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CHILDREN'S ONCOLOGY GROUP

ACCL1034

Impact of Cleansing with Chlorhexidine Gluconate (CHG) on Reducing Central Line Associated Bloodstream Infection (CLABSI) and Acquisition of Multi-drug Resistant Organisms (MDRO) in Children with Cancer or Those Receiving Allogeneic Hematopoietic Cell Transplantation (HCT)

A Groupwide Study (Limited to US and Canada sites)

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AGENT NSC# AND IND#
Chlorhexidine gluconate (CHG)

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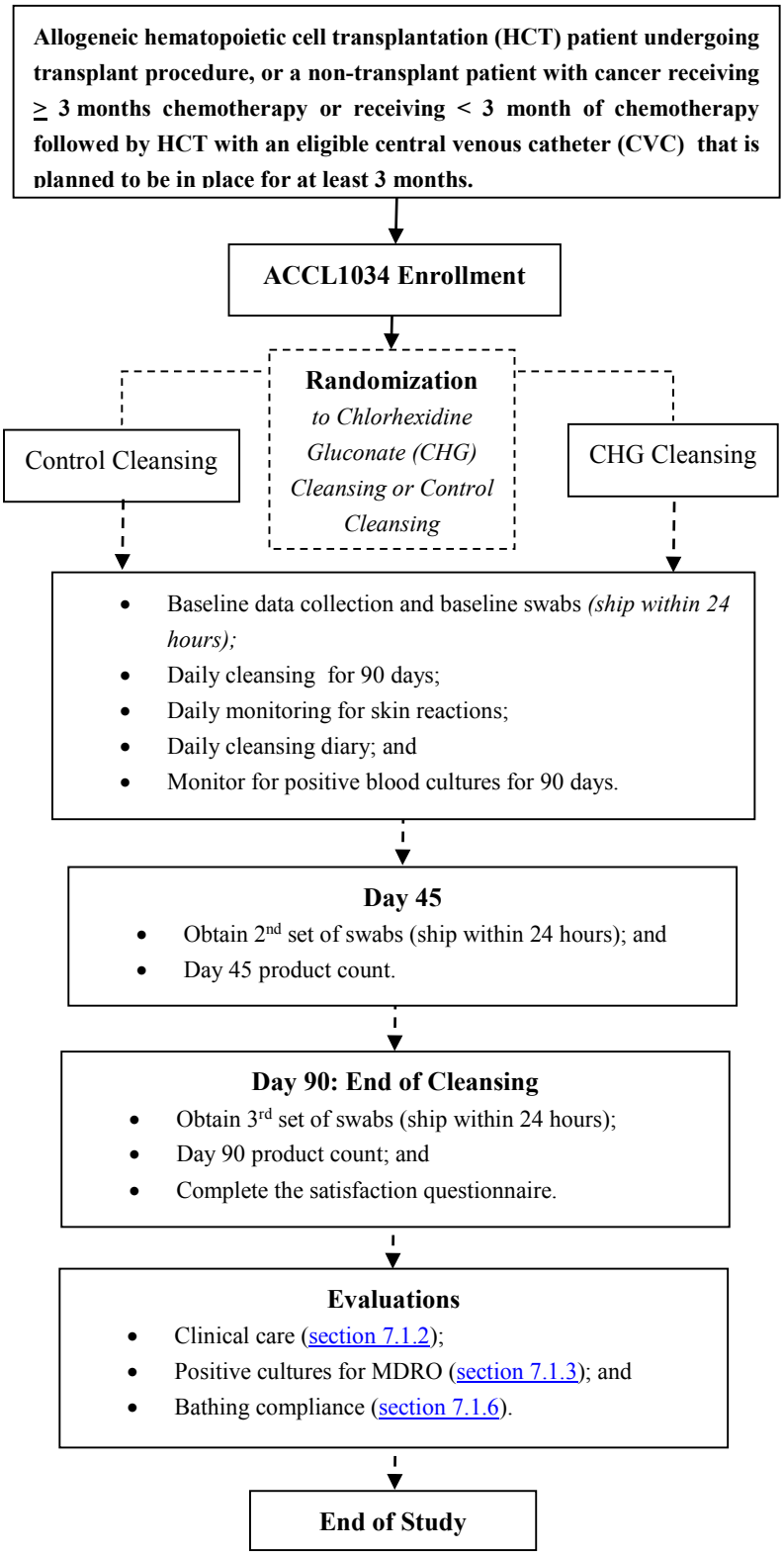
ABSTRACT

Reducing the frequency of healthcare-associated infections (HAI) is a national healthcare priority. Central line associated bloodstream infections (CLABSI) and infections due to multidrug resistant organisms (MDRO) are two of the most prevalent and serious HAI experienced by patients with cancer. Chlorhexidine gluconate (CHG) is more effective than other antiseptics in lowering cutaneous microbial levels and daily bathing or cleansing the skin with CHG has been shown to reduce CLABSI and MDRO acquisition in critically ill adults. This study is a randomized, double-blinded, controlled trial to evaluate the efficacy of CHG cleansing in preventing CLABSI and MDRO acquisition in children with cancer or those receiving allogeneic hematopoietic cell transplantation (HCT). Eligible patients include those between 2 months and 21 years of age with an eligible central venous catheter which is planned to be in place for at least 3 month; the reason for the catheter can be a planned allogeneic transplant, or an oncology diagnosis requiring chemotherapy for $\geq$ 3 months or an oncology diagnosis requiring < 3 months of chemotherapy followed by transplantation (allogeneic or stem cell rescue) during the study period. A total of 450 subjects will be randomized to CHG or control cleansing up to 10 days before to 7 days after starting a cycle of chemotherapy or conditioning. Subjects will receive study cleansing daily, beginning after randomization and continuing for 90 days. Skin swabs will be collected in order to track CHG and antimicrobial resistance in skin microorganisms. Bacterial isolates from any positive blood cultures will also be collected. The primary outcome will be the occurrence of CLABSI. Secondary outcomes include any bloodstream infection, acquisition of MDRO, and CHG and antimicrobial resistance in skin and bloodstream microorganisms.

EXPERIMENTAL DESIGN SCHEMA



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary

To determine whether chlorhexidine gluconate (CHG) cleansing decreases central line associated bloodstream infection (CLABSI) in children with cancer or those receiving an allogeneic hematopoietic cell transplantation (HCT).

1.2 Secondary

1.2.1 To determine whether CHG cleansing decreases acquisition of multi-drug resistant organisms [MDRO: vancomycin resistant enterococci (VRE), methicillin resistant *Staphylococcus aureus* (MRSA), etc.] in children with cancer or those receiving allogeneic HCT.

1.2.2 To determine whether CHG cleansing in children with cancer or those receiving allogeneic HCT is associated with cutaneous bacterial isolates with reduced susceptibility to CHG.

1.2.3 To determine whether CHG cleansing decreases positive blood cultures in children with cancer or those receiving allogeneic HCT.

2.0 BACKGROUND

2.1 Overview and Significance of the Problem and Rationale for Selected Outcomes

Reducing the frequency of healthcare-associated infections is a national healthcare priority.[1] Central line associated bloodstream infections (CLABSI) and infections due to epidemiologically important multidrug resistant organisms (MDRO) are two of the most prevalent and serious healthcare associated infections experienced by patients with cancer.

CLABSI is the single most common healthcare-associated infection in patients with cancer and carries the highest attributable morbidity and mortality.[2,3] Up to 25-50% of HCT recipients will experience a bloodstream infection in the first year after transplantation.[2,3] Approximately 50% of these occur in the pre-engraftment period, where attributable mortality is estimated to be 12.5%.[2] As a result, patients with a pre-engraftment bloodstream infection have a one-year post-transplant survival rate of 46.8% versus 64.1% in those without.[2] High bloodstream infection rates are not restricted to patients receiving transplantation. In a phase 3 pediatric acute myeloid leukemia trial (Children's Cancer Group 2891), 39-58% of patients experienced a bacterial infection during induction chemotherapy and fatal infections occurred in 1-5%, depending on the intensity of the chemotherapy.

Evidence-based best practices aimed at reducing CLABSI are well documented in the literature, including hand hygiene, maximal barrier precautions, CHG skin antisepsis, optimal catheter site selection, and daily review of line necessity.[4] Unfortunately, despite the evidence and application of these interventions, rates of hospital-associated bloodstream infection remain unacceptably high. Additional measures are required to further reduce CLABSI, especially in high-risk populations.

Epidemiologically important MDRO include methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococcus* (VRE), extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae,* and multi-drug resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* Immunocompromised patients are especially vulnerable to MDRO infections and high rates of morbidity and mortality have been documented for a number of the organisms including multi-drug resistant *Pseudomonas*,[5] ESBL-producing *Enterobacteriaceae*,[6] and VRE.[7,8] VRE is the most common and best-studied MDRO in immunocompromised populations. VRE outbreaks and high-level endemic infection are well-documented in adult and pediatric oncology settings.[9,10] In a study of adult allogeneic HCT recipients, VRE colonization was detected in 40% of patients; 75% of these were identified on the first surveillance stool culture and the remaining 25% were identified on subsequent cultures.[8] A VRE bloodstream infection developed in 34% of colonized patients by day 35 post-transplantation, compared to 1.8% without VRE colonization ($p<0.01$). Despite appropriate treatment, a VRE bloodstream infection was associated with microbiological failure (28% of cases) and high mortality. Mortality was judged to be directly attributable to the VRE in 2 of the 14 patients, and in an additional 3 patients, VRE was judged to contribute to mortality. Another study of allogeneic transplant recipients found that VRE bloodstream infection developed in 12 (4.3%) of 281 patients with unknown colonization status. All 12 patients with VRE bloodstream infection died within 73 days despite appropriate therapy.

Guidelines for control of MDRO have been published.[11,12] However, despite implementation of such practices, most centers continue to have patients that acquire these organisms. Additional effective interventions are needed to reduce the frequency of these infections.

2.2 Rationale for Selection of CHG Cleansing

CHG is an antiseptic bactericidal to Gram-positive and Gram-negative bacteria, including MDROs. The mechanism of action involves bacterial membrane disruption; the onset of action is relatively rapid and the effect is persistent. CHG is commercially available in oral rinses, skin and hand cleansers, surgical scrubs, and skin preps. CHG 2% impregnated cloths have been shown to significantly reduce bacterial levels on the skin for at least 6 hours after application.[13] Longer post-application durations have not been studied. However, 2% CHG in a formulation with 70% isopropyl alcohol (ChloraPrep, Cardinal Health, Inc.) has been shown to have activity for up to 48 hours on the skin[14] and CHG is the component presumed to provide the persistent effect. CHG requires several applications to attain maximum antimicrobial benefit and repeated applications are often recommended.[15] CHG has repeatedly been shown to be more effective than other antiseptics (i.e. povidone-iodine and triclocarban) in lowering cutaneous microbial levels, including when used for pre-operative bathing or cleansing.[16-18]

CHG has also been studied as site preparation for placement of central venous catheters (CVC) and was shown to reduce CLABSI incidence, when compared to ethanol or povidone-iodine.[19]

A 2% CHG-impregnated cloth product (Sage Products, Inc., Cary Illinois) was licensed by the FDA in 2005 for pre-operative skin preparation. This same product has been studied as

a cleansing or waterless bathing product in the adult critical care setting.[20-22] A single-center, 1-arm cross-over study comparing daily cleansing with CHG-impregnated cloths to cleansing with non-medicated cloths or bathing with soap and water, demonstrated that CHG cleansing resulted in decreased VRE levels on patients' skin, healthcare workers' hands, and environmental surfaces.[22] In addition, with CHG cleansing, the incidence of new acquisition of VRE rectal colonization decreased from 26 colonizations per 1000 patient-days to 9 per 1000 patient days. A subsequent 2-arm, cross-over study comparing daily CHG cleansing to daily bathing with soap and water bathing, demonstrated that patients receiving CHG were significantly less likely to acquire a CLABSI.[20] More recently, a multicenter study of critically ill adults compared a 6-month period of routine bathing with soap and water with a subsequent 6-month period bathing with CHG solution, and evaluated for MDRO acquisition (new colonization or infection).[21] CHG bathing was associated with a 32% decrease in MRSA acquisition and a 50% decrease in VRE acquisition. In addition, patients colonized with VRE had a 70% reduced risk of developing VRE bacteremia.[21] Another study in critically ill adults demonstrated a significant decrease in CLABSI and blood culture contamination after implementation of cleansing with CHG.[23] Currently, there are no published studies of the effect of CHG cleansing on occurrence of healthcare associated infections in children or in an oncology population. However, there is a multicenter study of critically ill pediatric patients that has demonstrated that CHG cleansing results in a reduced risk of bacteremia.[24] Results from this study have been submitted for publication.

CHG has a very favorable safety profile. One of the common concerns about CHG use is skin reaction. In a clinical study of CHG cleansing in critically ill adults, there were no serious adverse reactions related to CHG and a higher proportion of subjects had deterioration in skin condition during soap and water bathing than during CHG cleansing (18% vs. 3%; $p = 0.02$).[22] There are currently no publications describing safety or tolerability of CHG bathing for longer durations (e.g. > 1 week) in the proposed pediatric population. However, the multicenter study of CHG cleansing in pediatric ICUs (referenced above) has provided reassuring preliminary data. Their data indicates that 1864 children received CHG cleansing: 188 for > 2 weeks, 51 for > 4 weeks, and 16 for > 8 weeks. There were no serious adverse events reported. The only reported events were skin rash. Overall, 63 rashes were reported: 43 in the CHG group and 20 in the control group. Of the 43 events in patients receiving CHG, 14 were judged to be related to CHG bathing. All CHG-related skin reactions were mild dermatitis including macular or maculopapular erythema[24]. In high concentrations, CHG can be toxic to the eyes and inner ear. Ocular damage has been reported to occur when CHG entered and remained in the eye during surgery and middle ear damage has been reported after direct instillation of CHG into the middle ear through a perforated tympanic membrane. The proposed protocol calls for cleansing with CHG cloths from the neck down. It is very unlikely that CHG would enter the eye or middle ear when delivered by this method. Finally, it is important to note that over-the-counter preparations of CHG include a 4% formulation (Hibiclens®), which is FDA-approved as a general skin cleanser, as well as the 2% CHG cloths (Sage Products, Inc.) proposed for the study.

With any antimicrobial or antiseptic, it is important to understand the epidemiology and clinical relevance of resistance. In the case of CHG, what constitutes "resistance" and its associated clinical implications remains undefined. Higher minimum inhibitory

concentrations (MICs) to CHG have variably been associated with higher CHG minimum bactericidal concentrations (MBCs) and measures of killing activity. Whether these high MICs result in a reduction of the effect of CHG used at clinical concentrations is unclear. However, there are data suggesting that higher CHG MICs may be associated with resistance to commonly-used antibiotics,[25-36] though it should be noted that these data are derived from cross-sectional and/or *in vitro* studies.

One study of *S. aureus* demonstrated an association between MICs and bactericidal action of CHG in growth and time-kill studies,[37] although another study of *S. aureus* was unable to demonstrate this association.[38] A more recent study of *S. aureus* found that the presence of *qacA/B* was associated with higher MICs and MBCs to CHG.[33,34]

There are also data suggesting that a potential association between CHG resistance and commonly used antimicrobials may extend beyond *S. aureus*. A recent cross-sectional study of 70 distinct clinical isolates of *E. coli, K. pneumoniae, P. aeruginosa, A. baumannii, S. aureus, S. pyogenes,* and *E. faecalis* demonstrated that among Gram-negative organisms, there was a positive correlation between CHG MIC and MBC values and the MIC of all antibiotics tested.[28] Similarly, for Gram-positive bacteria, there was a correlation between MBC values for CHG and several of the antibiotics tested. There are also limited data suggesting that *in vitro* exposure to CHG may result in CHG and antibiotic resistance. For instance, repeated passaging of *Acinetobacter* species in sub-inhibitory concentrations of CHG resulted in an elevation of MICs.[27] Similarly, stable resistance to chlorhexidine diacetate was induced in *Pseudomonas stutzeri* strains by exposure to increasing concentrations of the agent.[35] The chlorhexidine diacetate-resistant strains variably showed reduced sensitivity to certain other antiseptics (e.g., triclosan) as well as to certain antibiotics, but this varied by strain.[35] A study involving one clinical MRSA isolate and one laboratory MRSA isolate demonstrated an increase in MICs to tested antibiotics following exposure to surface-dried CHG residues.[36]

In a study of CHG cleansing in critically ill adults, the median CHG MIC was slightly higher for bloodstream isolates identified in the CHG arm compared to those in the soap-and-water arm.[20] However, this appeared to be due to the less frequent recovery of highly CHG-susceptible, gram-positive bacteria in the CHG arm, rather than to an increase in the absolute number or rate of isolates with elevated CHG MICs. In another study of CHG cleansing in adults, the median CHG MICs for VRE were similar across the 3 periods (soap and water, CHG impregnated cloths, and cloths without CHG). The highest MIC, 8µg/mL, was from an *E. faecalis* strain that was collected during the non-medicated cloth period.[22] A longitudinal study of both skin isolates and BSI breakthrough isolates obtained from patients exposed to CHG and controls is needed to better understand to what extent if any, clinical CHG exposure is associated with CHG susceptibility and susceptibility to commonly used antibiotics. Results from this study have the potential to lead to practice changes in the care of pediatric cancer patients and will likely lead to a better understanding of the clinical ramifications of CHG resistance.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix IV for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206), E-mailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.4 Timing

Patients must be enrolled before protocol therapy (use of study cleansing product) begins. Patients must be enrolled and randomized no more than 10 days before or 7 days after day 1 of a conditioning regimen or day 1 of any chemotherapy cycle. Protocol therapy (use of study cleansing product) must be started within ***five*** **(5)** calendar days of the date of study enrollment.

3.1.5 Inclusion of Women and Minorities

Both male and female children of all races and ethnic groups are eligible for this study.

3.1.6 Randomization

Randomization will take place at the time a patient is enrolled. Patients will be assigned to either CHG or control cleansing product in a 1:1 ratio. Randomization will be stratified by myeloablative or reduced intensity allogeneic transplantation versus non-myeloablative allogeneic transplantation versus oncology patients receiving chemotherapy with or without a subsequent transplantation (see Appendix I for definitions). The randomization sequence will remain concealed to the site study team. Each site will be provided with a starter kit, containing identically packaged CHG and control product. Lot numbers will be used to differentiate between study and control product. After randomization of a subject, the site will be informed which lot number to use from the starter kit. Subsequently, patient-specific kits containing the appropriate product will be shipped by the coordinating site (Seattle) to the study site. Site-specific research staffs are to refer to the "Drug Management" document on the protocol web page.

3.1.7 Blinding

The subject, investigators, and site-specific research and clinical staff who are involved with the conduct of the study will remain blinded to the treatment. Sage Products, Inc. will supply identically packaged CHG and control product to the coordinating site (Seattle). Lot numbers will be used to track CHG and control products. Only Sage and Seattle Children's Investigational Drug Service will know what product is assigned to each lot number. The coordinating site (Seattle) will label each subject's product with the subject-specific study number and ship the labeled product to the subject's site.

3.1.8 Accountability

To ensure that the subject receives appropriate product, each site will maintain accurate records of all study products received and dispensed. The site will use the accountability record to document which product was given to the patient from the study pack. The study product will be packaged in a box which will have a two-part tear off label. Before the box is given out to the subject, one part of the label will be torn off and affixed to the patient specific accountability record. This tear off label will, at minimum, contain information as to study product dispensed (lot #, date and COG patient ID #). The accountability records will be reviewed at regular intervals by the coordinating site (Seattle).

3.2 Patient Eligibility Criteria

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Age

Patients must be ≥ 2 months of age and ≤ 21 years of age at enrollment.

3.2.2 Diagnosis

3.2.2.1 Transplant Patients

All patients undergoing planned allogeneic transplant (both malignant and non-malignant diagnoses).

3.2.2.2 Oncology Patients

- Patients with an oncology diagnosis that **are or will be on** a chemotherapy regimen that will last for an additional ≥ 3 months or **are on** or will be on a chemotherapy regimen for < 3 months and then proceed to transplant (allogeneic or autologous stem cell rescue) during the 3-month study period.

3.2.3 Central venous catheter

3.2.3.1 Transplant Patients

Patients undergoing allogeneic transplant must have, or be scheduled to have, an external tunneled central venous catheter (CVC) (Broviacs, Hickmans, **tunneled** percutaneously inserted central catheter (PICCs), etc.) and/or non-tunneled percutaneously inserted central catheter (PICC) that is expected to remain in place for an additional ≥ 3 months.

3.2.3.2 Oncology Patients with AML or relapsed ALL

Patients with AML or relapsed ALL that will receive chemotherapy with/without transplant must have, or be scheduled to have, an external tunneled central venous catheter (CVC) (Broviacs, Hickmans, **tunneled** percutaneously inserted central catheter (PICCs), etc.) and/or non-tunneled percutaneously inserted central catheter (PICC) that is expected to remain in place for an additional ≥ 3 months.

3.2.3.3 Other Oncology Patients

All other oncology patients that will receive chemotherapy with/without transplant must have, or be scheduled to have, an external tunneled central venous catheter (CVC) (Broviacs, Hickmans, **tunneled** percutaneously inserted catheter (PICCs), etc. that is expected to remain in place for an additional ≥ 3 months.

EXCLUSION CRITERIA

3.2.4 Patients with a previous or current line infection are ineligible until 14 days after the completion of antibiotics.

3.2.5 Patients with only totally implanted CVCs (i.e. ports) are ineligible.

3.2.6 Patients with a known allergy or hypersensitivity to CHG are ineligible.

3.2.7 Patients with chronic, severe, generalized skin breakdown (such as generalized blistering, burns, severe graft versus host disease (GVHD) with open sores, etc.) are ineligible.

3.2.8 Patients currently enrolled on COG study **ACCL0934** are not eligible until they have completed the infection observation period of that study.

3.2.9 Patients scheduled to receive broad-spectrum prophylactic antibacterial therapy are ineligible. Patients only receiving prophylaxis for PCP (TMP/SMX) or encapsulated organisms (penicillin) are eligible.

3.2.10 Patients receiving sorafenib at the time of enrollment and those who are scheduled to receive sorafenib as part of a treatment plan are ineligible

3.2.11 Patients using prophylactic antimicrobial locks in the CVC at the time of enrollment and those who are scheduled to receive antimicrobial locks in the CVC as part of a treatment plan are ineligible.

3.2.12 Patients previously enrolled on this trial are ineligible.

3.2.13 Females who are pregnant or breastfeeding are ineligible.

REGULATORY

3.2.16 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.17 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

This study is a randomized double-blind trial comparing cleansing with 2% CHG impregnated cloths (Sage Products, Inc.) to control cleansing with similar cloths that are impregnated with mild cleansers and moisturizers (Comfort Bath, Sage Products, Inc.) in children, adolescents, and young adults undergoing chemotherapy or conditioning for allogeneic HCT.

At the time of enrollment and within 10 days before or 7 days after starting a cycle of chemotherapy or conditioning for HCT, patients will be randomized to receive either CHG cleansing or control cleansing (see Section 3.1.6) for 90 days. All patients and their healthcare providers will be blinded to the intervention. The CHG and control cleansing cloths will be packaged in an identical fashion to maintain blinding.

Once-daily cleansing with the assigned study cloths will take place throughout the course of the treatment period of the study (90 days). Study cleansing will occur both while patients are hospitalized and when they are outpatients. Cleansing with study cloths will occur after, or instead of, usual bathing, and will include the whole body, except the face/head. Standardized instructions for cleansing with the study cloths are available on the protocol page on the web. Additionally, each package of study product (CHG or control) will include standardized cleansing instructions (See protocol webpage).

4.1.1 Tracking Compliance

To track cleansing compliance, families will be given a daily diary formatted like a calendar where they will record whether study cleansing has taken place on a daily basis. Patients who go off protocol therapy will continue to complete daily diaries. Nursing diaries will also be used for inpatients. Families will also be contacted at day 45 and at the completion of the study and a cloth use and product count survey will be obtained. During the survey, families will be asked to provide a count of remaining product as well as provide the average number of baths missed since enrollment at Day 45 and since the last survey at Day 90, and provide the number of baths missed in the last week. Patients who go off protocol therapy (either prior to Day 45 or Day 90) will complete a final cloth use and product count survey when they are removed from protocol therapy.

4.1.2 CHG-compatible soaps and lotions

Patients receiving protocol therapy in either arm of the study can only use approved CHG-compatible soaps for bathing and apply approved CHG-compatible lotions to the body. Approved soaps and lotions will be provided to each patient for their use while inpatient and outpatient.

4.1.3 Non-study Daily CHG Bathing

Patients receiving protocol therapy in either arm of the study should not use non-study CHG products (CHG cloths or liquid soap) for daily bathing. Patients should only use approved CHG products as outlined in sections 4.2.1-4.2.3.

4.1.4 Subjects who develop a positive blood culture

Subjects who develop a positive blood culture will continue the assigned study cleansing intervention throughout the course of the study (90 days) whether or not their catheter is removed. Patients who have their eligible catheter removed for any reason and do not have it replaced will not be followed for CLABSI beyond 2 days immediately following the loss of their eligible catheter, but will continue to be followed for MDRO, CHG resistance, and positive blood culture endpoints throughout the course of the study. Patients who maintain an eligible catheter will continue to be followed for all endpoints throughout the course of the study.

4.1.5 Subjects with treatment plan changes

Oncology subjects who have a change in their original treatment plan will stay on protocol and receive study cleansing as long the central line remains in place and the patient continues to receive some form of chemotherapy.

4.2 Concomitant Therapy Restrictions

4.2.1 CVC Care (Dressing Changes and Hub Cleaning)

Institutions may follow their standards for CVC care, which may include local application of CHG.

4.2.2 Surgical Procedures

Institutions may continue to follow their standard processes for CHG cleansing or bathing prior to operative procedures (typically 1-2 uses prior to the surgical procedure). Institutional procedures should be followed for the care of the incision.

4.2.3 CHG Cleansing During ICU stay

If the subject is admitted to the ICU, it is preferred that cleansing with the assigned study cloths are continued throughout the ICU stay. However, it is permissible for the patient to receive CHG cleansing during the ICU hospitalization only (and temporarily hold the assigned intervention) if this practice is standard of care at that institution.

4.2.4 Antibiotic/Antifungal Administration

There are no restrictions to the administration of systemic antibiotics used for treatment and no restrictions to the administration of anti-fungals. These data will be recorded on the appropriate case report forms. Study cleansing will continue while a patient is receiving systemic antimicrobials.

4.2.5 Radiation Therapy

- Patients undergoing HCT, or other treatment regimens that require short duration (e.g. 3-4 days) radiation therapy will have study cleansing held on all days in which radiotherapy is administered. If indicated, patients will bathe with regular soap and water on the days radiation is received. Study cleansing product should resume if radiation therapy is interrupted (for example, on weekends) and re-started the day after completion of radiation therapy.
- Patients who require long-term focal radiation therapy (such as those with neuroblastoma) will continue study cleansing except the focal area being irradiated will be avoided and bathed with regular soap and water if indicated.

4.2.6 Thiotepa therapy

Patients receiving thiotepa will not be bathed with study product the day of and the day after administration of thiotepa. Institutions typically have specialized bathing instructions for patients receiving thiotepa. These institutional bathing protocols will be followed the day of and the day after receipt of thiotepa.

4.2.7 High-dose Cyclophosphamide

Patients receiving high-dose cyclophosphamide ($\geq$ 50 mg/kg/dose) will not be bathed with study product the day of and the day after administration of high-dose cyclophosphamide. If indicated, patients will bathe with regular soap and water the day of and the day after receiving high-dose cyclophosphamide.

4.3 Schedule for CHG/Control Cleansing

Either 2% CHG or control cleansing cloths will be used daily for 90 days. Intervention and control cleansing products will be provided in identical packages, each containing 2 cleansing cloths.

TREATMENT	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
2% CHG or control cleansing	Topical skin cloths	Cloths impregnated with 2% CHG or cloths impregnated with mild soap and moisturizers	Once daily. Daily times may vary. Any missed doses do not need to be made up.	Start within 5 days of enrollment. Use from the neck down only. Do not use on the head and face. Use regular "approved" soap for the face and wash the hair with shampoo. Use only once/day. If another bath is required, use regular soap and water. Use only soap provided or another "approved" soap. If a regular soap and water bath is desired on a routine basis, wash first with water and an approved soap. After the soap and water bath, allow the skin to dry and cool for several minutes. After the skin has cooled, the cloths may be used as directed. Do not apply lotions to the whole body that are not provided by study staff or are not "approved". Any lotion may be applied to the face or hands. Do not use for preparation for lumbar punctures or in scenarios where the product may come in contact with the meninges.	a. Baseline collection history, demographics and institutional standard of care. b. Collection of clinical care data throughout the treatment period. c. Monitor for cleansing compliance. (See section 7.1.6). d. Record any positive blood cultures during the study period. (See section 7.1.6). e. Collection of leftover blood isolates (See section 13.0). f. Record any positive cultures with an MDRO during the study period.(See section 7.1.3). g. Collection of skin (axilla and neck) swabs (See sections 7.1.8 and 14). h. Optional nares and perirectal swab or stool specimen. (See section 7.2).

For COG Supportive Care Guidelines see: https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols. **See Section 5.0 for Dose Modifications based on Toxicities.** For details regarding criteria for determining CLABSI, see Section 13.0

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Skin Breakdown

Subjects will discontinue the skin cleaning intervention and be removed from protocol therapy if they develop severe generalized skin breakdown (such as severe skin disruption from GVHD) judged by the attending physician to warrant discontinuation of the study cleansing intervention. Any localized wounds or areas of skin breakdown should be avoided while bathing.

Skin Reaction
Subjects will discontinue the skin cleaning intervention and be removed from protocol therapy if they develop any skin reaction thought to be caused by allergy to the cleansing product or any non-allergic skin reaction $\geq$ Grade 3 possibly, probably, or definitely related to the cleansing product.

5.2 Emergency Un-Blinding

If emergency un-blinding is required, the local study staff will complete an emergency un-blinding CRF that will be forwarded to Seattle's Investigative Drug Service. The Seattle Investigative drug service will contact the site investigator and provide the information. The Study Chair and research coordinator at the central coordinating site (Seattle) will remain blinded. In the event of un-blinding, the patient will be removed from protocol therapy (bathing cloths) but will continue to be followed for CLABSI, MDRO, CHG resistance, and positive blood culture endpoints.

6.0 AGENT INFORMATION

Chlorhexidine Gluconate cloth, 2%
NSC #753971 (04/16/12)

6.1 Source and Pharmacology

Chlorhexidine gluconate is an antiseptic that exerts its bactericidal activity against Gram-positive and Gram-negative bacteria through bacterial cell membrane disruption. The use of cloths impregnated with 2% chlorhexidine gluconate has demonstrated significant reduction of bacterial levels on the skin for at least 6 hours after application. Chlorhexidine gluconate requires several applications to achieve its maximum antimicrobial benefit; repeated applications are often recommended. Chlorhexidine gluconate has been shown to be more effective than other commonly used antiseptics (eg, povidone-iodine) in lowering cutaneous microbial levels.

6.2 Toxicity

Toxicities of chlorhexidine gluconate cloths may include the following (frequency and timing unknown)

- Allergic reaction
- Edema – face
- Nasal congestion
- Dyspnea
- Dry skin

- Skin and subcutaneous tissue disorders - Other, [skin redness]
- Skin and subcutaneous tissue disorders - Other, [skin roughness]
- Skin and subcutaneous tissue disorders - Other, [skin sensitization]

6.3 Formulation and Stability

Each packet (CHG and placebo) contains 2 cloths. The quantity of packets in each shipment will vary by the size of the patient. Each polyester cloth contains 500 mg chlorhexidine per cloth. The following inactive ingredients are included in each cloth: aloe vera, dimethicone, fragrance, glucono-delta-lactone, glycerin, Igepal®, polysorbate 20, propylene glycol, USP, and purified water. Chlorhexidine gluconate 2% cloths do not contain any alcohol. Store the product flat at controlled room temperature [between 20-25°C (68-77°F)]. Avoid excessive heat above 40°C (104°F).

The placebo product for ACCL1034 will be similarly packaged and should be similarly stored.

6.4 Guidelines for Administration

To open a package containing a cloth (for this trial only):

- Hold the top of the package in one hand and lift flap on backside of package with the other hand. Grasp flap at top and pull down to tear flap along the middle (long axis) and expose blue foam insulator. Do not tear across the top.
- Remove and discard the blue foam.
- Take the cloths out one at a time. Do not remove the second cloth until the first cloth has been used and discarded.

For external use only. Keep out of eyes and ears. Avoid contact with meninges; do not use as preparation for lumbar punctures. Discard each cloth after a single use. Once an individual package has been opened, the cloth must be used then discarded. If only one of the two cloths in the package is used, the other cloth must be discarded. Do not open and repackage cloths for future use. Do not microwave cloths. Do not flush cloths in the toilet.

6.5 Supplier

Sage Products, Inc. Supplied by the Investigational Pharmacy Services of Seattle Children's Hospital.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required Clinical, Laboratory and Disease Evaluations

STUDIES TO BE OBTAINED	Baseline[a]	Study Period (90 days)
History [a]	X	
Ht, Wt, BSA[a]	X	
Performance status [a]	X	
MDRO and associated clinical data (MDRO worksheet) [b, h]	X	Each culture positive with a targeted organism
Monitoring of patient census [c]		X
Patient cleansing diary [d, h]		X
Cleansing Cloth Use and Product Count Survey [d]		At Day 45 and Day 90 (+/- 7 days) or at the time patient goes off protocol therapy
Positive blood culture worksheet [e, h]		Whenever the patient has a positive blood culture during the study period.
Leftover bacterial isolates from patients with positive blood cultures during the study period [f]		Whenever a patient has a positive blood culture during the study period. Should be monitored real-time.
Patient satisfaction questionnaire [d, h]		At Day 90 (+/- 7 days) or at time patient goes off protocol therapy/off study
Required Skin swabs (axilla and neck) for MDRO Acquisition and Resistance to CHG [g]	X	at Day 45 and Day 90 (+/- 7 days)
Optional Nasal swabs and Perirectal or Stool Specimen swabs for MDRO Acquisition [g]	X	at Day 45 and Day 90 (+/- 7 days)

a. This data and baseline swabs and data will be obtained prior to the start of cleansing.
b. Can be assessed at Day 90 (retrospective) (See section 7.1.2 and 7.1.3).
c. See product management document on protocol webpage for details.
d. See section 7.1.6.
e. Presence of positive blood cultures will be assessed real-time so that isolates can be collected. CLABSI will be defined using CDC criteria by coordinating site (Seattle) (see Sections 7.1.4 and 13.0 for details). This is ideally accomplished within 7 days after collection of the positive blood culture.
f. Blood isolates to be saved every time a patient has a positive culture (See section 7.1.5 for details. See section 13.2 for collection and shipping details).
g. See section 14.0 for collection and shipping details.
h. Once completed and received, must be uploaded into RAVE (See sections 7.1.3, 7.1.4, 7.1.6.and 7.1.7).

7.1.1 History and Demographic Information

Demographic information collected at baseline will include age, gender, race, ethnicity, payment status, performance status, height, weight, cancer diagnosis, presence of down syndrome, presence of short bowel syndrome or severe malabsorption disorder, presence of colostomy or ileostomy, episodes of BSI within 30 days of enrollment, history of targeted organism (potential MDRO) within the last year, and number of days CHG bathing received in the 2 weeks prior to enrollment (0-14). For HCT recipients, the following will also be collected: cell source, donor type, donor HLA match, conditioning regimen, and reason for transplantation for benign conditions.

7.1.2 Clinical Care Data Collection

Clinical care information will include any of the following that occur during the study period: number of positive blood cultures and number of positive cultures with a targeted organism (potential MDRO) with additional data for central review (see section 7.1.3 and 7.1.4), type of chemotherapy, type of radiation (TBI vs. focal), location of focal radiation, the number of days of radiation, dates of receipt of total parenteral nutrition (TPN), start and stop dates of periods of neutropenia (first day ANC < 500 and first day of 3 consecutive measurements with ANC > 500), dates of platelet transfusions, hospitalizations (admission and discharge dates), ICU admissions (admission and discharge dates), use of non-study CHG bathing while admitted in the ICU, dates and types of systemic antibiotics and/or antifungals including non-absorbable gut decontamination, and any clinical application of CHG for line accesses, line dressing changes, CHG impregnated line dressings (eg Biopatch etc.), and skin preparation for surgery; for HSCT patients, regimen for GVHD prophylaxis and treatment if any. For stratum 3 patients that receive a transplant during the study period, the following will also be collected: cell source, donor type, donor HLA match, conditioning regimen, and GVHD prophylaxis and treatment if any. Clinical data collection on the CVC during the study period include date of CVC placement, type and size of CVC (the circumference in mm as reported by the "French Size" eg. 6 French Broviac etc), number of lumens of CVC, any clinical application of CHG during the line placement, date of CVC removals, reason for CVC removal, and dates of any CVC repairs.

7.1.3 Positive Cultures for MDRO

The patient's microbiology laboratory records will be reviewed for any cultures positive with a targeted organism (potential MDRO, see Appendix III) at any site that occurs during the study period and within 1-year prior to enrollment. A MDRO worksheet will be completed for each positive culture with a targeted organism (potential MDRO). Worksheets (paper) will be available on the protocol website. The worksheet includes date(s) of positive culture(s), site of culture(s), associated infection, and severity of infection (using CTCAE criteria). Worksheets should be completed and uploaded to RAVE. Additionally, microbiology laboratory records, complete with susceptibilities, must also be uploaded in RAVE along with the worksheet. Investigators at the coordinating site (Seattle) will review the

worksheet and microbiology laboratory results and determine if the targeted organism is a true MDRO and enter this data in RAVE.

7.1.4 Presence of CLABSI

Patients will be monitored for positive blood cultures real-time. Data will be collected on all positive blood cultures that occur during the study period. A "positive blood culture" worksheet will be completed for each positive blood culture. Worksheets may be printed from the protocol website. The worksheet includes date and time of culture, presence of a central line, whether patients was hospitalized at time of positive culture, whether the patient had evidence of infection at another site of the body, whether the patient had a positive culture at another site of the body, and other information required for CLABSI determination. Worksheets should be completed and uploaded to RAVE within 7-14 days after the positive blood culture (to allow time for other infections to be identified). Additionally, supporting microbiology laboratory records, complete with susceptibilities, must also be uploaded in RAVE along with the worksheet. Investigators at the coordinating site will review the worksheet and microbiology laboratory results and determine if the infection meets criteria for CLABSI using CDC definitions as outlined in section 13.1 and enter this data in RAVE.

7.1.5 Clinical Blood Culture Isolates

Patients will be monitored for positive blood cultures real-time. Leftover positive clinical blood culture isolates will be retrieved from the clinical microbiology laboratories and sent to the coordinating site (Seattle) after the patient completes the study (See section 13.2 for details).

7.1.6 Cleansing Compliance Data

7.1.6.1 Patient cleansing Diary

Families will be given a daily diary formatted like a calendar where they will record whether study cleansing has taken place on a daily basis. Much of this trial will occur in the outpatient setting where the patient/family will be responsible for performing study cleansing. It is critical to be able to assess patient/family compliance with the intervention. Moreover, the daily diary conveys the importance of the intervention to families and will further engage them in the intervention. The diaries will be collected from the patients by the local research team at Day 45 and Day 90 at the time of swab collection. During periods of hospitalization, additional daily bathing diaries will be placed in the patient's charts and completed by the clinical nurses. Families will continue to complete the patient diaries. Patient diaries and nursing diaries will be compared. Any discrepancies will be resolved by the local study team and the patient diary will be edited as necessary. Patient and Nursing diaries will be available in the starter packs provided to each site. Completed patient diaries will be uploaded to RAVE at Day 45 and at completion of the study. Nursing diaries will not be uploaded. Diary data will be reviewed by the coordinating site (Seattle).

7.1.6.2 Cleansing Cloth Use and Product count Survey:

As an additional means to assess compliance, families will be contacted at day 45 and at completion of the study and a Cloth Use and Product Count Survey will be obtained. During the survey, families will be asked to provide a count of their remaining study product as well as provide the average number of baths missed since enrollment at Day 45 and since the last survey at Day 90 and provide the number of baths missed over the last week. Patients who go off protocol therapy (either prior to Day 45 or Day 90) will complete a final cloth use and product count survey when they are removed from protocol therapy.

7.1.6.3 Non-study Daily CHG Bathing

Patients receiving protocol-therapy in either arm should not use non-study CHG products (CHG cloths or liquid CHG soap) for daily bathing. Patients should only use approved CHG products as outlined in sections 4.2.1-4.2.3. Use of any non-study CHG bathing will be assessed using the daily diary.

7.1.7 Use of compatible soaps and lotions & patient satisfaction questionnaire

Study participants can only use CHG compatible soaps on areas except the face and hand during study cleansing days. Any soap may be used to wash the hands or face. Additionally, only CHG compatible lotions can be applied to areas except the face and hand during study cleansing days. Any lotion can be applied to the hands or face. Incompatible soaps and lotions may inactivate CHG. Each starter pack and subsequent product shipment will include CHG compatible soap and lotion for each participant. If a family wishes to use their own soaps and lotions they may do so if they are CHG compatible. A comprehensive list of commercially available compatible products is located on the protocol webpage. If an institution or family wishes to use a soap or lotion and compatibility is unknown, see 'Product Management' document on the protocol webpage for additional information. Use of products other than those provided by the study will be assessed using the daily diary and the patient satisfaction questionnaire referenced below.

At Day 90 or when the patient is off protocol therapy/off study, study staff will administer a questionnaire to the family to assess usability of the study cloths and satisfaction with the product. This questionnaire will be a paper form (available on the protocol webpage) that can be administered in person or over the phone. Completed questionnaires must be uploaded to RAVE for review.

7.1.8 Skin Swabs

Skin swabs (neck and axilla) will be collected at baseline, Day 45 (+/- 7 days) and Day 90 (+/-7 days) to assess CHG and antimicrobial resistance in skin microorganisms and changes in MDRO colonization. These should be sent to the coordinating site (Seattle) within 24 hours. See section 15.0 for details.

7.2 Optional Study

As part of the ACCL1034 trial, an ancillary study will assess whether CHG cleansing decreases acquisition MDRO in children with cancer those receiving allogeneic HCT. Nasal and perirectal swabs (or stool samples) will be collected at baseline, Day 45 (+/- 7 days) and Day 90 (+/- 7 days) to assess changes in MDRO colonization.

All patients enrolled in ACCL1034 will be offered the opportunity to participate in this ancillary study. Presence of MDRO will be determined by nasal and perirectal swabs (or stool samples). Perirectal swabs are preferred to stool samples in many COG institutions and have increased sensitivity for detecting MRSA. Consequently, perirectal swabs will be the preferred method of MDRO screening, although an institution or individual patient may choose to use stool specimens as long as the method of collection is consistent within an individual patient. If a stool specimen cannot be provided during a sampling period (such as constipation), a perirectal swab may be substituted.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) A problem with skin integrity (generalized skin breakdown such as severe skin GVHD or other severe generalized skin disruption) judged by the attending physician to warrant discontinuation of study treatment.
b) Any skin reaction thought to be caused by allergy to the cleansing product.
c) Any non-allergic skin reaction $\geq$ Grade 3 possibly, probably, or definitely related to the cleansing product.
d) Patient receives Sorafenib after study enrollment.
e) Physician determines it is in the patient's best interest.
f) Emergency un-blinding.
g) Refusal of further protocol therapy by patient/parent/guardian.

Patients who are off protocol therapy are to be followed for positive blood cultures, targeted organisms (potential MDRO), all clinical data collection outlined in section 7.1.2, swab collection, and continuation of daily diary until they meet the criteria for Off Study (see below).

8.2 Off Study Criteria

a) Withdrawal of consent for any further data submission
b) Death
c) Completion of planned study assessments
d) Enrollment onto COG study ACCL0934
e) Lost to follow up

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

This study is a randomized, double blind study that aims to examine the effect of CHG cleansing on occurrence of CLABSIs (primary aim), acquisition of MDRO, susceptibility to CHG, and bacteremia in pediatric patients with cancer or those receiving an allogeneic HCT. Randomization between CHG and control cleansing will be stratified by myeloablative or reduced intensity allogeneic transplantation versus non-myeloablative allogeneic transplantation versus oncology patients receiving chemotherapy with or without subsequent transplantation.

9.2 Patient Accrual and Expected Duration of Trial

The study aims to accrue up to 450 patients, age 2 months to 21 years, with a planned CVC for at least 3 months. We do not have a good estimate for the expected COG accrual rate on this study as we have no prior COG studies on similar patients. As we estimate that the potential patient pool with such CVC duration should be large hundreds per year within COG), we anticipate accruing 450 patients in 4 years.

9.3 Statistical Analysis Methods

9.3.1 Study Endpoints

The primary endpoint is the number of CLABSI events during the at-risk days (within the 90-day study period). Days that the patient is at risk for CLABSI are defined as the days when the patient has an eligible CVC plus 2 days following the loss of an eligible tunneled CVC. In other words, an event occurred during the 2 days immediately following the loss of an eligible CVC (without a replacement) will be attributed to the lost CVC. CLABSI will be defined by a central review committee blinded to the study treatment (see Section 13).

Secondary endpoints include acquisition of MDRO, susceptibility to CHG, and the number of bacteremia episodes during the at-risk days.

9.3.2 Sample Size and Power Consideration

For the primary endpoint of CLABSI, rates of 3.3 - 4.6 CLABSI per 1000 catheter days have been documented in pediatric patients with cancer.[39,40] Higher risk diagnoses, such as AML, however, have much higher rates of CLABSI. Assuming the patients in the control arm have a constant rate of CLABSI at 5 per 1000 catheter days compared to a constant rate of 3 per 1000 catheter days in the CHG arm, 400 patients (200 per arm) will provide at least 85% power in a Poisson regression model to detect the difference in the rate of CLABSI between the 2 arms at 2-sided alpha of 0.05 if all patients have 90 at-risk days for CLABSI. Power estimation is based on simulations. The maximum enrollment is increased to 450 randomized patients to account for ineligible enrollments and loss of at-risk days in some patients during the 90-day period because of days without a CVC.

Based on the effective sample size of 200 per arm with 90 at-risk days, for the secondary endpoint of bacteremia, assuming a constant rate of 7 per 1000 catheter days in the control arm compared to 4.5 per 1000 catheter days in the CHG arm, the study will provide at least 88% power in a Poisson regression model for detecting the reduction in the rate of bacteremia at 2-sided alpha level of 0.05.

For the secondary endpoint of acquisition of MDRO, the power estimation is based on comparing the percentage of patients with MDRO acquisition between the 2 arms. Estimates for MDRO acquisition are lacking in pediatric oncology patients. Assuming 15% of patients in the control arm acquire MDRO, with 200-225 patients per arm, the study will provide 84-88% power for detecting a 6% MDRO acquisition in patients in the CHG arm (a decrease of 9% from the control arm); if 20% of the patients in control arm acquire MDRO, the power will be 80-85% for detecting a 10% MDRO acquisition for patients in the CHG arm (a decrease of 10% from the control arm).

For the secondary endpoint on susceptibility to CHG, the power estimation is based on comparing the percentage of patients with blood culture or swab that shows reduced susceptibility to CHG (defined by MIC and MBC cutoffs) between the 2 arms. Assuming 5% of patients in the control arm have reduced susceptibility of CHG, with 200-225 patients per arm, the study will provide 80-85% power for detecting a 13% patients with reduced susceptibility to CHG in the CHG arm (an increase of 8% compared to the control arm); if 10% of the patients in control arm have reduced susceptibility to CHG, the power will be 80-85% for detecting 20% patients with reduced susceptibility in the CHG arm (an increase of 10% compared to the control arm).

9.3.3 Analysis Plan

The primary analysis for CLABSI will be based on intent-to-treat analysis. The rate of CLABSI when the patient is at risk will be estimated and compared between the 2 arms by a Poisson regression model adjusting for the randomization stratification factor on treatment/diagnosis. Patient specific at-risk days will be included as offset in the Poisson regression. We will also consider adjustment for potential confounders and potential interaction between risk factors and treatment in the analysis. Secondary analyses of time to first CLABSI event will be performed using survival analysis methodology including log rank test and Cox proportional hazards models. Such analyses include only the first CLABSI event rather than all events. They are useful alternative approaches as the delay of first CLABSI is clinically important and the chance of multiple CLABSI events is expected to be low. Given the expected rate of CLABSI, the chance of a patient having more than one qualifying event during the study period should be small. If we observe a higher than expected number of patients having multiple CLABSI, we will examine the risk for second or later events to see if there are any suggestions of a higher risk than that for the first event.

The study will also examine whether CHG cleansing changes the acquisition of new MDRO by Day 45 (half way through the treatment period) and by the end of the study. Clinical data reported by the site as well as swab specimens analyzed by the coordinating site (Seattle) will be used to determine acquisition of epidemiologically important MDRO. Patients with a past infection or known colonization status with a particular MDRO will not be able to acquire that MDRO at a later time during the study period. The consequence is that later outcomes are actually determined by previous outcomes. Such a deterministic relationship makes a longitudinal analysis of MDRO status at all 3 time points (baseline, Day 45, and Day 90) infeasible, therefore we will evaluate acquisition of epidemiologically important MDRO by Day 45 and by the end of the study (if a patient is infected or colonized by Day 45, then the patient is also considered infected or colonized by the end of the study). The effect of CHG cleansing on the proportion of patients acquiring MDRO by Day 45 or by the end of the study will be compared between the two arms using logistic regression, adjusting for the randomization stratification factor on treatment/diagnosis and other potential confounders such as baseline patient characteristics. Non-linear mixed effects models will also be used to examine the effect of CHG on the proportion of patients acquiring MDRO with adjustment for the treating institution as random effects. This outcome will be evaluated in aggregate as well as by organism (MRSA, VRE, etc.). In addition, this outcome will be evaluated using data from the swabs alone.

This study will also evaluate whether use of CHG is associated with skin and bloodstream microorganisms demonstrating reduced susceptibility to CHG, which will be measured by MICs and MBCs. Analyses will be done separately for skin and bloodstream isolates. For skin isolates, MIC and MBC medians, interquartile ranges, and ranges will be described for each arm at baseline, Day 45, and Day 90 time points for *S. aureus* and coagulase negative staphylococci in aggregate and separately. We will describe the frequency of patients in each arm with a skin isolate demonstrating reduced susceptibility to CHG (defined both by MIC and MBC) at each time point. Comparison of CHG susceptibility status from skin isolates (yes/no based on chosen cutoff point) across study arms at Day 45 and Day 90 will be based on logistic regression, with adjustment for the randomization stratification factor on treatment/diagnosis and other potential confounders. In addition, we will apply nonlinear mixed models to explore the association between CHG cleansing and reduced susceptibility to CHG over the longitudinal assessments. These models will account for the correlation of repeated measures over time. We will also evaluate the association between reduced susceptibility to CHG and resistance to commonly used antimicrobials in cutaneous staphylococci, overall and by species, using both chi-square test and logistic regression where resistance to commonly used antimicrobials will be modeled as the outcome and reduced susceptibility to CHG as the predictor of interest. We will stratify analyses by whether or not qacA/B was detected. For bloodstream isolates, we will compare the frequency of bloodstream isolates resistant to CHG at any time during study period between those who received CHG cleansing versus those who received control cleansing using similar analysis as described above.

Daily compliance data based on the patient diary on whether protocol cleansing was completed (and if not, the reason) and on usage of unauthorized soap and

location will be captured. In addition, product count and an estimate by the family for number of missed cleansing will be obtained at day 45 and at completion of study. We will describe the compliance with protocol-cleansing/usage of unauthorized soap or location and the reasons for missed protocol cleansing using appropriate summary and descriptive statistics. Summary variable on compliance with protocol cleansing or on usage of unauthorized soap/location will be created, such as the number/percentage of days with compliance or a binary variable for compliance based on a cutoff. We will examine whether there are differences in compliance between the 2 arms on such summary compliance variables by appropriate two sample tests. We will also include such summary compliance variables in the regression models as covariate to explore whether the treatment effect of CHG is associated with such compliance measures.

Descriptive statistics will be used to summarize the responses to the patient satisfaction survey collected at the end of the study. Counts/percentages of patients who consider the study cleansing easy/difficult to use and those of patients satisfied/unsatisfied with the cleansing cloths will be tabulated. The reasons provided for dissatisfaction will also be tabulated. These descriptive statistics will be generated for the entire study population across the 2 arms first and then by each arm.

9.3.4 Interim monitoring

Interim efficacy monitoring on the rate of CLABSI will be performed once after about half of the patients complete study observation. Monitoring boundary will be based on Lan-Demet's method with spending function αt^2. No interim futility monitoring is planned because reduction in the risk of MDRO acquisition, if any, is also considered an important effect of CHG even if the rate of CLABSI is not reduced by CHG cleansing. Informal interim analysis on incidence and severity of skin rash will be performed annually. If such informal analysis suggests a significantly higher incidence of rash for CHG patients compared to the control patients at the alpha level of 0.05, the study committee will perform a review of the data on rash and report the findings and study committee recommendation to the DSMC. The DSMC may also make their assessment and recommendation regarding the study at any time.

9.3.5 Potential Confounders and Effect Modification Factors

Potential confounders that influence the underlying risk of CLABSI and factors that may modify the effect of CHG treatment will be collected on the study participants. Such factors include some patient and/or disease characteristics as well as clinical care practices. These data collection are described in Section 7.1.1 and Section 7.1.2. These factors will be explored in the adjusted regression analyses. Such potential confounders and effect modification factors on patient or disease characteristics will be considered for inclusion as covariates in the Poisson regression models for analyzing incidence of CLBASI and in the logistic regression models and nonlinear mixed models for analyzing acquisition of MDRO or reduced susceptibility to CHG at Day 45 and Day 90. Time-dependent factors will be considered for inclusion as time-dependent covariates in analyzing time to first CLABSI; for acquisition of MDRO or reduced susceptibility to CHG

at Day 45 and Day 90, these time-dependent factors prior to Day 45 and Day 90 will first be summarized and the summary variables be considered as covariates in the modeling. Alternative modeling of CLABSI incidence which might accommodate time-dependent factors will also be explored. One possible approach might be to model the daily outcome on CLABSI as a binary variable with dependence within patients across the daily outcomes, and to incorporate some summary variable for the time-dependent factors up to the particular day as covariate for the binary outcome.

9.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	44	66	110
Not Hispanic or Latino	129	211	340
Ethnic Category: Total of all subjects	173	277	*450
Racial Category			
American Indian or Alaskan Native	2	1	3
Asian	5	9	14
Black or African American	18	37	55
Native Hawaiian or other Pacific Islander	0	5	5
White	148	225	373
Racial Category: Total of all subjects	173	277	*450

* These totals must agree

The estimates are based on Children's Oncology Group (COG) patient demographics, assuming 15% of subjects with acute myeloid leukemia (AML) (race/gender distribution estimated from AAML0531), 35% of subjects with relapsed acute lymphoblastic leukemia (ALL) (projected race/gender distribution for AALL07P1), and 50% of subjects being allogeneic hematopoietic cell transplant recipients (race/gender distribution estimated from allogeneic transplant patients on ACCL0331).

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (i.e., v4.02 and all subsequent iterations prior to version 5.0).

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- ***the current known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or***
- ***the drug package insert.***

11.3 Reporting of Adverse Events for Commercial Agents - via CTEP-AERS

Expedited AE reporting must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via https://eapps-ctep.nci.nih.gov/ctepaers

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study

Committee roster.

- COG requires the CTEP-AERS report to be submitted **within 5 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS
[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.			

11.4 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all CTEP-AERS reportable events and all Grade $\geq$ 1 CTCAE v.4 skin reactions (System Organ Class "Skin and Subcutaneous Tissue Disorders") with the following adverse event headings: skin induration, skin ulceration, rash maculo-papular, urticaria, skin and subcutaneous tissue disorders – others, specify, stevens-johnson syndrome and toxic epidermal necrolysis.

12.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

13.0 Central Line Associated Bloodstream Infection (CLABSI) and collection of left over clinical blood culture isolates

Patients will be followed for positive blood cultures real-time. Each positive blood culture will prompt collection of the data necessary to determine whether it meets criteria for CLABSI as defined by CDC criteria (see appropriate case report form for variables to collect). Determination of CLABSI will be accomplished by 2 investigators blinded to the cleansing product that the subject is receiving. Additionally, the 2 investigators will be blinded to each other's responses while making this determination. Discordant decisions will be resolved by consensus. Final determinations will be recorded on the central review form by the coordinating site (Seattle). Peripheral blood culture is not required to perform this classification. The clinical blood isolate will be sent to Seattle for further testing.

13.1 CDC Criteria for Central Line Associated Bloodstream Infection (CLABSI). To be used by the investigators coding CLABSI

Investigators will use the most current CDC definition for coding CLABSI.

13.1.1 Additional considerations not included in the CDC criteria

a. We will include criteria for recurrence of infection and recurrent infections will not be counted as new infections. These criteria will include: 1) the subsequent positive culture occurs in association with the same CVC as the previous infection (the CVC was not replaced with the previous infection), 2) the subsequent positive culture is due to the same organism/s as the previous infection without new organism/s cultured, and 3) the subsequent positive culture occurs within 4 weeks of the first infection. All 3 criteria must be present for a positive culture to be deemed a recurrent infection. Different species isolated within a week of an initial isolate will be counted as one infection episode. Different species identified at least one week after the initial isolate will be categorized as a new infection.

13.2 Positive clinical blood culture isolates

13.2.1 Sample collection

Any positive blood cultures that occur during the study period will be sent to Seattle for CHG and antimicrobial susceptibility testing. See the laboratory manual on the protocol webpage for additional information.

13.2.2 Obtaining clinical blood culture samples

- Use a sterile cotton swab to touch 2-5 colonies of pure growth on Sheep Blood or MacConkey Agar.
- Place swab in cryovial with 1 ml of BBL trypticase Soy Broth with 20% glycerol (or freezing media of your choice) and agitate.
- Remove swab and freeze liquid sample in cryovial at -70ºC.
- Isolates will be affixed with a freezer-safe label provided by the coordinating site (Seattle).
- Isolates will be labeled with the protocol number, patient's COG ID number, BPC number and date of collection.

13.2.3 Sample shipping.

Blood culture samples will be shipped to Seattle for further testing. Each center will use shipping kits provided by Seattle Children's. These kits will contain a Styrofoam-line insulated shipper, biohazard bag, isolate shipping inventory sheet

Shipping form: Complete an isolate shipping inventory sheet for each isolate in the shipment. Site should retain copies.

Packaging:

- Assure all specimens are labeled correctly and legibly.
- Place all labeled isolates in the biohazard bag and seal. The biohazard bag is provided in the shipping kit.
- Ship isolates in the box provided in the shipping kit along with 3kg of dry ice.
- Place the biohazard bag containing the isolates in the box and surround with dry ice.
- Replace the Styrofoam lid on the box but do not tape the lid of the Styrofoam box.
- Place the completed isolate shipping inventory sheet on top of the Styrofoam liner.
- Tape the cardboard box.

Shipping Instructions:

- To optimize efficiency, these specimens should be shipped at the end of the patient's participation (day 90 or when the patient is off study).
- Ship isolates on Monday-Friday. Friday shipments must be completed prior to final FedEx pick-up time at the respective site. Please do not ship the day preceding a holiday.

- Fax a shipment notification form located on the protocol page to the Qin laboratory at Seattle Children's Hospital (see Specimen Shipping forms on the protocol webpage).
- All isolates are shipped via FedEx Priority Overnight.
- Generate a shipping label via the FedEx website (www.fedex.com). Account information is provided on the shipment notification form that can be found on the protocol webpage.

- Ship specimens to :

  Dr. Xuan Qin
  4800 Sandpoint Way NE, A-6901
  Seattle, WA 98105
  Phone: (206) 987-2586
  Fax: (206) 987-3840
  Contact: Jessica Berry jessica.berry@seattlechildrens.org

14.0 MDRO Data Collection

Historical and ongoing clinical cultures will be used to determine acquisition of epidemiologically important MDRO. In addition, to enhance sensitivity of MDRO detection, nasal and perirectal swabs will be obtained at baseline and 45 and 90 days after enrollment (See Section 15). Patients with any past cultures or a baseline swab positive for MDRO will be designated as a known MDRO carrier. MDRO acquisition will be defined by any positive clinical culture or screening swab cultures obtained subsequent to the baseline swab in a patient that is not an MDRO carrier. MDRO will be analyzed in aggregate and for each organism separately (MRSA, VRE, etc.). An MDRO worksheet will be completed for any positive culture with a targeted organism (potential MDRO). Both historical (year prior to enrollment) and occurrences during the study period will be collected. Data included on the MDRO worksheet includes culture date, culture site, clinical information regarding infection, severity of infection (if obtained during the study period). Completed worksheet as well as the microbiology laboratory record, including susceptibilities, will be uploaded to RAVE. The coordinating site will evaluate the worksheet and microbiology laboratory results and determine if the targeted organism is a true MDRO. Central review forms will be completed by the coordinating site for those judged to be true MDRO.

14.1 **Any cultures with the targeted organisms listed in Appendix III will be evaluated as potential MDRO.**

15.0 SPECIMEN REQUIREMENTS

15.1 Screening Swabs

The screening swabs (nares, axilla and neck, and perirectal) will be obtained at study entry (before day 1 of cleansing), Day 45, and at Day 90. The swabs will be processed for the bacterial counts, MDRO and CHG resistance.
Screening swabs will be collected using kits provided by Seattle Children's Hospital. Each kit will contain:

1) Three (3) Copan swabbing systems in 1mL bacterial transport media;
2) 3 ampules of saline;
3) Labels;
4) A plastic biohazard bag; and
5) Instructions for obtaining swabs (See Section 15.1.1).

15.1.1 Swab Collection

Each swab should be collected as follows. A detailed instruction sheet is also available on the protocol webpage.

Axilla and Neck (Required study)

1) Remove the swab from the pouch.
2) Moisten the swab with the saline.
3) Rub the swab on the side or back of the neck over a 3x3cm area, for 20 seconds.
4) Rub the same swab in the axilla over a 3x cm area, for 20 seconds.
5) Remove the lid from the vial containing the bacterial transport media.
6) Place the swab all the way to the bottom of the tube, place the swab against the side of the vial and break the applicator shaft at the molded breakpoint (marked by a pink line). Screw the cap down tightly on the vial.
7) Label the tube with the patient's study ID number, collection date, and collection site (skin).
8) Place the labeled tube in the biohazard bag.

Nares (Optional study)

1) Remove the swab from the pouch.
2) Moisten the swab with the saline.
3) Rotate the swab 5x clockwise and counterclockwise in each anterior nare (nostril).
4) Remove the lid from the vial containing the bacterial transport media.
5) Place the swab all the way to the bottom of the tube, place the swab against the side of the vial and break the applicator shaft at the molded breakpoint (marked by a pink line). Screw the cap down tightly on the vial.
6) Label the tube with the patient's study ID number, collection date, and collection site (nares).
7) Place the labeled tube in the biohazard bag.

Perirectal/stool (Optional study)

1) Remove the swab from the pouch.
2) Moisten the swab with the saline.
3) Using the swab from the saline system, gently rub the swab in the perirectal region for 20 seconds. If obtaining a stool swab, dip the swab directly in the stool sample.
4) Remove the lid from the vial containing the bacterial transport media.
5) Place the swab all the way to the bottom of the tube, place the swab against the side of the vial and break the applicator shaft at the molded breakpoint (marked by a pink line). Screw the cap down tightly on the vial.
6) Label the tube with the patient's study ID number, collection date, and collection site (perirectum or stool).
7) Place the labeled tube in the biohazard bag.

15.1.2 Sample Processing

As a means to ensure the highest level of bacterial recovery, swabs should be shipped to Seattle Children's Hospital on the day they are collected. If that is not possible, they should be refrigerated overnight and shipped no later than the next day. Swabs can be shipped Monday-Friday. If shipping on Friday, shipments must me made prior to the last FedEx pick-up time at the respective site.

15.1.3 Shipping

- Swabs will be shipped using kits provided by Seattle Children's Hospital. Each kit will contain a Styrofoam lined shipping box, cold pack, and swab shipping inventory sheet.
- Shipping form: Complete a swab shipping inventory sheet for each isolate in the shipment. Site should retain copies.

Packaging:

- Assure all specimens are labeled correctly and legibly.
- Assure all specimens are in a sealed plastic biohazard bag.
- Ship isolates in the box provided in the shipping kit along with the cold pack that should be frozen.
- Place the frozen cold pack into the Styrofoam liner. This cold pack will ensure specimen integrity during overnight shipping.
- Place the plastic biohazard bag containing the swabs directly on top of the frozen cold pack.
- Replace the Styrofoam lid on the box.
- Place the completed swab shipping inventory sheet on top of the Styrofoam box.
- Tape the cardboard box.

Shipping Instructions:

- Ship isolates on Monday-Friday. Friday shipments must be completed prior to final FedEx pick-up time at the respective site.
- Please do not ship the day preceding a holiday.
- Fax a shipment notification form located on the protocol page to the Qin laboratory at Seattle Children's Hospital (see Specimen Shipping forms on the protocol webpage).
- All isolates are shipped via FedEx Priority Overnight.
- Generate a shipping label via the FedEx website (www.fedex.com).
- Account information is provided on the shipment notification form that can be found on the protocol website.

APPENDIX I: Definitions for the Intensity of a Hematopoietic Stem Cell Transplant Conditioning Regimen

In order to assist in the proper classification of SCT Conditioning Regimens for stratification purposes, please utilize the following definitions.[41]

1. Myeloablative: A combination of agents expected to produce profound pancytopenia and myeloablation within 1-3 weeks from administration; pancytopenia is long lasting, usually irreversible, and in most instances fatal, unless hematopoiesis is restored by hematopoietic stem cell infusion.
   Examples:
   a. Total Body Irradiation (TBI) ≥5 Gy as a single dose or ≥8 Gy a fractionated doses, generally in combination with other agents
   b. Busulfan >8 mg/kg total dose, generally in combination with other agents

2. Non-myeloablative (also termed "Immunoablative"): A regimen that will cause minimal cytopenias and does not require stem cell support.
   Examples:
   a. TBI ≤2 Gy ± a purine analog (i.e. Fludarabine)
   b. Fludarabine + Cyclophosphamide ± Serotherapy (ATG or Alemtuzumab)
   c. Fludarabine + Cytarabine + Idarubicin
   d. Cladribine + Cytarabine
   e. Total Lymphoid Irradiation + Serotherapy

3. Reduced intensity (also termed "RIC"): A regimen that cannot be classified as non-myeloablative or myeloablative.
   Examples:
   a. Fludarabine + Melphalan ≤140 mg/m^2
   b. Cyclophosphamide 200 mg/kg ± Serotherapy

If it is not clear what definition should be applied to a specific conditioning regimen, centers are encouraged to discuss with the Study Chair and Committee prior to enrollment in order to ensure uniformity of the stratification system.

APPENDIX II: STANDARDIZED INSTRUCTIONS FOR USE OF STUDY CLEANSING CLOTHS

(Package label)

- **Cloths can be used at room temperature or warmed.**
- **DO NOT microwave cloths.**
- **If warm cloths are preferred, fill a large bowl or basin with warm water (temperature you would use for bathing) and immerse the pack of cloths in water and hold for 30-60 seconds. OR, if hospitalized, an appropriate warmer may be used. ONLY use warmers that are designed for bathing cloths.**
- **KEEP Cloths out of eyes, ears, and mouth. Use regular approved soap for washing the face.**
- **Wipe the cloths in a circular or back and forth motion over the part of the body to be cleaned. Use the chart below to determine which part of the body should be cleaned with each cloth.**
- **DO NOT rinse the skin.**
- **DO NOT apply any unapproved lotions.**
- **DO NOT apply more than once/day. If second bath is needed, use water and approved soap.**
- **If a regular soap and water bath is desired on a routine basis, use the study cloths after the regular bath. After the soap and water bath, allow the skin to cool for a few minutes before using the study cloths.**

	<22lbs (10kg)	22-66lbs (10-30kg	>66lbs (>30kg)
CHG Cloth 1	Neck, Chest, Abdomen, Both Arms, and Back	Neck, Chest, Abdome and Both Arms	Neck, Chest, Abdomen
CHG Cloth 2	Both Legs, Buttocks, and Genital/anal area	Back and Buttocks	Both Arms
CHG Cloth 3	----------	Both Legs	Right Leg
CHG Cloth 4	----------	Genital/anal Area	Left Leg
CHG Cloth 5	----------	----------	Back and Buttocks
CHG Cloth 6	----------	----------	Genital/anal Area

APPENDIX III: TARGETED ORGANISMS

- ***Staphylococcus aureus-*** resistant to oxacillin, nafcillin, or methicillin
- ***Enterococcus faecalis*** or ***Enterococcus faecium*** resistant to vancomycin
- ***Escherichia coli (E. coli)*** resistant or intermediately susceptible to ceftriaxone, ceftazidime, cefepime or any carbapenem (meropenem, imipenem, ertapenem) OR those identified by your laboratory as being multi-drug resistant or "ESBL" organisms
- ***Klebsiella pneumoniae*** or ***Klebsiella oxytoca*** resistant or intermediately susceptible to ceftriaxone, ceftazidime, cefepime or any carbapenem (meropenem, imipenem, ertapenem) OR those identified by your laboratory as being multi-drug resistant or "ESBL" organisms
- Any ***Serratia***, ***Enterobacter***, *or* ***Citrobacter*** species resistant or intermediately susceptible to cefepime or any carbapenem (meropenem, imipenem, ertapenem)
- Any ***Acinetobacter baumannii***
- Any ***Pseudomonas aeruginosa***
- Any ***Clostridium difficile***

APPENDIX IV: CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements for ACCL1034 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

APPENDIX V: Youth information sheets

INFORMATION SHEET REGARDING RESEARCH STUDY – ACCL1034
(for children from 7 through 12 years of age)

A Study of Cleansing Cloths to Prevent Central Line Infections in Children

1. We have been talking with you about your central line. An unwanted problem with central lines is that they can get infected and cause an infection in your blood.

2. We are asking you to take part in a research study because you have a central line. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to keep central lines from getting infected. We will do this by trying a new way to help prevent these infections.

3. Some children in this study will be given a skin cloth that has an ingredient called CHG in it. CHG kills germs. Some children will get skin cloths to use that do not have CHG in them, but have other ingredients in them to help clean your skin. You have the same chance of getting the CHG cloths or the other cloths. You will be asked to use the skin cloths every day. You will be asked to clean yourself from the neck down with the cloths instead of or after you have done your normal soap and water bathing. You will be asked to use the cloths for 90 days.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is a better chance of keeping an infection from happening, if you get the CHG cloths. If you get the other cloths, we hope a benefit to you is helping study doctors learn more about how to keep central line infections from happening. But, we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risk to you from this study could be a health problem from the CHG cloths, like a rash on your skin. If you get the other cloths, the risks to you is that you many get a rash and you may not get a treatment that is better at helping keep central line infections from happening. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We would also like to take a swab of your skin on your neck and in your armpit as part of this study. This swab would happen at 3 times during the study – when you start, halfway through the study (at 6 weeks), and when you finish the study. We want to see what kind of germs are living on your skin and if they are affected by the CHG. If your central line gets infected while you are in the study, we would like to test the germs in your blood to see if they are affected by the CHG. We will not draw your blood for this study.

8. We will give you a daily calendar to tell us if you used the cleansing cloths each day. We will also ask you to tell us if you took a regular bath with soap and water each day and we will ask you about the soaps and lotions you use each day. Half-way through the study and at the end of the study, we

will ask you to tell us how many cleansing cloths you used. Also at the end of the study, we will ask you questions about if you liked the cloths.

9. There is also an optional part of this study that will find out if you have germs on your skin that are resistant to germ-killing medications. We also want to find out if the CHG cloths can help keep you from getting these germs. For this sub-study, we would like to take swabs from inside your nose and your peri-rectum (just outside your rectum) or a stool sample (a sample of feces when you have a bowel movement). We would collect these swabs at the same time as the skin swab of your armpit. Your family can choose to be a part of this optional sub-study or not.

INFORMATION SHEET REGARDING RESEARCH STUDY – ACCL1034
(for teens from 13 through 17 years of age)

A Study of Cleansing Cloths to Prevent Central Line Infections in Children and Teens

1. We have been talking with you about your central line. An unwanted problem with central lines is that they can get infected and cause an infection in your bloodstream.

2. We are asking you to take part in a research study because you have a central line put in for your treatment. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to prevent central line infections, in children and teens undergoing treatment for cancer. We will do this by trying a new way to prevent central line infections.

3. Some children and teens in this study will receive cleansing cloths with CHG in them. CHG is an ingredient that kills germs. Others will receive cleansing cloths that do not have CHG in them, but have other ingredients to help clean your skin. They are called comfort bath cloths. If you agree to be in this study you have a 50-50 chance that you will receive the CHG cloths, and a 50-50 chance that you will receive the comfort bath cloths. You will be asked to use the cleansing cloths every day. You will be asked to clean yourself from the neck down with the cloths instead of or after you have done your usual soap and water bathing. You will be asked to use the cloths for90 days.

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is that you will be less likely to have a central line infection if you receive the CHG cloths. If you receive the comfort bath cloths, we hope a benefit to you is knowing that you will help doctors learn more about how to prevent central line infections. But, we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” If you receive the CHG cloths, the risk to you from this study could be the chance of unwanted effects from the CHG such as a skin rash, but this is not very likely. If you receive the comfort bath cloths, the risks to you is that you may get a skin rash and you may not receive a treatment that is better at helping prevent line infections. Other things may happen to you that we don’t yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We would also like to take a swab of your skin on your neck and in your underarm as part of this study. This swab would happen at 3 times during the study – when you start, halfway through the study (at about Day 45), and when you finish the study (at about Day 90). We want to see what kind of germs are living on your skin and if they are affected by the CHG. If your central line gets

infected while you are in the study, we would like to test the germs in your blood to see if they are affected by the CHG. We will not draw your blood for this study.

8. We will give you a daily calendar to tell us if you used the cleansing cloths each day. We will also ask you to tell us if you took a regular bath with soap and water each day and we will ask you about the soaps and lotions you use each day. Half-way through the study and at the end of the study, we will ask you to tell us how many cleansing cloths you used. Also at the end of the study, we will ask you questions about if you liked the cloths.

9. There is also an optional part of this study that will find out if you have germs on your skin that are resistant to germ-killing medications. We also want to find out if the CHG cloths can help keep you from getting these germs. For this sub-study, we would like to take swabs from inside your nose and your peri-rectum (just outside your rectum) or a stool sample (collecting a sample of feces when you have a bowel movement). We would collect these swabs at the same time as the skin swab of your armpit. Your family can choose to be a part of this optional sub-study or not.

REFERENCES

1. Klevens RM, Edwards JR, Richards CL, Jr., et al: Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep 122:160-6, 2007
2. Almyroudis NG, Fuller A, Jakubowski A, et al: Pre- and post-engraftment bloodstream infection rates and associated mortality in allogeneic hematopoietic stem cell transplant recipients. Transpl Infect Dis 7:11-7, 2005
3. Sung L, Gamis A, Alonzo TA, et al: Infections and association with different intensity of chemotherapy in children with acute myeloid leukemia. Cancer 115:1100-8, 2009
4. Perencevich EN, Pittet D: Preventing catheter-related bloodstream infections: thinking outside the checklist. JAMA 301:1285-7, 2009
5. Micol JB, de Botton S, Guieze R, et al: An 18-case outbreak of drug-resistant Pseudomonas aeruginosa bacteriemia in hematology patients. Haematologica 91:1134-8, 2006
6. Gudiol C, Calatayud L, Garcia-Vidal C, et al: Bacteraemia due to extended-spectrum beta-lactamase-producing Escherichia coli (ESBL-EC) in cancer patients: clinical features, risk factors, molecular epidemiology and outcome. J Antimicrob Chemother 65:333-41, 2010
7. Avery R, Kalaycio M, Pohlman B, et al: Early vancomycin-resistant enterococcus (VRE) bacteremia after allogeneic bone marrow transplantation is associated with a rapidly deteriorating clinical course. Bone Marrow Transplant 35:497-9, 2005
8. Weinstock DM, Conlon M, Iovino C, et al: Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant. Biol Blood Marrow Transplant 13:615-21, 2007
9. Sample ML, Gravel D, Oxley C, et al: An outbreak of vancomycin-resistant enterococci in a hematology-oncology unit: control by patient cohorting and terminal cleaning of the environment. Infect Control Hosp Epidemiol 23:468-70, 2002
10. Singh-Naz N, Sleemi A, Pikis A, et al: Vancomycin-resistant Enterococcus faecium colonization in children. J Clin Microbiol 37:413-6, 1999
11. CDC: Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep 49:1-125, CE1-7, 2000
12. Siegel JD, Rhinehart E, Jackson M, et al: Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control 35:S165-93, 2007
13. Edmiston CE, Jr., Seabrook GR, Johnson CP, et al: Comparative of a new and innovative 2% chlorhexidine gluconate-impregnated cloth with 4% chlorhexidine gluconate as topical antiseptic for preparation of the skin prior to surgery. Am J Infect Control 35:89-96, 2007
14. Garcia R, Hibbard JS, Mulberry GK, et al: Comparison of chloraprep and betadine as preoperative skin preparation antiseptics. Presented at the 40th Annual Meeting of the Infectious Disease Society of America;, Chicago, Ill, 2002
15. Kaiser AB, Kernodle DS, Barg NL, et al: Influence of preoperative showers on staphylococcal skin colonization: a comparative trial of antiseptic skin cleansers. Ann Thorac Surg 45:35-8, 1988
16. Garibaldi RA: Prevention of intraoperative wound contamination with chlorhexidine shower and scrub. J Hosp Infect 11 Suppl B:5-9, 1988
17. Hayek LJ, Emerson JM, Gardner AM: A placebo-controlled trial of the effect of two preoperative baths or showers with chlorhexidine detergent on postoperative wound infection rates. J Hosp Infect 10:165-72, 1987
18. Paulson DS: Efficacy evaluation of a 4% chlorhexidine gluconate as a full-body shower wash. Am J Infect Control 21:205-9, 1993
19. Maki DG, Ringer M, Alvarado CJ: Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. Lancet 338:339-43, 1991
20. Bleasdale SC, Trick WE, Gonzalez IM, et al: Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. Arch Intern Med 167:2073-9, 2007

21. Climo MW, Sepkowitz KA, Zuccotti G, et al: The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. Crit Care Med 37:1858-65, 2009
22. Vernon MO, Hayden MK, Trick WE, et al: Chlorhexidine gluconate to cleanse patients in a medical intensive care unit: the effectiveness of source control to reduce the bioburden of vancomycin-resistant enterococci. Arch Intern Med 166:306-12, 2006
23. Popovich KJ, Hota B, Hayes R, et al: Effectiveness of routine patient cleansing with chlorhexidine gluconate for infection prevention in the medical intensive care unit. Infect Control Hosp Epidemiol 30:959-63, 2009
24. Milstone AM, Elward A, Song X, et al: Daily Chlorhexidine Bathing To Reduce Bacteremia in Critically Ill Children: a Multicenter, Cluster-Randomized, Two-Period Crossover Trial. Lancet, In press.
25. Alam MM, Kobayashi N, Uehara N, et al: Analysis on distribution and genomic diversity of high-level antiseptic resistance genes qacA and qacB in human clinical isolates of Staphylococcus aureus. Microb Drug Resist 9:109-21, 2003
26. Fang CT, Chen HC, Chuang YP, et al: Cloning of a cation efflux pump gene associated with chlorhexidine resistance in Klebsiella pneumoniae. Antimicrob Agents Chemother 46:2024-8, 2002
27. Kawamura-Sato K, Wachino J, Kondo T, et al: Reduction of disinfectant bactericidal activities in clinically isolated Acinetobacter species in the presence of organic material. J Antimicrob Chemother 61:568-76, 2008
28. Koljalg S, Naaber P, Mikelsaar M: Antibiotic resistance as an indicator of bacterial chlorhexidine susceptibility. J Hosp Infect 51:106-13, 2002
29. Maseda H, Hashida Y, Konaka R, et al: Mutational upregulation of a resistance-nodulation-cell division-type multidrug efflux pump, SdeAB, upon exposure to a biocide, cetylpyridinium chloride, and antibiotic resistance in Serratia marcescens. Antimicrob Agents Chemother 53:5230-5, 2009
30. Mayer S, Boos M, Beyer A, et al: Distribution of the antiseptic resistance genes qacA, qacB and qacC in 497 methicillin-resistant and -susceptible European isolates of Staphylococcus aureus. J Antimicrob Chemother 47:896-7, 2001
31. McDonnell G, Russell AD: Antiseptics and disinfectants: activity, action, and resistance. Clin Microbiol Rev 12:147-79, 1999
32. Noguchi N, Suwa J, Narui K, et al: Susceptibilities to antiseptic agents and distribution of antiseptic-resistance genes qacA/B and smr of methicillin-resistant Staphylococcus aureus isolated in Asia during 1998 and 1999. J Med Microbiol 54:557-65, 2005
33. Sheng WH, Wang JT, Lauderdale TL, et al: Epidemiology and susceptibilities of methicillin-resistant Staphylococcus aureus in Taiwan: emphasis on chlorhexidine susceptibility. Diagn Microbiol Infect Dis 63:309-13, 2009
34. Smith K, Gemmell CG, Hunter IS: The association between biocide tolerance and the presence or absence of qac genes among hospital-acquired and community-acquired MRSA isolates. J Antimicrob Chemother 61:78-84, 2008
35. Tattawasart U, Maillard JY, Furr JR, et al: Development of resistance to chlorhexidine diacetate and cetylpyridinium chloride in Pseudomonas stutzeri and changes in antibiotic susceptibility. J Hosp Infect 42:219-29, 1999
36. Vali L, Davies SE, Lai LL, et al: Frequency of biocide resistance genes, antibiotic resistance and the effect of chlorhexidine exposure on clinical methicillin-resistant Staphylococcus aureus isolates. J Antimicrob Chemother 61:524-32, 2008
37. Irizarry L, Merlin T, Rupp J, et al: Reduced susceptibility of methicillin-resistant Staphylococcus aureus to cetylpyridinium chloride and chlorhexidine. Chemotherapy 42:248-52, 1996
38. Cookson BD, Bolton MC, Platt JH: Chlorhexidine resistance in methicillin-resistant Staphylococcus aureus or just an elevated MIC? An in vitro and in vivo assessment. Antimicrob Agents Chemother 35:1997-2002, 1991

39. Adler A, Yaniv I, Steinberg R, et al: Infectious complications of implantable ports and Hickman catheters in paediatric haematology-oncology patients. J Hosp Infect 62:358-65, 2006
40. Simon A, Ammann RA, Bode U, et al: Healthcare-associated infections in pediatric cancer patients: results of a prospective surveillance study from university hospitals in Germany and Switzerland. BMC Infect Dis 8:70, 2008
41. Bacigalupo A, Ballen K, Rizzo D, et al: Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 15:1628-33, 2009

SAMPLE INFORMED CONSENT / PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document that are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the local IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ACCL1034, *Impact of Cleansing with Chlorhexidine Gluconate (CHG) on Reducing Central Line Associated Bloodstream Infection (CLABSI) and Acquisition of Multi-drug Resistant Organisms (MDRO) in Children with Cancer or Those Receiving Allogeneic Hematopoietic Cell Transplantation (HCT)*

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say "you" in this consent form, we mean you or your child; "we" means the doctors and other staff.

Why am I being invited to take part in this study?

You are being asked to take part in this research study because you about to undergo chemotherapy for more than 3 months or you are about to start treatment to prepare for a stem cell transplant. You also have a central line, a thin plastic tube placed in a vein in the upper chest or neck, which is used for intravenous (IV) medications.

In this study, we want to test if using CHG cleansing cloths can help prevent central line associated bloodstream infections (CLA-BSIs). Having a central venous catheter can increase the risk of bloodstream infections, CLA-BSIs are often a problem for children and young adults undergoing treatment for cancer. CHG stands for chlorhexidine gluconate. This is a special liquid cleaner that is used on the skin. CHG is a FDA approved for cleaning the skin before surgery. Studies have shown that daily bathing with CHG decreases bloodstream infections in critically ill children and adults. Daily bathing with CHG has not been studied in children or adults with cancer or those having a stem cell transplant.

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between other treatments to help prevent a central line infection and this clinical trial.

Please take your time to make your decision. You may want to discuss it with your friends and family. We encourage parents to include their child in the discussion and decision to the extent that the child is able to understand and take part.

What is the current standard of treatment for this problem?

Current treatments that are used to help prevent CLA-BSI include: hand washing before the central line is placed, having a sterile environment while putting the central line in place, cleaning the skin with antimicrobials (germ killing ingredients) such as CHG before the central line is placed, and cleaning the skin with CHG with central line dressing changes. Participation in this trial would not effect these standard treatments.

Why is this study being done?

The overall goal of this study is to compare the effects, good and/or bad, of CHG cloths with a control cloth (a cloth without the active ingredient CHG in it) for the prevention of CLA-BSI in children and young adults with central lines undergoing treatment for cancer, to find out which is better. In this study, you will use either the CHG cloths or the control cloths. You will not use both.

Preventing CLA-BSI is important for the following reasons:

- CLA-BSI is one of the most common and serious infections patients get; and
- Many patients with CLA-BSI will need to have their central lines removed and/or replaced.

CHG cloths have been researched in adult patients, and these studies have shown that use of CHG, either in cloths or as a liquid wash, helped reduce the chances of getting CLA-BSIs in patients with central lines. These studies also showed that the use of CHG reduced the chance of a patient acquiring bacteria (germs) resistant to multiple antibiotics.

The use of CHG cloths is experimental in children and adolescents with cancer. Study doctors would like to know how effective CHG cloths are for preventing CLA-BSI in children, adolescents and young adults undergoing treatment for cancer.

What will happen on this study that is research?

Summary of Study Treatments
In this study you will get 1 of 2 treatment plans. The 2 treatment plans are the same except for the different cleansing cloths you will use. You will not know which treatment you are receiving. The treatment on this study will take about 90 days.

The treatment involves the use of CHG cloths or control cleansing cloths in addition to or instead of your usual cleansing/bathing. You will be asked to use the cloths once per day, after or instead of your usual bathing. Cleansing with the CHG cloths or control cloths will continue for 90 days.

Some soaps and lotions can cause the CHG cloths to not work. You will be asked to only use soaps and lotions that work well with CHG regardless of which treatment plan you are receiving. A list of compatible soaps and lotions will be provided for you.

The 2 treatment plans are called Arm A and Arm B, as follows:

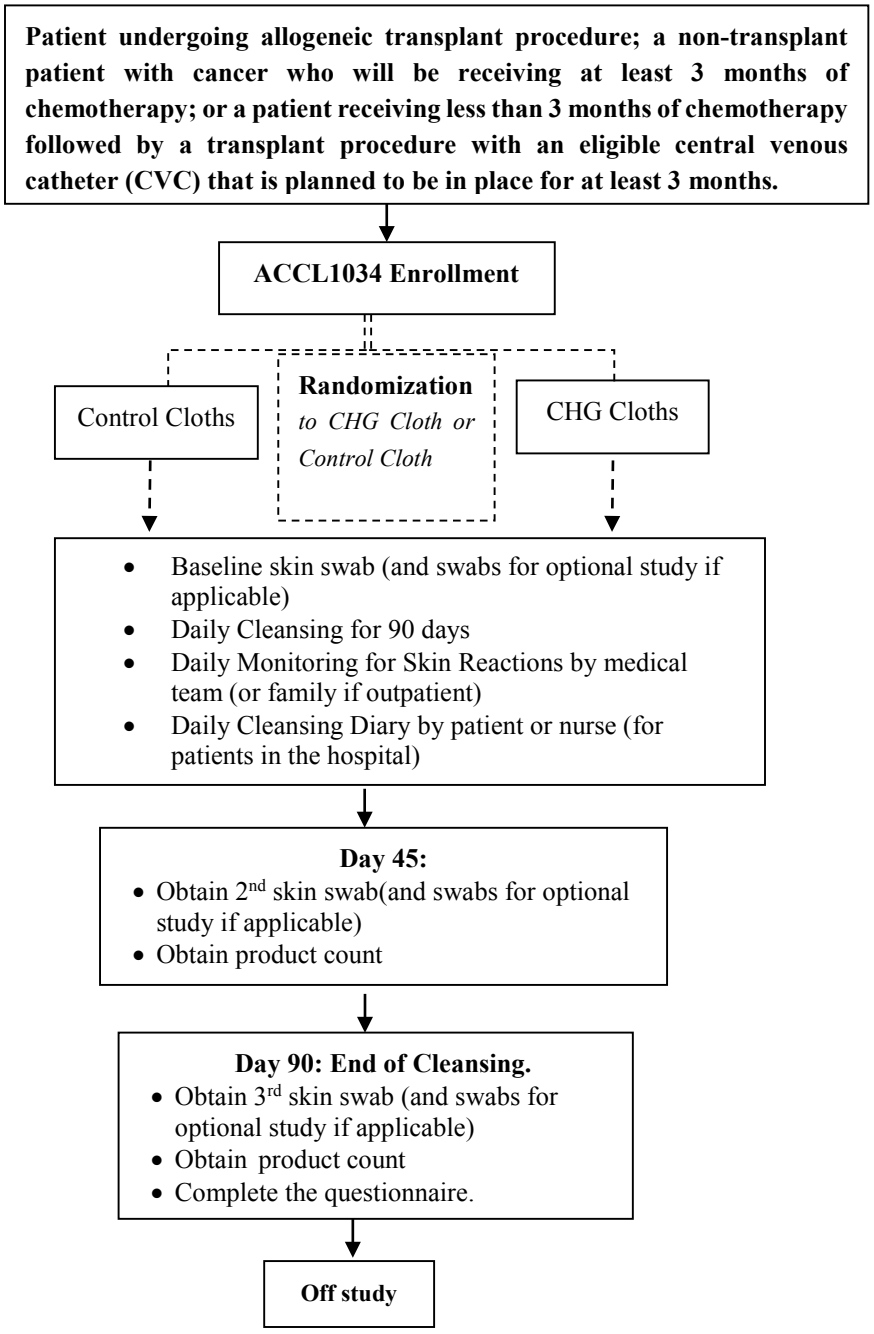
- Arm A (CHG Cleansing):Subjects will use the study cloth that contains CHG
- Arm B (Control Cleansing): Subjects will use the control cloth that does not contain CHG.

Random Assignment
You will receive 1 of 2 different treatment plans. The treatment plan that you receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer. You and your doctor will not pick which treatment you get. The randomization process is described in the COG Family Handbook for Children with Cancer.

Some subjects will be randomized to use the CHG cloths; others will be randomized to use the control cloths.

The cloths look the same. You and your doctor will not know which treatment plan you have been assigned to. This information will be kept by the pharmacists at the study coordination site.

Diagram of Treatment
This chart shows the treatments on this study.


Patient undergoing allogeneic transplant procedure; a non-transplant patient with cancer who will be receiving at least 3 months of chemotherapy; or a patient receiving less than 3 months of chemotherapy followed by a transplant procedure with an eligible central venous catheter (CVC) that is planned to be in place for at least 3 months.
ACCL1034 Enrollment
Control Cloths
Randomization
to CHG Cloth or Control Cloth
CHG Cloths
Baseline skin swab (and swabs for optional study if applicable)
Daily Cleansing for 90 days
Daily Monitoring for Skin Reactions by medical team (or family if outpatient)
Daily Cleansing Diary by patient or nurse (for patients in the hospital)
Day 45:
Obtain 2nd skin swab(and swabs for optional study if applicable)
Obtain product count
Day 90: End of Cleansing.
Obtain 3rd skin swab (and swabs for optional study if applicable)
Obtain product count
Complete the questionnaire.
Off study

Treatment that is Research

Treatment for subjects who are on Arm A (CHG Cloths)

Cloth	How the treatment will be given	For How Long
CHG cloth	Daily, after (or instead of) your usual bathing	90 days

Treatment for subjects who are on Arm B (Control Cloths)

Cloth	How the treatment will be given	For How Long
Control cloth	Daily after (or instead of) your usual bathing	90 days

If your chemotherapy treatment changes during the course of this study, as long as you still have a central line in place and plan to continue chemotherapy, you may remain on study.

Study Tests and Procedures

The following tests will be done because you are part of this study. If you were not in the study you would probably not have these tests.

1) Skin Swab to Check for Resistance to CHG

We would like to do some tests to check for the presence of bacteria on your skin. These tests are important to help us learn more about CHG cloths and how using them affects the bacteria on your skin. These tests will also help us learn more about whether bacteria can develop a resistance to CHG. These tests may also help children and young adults who use these cloths in the future. The information learned would not change the way you are treated, and the results of these tests will not be given to you.

We would take this swab sample at three times: when you enter the study (before treatment has started); half-way through the study (about Day 45); and when you finish the study (about Day 90). We would take this swab sample from the skin on your neck and in your underarm.

2) Testing the Bacteria that Cause Bloodstream Infections

As part of routine clinical care your blood may be drawn to check to see if you have a bloodstream infection. We will not draw your blood for the study. If you have a bloodstream infection while you are in the study, we will check to see if the bacteria in your blood are resistant to (or not destroyed by) CHG and commonly used antibiotics. You will receive standard clinical treatment for your bloodstream infection.

3) Daily Cleansing Diary

You will be given a daily diary that is like a calendar with checkboxes. You will be asked to mark if study cleansing was done each day. We will also ask you to mark if a regular soap and water bath was performed each day and we will ask you about any soaps and lotions you used each day.

4) Product Count and Satisfaction Questionnaire

Half way through the study and at the end of your participation in the study, we will ask you to count the packets of cleansing cloths you have left. This will give us an idea of how often you used the cleansing cloths. The product count should take about 5-10 minutes to complete. Additionally, at the end of the study we will ask you to fill out a short survey about the cleansing cloths. The survey should take about 5-10 minutes to complete.

Optional Research Study Tests

We would also like to do some other tests. Some bacteria are able to survive treatment with antibiotics. This is called antibiotic resistance. We would like to look for bacteria that are resistant to antibiotics. These tests are important to help us learn more about CHG cloths and whether using them can help decrease your risk of acquiring bacteria that are resistant to antibiotics.

These tests may also help children and young adults who use these cloths in the future. The information learned will not change the way you are treated, and the results of these tests will not be given to you. You do not have to do these tests if you do not want to. You can still be in the study if you do not want to do these tests. And the end of the consent form, there is a specific place to record your decision about taking part in each test.

We would like to collect swab samples from just inside your nose and your peri-rectum (just outside your rectum). Instead of a peri-rectum sample, you can choose to provide a stool specimen (collecting a sample of your feces when you have a bowel movement). These methods of collecting a sample from you will not cause you any pain. The peri-rectum swab (or stool sample) and the nose swab would happen when we are obtaining the skin swab.

What side effects or risks can I expect from being in the study?

Risks for subjects that receive CHG cloths (study risk)

Because there is very limited information about how well-tolerated the long-term use (more than 1 week) of the CHG cleansing cloths is in children, adolescents, or young adults undergoing treatment for cancer, there might be side effects that study doctors can not anticipate. The use of CHG cloths instead of control cloths may cause complications. The most common risk of using CHG cloths is skin rash or itching of the skin, but rare cases of severe allergic reactions, which may be life threatening, have been reported If this happens, you will stop using the CHG cloths. No serious allergic reactions were reported in recent studies using CHG cloths, including the study of CHG in children in the intensive care unit. There were a few skin reactions judged to be related to the CHG. All were mild.

Risks for subjects that receive Control cloths (study risk):

Subjects that receive the control cloths will be using a cloth without any active medication to prevent infections in it. Patients who use the control cloths may also get a mild rash.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

Are there benefits to taking part in the study?

We hope that this study will help you personally, but we do not know if it will.

A potential benefit to you could include being less likely to have an infection in your blood because of a central line infection.

We expect that the information learned from this study will benefit other patients in the future.

What other options are there?

Instead of being in this study, you have these options:

- **Taking part in another study.**

Please talk to your doctor about these and other options.

How many people will take part in the study?

The total number of people enrolled on this study is expected to be 450.

How long is the study?

People in this clinical trial are expected to receive treatment on this study for about 90 days. After treatment, you will not have any follow-up examinations or medical tests for this study.

You can stop taking part in the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first. They will help you stop safely.

Your doctor or the study doctor may decide to take you off this study:
- if he/she believes that it is in your best interest;
- if your disease comes back during treatment;
- if you experience side effects from the treatment that are considered too severe; or
- if new information becomes available that shows that another treatment would be better for you.

What about privacy?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included in **Attachment #1**.

Organizations that may look at and/or copy your research or medical records for research, quality assurance and data analysis include groups such as:

- **Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this hospital**
- **Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**
- **Seattle Children's Hospital**

What are the costs?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

The study bathing cloths are being provided at no charge to you. Neither you nor your insurance company will be charged for the study bathing cloths.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

Funding support

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to do the research. There are no plans to pay you for taking part in this study.

This study includes providing specimens to the researcher. There are no plans for you to profit from any new product developed from research done on your specimens.

What are my rights as a participant?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies COG if changes must be made to the study. Members of COG meet twice a year to discuss results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years from now since all people on the study need to have completed treatment.

Whom do I call if I have questions or problems?

For questions about the study or if you have a research related problem or if you think you have been injured in this study, you may contact Dr. *XXXX* or your doctor at *XXXX*.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call *XXXX* IRB Administrator at *XXXX*.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at *XXXX*.

Where can I get more information?

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

The COG Family Handbook for Children with Cancer has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org/.

Visit the NCI's Web site at http://www.cancer.gov.

If you are in the United States, you may call the NCI's *Cancer Information Service* at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.

Information about long term follow-up after cancer treatment can be found at: http://www.survivorshipguidelines.org/.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Specimens for optional research tests

The choice to let us use specimens for research is up to you. No matter what you decide to do, it will not affect your care. You can still be a part of the main study even if you say 'No' to taking part in any of these optional research studies.

If you decide now that your specimens can be used for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then, any specimens that we have will be destroyed.

Please read the information below and think about your choices. After making your decisions, check "Yes" or "No", then add your initials and the date after your answer. If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number included in this consent.

#1 Swabs of my nose and peri-rectum or stool may be sent to a laboratory and studied to see if special tests can identify germs on my skin and if they have developed a resistance to germ-killing substances.

Yes_____ No_____ _____ / _____
Initials Date

Signature

I have been given a copy of all _____ pages of this form. The form includes one (1) attachment.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant_____Date _____

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____

IRB# _____ IRB Approved: _____

Attachment #1

Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.