STUDY PROPOSAL

Title: SQ53 disinfectant wipes for prevention of catheter related blood stream infection in patients receiving home parenteral nutrition: A Single Blind Randomized Placebo-controlled Clinical Trial (NCT04822467)

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Introduction:

Parenteral nutrition (PN) therapy is an essential component of medical management of patients suffering from intestinal failure. Depending on the underlying etiology and the type of intestinal failure, the duration of parenteral nutrition therapy could range from several weeks to several years, although a substantial proportion of these patients also require lifelong parenteral nutrition support. These patients continue the infusion of PN at their homes and are managed by the Cleveland Clinic's Home PN support team. These patients require Central Venous Catheters (CVC) for prolonged period of time for infusion of parenteral nutrition. The two most commonly used central catheters for TPN infusion are the Peripherally Inserted Central Catheter (PICC) and Tunneled CVCs. Catheter related blood stream infection (CRBSI) is a major complication of long-term CVCs. CRBSI is associated with high morbidity, mortality and healthcare

cost. Additionally, CRBSI can also lead to an interruption in nutrient delivery, loss of work and productivity, premature vascular access device removal, and poor quality of life.

Prevention of CRBSI is an important component of clinical management of patients receiving home PN therapy. Several strategies have been adopted to reduce the incidence of CRBSI. A heparin lock solution was used in the past for many years; however, current nutrition society guidelines recommend normal saline locks instead of heparin locks. Published data has suggested that heparin locks have not proven to have a substantial effect on CRBSI prevention, and it paradoxically increases the infection risk due to biofilm production. Antibiotic locks have also been used, although this practice is largely not preferred due to increased risk of infections with resistant microorganisms. Taurolidine is another lock solution which has been studied in the countries outside the United States such as Canada; however, it has not been approved for the use in the U.S. yet.[1]

We currently use the ethanol lock therapy which consists of 2ml of 50% ethanol. Multiple single center studies, meta-analysis and the systematic reviews have reported the effectiveness of ethanol lock therapy in prevention of CRBSI. In a retrospective study on the cohort of PN patients from the Cleveland Clinic, we found that Ethanol Lock therapy (ELT) was associated with a decrease in the number of CRBSI-related hospitalizations (10 vs 6 per 1000 catheter days), reduced number of confirmed CRBSI diagnoses with positive culture (3.5 vs 1.6 per 1000 catheter days) and decrease in the number of new catheter requirements.[2] A study by Zhang et al. reported in their systematic review that ethanol lock was associated with lower CRBSI rates when compared to heparin or normal saline lock.[3]

By strategically using the ethanol lock therapy daily in our home PN patients, we have been successful in reducing the incidence of the CRBSI in our patient population. However, ethanol lock solution will no longer be available to our patients due to changes in the supply network. The sterile ethanol solution is redirected to a breakthrough use for patients with cardiac hypertrophy which has driven its cost substantially high. Our center had earlier reported a spike in CRBSI in our patients when the ethanol lock solution became unavailable temporarily due to national shortage.[4] Therefore, it is very important to study and to assess the effectiveness of newer strategies for prevention of CRBSI.

SQ53 is a novel antimicrobial, sporicidal aqueous solution that is based on a platform of quaternary ammonium chloride compounds. Other active components include polymeric biguanide, chlorocresol, bronopol and ethanol. It has been tested against a wide range of bacteria, viruses, spores and fungal pathogens. Extensive laboratory testing has demonstrated the effectiveness of SQ53 impregnated wipes in cleaning surfaces including catheters over a 24 hour plus time period. In addition, it includes no development of VNBC (Viable-but non culturable bacterial colonies) populations or evidence of resistance to the active compounds. SQ53 also received an in vitro evaluation of the irritancy potential using a tissue engineered human skin model and was found to have no potential for skin irritation. In Europe, SQ53 currently has a class 1 CE mark and is cleared and registered under European Union Biocidal Product Regulations in UK, Germany, France, Belgium and Austria. SQ53 is available as a single wipe per pack which is prepared in biocide driven sterilized environment. The pack is easy to open by tearing off the top end and presenting the contents to the operator to remove under sterile conditions.

SQ53 has been studied in India in 148 patients in two groups. Group 1 had the patients who required long term CVC for PN (n = 42, 31 adults and 11 pediatric patients) and dialysis (n=106). Group 2 had the patients who required PN for short duration for postop complications (n=14). The study findings (which are in the publication process) support a substantial improvement in the CRBSI rates **from 131 episodes per 1000 (48 per 365 days) days to 9 episodes per 1000 (3 episodes per 365 days) resulting in an overall 94% reduction**. None of the enrolled patient's experienced local or systemic adverse effect with the use of SQ53 wipes.

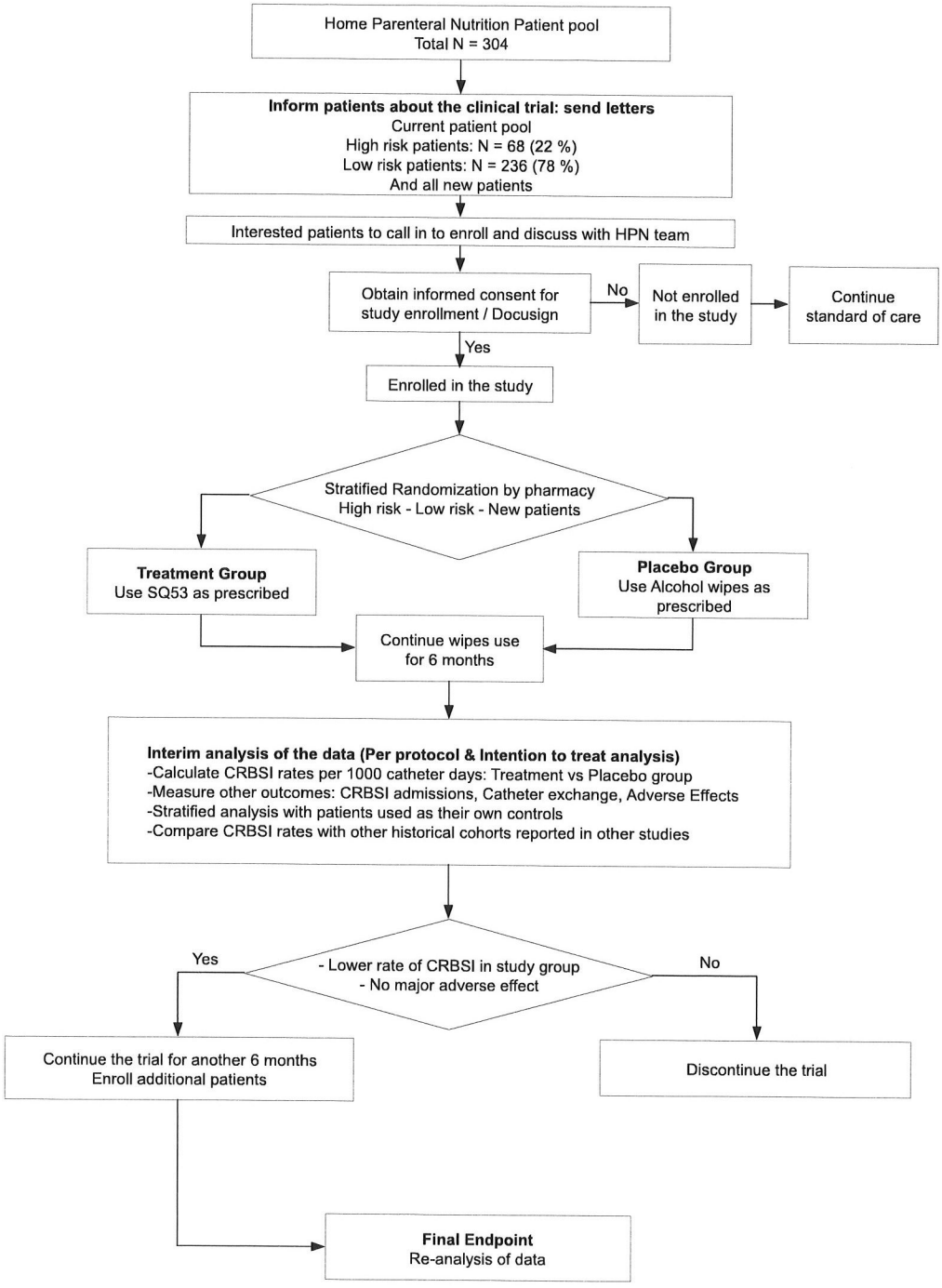
Study significance:

1. Ethanol Lock Therapy (ELT) which is currently used for prevention of CRBSI is an off-label usage of a commercially available product that will no longer be readily available for patients receiving home parenteral nutrition. Another breakthrough use of ELT has precluded the possibility of ELT use for PN patients. It is critical to identify and explore other agents and alternate therapeutic

approaches to prevent excess morbidity and mortality resulting from preventable CRBSI. SQ53 has shown promising results in CRBSI prevention trial conducted outside the United States.

2. The current study will be a randomized single-blinded placebo-controlled phase III clinical trial for this Investigational new device (SQ53 wipes) intended for the catheter cleaning in patients receiving home parenteral nutrition.
3. With ethanol lock therapy being phased out, there is no currently approved effective and readily available modality available in the United States to prevent CRBSI. On compassionate grounds it is imperative to use and to study SQ53 so that patients can benefit from this clinical trial.

Study design: Prospective randomized single-blinded placebo-controlled clinical trial



*Please note that the randomization will also be stratified by PICC/Tunneled catheter type.

Protocol version: 1.27.2022

Study objectives:

Primary objective:

1. To determine the effectiveness of SQ53 wipes in prevention of CRBSI in patients receiving home parenteral nutrition.

Secondary objectives:

1. To identify if there are any major or minor adverse effects such as skin irritation associated with the use of SQ53 wipes.

Inclusion criteria and patient recruitment:

1. Adult (age>18) patients requiring home parenteral nutrition support via PICC line or tunneled CVC.
2. Patients will be included via following process:
    a. All patients managed by CCF HPN team, meeting the inclusion criteria will be sent a letter of information and full informed consent form.
        i. Letter of information will be a cover letter informing patients about the clinical trial (letter attached)
        ii. Informed consent form: Standard informed consent form with detailed information about the study as per the Cleveland Clinic guidelines.
        iii. Letters will be sent in an alphabetical order for 10-15 patients each week to evenly distribute the work burden overtime.
    b. Patients who are interested to enroll in the study will call our HPN team, and we will answer any questions that these patients might have.
        i. The consent form will be again sent via email.
        ii. HPN dietitian will take consent over the phone by using DocuSign and will document it in patient's chart in HPN database
        iii. HPN dietitian will notify caring NST physician regarding patient's enrollment in the trial.

c. HPN dietitian (or NST physician or both) will classify patient in either a High Risk, Low Risk or New Patient Category via specific criteria.
    i. **Identification of high-risk patients** which will be determined by the following criteria:
        1. History of one or more CRBSI infection in the past 6 months
        2. Immunocompromised state increasing the infection risk
            a. Clinical determination based on comorbidities such as HIV, immunosuppressant medications, and steroids (prednisone >40mg per day)
        3. History of multiple catheter exchange in the past (greater or equal to 2 within the past 6 months) with difficult access
            a. This determination to be made based on patient's history
    ii. Identification of Low risk patients:
        1. Patients who do not meet High-risk criteria will be classified as Low risk patients
    iii. New patients:
        1. New patients are the patients who are newly started on PN during their in-patient stay and those who have been on PN less than 6 months unless they had CRBSI in the time frame.
        2. These patients will receive information about the clinical trial by RNs who provide education as standard of care.
d. Patients can also be enrolled in the study at the time of outpatient visit, or before discharge from the hospital.

3. Cleveland Clinic Home Infusion Pharmacy (CCHIP) will be informed about patient's enrollment and the risk category (High vs Low vs New patient) and the catheter type (PICC or tunneled)
    a. CCHIP will perform stratified randomization and assign the patient to either Treatment (SQ53) or PLACEBO (Alcohol wipes) group.
4. Treatment group will also have the SQ53 impregnated wipe used on a remote site to check for hypersensitivity and any other skin reactions before it is be deemed safe to use routinely in that patient.

5. All enrolled patient will need to agree to reach out to Home Nutrition Pager which is available 24x7 in case of noted adverse effect – this is standard of care for home PN patients.

Exclusion criteria:

1. Age less than 18 years
2. Women known to be pregnant (patient will be asked verbally- no pregnancy test will be performed)
3. Women of childbearing age who are planning a pregnancy
4. Women who are breastfeeding
5. Patient's refusal to enroll in the study at any point in time
6. Patients who refuse to use disinfectant wipes daily.
7. Patients who use port for their PN infusion.
8. Patients who are enrolled in other clinical trials with investigational drugs or device

Blinding and Randomization:

- **Blinding:** This will be a single blinded study and the NST-providers will be blinded to the treatment arm that the patient is assigned to. A clinician will initially interview the patient and at the time of enrollment into the clinical trial, obtain an informed consent after which the patient will be enrolled in the study.
- **Blinding the patients is not possible** due to several reasons:
    - SQ53 and alcohol wipes will have labels on them
    - differences in physical characteristics (smell) which are distinct for alcohol wipes and SQ53
    - therefore, it is unfeasible to blind patients to the intervention.
- **However,** despite being an unblinded study, outcome of our study is not likely to be affected as the primary outcome measure is diagnosis of CRBSI which is based on the Positive Blood Culture and is not very likely to be impacted by a placebo effect.
- **Randomization with a placebo:** Once patients are enrolled into our study, patient's information will be discussed with the pharmacy who will assign the patient to either a treatment or a placebo group.

- Patients will be randomized in 1:1 ratio to receive either SQ53 or placebo. The randomization process will be stratified randomization, followed by blocked randomization in each stratum. Stratification will be done on two factors: CRBSI risk category and catheter type. CRBSI risk categories will be determined by the clinicians or NST staffs 1. High risk (1 or more CRBSI in previous 6 months) 2. Low risk (no CRBSI in previous 6 months 3. New patient. Catheter types will be 1. Tunneled central catheters 2. Non-tunneled central catheters. The design has 3 x 2 = 6 strata. Blocked randomization will subsequently done in order to avoid serious imbalance in the number of participants assigned to treatment or placebo group. The block sizes will be determined by Cleveland Clinic Home Infusion Pharmacy.

Intervention:

Patients who qualify to enroll in the trial and sign an informed consent will be enrolled and will be eligible to receive either the intervention or the placebo. Providers will be blinded to which group patient is assigned to.

- Pharmacy (Cleveland Clinic Home Infusion Pharmacy will perform randomization and will assign patients to the groups)
- **All patients in the study will receive the wipes (Treatment group = SQ53 wipes, Placebo = alcohol wipes)**
    - Provide packs of sterile wipes to the patient for daily use **(external use only)**
    - Wipes should be used daily, as well as, when the dressing is changed, by wiping the catheter surface and hubs for at least 15 seconds
    - **Daily use:** Patients will be given instruction to clean the exterior and the caps of the intravenous catheters by following a sterile technique. This should be done before and after each use (i.e. PN infusion)
    - **At the time of dressing change:** Standard practice is to change the dressing every week. At this time the patient will use wipes to clean the catheter exit site and skin around the catheter exit site, catheter exterior and catheter caps prior to applying the new dressing
    - Wipes will be provided to the patient free of cost (material will be sponsored by the JVS company)

- Patients in both the groups will continue to use the standard care: i.e. ethanol (curos) caps, saline locks.

Data collection:

1. A registry of enrolled patients will be prepared. CCF HPN service has an approved database of patients receiving home parenteral nutrition. There are no additional HPI that will be collected as a part of enrollment in the study. The patient data is already collected into a password protected HPN database as current standard of practice. This data is routinely collected and updated by HPN dietitians.

Sample data sheet of primary objectives ***(data in italics blue font is for example):***

Patient Nomenclature: **SQ53/Treatment Group: Patient T1, Patient T2....** **Placebo Group: Patient C1, Patient C2....**				
	Pre vs Post SQ53 trial enrollment	**Number of Confirmed CRBSI in 6 months**	**Number of total admissions for CRBSI in 6 months**	**Number of catheters changed due to CRBSI in 6 months**
Patient T1	**Pre**	*2*	*3*	*0*
	Post	*0*	*1*	*0*
Patient T2	**Pre**			
	Post			
Patient C1	**Pre**	*0*	*1*	*0*
	Post	*1*	*1*	*1*

Patient C2	Pre			
	Post			
Patient C3	Pre			
	Post			

Data protection, processing and, analysis of the data:

1. CCF HPN service has an approved database of patients receiving home parenteral nutrition. The patient data is already collected into a password protected HPN database as current standard of practice. We will use REDCap for data entry for analysis. All data will be password protected.
2. We plan to perform both **"Per Protocol"** and **"Intention to treat analysis".**
3. Patients whose compliance is less than 90 percent will be excluded from Per Protocol analysis; however, those patients will be accounted in intention to treat analysis. Patients who developed skin reaction in remote site (e.g., forearm) will be excluded from Per Protocol analysis, but will be included in intention to treat analysis
    a. Compliance will be determined by HPN dietitian at the time of phone/virtual visit encounters: patient will be asked about their disinfectant wipe use and compliance.
4. Our primary outcome measure (as listed in above data sheet) will be differences in the CRBSI rate at 6 months after patient enrollments into the trial (i.e. SQ53 use). We will also perform sub-analysis by utilizing patients as their own controls. Please see the detailed timeline below.
5. We will also analyze the differences in the number of admissions for CRBSI (which would include admission with suspect CRBSI), as well as, overall number of catheters changed for confirmed and suspected CRBSI.
6. We will perform Poisson Regression analysis to compare the rates and 95 % confidence interval of the differences in CRBSI rates and CRBSI admissions.
7. We will also perform a descriptive analysis identifying the most common microorganisms causing the CRBSI in the periods both before and during the SQ53 therapy.
8. We will also perform a survival analysis to plot a Kaplan-Meier curve

9. We will collect mortality data of patients. We will report an overall mortality, as well as, CRBSI-specific mortality in patients using SQ53 for CRBSI prevention.

Sample size and power calculation:

1. In the un-published study conducted in India SQ53 has been reported to reduce the CRBSI rate by 94%. We expect this effect size to be lower in our cohort. We performed our sample size calculation by utilizing the data reported in our previous study which reported CRBSI rates in high risk PN patients (Pre-ELT CRBSI rate= 3.53 and post-ELT 1.65 per 1,000 catheter days). Considering current CRBSI rate in our high-risk population to be 1.65 per 1000 catheter days, we will need a sample size of 46 patients to identify a 50% reduction in CRBSI rate with alpha of 0.05 and 80 % power.
2. To account for the patient attrition due to mortality, lost follow up and non-compliance (for per-protocol analysis), we would like to increase our sample size by 30% to this estimated calculation and would need to enroll 30 patients in each group of our study to make determinations of differences with statistical significance.

Safety concerns: Risk to the study participants: Minimal

1. Our study is a single blinded randomized placebo-controlled phase III clinical trial which utilizes disinfectant wipes which are meant for external use only. These wipes have proven to be safe in the in-vivo and in-vitro studies.
2. No major adverse effect has been reported in previous clinical trial.
3. Current data suggest that SQ53 has no potential for skin irritation; however, if a patient experiences hypersensitivity skin reaction to any of the ingredients in the formula, then those patients will be excluded from the study and use of wipes will be discontinued.
4. Collected PHI data will be securely protected on the Cleveland Clinic Network drive.

Timeline:

Please see below a simplified timeline for this project.

Time Period	Activity

	Project Lead: Donald Kirby Project mentors: Gail Cresci and Mandy Corrigan Project team members: Mohamed Tausif Siddiqui, Allison Doriot, Ji Seok Park and Richard Benjamin, Eileen Hendrickson, Anil Vaidya
June 2020 - Sept 2020	1. Protocol and team development 2. Investigational New Drug (IND exemption process) 3. FDA exemption given by CCF IDE office considering the wipes as low risk device **Personnel responsibility:** Above steps have been completed
Oct 2020 – Nov 2020	1. Protocol submission to CHN & budget acquisition 2. Protocol submission to DDSI 3. Protocol submission to IRB **Personnel responsibility:** Above steps have been completed. - Protocol for IRB/CHN/DDSI submission is ready - Cover letter is ready - Informed consent document is ready - Budget is done
Nov 2020 – Dec 2020	1. Once IRB is approved: send letters to patients 2. Obtain informed consent and enroll patients 3. Risk category assessment 4. Baseline data collection 5. Randomization 6. Shipment of SQ53 or Placebo supply **Personnel responsibility:** 1. Sending letters to patients: - Letter has been drafted and ready, to be printed and mailed to the patients by study coordinator

	2. Obtain informed consent - HPN dietitian 3. Risk category assessment - HPN dietitian & NST staff 4. Baseline data collection - HPN team, Nutrition Fellows, Study coordinator 5. Randomization - DDSI statistician / CC Home infusion Pharmacy 6. Supplying SQ53 and placebo wipes - CC Home infusion pharmacy
Dec 2020 to June 2021	1. Continuation and monitoring phase of the study 2. Answer patient's concerns and collect data regarding specific side effects (if any) 3. Continue standard routine follow up: i.e. with labs, or during phone encounters **Personnel responsibility:** - HPN dietitian, NST staff and Nutrition fellows
June 2021	1. Perform interim analysis of the data **Personnel responsibility:** - DDSI statistician
July 2021 to Dec 2021	1. Continue the study for another 6 months and continue to enroll the patients **Personnel responsibility:** - HPN dietitian, NST staff and Nutrition fellows
Jan 2022	1. Final Analysis of the data 2. Reporting of the study findings **Personnel responsibility:** - Statistical analysis: DDSI statistician

	- Reporting: All investigators

References:

1. John BK, Khan MA, Speerhas R, et al. Ethanol lock therapy in reducing catheter-related bloodstream infections in adult home parenteral nutrition patients: results of a retrospective study. JPEN J Parenter Enteral Nutr. 2012;36(5):603-610. doi:10.1177/0148607111428452
2. Zhang J, Wang B, Wang J, Yang Q. Ethanol locks for the prevention of catheter-related infection in patients with central venous catheter: A systematic review and meta-analysis of randomized controlled trials. PLoS One. 2019;14(9):e0222408. Published 2019 Sep 12. doi:10.1371/journal.pone.0222408
3. Corrigan M, Kirby DF. Impact of a national shortage of sterile ethanol on a home parenteral nutrition practice: a case series. JPEN J Parenter Enteral Nutr. 2012;36(4):476-480. doi:10.1177/0148607111428453