COMMUNITY CENTRAL LINE INFECTION PREVENTION (CCLIP) Trial

SUPPLEMENT A

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Study Protocol

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1. Synopsis:

The overall goal of this Community Central Line Infection Prevention (CCLIP) trial, supported by grant R01 HS022870 from the Agency for Healthcare Research and Quality, is to determine whether use of a promising new intervention, namely 70% isopropyl alcohol embedded protective caps on central lines, in the home setting is associated with a reduction in ambulatory central line-associated bloodstream infections (CLABSI) in a high-risk population of pediatric hematology/oncology patients. The National Association of Children's Hospitals and Related Institutions (NACHRI), now renamed the Children's Hospital Association (the Association), a 200+ member, not-for-profit organization of children's hospitals, has developed, sustained and spread several quality transformation efforts focused on CLABSI elimination in hospitalized settings. The Association's CLABSI prevention work in hospitalized, non-intensive care unit (ICU) children with chronic conditions was supported by an Agency for Healthcare Research and Quality (AHRQ) grant (R18 HS019590 "Eliminating CLABSIs in Chronic Central Lines"). Preliminary analyses show a nearly 30% decrease in CLABSI rates in this high-risk non-ICU population. The Association's Pediatric ICU CLABSI effort, operating since 2006 and involving over 70 PICUs, has resulted in CLABSI rates dropping dramatically from 5.5 infections per 1,000 central line days to approximately 1 infection per 1,000 central line days. Despite these successes, it remains unknown what generalizable best practices should be with chronic central lines in the home setting and how effective involving patients and caregivers across multiple institutions in CLABSI reduction efforts will be. This proposed research, working with an anticipated 24 children's hospitals, will layer a cluster-randomized, cross-over design, clinical trial on the learnings and foundation of the prior AHRQ-supported grant to standardize and spread best-practice care bundles among caregivers for children with chronic hematologic/oncologic conditions. This proposal will be first prospective trial of a promising new intervention and will focus on the caregivers integral to ambulatory pediatric central line care: patients and families. Successful completion of this project will give AHRQ, healthcare providers, patients, payers, and policymakers generalizable and effective tools for spreading CLABSI eradication efforts outside hospitalized settings.

2. Background and Rationale:

A. Background:

The proposed study addresses the salient topic of central line-associated bloodstream infections (CLABSI) in chronic central lines at home for children with chronic hematologic and oncologic diagnoses. Evidence-based practice can, we believe, dramatically reduce patient risk of CLABSI and the resulting morbidity in this high-risk population. Childhood survival after a cancer diagnosis has significantly increased over the past 25 years in the United States.[1,2] One reason is intensive chemotherapy regimens delivered through implanted and non-implanted central lines.[1,2] Unfortunately, these same central lines put many immune-compromised children at risk for healthcare associated infections such as CLABSIs. Much research has been accomplished on reducing CLABSIs in the hospitalized patient but relatively none has been done for CLABSIs occurring at home.[3,4,5,6] In high risk populations, such as children with hematologic/oncologic diagnoses, a recent study noted a 2-fold increase in the number of ambulatory pediatric oncology CLABSIs as compared to inpatient pediatric oncology CLABSIs.[7] Our own single institutional research (AHRQ grant K08 HS021282 "CLABSIs in Ambulatory Pediatric Oncology Patients) found a 3-fold higher incidence of CLABSI in ambulatory settings as compared to inpatient settings for children with oncologic diagnoses.[8] These data suggest a higher burden of CLABSI disease in the ambulatory setting. Furthermore, the impact of a CLABSI at home is substantially greater than as an inpatient as these events most often result in a hospitalization, active treatment for the infection, as well as missed time from school and work for the patient and caregivers. Central lines in the home setting have unique attributes that hamper translation of known best practices in the inpatient setting. Three examples illustrate these unique attributes: 1. the caregivers handling the central line at home are patients and families as opposed to medically trained nurses and physicians; 2. one strategy to reduce inpatient CLABSI is to remove the central line as soon as possible; in the ambulatory setting, the express purpose of the central line is to leave it in for extended duration; and 3. the central line in a home setting is subject to realities not encountered in hospitals such as patients playing sports or exercising, routinely showering, and pets. The recent development of 70% isopropyl alcohol embedded protective caps for central lines opens the door to a relatively easy to use, inexpensive, and therefore, amenable to use in the home setting, medical device to reduce CLABSI. Initial studies on these 70% isopropyl alcohol embedded protective caps suggest significant reductions in inpatient CLABSI rates.[9,10,11] This proposal will be the first prospective trial of the use of these promising 70% isopropyl alcohol embedded protective caps to reduce CLABSI in the home setting and also be one of the first prospective trials of any interventions to reduce CLABSI in the home setting.

B. Rationale:

Central line-associated blood stream infections (CLABSI)

CLABSIs are common.[3,4,5] The overwhelming majority of CLABSI research to date derives from intensive care units and a 2011 report from the Centers for Disease Control and Prevention (CDC) attests to the dramatic reductions in ICU CLABSI cases over the last 10 years.[3,6] What this recent CDC report also highlights however is that the burden of CLABSIs is now centered on outpatient settings and non-ICU inpatient wards. The last several reports from the CDC on CLABSI rates have consistently shown that across all types of settings and patients, children are at the high end of CLABSI rates.[12,13,14] The most recent estimates from December 2009 show that Pediatric ICUs continue to have the third highest rate compared to 13 other types of ICU, and among 20 types of non-ICU inpatient wards pediatric medical/surgical wards have the highest CLABSI rates.[15] This higher rate in pediatric settings likely derives from intrinsic differences in how central lines are handled between adult and pediatric patients and makes pediatrics an ideal learning environment. What is equally important to stress however is the 2011 CDC report highlights for the first time that that highest rates of CLABSI in the United States at present are in outpatient settings. None of the nearly annual CDC reports on CLABSIs nor data in the CDC's National Healthcare Safety Network (NHSN) at present systematically includes data on outpatient CLABSIs. Given the trend in ICU and non-ICU inpatient settings, it is highly likely that children have some of the highest rates of outpatient CLABSIs.

CLABSIs are also costly, averaging $45,000 per event, and potentially lethal.[13] Looking at the decline in ICU CLABSI from 2001 to 2009, the CDC recently estimated that the success of CLABSI reduction efforts in ICUs has saved over 6,000 lives and $1.8 billion in cumulative excess healthcare costs.[3] The lives and cost savings achievable among chronic central lines outside the ICU are unknown, but are likely greater in magnitude given

the shift in healthcare to increased survivability with chronic conditions and the advances in chronic delivery of medications via central lines both outside the ICU and even outside hospitals.

CLABSI's are a significant source of morbidity, mortality and added medical costs for pediatric hematology/oncology patients.[16,17,18,19,20,21,22,23] According to the most recent NHSN data, the rate of CLABSI's among pediatric oncology patients is higher than CLABSI rates among 10 types of ICUs. In addition, pediatric rates of CLABSI among temporary central lines in oncology are the highest compared to all adult oncology patients, including bone marrow transplant recipients, with a rate of 4.6 infections per 1000 central line days.[15]

Evidence of 'what works' for chronic central line CLABSI prevention can be best discovered with pediatric central lines, building on prior research

Compared to adult ICU efforts, diligent focus in the mid 2000s on solely central line insertion practices in Pediatric ICUs had yielded much smaller reductions in CLABSI.[6,24,25] The reasons behind this historic reality are multi-faceted. First, key differences exist in the evidence behind some central line-related insertion factors that are important in adult CLABSI reduction, namely a lack of evidence that the femoral site is problematic in children.[26,27,28] In addition, pediatric healthcare providers recognize that children have unique risks factors for CLABSI compared to adult patients. For example, pediatric providers utilize central lines differently than adult-focused providers, with a greater reliance on maintaining central lines to obtain needed blood samples or keeping lines in place longer to ensure secure venous access in an emergency given the difficulty of venous access especially in small children. Based on the initial 12 months of work of first 29 PICUs participating in the National Association of Children's Hospitals and Related Institutions (NACHRI) Pediatric ICU CLABSI reduction effort from October 2006 through September 2007, we now know that for children in ICUs the main driver for reducing CLABSI is safe day to day handling of the central line, known as Maintenance Care, not the practices around insertion of central lines.[29,30] In short, while adult-focused ICU providers can nearly eliminate the risk of CLABSI by focusing on best practices when central lines are inserted, pediatric providers need to instead focus on the day to day handling of central lines in the ICU in order to reduce CLABSI. For every one central line insertion there are literally hundreds of episodes of day to day handling of the central line for each patient. This pediatric driven evidence that the day to day maintenance care of central lines leads to CLABSI reduction, opens the door to expanding CLABSI reduction efforts to chronic outpatient central lines, where maintenance care is paramount.

Compounding the 'unknown' on how best to handle chronic, outpatient central lines is the reality that ICU efforts on reducing CLABSI include a focus on 'removing' central lines as fast as clinically possible. In chronic outpatient central lines, such as with chronic oncologic or hematologic conditions, the express purpose of the central line is to keep the central line in place for weeks and even months. It is undoubted that a more robust daily maintenance care bundle for chronic, outpatient central lines will need to be developed and evaluated than has been shown effective for maintenance in acute central lines in ICUs. It is imperative, therefore, that research of the type we propose is undertaken to develop and evaluate promising new practices, such as the reliable use of 70% isopropyl alcohol embedded protective caps on central lines, for day to day handling of chronic, outpatient central lines by patients and families so that CLABSI rates in the outpatient setting can finally be reduced.

The outpatient setting introduces numerous complexities not encountered in the ICU setting, namely patients and non-clinical caregivers doing a majority of the day-to-day central line care. Focused research needs to be done to understand how to extrapolate and tailor ICU-based CLABSI reduction efforts to chronic, outpatient central lines. Given that children with oncologic conditions have one of the highest burdens of CLABSIs among chronic central lines and over 60% of these children have a central line, they represent an ideal population for this research.

70% isopropyl alcohol embedded protective caps to reduce CLABSI are a new and ideal intervention for patients and families to implement

In 2012 and 2013, three published studies have shown promising impact of 70% isopropyl alcohol embedded protective caps to reduce CLABSI and overall positive blood culture rates, likely due to reduced central line hub contamination, within the hospital.[9,10,11] These studies have, respectively, been conducted on an inpatient adult oncology unit, 2 adult ICUs, and all adult inpatient units, each within a single health system. The reported dramatic and statistically significant CLABSI rate decreases were, respectively, as follows: 2.3 CLABSI/1,000 central line days down to 0.3 CLABSI/1,000 central line days; 1.9 CLABSI/1,000 central line days down to 0.5

CLABSI/1,000 central line days; and 1.43 CLABSI/1,000 central line days down to 0.69 CLABSI/1,000 central line days. The dramatic and statistically significant decreases in rates of positive blood cultures due to contaminated central line hubs were, respectively, as follows: 2.5% decreased to 0.2%, and 12.7% decreased to 5.5%. These data suggest approximately 50-80% decreases in inpatient CLABSI rates and positive blood culture rates due to hub contamination due to use of 70% isopropyl alcohol embedded protective caps. Each of these studies, however, was only done within a single institution and only done on the inpatient side. While clearly showing a significant inpatient CLABSI and positive blood culture rate impact, these 70% isopropyl alcohol embedded protective caps are an ideal intervention for the more chaotic and less controlled home setting. These protective caps are applied to central lines in a few seconds, luer lock onto the central line cap for safety, and then passively protect the central line by continuously bathing the central line cap in 70% isopropyl alcohol. These protective caps disinfect the central line access port within 3 minutes and can keep the central line access port clean for up to 7 days before needing to be changed. In the home setting, the likelihood of the central line access port touching non-sterile surfaces or, for example, inadvertently slipping inside the diaper of a small child, is much greater than the more controlled inpatient setting. These 70% isopropyl alcohol embedded protective caps would provide an easily applied and consistent barrier of protection for the central line access ports to prevent catheter hub contamination, subsequent bacteremias, and CLABSIs.

C. Significance of the Proposed Research:

New research, focused on pediatric care has proven that once we achieve ideal central line insertion-related practices that the most important driver for further reducing CLABSIs is the daily maintenance care.[29,30] Furthermore, a 2011 CDC report highlights that the greatest burden of CLABSI is now the outpatient setting due to 10+ years of successful research on reducing ICU CLABSI.[3] This project can and would change healthcare by finally broadening the focus on preventing CLABSI from just acute central lines utilized in ICU to the chronic central lines in the ambulatory setting. Although hard estimates are difficult to obtain, there exist substantially more central lines in outpatient settings than inpatient due to the advances in healthcare and home care. Our proposed study will be the first prospective trial of a promising new intervention, 70% isopropyl alcohol embedded protective caps, to reduce CLABSI in the home setting. This work will scientifically address the silence in baseline data on outpatient CLABSI rates and the silence on effective national recommendations regarding best practices, such as 70% isopropyl alcohol embedded protective caps on central lines, for management of chronic, outpatient central lines. Given the high burden of chronic, outpatient central lines and infections in the community, the time has come for innovative efforts to tackle the CLABSI problem in environments outside the well-investigated ICUs.

3. Study Purpose, Objective and Hypotheses:

A. Purpose: The goal of this project is to determine the effectiveness of 70% isopropyl alcohol embedded protective caps to reduce CLABSIs, secondary bloodstream infections (BSI), and single positive blood cultures (SPBC) at home for chronic central lines in pediatric hematology/oncology patients.

B. Objectives: To compare the effectiveness of 70% isopropyl alcohol embedded protective caps to "usual care" on reducing CLABSIs, secondary BSI, and SPBC at home for chronic central lines in pediatric hematology/oncology patients.

C. Primary Hypothesis: Use of 70% isopropyl alcohol embedded protective caps on central lines will be associated with at least a 25% reduction in the ambulatory CLABSI rate for pediatric hematology/oncology patients.

D. Secondary Hypotheses:

- **i.** Use of 70% isopropyl alcohol embedded protective caps on central lines will be associated with at least a 25% reduction in the positive blood culture rate (defined as sum of CLABSI + BSI + SPBC) at home for pediatric hematology/oncology patients.
- **ii.** Use of 70% isopropyl alcohol embedded protective caps on central lines will reduce Gram-positive CLABSI, secondary blood steam infections, and single positive blood cultures at home for pediatric hematology/oncology patients.

4. Study Procedures:

A. Design Summary:

The proposed Community Central Line Infection Prevention (CCLIP) trial is an investigator-initiated, cluster-randomized, 2 period crossover, clinical trial to evaluate the effectiveness of 70% isopropyl alcohol embedded protective caps in reducing CLABSIs, secondary BSI, and SPBC at home for chronic central lines in pediatric hematology/oncology patients. The Control Arm will involve reliable use of the best practice "usual care" for ambulatory central lines and the Intervention Arm will add use of 70% isopropyl alcohol embedded protective caps in addition to "usual care". Each participating institution will be randomly assigned to either the intervention or control phase of the design for the first 12 months of the study. There will then be a 3 month wash out period, followed by each institution then implementing either the control or intervention phase for another 12 months such that each institution will complete 12 months each in the intervention arm and the control arms of the study.

B. Study Organization:

The work will build on the partnership between the pediatric quality improvement research group at Johns Hopkins University which will serve as the CCLIP Trial Coordinating Center, the 12-24 individual institutional teams comprised of pediatric hematology/oncology clinics across the USA, and the vendor 3M Corporation, maker of the CUROS® brand 70% isopropyl alcohol embedded protective caps for central lines.[31,32]

The CCLIP Trial Coordinating Center will be at Johns Hopkins University. Dr. Miller is Principal Investigator. The Coordinating Center also includes: Dr. Aaron Milstone at Johns Hopkins University, director of pediatric hospital epidemiology and infection control; Dr. Elizabeth Colantuoni a Biostatistician and Assistant Scientist in the Johns Hopkins Bloomberg School of Public Health; Nichole Persing, a Research Assistant who will focus on data collection and quality assurance, and a To Be Determined Research Assistant who will focus on support of the 12-24 individual institutional teams participating in this trial. In addition, the CCLIP Trial Coordinating Center will work in partnership with the Johns Hopkins Bloomberg School of Public Health Biostatistics Consulting Center for final data analysis of this trial.

Each of the anticipated 12-24 individual pediatric hematology/oncology institutional teams from across the USA will designate a Principal Investigator for their site as well as a Nurse Champion and clinic team to work on this trial.

C. Study Timeline:

The work will span four years. Year 1 Preparatory work will include establishing Institutional Review Board approval at participating institutions, setting up distribution mechanisms for the intervention both to the clinics and then within each clinic to the homes, and educating providers, patients, and families on how to apply the CUROS® cap across all the participating institutions. (Table 1)

Table 1: Proposed Timeline

STUDY YEAR	1				2				3				4			
Calendar Year	2014-2015				2015-2016				2016-2017				2017-2018			
Quarter	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2
Year One preparatory work	X	X	X	X												
Hypothesis #1 and #2					X	X	X	X			X	X	X	X		
Hypothesis #3					X	X	X	X			X	X	X	X		
Wash out period between crossover									X							
Intervention ramp up for crossover teams									X	X						
Analysis/Manuscript preparation															X	X

D. Intervention Arm:

i. Intervention:

The intervention we will deploy in the CCLIP Trial is the CUROS® brand of 70% isopropyl alcohol embedded protective caps for central lines. (Figure 1 and 2) These caps are manufactured by 3M Corporation. As in kind contribution to this proposed study, 3M Corporation has agreed to donate and distribute all needed CUROS® caps to the participating institutions for the duration of this study. 3M Corporation had no role in study design and will have no role in the data collection, data analysis, data interpretation, writing of the report, or decisions regarding publication.

Figures 1 and 2: Photographs of the green CUROS® 70% Isopropyl Alcohol Embedded Protective Cap for Central Lines

ii. Alternative Acceptable Intervention:

It is possible that some teams interested in participating in this CCLIP trial may prefer to use a comparable brand of 70% isopropyl alcohol embedded protective caps for central lines (e.g. DualCap or SwabCap). If the CCLIP Trial Coordinating Center finds this to be the preference of some of the teams, these teams would be permitted to enroll in this trial, assuming they agree to the full protocol as written here. These teams using a comparable brand of 70% isopropyl alcohol embedded protective caps for central lines (e.g. DualCap or SwabCap) would not receive in kind contribution of the intervention central line caps via 3M Corporation. These teams would be expected to supply their own chosen brand of 70% isopropyl alcohol embedded protective caps for central lines. All sites using an alternative acceptable intervention must agree to fully participate in both arms of the trial, the Intervention Arm and Control Arm.

iii. Intervention Distribution to Clinics:

Distribution of the CUROS® caps will be accomplished via 3M Corporation directly to the clinics of each participating institution. Each participating clinic site will need to establish contact staff for receipt, storage and distribution of CUROS® caps.

iv. Intervention Distribution via Clinics to Patients/Families:

Children with chronic hematologic/oncologic conditions are seen frequently in pediatric hematology/oncology clinics, often up to several times per week. Subjects (pediatric patients of the hematology/oncology clinics with external central lines) and their parents/caregivers will receive supplies of the 70% isopropyl alcohol embedded protective caps for central lines as well as standardized instructions for use from the clinic staff/local institutional research team at their usually scheduled recurring clinic visits. There will not be any required clinic visits solely for the purposes of this CCLIP Trial.

Clinic staff will distribute and track the volume of CUROS® caps dispensed to each family/patient, with the family/patient reporting back each subsequent visit on the remaining volume of CUROS® caps. This will ensure reliable distribution to the families/patients, provide a face-to-face educational opportunity to ensure proper application of the CUROS® cap, and provide opportunities to assess compliance via volume of CUROS® caps utilized.

v. Instruction on Intervention to Clinics:

The CCLIP Trial Coordinating Center in partnership with 3M Corporation will facilitate staff education on the use and disposal of CUROS® caps. This will be tailored to the needs of each participating clinic and may include the following: brochures, video demonstrations, conference calls, and site visits.

vi. Instruction on Intervention via Clinics to Patients/Families:

The CCLIP Trial Coordinating Center in partnership with 3M Corporation will facilitate clinic staff on developing their patient/family educational materials for the use and disposal of CUROS® caps. The instructions will entail teaching that the hub of the central line is to be protected via luer-lock placement of the 70% isopropyl alcohol embedded protective caps for central lines at all times while the patient is in the ambulatory setting (e.g. home, school, work, etc). If there is the need to infuse medications, parenteral nutrition, flush solutions, or fluids, the 70% isopropyl alcohol embedded protective cap is to be removed and discarded. After completion of the infusion, a new 70% isopropyl alcohol embedded protective cap will be luer-locked onto the central line hub by the patient or parent/caregiver. Any single 70% isopropyl alcohol embedded protective cap can only stay in place for 7 consecutive days. Therefore, instructions will also include changing the 70% isopropyl alcohol embedded protective caps for central lines at 7 days.

E. Control Arm:

Each participating institutional team will participate in both the Intervention Arm and the Control Arm for 12 months time each. During the Control Arm, the care of the central line while the patient is in the ambulatory setting will be per individual institutional policy for ambulatory central line care.

F. Enrollment and Ongoing Participation of Patients/Families via the Clinics:

i. Patient Eligibility:

All patients of the participating pediatric hematology/oncology clinics who have an external central line (e.g. Hickman, Broviac, central PICC, non-tunneled central lines) will be eligible for participation in this trial. Given that the intervention is a protective cap for central line access connectors, patients who only have a totally implanted port as their central venous access will not be eligible for this study as the intervention is not physically applicable to such central lines when they are not accessed. There are no other exclusion criteria.

ii. Patient Recruitment:

The individual institutional clinic team will pre-screen patients for eligibility at the start of each clinic session. A member of the study team will approach the patient/parent/caregiver unit in their clinic room and inform them about the clinic's participation in this minimal risk trial as outlined in the next sections. During each institutional clinic teams participation in the 12 month long Intervention Arm, all existing and new clinic patients during that 12-month time period will be informed about trial participation.

iii. Patient Consent:

Given the minimal risk of the trial, the CCLIP Trial will operate with a consent waiver although each participating site is required to comply with their own Institutional Review Board recommendations. This waiver will not adversely affect the rights and welfare of the participants given two factors: 1. it is acceptable for individual patients/families to decline to participate; and 2. this trial is focused on patients/families complying with an intervention while the child is at home that the patients/families

themselves are responsible for doing (e.g. if patients/families do not wish to participate in trial they have full control to not do so given they are the mediators of the trial's intervention).

A Patient Information Sheet, drafted by the CCLIP Trial Coordinating Center, will be provided to all eligible clinic patients.

iv. Patient Refusal to Participate:

Patients/parent/caregiver units may choose to not participate in this CCLIP trial. These patients will continue to receive the usual ambulatory care for central lines as per institutional policy.

v. Patient Withdrawal from Trial:

Patient/parent/caregiver units may discontinue participation in the Intervention Arm if they choose. In these cases, they will be instructed by clinic staff to resume the standard ambulatory care of their central line as per individual institutional policy.

vi. Change in Patient's Ambulatory Status during the CCLIP Trial:

If during the Intervention Arm phase of the CCLIP trial an individual participant is admitted to the hospital, the use of the 70% isopropyl alcohol embedded protective cap will be discontinued and care of the central line will be per individual institutional inpatient policy.

Upon discharge from that hospital admission, that individual participant can re-enter the CCLIP trial, using their home supply of 70% isopropyl alcohol embedded protective caps..

5. Primary and Secondary Outcomes:

A. Primary Outcome:

Primary outcome is ambulatory central line associated bloodstream infections (CLABSI) during either the 12-month Intervention Arm or the 12-month Control Arm phase of this trial. CLABSIs will be defined according to Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC NHSN) criteria. An ambulatory CLABSI is defined as a CLABSI that occurs more than 48 hours after hospital discharge or within 48 hours of hospital admission.

Primary outcome ascertainment – Each participating institutional clinic team will work with their Infection Control staff to determine which ambulatory positive blood cultures meet definitional criteria for CLABSI.

B. Secondary Outcomes:

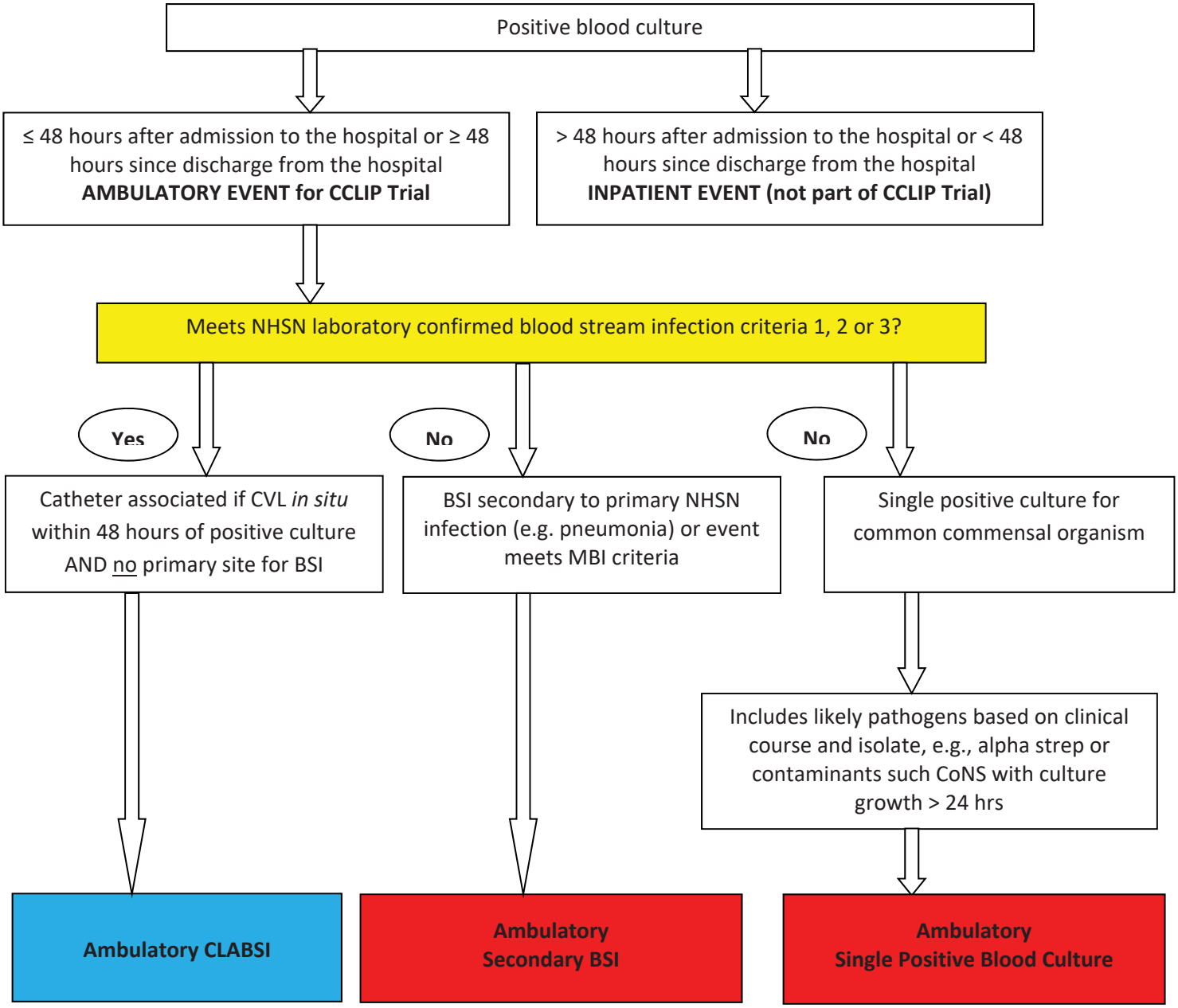
i. Ambulatory secondary bloodstream infections (secondary BSI) during either the 12 month Intervention Arm or the 12 month Control Arm phase of this trial. Secondary BSI will be defined as BSIs that meet the CDC NHSN's criteria for BSIs with a secondary source (such as pneumonia, abscess, etc.). Secondary BSIs will also include those BSIs that meet the laboratory-confirmed mucosal barrier injury (LC-MBI) criteria.

ii. Ambulatory single positive blood cultures (SPBC) during either the 12 month Intervention Arm or the 12-month Control Arm phase of this trial. Single positive blood cultures will be defined as any single positive blood culture that grows an organism on the CDC NHSN's list of common commensal organisms (such as coagulase-negative Staphylococci, *Bacillus* spp.).

iii. Microorganism speciation name for any CLABSI, secondary BSI, or SPBC event.

Secondary outcomes ascertainment – Each participating institutional clinic team will work with their Infection Control staff to determine which ambulatory positive blood cultures meet definitional criteria for CLABSI

C. Decision flow when adjudicating primary versus secondary BSI:



6. Institutional Clinic Data Collection and Submission:

A. Required Monthly Data for CCLIP Trial:

Each participating institutional clinic will set up procedures to collect and submit aggregate clinic level data required for this CCLIP trial. Aggregate clinic data will be collected and submitted as an "intention to treat at the clinic level" approach. This means that if some patients with external central lines decline to participate in this trial, the aggregate clinic data for that site will still include the primary and secondary outcomes as well as the central line day counts for these non-participating patients. No patient identifiable or protected health information will be submitted to the CCLIP Trial Coordinating Center at Johns Hopkins University. The data to

be submitted by each institutional team to Johns Hopkins University and encompassing only their CCLIP Trial eligible and participating patients include:

i. Overall count of CLABSI, secondary BSI and single positive blood cultures for their entire eligible ambulatory patient population each month (participating and non-participating patients).
ii. Monthly aggregate external central line day count for their entire eligible patient population (participating and non-participating patients). If any given patient is admitted to the hospital during any month, the contribution of that patient's ambulatory central line days to the clinic aggregate ambulatory central line day tally will exclude the inpatient days for that patient.
iii. Monthly tally of named microorganisms in each positive CLABSI, secondary BSI and single positive blood culture (e.g. Streptococcus Group C, Klebsiella pneumonia) for their entire eligible ambulatory patient population (participating and non-participating patients).

The CCLIP Coordinating Center at Johns Hopkins University will create a REDCap database, which is a secure, web-based application designed exclusively to support data capture for research. The Johns Hopkins University is a member of the REDCap consortium. Participating institutional clinics will upload their monthly data directly into the REDcap database for this CCLIP Trial.

For institutional clinics that happen to also be participating in the Children's Hospital Association Pediatric Hematology/Oncology Quality Transformation Network effort, the required data for this CCLIP Trial are completely encompassed in the data those sites already submit monthly to the Children's Hospital Association. For such institutional clinic teams, the CCLIP Coordinating Center at Johns Hopkins University has arranged the cooperation of the Children's Hospital Association to, with institutional clinic approval, directly send to the CCLIP Coordinating Center.

B. Annual Data for CCLIP Trial:

In order to facilitate understanding the demographics of patients at the participating institutional clinics as well as adjusting for any significant variations in patient populations by clinic, the CCLIP Trial Coordinating Center will annually, in Year 1-3 of the trial, send out an electronic survey to participating institutional clinics to capture overall clinic patient demographics such as gender distribution, race distributions, age distributions, diagnosis group distributions, overall number of clinic visits per year, and overall number of unique patients seen in clinic per year. In addition this survey will query clinics to report on other infection prevention strategies used in some or all of their ambulatory patients. These other strategies will include items such as biopatches, antibiotic coated catheters, antibiotic/non-antibiotic locks in central lines, and chlorhexidine baths in ambulatory setting.

C. Compliance Data:

Assessing compliance of the patients/families/caregivers with the use of the 70% isopropyl alcohol embedded protective caps on central lines while patients are not hospitalized will be difficult but important to the CCLIP Trial. Given the clinic staff will distribute and track volume of CUROS® caps dispensed to each family/patient, with the family/patient reporting back at each subsequent visit on the remaining volume of CUROS® caps, we will use this information as a qualitative view into home compliance via relative counts of CUROS® caps utilized by each patient. The CCLIP Trial Coordinating Center will monthly query each participating institutional clinic for overall compliance assessment of their patient population and, if the clinic is able to quantify this, monthly percentage of patients determined to be poorly or non-compliant with use of the 70% isopropyl alcohol embedded protective caps on central lines while patients are not hospitalized.

D. Adverse Event Data:

We do not anticipate any adverse events from the use of these 70% isopropyl alcohol embedded protective caps on central lines in the home setting. However, the CCLIP Trial Coordinating Center will monthly query each participating institutional clinic for any reports of potential adverse events related to use of the 70% isopropyl alcohol embedded protective caps on central lines in the home setting.

7. Risks and Benefits:

A. Potential Risks:

The CUROS® port protector is a single use, sterile device that contains 70% isopropyl alcohol and is intended to be used as a disinfectant for needleless luer activated valves such as central line access ports. The Food and Drug Association (FDA) has classified the CUROS® device as a Class II device under product code LKB, subjected to premarket clearance under the 510(k) clearance process. The FDA has reviewed and cleared the CUROS® device under 510(k) number K111992. Examples of other Class II devices include powered wheelchairs, infusion pumps, and surgical drapes.

As background, under the Food, Drug, and Cosmetic Act, the FDA recognizes three Classes of medical devices, based on the level of control necessary to assure safety and effectiveness. These are Classes I, II, and III. The FDA also permits two regulatory pathways for medical devices. The first and most common is the premarket notification 510(k) process, which applies to the CUROS® cap. The 510(k) process requires that a new medical device demonstrate that it is "substantially equivalent" to a previously legally marketed device. If this proof is achieved, the device can be cleared by the FDA for marketing. Given the relative safety of Class 1 and Class II devices compared to Class III devices, the 510(k) pathway rarely requires clinical trials. The second regulatory pathway, which applies to Class III new medical devices, is the Premarket Approval process, which is similar to the pathway for a new drug approval. Typically, clinical trials are required for Class III devices, as well as scientific review, to ensure the device's safety and effectiveness. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.

Given the relative safety of Class II devices, there are no special FDA controls required for the CUROS® device. There are no mandatory standards imposed by the FDA for this device. The Curos, like any legally marketed device, is required to meet the post market surveillance requirements established by the FDA. 3M Corporation has quality system procedures in place to meet these requirements.

The CUROS® device to be used in this proposal is the exact same device that is currently sold throughout the USA. The use of the CUROS® device in this evaluation is consistent with the intended use and labeling of the currently marketed device. This evaluation does not involve any off label use, or any alteration of the legally marketed device. In the CUROS® 510(k) review, the FDA intended use indications confirmed that test data for disinfection shows effect after 3 minutes of application of the CUROS® cap and this protection stays up to 7 days (168 hours). The FDA Indications statement states that the CUROS® port protector may be used in the home or healthcare facility for all age patients.

B. Protection against Risks:

One minimal risk, given the patients are children, is a choking hazard since the CUROS® cap is a relatively small device. Given this, the CUROS® cap luer locks onto the central line hubs much like other central line devices used in the home and hospital setting. The FDA has not restricted the indications for the CUROS® cap based on patient age.

An additional risk is the identification of individual patients. The data to be collected for this study for CLABSI, secondary BSI, and SPBC encompass only aggregate, institutional-level infection rates. The data regarding microorganism speciation are not identifiable to individual patients. None of these data contain Protected Health Information, making the risk of individual patient identification negligible.

Given the relative safety of this device, as a FDA Class II device, additional adverse events are not anticipated. We will serially query the institutional clinic teams participating in this trial for any potential adverse events.

The study team also recognizes that subjects may seek advice about issues beyond the scope of this study and will refer all non-study related health issues to the patient’s treating clinician.

C. Potential Benefits:

The potential benefits of this study to the subjects are decreases in the occurrence of central line infections, either CLABSI, secondary BSI, or SPBC. Given the immunocompromised nature of these patients, any of these central line infections typically cause a hospitalization, antibiotic therapy, and possibly removal of the

central line. Preventing these infections therefore has substantial benefit to the patients, families and caregivers. The benefits to the healthcare staff at the participating institutions is the ready identification of easy to use interventions that can prevent central line infections in their vulnerable pediatric patients.

8. Statistical Plan:

A. Sample size and power estimates:

Expected Power/Sample Size: Data from January 2013 from the 24 units already submitting data on ambulatory central line infections to the Children's Hospital Association was used to simulate two 12-month periods, with a crossover, for a total study period of 24 months. In the crossover design, each of the 24 units would receive both treatments (Control and Intervention), and the order that the units received the treatments was randomly assigned. Monthly line-days were simulated from a uniform distribution on the range 20% lower and 20% greater than those reported in January 2013. The monthly number of infections were sampled from a Poisson distribution assuming the following: a) the CLABSI rate for the Control treatment would be the same as the observed rate in January 2013, b) the Intervention treatment would decrease the rate by 25, 35 or 50%, and c) that units receiving the Intervention treatment first would have infection rates on this treatment that were 5% lower than the corresponding rates among units that received this treatment second (cross-over effect) and d) each unit has a unit-specific effect (random intercept assumed to follow a normal distribution with mean 0 and standard deviation 0.6) which induces an exchangeable correlation structure over time. For each simulated study, we fit a generalized linear mixed Poisson regression model that included an indicator for treatment period, order of treatment, an offset for line-days and random intercept for unit and robust variance estimate. The power was estimated to be the proportion of simulated studies where the treatment effect was significant at the alpha = 0.05 level. We considered three cases where the full sample of 24 units would participate and then also assumed a 75% and 50% participation rate. Table 2 below displays the estimate power to detect the specified treatment effect (a relative reduction in CLABSI rate comparing Control to Intervention treatment after adjusting for order).

Table 2: Power to Detect CLABSI Rate Decreases in 24 Month Crossover Design Clinical Trial

Participation Rate by 24 Teams	Treatment Effect		
	25% Reduction	35% Reduction	50% Reduction
100%	0.78	0.91	0.92
75%	0.66	0.82	0.87
50%	0.56	0.72	0.79

Table 3 below displays the estimate power to detect the specified treatment effect (a relative reduction in the rate of any infection including CLABSI + secondary BSI + SPBC comparing Control to Intervention treatment after adjusting for order).

Table 3: Power to Detect Positive Blood Culture Rate (CLABSI + BSI + SPBC) Decreases in 24 Month Crossover Design Clinical Trial

Participation Rate by 24 Teams	Treatment Effect		
	25% Reduction	35% Reduction	50% Reduction
100%	0.92	0.98	0.98
75%	0.84	0.93	0.96
50%	0.72	0.85	0.90

Based on these simulations and the 3 recent studies showing 50-80% decreases in CLABSI rates with use of 70% isopropyl alcohol embedded protective caps for central lines, this cluster-randomized, 24 month cross over design, clinical trial is sufficiently powered to detect outcomes of interest for both the Primary Hypothesis and the first Secondary Hypothesis (decrease in rate of all positive blood cultures).

Given the current lack of published data relative to second Secondary Hypothesis (reduction in Gram Positive single positive blood cultures with common commensal microorganisms), this hypothesis is exploratory in nature and does not have power calculations underlying it. Minimal data exist on the distribution of organism causing CLABSI, secondary BSI and SPBC in ambulatory patients with chronic central lines. Based on data from previous studies in adults, we estimate a significant reduction in the proportion of CLABSI, secondary BSI and SPBC in ambulatory patients with chronic central lines. We anticipated seeing an increase in the proportion of CLABSI, secondary BSI and SPBC caused by Gram-negative organisms, because the overall numbers of events will decrease causing a perceived increase in the proportion, but no change in rate.

B. Statistical analysis plan:

The statistical analysis of CCLIP Trial data will be handled by the CCLIP Trial Coordinating Center at Johns Hopkins University in conjunction with the Johns Hopkins Bloomberg School of Public Health Biostatistical Consulting Center. The analysis plan includes:

Exploratory analyses: Descriptive statistics at the unit level will be calculated to summarize rates of infections (CLABSI and all infections) over time when the unit receives both the control and treatment arm. Scatterplots and line plots will be used to describe the trends in infection rates during the course of the study separately by treatment arm. In case missing data occurs in our analysis we will explore the relationship between missing data and the unit's observed data in months prior and our analysis methods will be valid under the assumptions that the missing data are generated completely at random or depend on the prior observed rates (missing at random). Our data integrity efforts and frequent contacts with this team will work to minimize any instances of missing data.

Multivariate analyses: Generalized linear mixed Poisson regression models will be used to test for a treatment effect. Specifically, the monthly count of CLABSI (Primary Hypothesis) or the monthly count of all positive blood cultures (first Secondary Hypothesis) will be modeled as a function of the dichotomous treatment assignment and an indicator for when the treatment arm was received (first or second 12 month period) with inclusion of an offset representing the monthly number of central line days and a random intercept for unit to account for the correlation of monthly rates of infections over time within the same unit. The models rely on two key assumptions: i) the infection rates follow a Poisson distribution where the mean rate is the same as the variance in the rate and ii) the correlation of the rates within a unit over time is exchangeable. These assumptions will be assessed via descriptive analyses and by adding a robust variance estimate clustering on the unit.

Relative to the second Secondary Hypothesis (reduction in blood cultures with Gram Positive microorganisms), the analysis would be a comparison of proportions of Gram positive organisms causing CLABSI, secondary BSI and SPBC between the control and intervention study arms. Given that Gram positive organisms are the most common organisms causing CLABSI and SPBC in children, achieving a reduction in Gram positive organisms would be an important additional finding of this clinical trial

9. Payments and Remuneration:

To encourage participation and support the added work needed to accomplish this clinical trial, we have included an annual payment to each participating institution of $5,000. These funds will be used by the sites to support the needed staff time for education of patients/caregivers, developing educational materials, distributing supplies to each participating family, and auditing family compliance with intervention.

Participating institutional clinic teams and the patients enrolled at that clinic will also receive a free supply of the CUROS brand of 70% isopropyl alcohol embedded protective caps for central lines during the 12 months their institution is active in the Intervention Arm of this trial.

10. Costs

There are no direct costs to the patient in this study. All study related supplies will be provided.

11. References:

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FINAL CCLIP Statistical Analysis Plan (SAP), (5/29/2019)

1. PURPOSE OF THE SAP

The goal of this document is to provide details on the analytic approach that will be used to perform data analysis of the final locked dataset (dated 5/29/2019) to inform the data analysis results.

2. STUDY SPECIFIC AIMS AND ENDPOINTS

Specific Aim #1: To evaluate whether use of 70% isopropyl alcohol embedded protective caps on central lines reduces the rate of central-line associated bloodstream infections (CLABSI) in ambulatory pediatric hematology/oncology patients.

Specific Aim #2: To evaluate whether use of 70% isopropyl alcohol embedded protective caps on central lines reduces the rate of all positive blood cultures in ambulatory pediatric hematology/oncology patients.

Specific Aim #3: To evaluate whether the use of 70% isopropyl alcohol embedded protective caps on central lines changes the distribution of bacteria isolated from blood cultures of ambulatory pediatric hematology/oncology patients.

A. PRIMARY ENDPOINT:

1. Primary dependent variable is ambulatory central line-associated bloodstream infections (CLABSI) rate. CLABSI is defined according to Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC NHSN) criteria outlined in the 2016 Patient Safety Component Manuel. "CLABSI: A laboratory-confirmed bloodstream infection (LCBI) where central line (CL) or umbilical catheter (UC) was in place for >2 calendar days on the date of event, with day of device placement being Day 1." Ambulatory CLABSI is defined as a CLABSI that occurs more than 48 hours after hospital discharge or within 48 hours of hospital admission.

B. SECONDARY ENDOINTS:

2. Mucosal Barrier Injury central line-associated bloodstream infections (MBI-CLABSI) rate. MBI-CLABSI is defined according to Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC NHSN) criteria outlined in the 2016 Patient Safety Component Manuel. "MBI-CLABSI: A Mucosal Barrier Injury Laboratory-Confirmed Bloodstream Infection (MBI-LCBI) where central line (CL) was in place for >2 calendar days on the date of event, with day of device placement being Day 1." An ambulatory MBI-CLABSI is defined as a CLABSI that occurs more than 48 hours after hospital discharge or within 48 hours of hospital admission.

3. Ambulatory secondary bloodstream infections (secondary BSI) rate. Secondary BSI is defined as BSI that meet the CDC NHSN's criteria for BSIs with a secondary source (such as pneumonia, abscess, etc.). An ambulatory secondary BSI is defined as a secondary BSI that occurs more than 48 hours after hospital discharge or within 48 hours of hospital admission.

4. Ambulatory single positive blood culture (SPBC) rate. Single positive blood culture is defined as any single positive blood culture that grows an organism on the CDC NHSN's 2016 list of common commensal organisms (such as coagulase-negative Staphylococci, *Bacillus* spp.). An ambulatory SPBC is defined as a SPBC that occurs more than 48 hours after hospital discharge or within 48 hours of hospital admission.

5. Ambulatory positive blood culture rate. Ambulatory positive blood culture rate is defined as the sum of CLABSI rate + MBI-CLBSI rate + secondary BSI rate + SPBC rate. Ambulatory positive blood cultures are defined as a positive blood cultures that occurs more than 48 hours after hospital discharge or within 48 hours of hospital admission

6. Proportion of acquired pathogens, classified as Gram positive bacteria, Gram negative bacteria, fungi, and other.

All rates will be calculated as the number of observed events over the number of central line days multiplied by 1000.

3. STUDY DESIGN SUMMARY

The CCLIP study is a cluster-randomized, 2 period crossover design to evaluate whether 70% isopropyl alcohol embedded protective caps used at home for chronic central lines (intervention) reduces CLABSIs and all positive blood cultures as compared to reliable use of best practice Maintenance Care Bundle (control) in pediatric hematology/oncology patients.

Prior to enrollment in the study, each of the participating institutions spent 15 months ensuring reliable performance of the best practice Maintenance Bundle in the ambulatory setting. The control phase of this trial, therefore, involves continued adherence to the proven best practice Maintenance Bundle while the treatment phase will entail the addition of the 70% isopropyl alcohol embedded protective caps Participating institutions are randomly assigned to start with either the intervention or control phase for the first period and then switched to the alternate group for the second period. After randomization, all sites will have a 2 month wash out period regardless of the initial treatment assignment. Each institution will then implement the period 1 treatment for 12 months followed by the period 2 treatment for an additional 12 months to ensure that each institution completes both intervention and control intervals.

Expected Power/Sample Size: Data on CLABSI rates from January 2013 collected from the 24 units that were candidates for participation in the trial while they were using the best practice Maintenance Bundle were used to estimate the control arm rates. At the time, available CLABSI rates were a composite of CLABSI + MBI-CLABSI. Simulation studies were used to simulate the cross-over design for a number of different scenarios while assuming that the monthly number of infections followed a Poisson distribution. For the control and intervention arms, we assumed that the CLABSI rate would be the same as the observed rate in January 2013 or decreased by a range of amounts (25, 35, 40, 45 or 50%), respectively. In addition, we assumed that the effect of intervention would be 5% lower among units receiving the intervention treatment first than among units that received this treatment second (i.e. a period effect). In addition, a unit-specific random intercept with mean 0 and standard deviation of 0.6 was incorporated in the data generation to induce an exchangeable correlation structure over time. For each simulated

study, we fit a generalized linear mixed Poisson regression model that included an indicator for treatment period, order of treatment, an offset for line-days and random intercept for unit and robust variance estimate. The power was estimated to be the proportion of simulated studies where the treatment effect was significant at the alpha = 0.05 level. We considered four cases based upon the proportion of the 24 units that would participate: 100%, 75%, 67% and 50% participation rate. Table 5 below displays the estimated power to detect the specified treatment effect (a relative reduction in CLABSI rate comparing Control to Intervention treatment after adjusting for order).

Table 1: Power to Detect CLABSI Rate Decreases in 24 Month Crossover Design Clinical Trial (Aim 1)

Participation Rate by 24 Teams	Treatment Effect				
	25% Reduction	35% Reduction	40% Reduction	45% Reduction	50% Reduction
100%	0.48	0.68	0.77	0.86	0.92
75%	0.41	0.62	0.73	0.81	0.87
67%	0.41	0.60	0.69	0.77	0.85
50%	0.38	0.53	0.62	0.71	0.79

Table 2 below displays the estimated power to detect the specified treatment effect (a relative reduction in the rate of any infection including CLABSI + MBI-CLABSI + Secondary BSI + SPBC comparing Control to Intervention treatment after adjusting for order).

Table 2: Power to Detect All Positive Blood Culture (CLABSI + MBI-CLABSI + Secondary BSI + SPBC) Rate Decreases in 24 Month Crossover Design Clinical Trial (Aim 2)

Participation Rate by 24 Teams	Treatment Effect				
	25% Reduction	35% Reduction	40% Reduction	45% Reduction	50% Reduction
100%	0.61	0.82	0.90	0.95	0.98
75%	0.53	0.75	0.84	0.91	0.96
67%	0.52	0.73	0.83	0.89	0.94
50%	0.48	0.68	0.74	0.83	0.90

Three recent studies have shown 50-80% decreases in CLABSI rates with use of 70% isopropyl alcohol embedded protective caps for central lines. Based upon our simulation studies, this cluster-randomized, 24-month cross-over design, clinical trial has between 79% and 85% power to detect decreases of 50% in CLABSI rates (Specific Aim #1) and between 90% and 94% power for all positive blood cultures (Specific Aim # 2), respectively, assuming 50 to 67% of clinics are enrolled.

Randomization: The study used a two-period crossover design with randomization at institution level with an initial run-in period. The participating institutions were randomized in 1:1 ratio to one of two arms during period 1: 1) standard of care for maintenance of external central lines (control period A), or standard of care for maintenance of external central lines with the addition of 70% isopropyl alcohol embedded protective caps (intervention period, B). After a 12 month period, units crossed to the alternative assignment. Each unit has one control period and one treatment period, either AB or BA.

The goal of randomization is to achieve balance between 2 study arms (AB vs. BA) with respect to the overall caseload of ambulatory external central lines and patient severity of illness. The caseload was operationalized by the total number of ambulatory external central line-days over two months of available data (May and June 2015) and was divided into 2 strata: below and

above the sample median. Analogously, for capturing patient severity of illness we calculated the total number of patients with bone marrow transplant (BMT) and/or stem cell transplant (SCT) patients and stratified the institutions into strata below versus above the median. In addition to these two covariates, attention was taken to ensure that the study arms were also balanced on ambulatory bloodstream infection rate (CLABSI, MBI-CLABSI, secondary BSI, and Single Positive Blood Cultures) for all patients with an external central line assessed for a two-month period (May and June 2015).

Stratified block randomization was used to generate the study arm assignments separately for each of the four randomization strata of caseload and patient severity.[1]

Blinding: Due to the nature of the study intervention blinding of the individual sites was not possible. The investigators were aware of the study arm assignment to monitor and implement each strategy.

4. STUDY SAMPLE AND TIMEFRAME

Inclusion Criteria for sites: pediatric hematology/oncology institutions with at least 12 month of baseline data on all types of ambulatory central line infections among children at home with central lines
Inclusion Criterion for patients: presence of an external central line
Exclusion Criteria for patients: patients who have a totally implanted port as their only central venous access. Patients for whom the caps pose a choking risk due to their age or developmental status will also be excluded.

5. Statistical Analyses

5.1. Initial Exploratory analyses: Events and line-days at the unit level will be calculated to summarize rates of infections (CLABSI and all infections) by treatment and period as well as by month to assess for any important trends. These trends will be evaluated using scatterplots and line plots, overall and separately by treatment arm and period. Summary statistics, such as mean, median, interquartile range and variance, for the monthly number of infection events and rates will be calculated for the overall sample and by treatment and period.

5.2. Baseline Annual survey data: Annual demographic surveys are distributed to all participating sites to collect data on inpatient and outpatient patient demographics receiving Hematology/Oncology service.

Data for annual survey variables, such as unit size, patient severity, use of other anti-infectives and others, will be reported for the analytic sample by survey year. Frequency of the use of infection prevention strategies, such as impregnated catheter, antibiotic locks, Biopatch and daily chlorhexidine gluconate bath use, as well as median and 25^{th}-75^{th} percentile (i.e. interquartile range, IQR) for annual patient days, inpatient admissions, ambulatory clinic visits, number of bone marrow transplant (BMT) and stem-cell transplant (SCT) patients, number of patients by gender and age category will be presented. These key characteristics will also be described for each team by survey year to assess for changes over time. Unit characteristics

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that vary over time to a significant degree will be included for inclusion in secondary analyses of the primary outcomes. Primary candidates include the use of biopatch and the number of BMT/SCT patients.

Since the survey data are available only annually, while the primary outcome data - monthly, the variable values for adjustment variables will be aligned with the year of primary outcome time period. For example, for all months for 2016, the reported 2016 annual survey results will be used for adjustment.

5.3. Analytic samples:

Primary Analytic ITT sample: The primary analysis will follow the principles of intention-to-treat (ITT). The analysis sample will include monthly events and line-day data from all randomized units.

Per Protocol (PP) sample / Protocol exceptions: This sample will include monthly events and line-days from all units, excluding events that occurred in patients that were not compliant with the assignment, i.e. use of protective caps on central lines during the control period or non-compliance with using caps during the treatment period. Data on protocol exceptions at the event level are collected. These exceptions will be reported by unit, month and infection event type.

Independent variable: The primary independent variable for these analyses will be the dichotomous treatment assignment to either control or intervention arms where unit will receive both arms. In addition to looking at the treatment assignment, the period during which the treatment is assigned (i.e. first or second 12-month period), will be taken into account.

5.4. Efficacy Analyses

Specific Aims #1 and 2: To evaluate whether use of 70% isopropyl alcohol embedded protective caps on central lines reduces the rate of central-line associated bloodstream infections (CLABSI) and all positive blood cultures in ambulatory pediatric hematology/oncology patients.

Primary, ITT analysis: Random effects Poisson regression models will be used to test for a treatment effect (equation 1). Specifically, the monthly number of CLABSI (Specific Aim #1) or the monthly number of all infections, μ (Specific Aim #2) will be modeled as a function of the dichotomous treatment assignment, with inclusion of an offset representing the monthly number of central line days, adjustment for time period (i.e. 1st vs. 2nd 12-month time period) and a random intercept for unit to account for the correlation of monthly rates of infections over time within the same unit. This model relies on two key assumptions: i) the infection rates follow a Poisson distribution where the mean rate is the same as the variance in the rate and ii) the correlation of the rates within a unit over time is exchangeable. These assumptions will be assessed via descriptive analyses. The two candidate distributions (Poisson vs. negative binomial) will be compared using AIC and the distribution associated with smallest AIC will be reported as the final model. Robust estimates of the variance will be calculated.

$$log(\mu_{i,j}) = \beta_0 + \beta_1 trt_{i,j} + \beta_2 period_{i,j} + \log(linedays_{i,j}) + u_j$$

for j = 1 through 16 sites and i = 1 through 24 months and u_j as the random intercept, $u_j \sim Normal(0, \sigma_u^2)$.

Secondary analysis: In addition to the unadjusted model described above, an adjusted model will be fit to the data that will include the following variables: 1) combined number of BMT/SCT patients dichotomized at the median value, and 2) the use of biopatch in ambulatory patients. Other potential confounding site-level variables measured in the annual site survey are: 1) prior use of impregnated catheter, antibiotic locks, chlorhexidine impregnated central line dressings, and chlorhexidine bathing, 2) volume of patients, admissions, beds, central line days or BMT/SCT patients. The distribution of and the change in these site-level variables between survey years 2015 and 16 will indicate potential time-varying confounding, since the majority of units started first period at the end of year 2015 and second period – at the end of year 2016 and these characteristics can potentially influence the number of infection events.

We will assess for the "order effect", specifically whether there is differential treatment effect by time period. This secondary model will include the dichotomous treatment assignment, indicator for time period (first or second 12-month period) and their interaction as the primary independent variables. The interaction term will test for "order effect" at 0.05 level of statistical significance, i.e. whether the treatment effect is different by period. If the interaction term is significant, the primary analysis will focus upon the first period only to avoid potential biases due to carry-over and period effects.

Exploratory hypotheses/analyses will assess monthly trends in the rates of infections. If an important trend in the rates of infections is detected in the visual analyses, a linear term for time in the study (i.e. month 0 through 24) will be added to the model, with a linear spline at 12 months to indicate the change in treatment assignment. This extended model will include the dichotomous treatment assignment, two linear terms for time and their interaction. A statistically significant interaction term will indicate a difference in the change in linear infection rate at 12 months by treatment order.

Missing data: Data availability for each unit by study-month will be summarized. Units with no eligible patients for a given month (i.e. zero line-days), will have missing CLABSI and infection rate data. All available data will be included in the primary analyses.

No imputation of the dependent variable data will be performed for the primary analysis. The primary analysis method results are valid under the assumption that the missing data are generated completely at random or depend on the prior observed rates (missing at random).

Per Protocol (PP) analyses:
In PP analysis, events that occurred in patients who were not compliant with the assignment will be excluded from the total count of the events in the regression model (1). Because central line day data were not collected at the patient-level, we perform multiple per protocol analyses both including all central line days for the given site/month in the as well as some removing varying number of days from the denominator for the site and month when exceptions occur (30 days or 15 days per patient who had an excluded event).

Patient refusals: depending on the unit and the site IRB submission requirements, the patients eligible for contributing their data to the trial might have been allowed to refuse their participation. Each team will be approached to assess whether 1) patients were allowed to refuse, 2) the number of patients refused their participation by treatment period, 3) whether the

central line days for these patients were reported as part of the trial data by treatment period. The number of patients who refused to participate will be reported by unit, treatment arm and time period. However, we cannot exclude these patients from the analyses, since event and line-day data are not collected at the person level.

Specific Aim #3: To evaluate whether the use of 70% isopropyl alcohol embedded protective caps on central lines changes the distribution of bacteria isolated from blood cultures of ambulatory pediatric hematology/oncology patients.

Distribution of Bacteria isolated from blood cultures: Organisms isolated for all blood cultures (CLABSI + MBI-CLABSI + Secondary BSI + SPBC) in patients involved in this study will be collected from participating teams during both the Control and Intervention arms of the clinical trial and sorted into Gram Positive bacteria, Gram Negative bacteria, and fungi. Organisms reported in “Other” category will be reclassified into one of these groups, where possible.

The analysis will compare the proportions of Gram positive bacteria organisms causing CLABSI and SPBC, and all positive blood cultures between the control and intervention study arms. Given that Gram positive organisms are the most common organisms causing CLABSI and SPBC in children, achieving a reduction in Gram positive organisms would be an important additional finding of this clinical trial.

The distribution of organisms by type (Gram Positive, Gram Negative, fungi and other) will be presented by treatment for CLABSI events, SPBC, and all positive blood cultures. The distributions of type of organism will be compared between treatment groups using chi-square test of association at 0.05 level of statistical significance.

Additionally, patients who were not compliant with the assignment will be excluded from the total count of organisms.

Log of Protocol and Statistical Analysis Plan Changes

Protocol Title: **COMMUNITY CENTRAL LINE INFECTION PREVENTION (CCLIP) Trial**	
Principal Investigator Name: Marlene Miller, MD, MSc	**IRB Protocol #** : IRB00046284
Current IRB approved protocol: Version 8, dated 10/20/2015	

Change Initiated by PI or IRB	Date of Protocol or Amendment	Summary of Protocol Changes
PI		None

Change Initiated by PI or IRB	Date of Statistical Plan Amendment	Summary of Statistical Analysis Plan Changes
PI	5/29/2019	1. After completion of the trial, we decided to update the outcomes to align with the current CDC NHSN definitions instead of those in place at the time the trial was proposed. There was no change to the primary outcome. Initially, the protocol proposed that bloodstream infections (BSIs) that met the CDC NHSN's laboratory-confirmed mucosal barrier injury (LC-MBI) criteria would be included as secondary bloodstream infections (secondary BSIs). Consistent with current CDC NHSN criteria, we updated the statistical analysis plan to include Mucosal Barrier Injury central line-associated bloodstream infections (MBI-CLABSI) as a stand-alone secondary outcome. 2. We also clarified that all positive blood cultures, a composite outcome, would be a secondary outcome. This composite outcome had been included in the protocol: 1) as secondary hypothesis i., 2) in the power calculations, and 3) in the statistical analysis section, but was accidently omitted from the list of secondary outcomes in the protocol. 3. Based on the enrollment of only 16 clinics, we added rows to the power calculation table in the final statistical analysis plan to show the power for 16 sites as the table in the initial protocol only included 12, 18 and 24 sites. 4. We added details to the final statistical plan.