval. Qualitative content analysis will inductively generate codes and categories rather than using an a priori coding scheme or researcher-generated coding scheme.[41] Line by line coding will be conducted to identify codes or statements of meaning (level I coding). Codes that emerge will be grouped into larger categories (level II, coding for themes).

*Patient Experience***:** After verification of transcription accuracy, team members will use VA-approved software to facilitate data organization, coding, and retrieval. Qualitative content analysis will inductively generate codes and categories rather than using an a priori coding scheme or researcher-generated coding scheme.[41,42] Line by line coding will be conducted to identify codes or statements of meaning (level I coding). Codes that emerge will be grouped into larger categories (level II, coding for themes).

Cost: Descriptive statistics will be used to describe nursing time frequencies and percentages. Paired t-tests will be used to compare average provider time for donning and doffing between the intervention and control units. We will use Royston's trend test to examine the monthly costs of supplies over time.

Provider-Patient Contact Surveys: We will compare the differences in reported contact between the intervention and control units.

Missing data: We will resolve all missing data using a case-wise analysis technique or multiple imputation solution.

5.9 Withdrawal of Subjects

Sites that are unable to meet performance measures such as a) obtaining a high rate of stool samples from admitted patients and b) collecting primary and secondary endpoint data may be withdrawn from the study at the PI's discretion.

A unit may withdraw voluntarily from the study at any point. Attempts will be made to collect all data for the duration of their participation in the intervention phase regardless if they were unit randomized to the intervention or standard care group including 30-day mortality occurring after participant withdraw or termination.

Since there is a short data collection period of only 15 months, the study team does not plan to replace any units who withdraw or terminate.

6.1 Reporting

6.2 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or disability, or a manifestation of a congenital anomaly/birth defect. An AE is also considered serious when medical, surgical, behavioral, social, or other intervention is required to prevent an above outcome.

All AEs will be assessed by the PI using the following guidelines:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study participation makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study participation, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

All SAEs that are unexpected and related to the study will be reported by the study team to the

IRB in writing within 5 business days of the team becoming aware of the SAE. A specific reportable event form will contain a detailed description of the symptoms observed and the concomitant treatment administered. Furthermore, the report must comment on a possible causative relationship between the AE and the research procedures. Each SAE must be followed until it is resolved or can be explained satisfactorily.

Any death that is unanticipated and potentially related to the research will be immediately reported to the IRB by the study team.

6.3 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Serious Problems that are both unanticipated and related to the research will be reported in writing within 5 days of becoming aware of the occurrence.

6.4 Protocol Deviations

Protocol deviations from the VA Central IRB are considered an act of noncompliance. Protocol deviations must be reported within 5 days of being made aware of the occurrence if they are likely to substantially adversely affect any of the following:

- The rights, safety, or welfare of the research participant
- The participant's willingness to continue participation, or
- The integrity of the research data, including VA information security requirements

7.1 Privacy and Confidentiality

Participant confidentiality and privacy is held in the highest regard by all study team members. This confidentiality is extended to cover all clinical information and testing of biological samples. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval. No individual results/PHI will be disclosed; only coded or aggregate data will be analyzed and only aggregate group-level data will be reported. Published study results will not identify individual units or subjects.

All study staff are up-to-date on VA privacy and information security trainings, specifically in ethical conduct, confidentiality protection, review of medical records, mandated reporting, and other topics of human research protections (including the Health Information Portability and Accountability Act (HIPAA). New staff will not be permitted to access any study data until they have completed all relevant trainings. Privacy will be maintained by conducting discussions and assessments in private rooms.

Removal of access to research study data will be accomplished for study personnel when they are no longer part of the research team. The Information Security Officer, Privacy Officer, and Associate Chief of Staff for Research will be notified immediately of any actual or suspected data breach.

VA REDCap may be used for entering patient-level clinical data, unit-level clinical and observational data, patient surveys, and Environmental Service worker surveys. VA REDcap is a 21 CFR Part 11-compliant data capture system provided by the VA Information Resource Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. No individual identifiers will be entered into VA REDCap, and only authorized staff will have access to the study REDCap project(s). No other web applications and no mobile devices will be used in this study. Unless otherwise specified as part of a valid DUA, no data will be stored on computer hard drives and sensitive data will not be removed from the VA-protected environment at any time; thus, no data will be stored at an alternative (non-VA) site. Original electronic VA data will be backed up regularly and stored behind the VA firewall.

At the end of the study, all VA research data and information will be retained in accordance with the applicable VA Records Control Schedule (NARA RCS 10-1). Prior to any destruction of research records, the PI will contact the Records Management Officer for current policy. Records will be destroyed, when allowed by shredding (paper records) and/or in a manner from which they cannot be retrieved (electronic/digital records).

Additional security measures for specific study procedures are described below.

Observations. We will follow usual infection control practices for observations of intervention fidelity/barrier precaution compliance using an audit tool. No identifiable information regarding the healthcare worker or the patient will be recorded, and only aggregate data will be shared with each site.

Interviews/Focus Groups. Interviews of patients will be administered in patient rooms at the VA. Interviews/focus groups of healthcare workers will be conducted in private conference rooms and/or over the phone, with both parties in a private setting. Patient interviewers will undergo training around human subject's protection, the interview guide, and engaging patients in a sensitive, respectful manner that promotes patients' engagement in the interview.

Furthermore, interviewers will participate in role playing to prepare for interviews and an expert qualitative researcher will observe their first actual interviews. The importance of privacy and discretion will be emphasized to participants during the sessions.

Researchers will notify participants that they are recording. Participants will be asked not to identify their names or other identifying information during interviews. Audio files will only be labeled with a unique number will be generated for each patient and healthcare worker and linked to a different unique letter representing the hospital unit. This identifier will be for purposes of this study only and will not include individually identifiable private information. Data will be stored in a password-protected database and accessed only by approved research personnel via password-protected computers in locked offices. Only aggregate data will be analyzed and presented; patient-, worker-, or facility-specific data will not be identified.

The Centralized Transcription Services Program (CTSP), based at the Salt Lake City VA, will transcribe interviews/focus groups. The CTSP will remove all identifying information, such as name or other personal identifiers, from the transcript prior to analysis. An investigator will upload the tapes to a transcriptionist at CTSP. Multiple levels of security will ensure the integrity and confidentiality of all data stored on the system. The computer system operates entirely within the VA network, which is protected by firewalls maintained by the VA Central Office. Authorized study team members are assigned an active, individually unique user identification code and individually unique password. The accounts and passwords comply with existing VA policies and procedures for computer access. User identification codes limit access to specific directories and files. The computer system is accessed via computers assigned to authorized investigators. These computers are secured through use of individually unique user identification codes and passwords.

All audio files, field notes files, and transcript files will be stored and transferred within the VA network which is protected by firewalls maintained by the VA Central Office. Only approved study team members and transcribers will have access to the audio files. The recordings will be appropriately destroyed at the end of the study, and the coded transcripts will be maintained according to VA policy.

Clinical Data Collection. Only the local site and minimum Madison staff necessary for replacing individual identifiers in patient-level data with the study ID number will have access to patient information, for example, the code key connecting patient name with the study ID number. All remaining data transferred to the Madison VA, including stool samples, will be coded. Each participant will be assigned a unique study ID, and all research data will be coded with ID numbers only, not names or social security numbers. The document ("key") linking names and ID numbers will be stored in a separate password-protected document on a password-protected server, to which only essential study staff (LSI, RA, and Madison staff responsible for coding patient-level data) will have access.

Unless otherwise specified as part of a valid DUA, research data for purposes of statistical analysis and scientific reporting will be stored at the Madison VA hospital. All identifiable data will be stored in locked drawers/file cabinets in the Madison VA Research Office or on a secure, password-protected server space in a research folder accessible only to trained and approved study personnel. All research data will be de- identified (i.e., all personally identifying information will be removed) prior to transfer to external parties of a valid DUA, data analysis and manuscript preparation; all identifiers will be replaced by study ID. All documents and databases will be stored on a secure server behind the VA firewall, and housed within a password-protected folder only accessible to approved research team members (unless otherwise specified by a valid DUA).

We will work with sites to determine their preferred method of data collection/transfer; i.e., whether the Madison study team will download these aggregate data from the Corporate Data Warehouse or whether the local study team will upload these data to the Madison study team using VA-secure methods behind the VA firewall. Regardless of collection/transfer method, all data will be kept behind the VA firewall at all times unless otherwise specified in a valid DUA. No study data will be shared in a non- secure manner. All data will be shared in accordance with VA regulations and via methods approved by the required officials (e.g., as outlined in a Enterprise Research Data Security Plan signed by the CIRB Information Systems Security Officer). All culture samples will be sent to the coordinating site at the central microbiology research laboratory at the Wm. S. Middleton Memorial VA Hospital. No patient identifiers will be received by the central laboratory, and no individual results will be shared back with facilities.

7.2 Specimen Banking

Stool specimens collected during this study will not be banked.

8.0 Communication Plan

Each participating site will have an assigned site PI (Local Site Investigator, LSI) and a Research Assistant (RA, 20% effort). These individuals will be responsible for monitoring local oversight and approvals, notifying appropriate stakeholders (including the facility director) about the study and its progress, and ensuring compliance to the study protocol. The LSI and RA will maintain a local site study binder with up-to-date documents and relevant approvals. The PI and Program Manager will ask the LSI and RA to confirm that these approvals are in place before beginning study procedures at the site.

The LSIs and RAs will meet regularly with the Madison-based study team, including the PI and Program Manager. Regular agenda items for these meetings will include discussing any Serious Adverse Events, Unanticipated Problems, interim results, or other factors that may impact conduct of the study. Any changes to the protocol will be discussed during this meeting to ensure understanding and compliance with updated procedures.

The Program Manager will be responsible for maintaining and updating a shared SharePoint site that houses up-to-date study documents, such as the protocol. Approved site personnel will have access to this SharePoint so that they can access the most current versions as needed. The Program Manager will notify site personnel by email if new documents have been added or if versions have been updated on SharePoint. The LSI and RA will be responsible for updating local binders (digital and/or physical) as required and reporting any changes or issues to the PI and Program Manager.

Site participation will end at the close of the up-to-24-month intervention period and

once all HCW and patient interviews have taken place at the site. At that point, we will notify the LSI and the facility director in writing that the study procedures at this site have ended.

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