Title: Maintaining Patency in Implanted Port Catheters with Saline Only Flushes

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Research Protocol

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Title: Maintaining Patency in Implanted Port Catheters with Saline Only Flushes

Principal Investigator: Sarah Pelgen, BSN, RN, OCN[1]
Sub-Investigators: Brian Singeltary, DO[2]

TriHealth Department Affiliation: [1]Nursing; [2] TriHealth Cancer Institute

UCMC Barrett Infusion Center Principal Investigator: Robbin Blau, BSN, RN, OCN

UCMC Barrett Infusion Center Sub-Investigator: Marsha Swango, BSN, RN, OCN, Dawn Grabill, RN, CRNI, OCN

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IRB Review Type: □ **Exempt** □ **Expedited** X **Full Board**

Purpose of Study: At TriHealth and at UCHMC Barrett Infusion Center, the majority of cancer patients have implanted port catheters. Maintenance of implanted port catheters is critical for the delivery of safe and effective care for cancer patients who need dedicated venous access for purposes of blood draws, blood product infusions, intravenous medications, intravenous fluids, and/or antineoplastic therapy. One of the most common complications of implanted port catheters is occlusion. The primary cause of catheter occlusion is the formation of a thrombus within or surrounding the catheter (McGee & Gould, 2003). The formation of a thrombus starts as a fibrin sleeve or sheath consisting of platelets and fibrin. Routine flushing of implanted port catheters is conducted as a measure to prevent the formation of a fibrin sleeve.

According to the TriHealth Nursing Policy and Procedure Intravenous Site Guidelines and the UC Health Nursing Policy for Central Venous Access Care and Maintenance, an implanted port catheter should be flushed with normal saline after IV medication, blood, or blood draws. Heparinized saline in the amount of 5 mL (concentration 100 units/mL) should be used as a final flush when no IV fluids are running and before de-accessing. However, routine use of heparinized saline flushes has been known to result in heparin induced thrombocytopenia (HIT), an immune reaction to heparin that can have serious consequences (Cooney, 2006). Additionally, heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots (Heparin Lock Flush Solution). It is recommended that the use of heparin be avoided or minimized whenever possible (Cooney, 2006).

While evidence in the literature is scant, there is no clear consensus on the need and efficacy of heparinized saline as the solution for maintaining patency in implanted port catheters (Camp-Sorrell, 2010). The investigators in this study examined the community standard, which revealed that while some area hospitals do use heparin in the final flush solution for implanted port

catheters, others adopted a saline only flush practice. This practice change does not appear to be based on evidence in the literature or the results of their own research. However, they do report anecdotally that there has been no increase in the use of alteplase (CathFlo: a thrombolytic) since the practice change.

The purpose of this study is to determine the safest and most effective flushing solution(s) for maintaining patency in implanted port catheters. The researchers also hope to conclude that the complication rate in patients whose ports are flushed with saline only is no greater than those of patients whose ports are flushed with the combination of saline and heparinized saline. These complications might include partial or complete obstruction, infection of the central line, and/or the onset of heparin induced thrombocytopenia.

Research Question(s):

1. Does a saline only flush maintain the patency of implanted port catheters at a rate comparable to a heparinized saline solution?

2. Is there any difference in the type and rate of complications among implanted port catheters flushed with saline versus heparinized saline?

Null Hypothesis:

We are proposing a non-inferiority trial. Thus, the null hypothesis is: Implanted port catheters flushed with saline only will experience an occlusion rate of more than 10% over the occlusion rate experienced in implanted port catheters flushed with a heparinized saline solution.

The alternative hypothesis is: Implanted port catheters flushed with saline only will experience an occlusion rate less than 10% over the occlusion rate experienced in implanted port catheters flushed with heparinized saline solution.

Background Information/Literature Review:

<u>Care of Implanted Port Catheters at TriHealth</u>

Currently at TriHealth, Inc. all implanted port catheters are flushed according to the TriHealth Nursing Policy and Procedure Intravenous Site Guidelines (See Appendix A). An implanted port catheter is flushed with normal saline after IV medication, blood, or blood draws. Heparinized saline in the amount of 5 mL (concentration 100 units/mL) is used as a final flush when no IV fluids are running and before de-accessing. This is intended to maintain patency of the catheter until the next use. The same process is used at University of Cincinnati Medical Center Barrett Infusion Center, a new site added to the study in January 2018.

TriHealth wide, there is no accurate data describing either the number of port catheters that are in use or the specifics of the complication rate. This data also is lacking UCMC wide. During the period of time between May 2, 2011 and April 30, 2012, the Out-Patient Cancer Care (OPCC) at TriHealth, utilized 134 doses of alteplase (Cath-Flo) to resolve occlusions. There is no easily accessible data describing whether these were partial (flushable but without a blood return) or complete (unable to flush) occlusions. There is no easily accessible information summarizing the type of central line that had to be de-clotted; however, the majority (>95%) of central lines

utilized by cancer patients in the OPCC are single lumen implanted port catheters. During this time period, there were two patients receiving care in the OPCC whose catheters were not flushed with a heparinized saline solution. One patient has documented HIT, and the other has a reported heparin allergy. Both patients have been able to maintain patent catheters with saline only flushes. Hospital wide, information related to the diagnosis of HIT, as it relates to type of Heparin exposure (e.g., subcutaneous or IV Heparin or the use of heparinized saline) is not available. There are no data available that demonstrates that patients with implanted port catheters who have developed a partial or complete occlusion developed bacteremia or central line infection due to the presence of fibrin on their catheter. Development of a fibrin sheath on the catheter is common after placement of an implanted port catheter (Gallieni, Pittiruti, & Biffi, 2008). The fibrin sheath may then become seeded with microorganisms which may disseminate into the blood stream. Both catheter-related thrombus and bacteremia are potentially life-threatening conditions.

Heparin induced thrombocytopenia (HIT) is an immune reaction to heparin. Through a series of steps, antibodies are produced in response to an immune complex, which in turn activates platelets. As activated platelets are destroyed, thrombocytopenia (low platelet count) occurs. This ultimately leads to a thrombotic state. Patients experiencing HIT can develop deep venous thrombosis, pulmonary emboli, stroke, or myocardial infarction. Patients developing HIT thrombotic syndrome may require limb amputation and are at increased risk for death. The actual incidence of HIT is 1-5% of patients exposed to heparin (Cooney, 2006). Many clinicians think that HIT is under-recognized and under diagnosed. The first response to the diagnosis of HIT is the discontinuation of all forms of heparin, including heparin flushes. The use of heparin should be avoided or minimized whenever possible. If saline only flushes were found to be as effective as heparinized saline flushes, it would significantly decrease the patient's exposure to heparin, and therefore the potential to develop HIT.

Frequency of flushing depends on the use of the implanted port catheter (ie. frequency of visits in the out-patient/in-patient units for blood draws or intravenous treatments). At TriHealth, implanted port catheters that are not in use are flushed a minimum of every three months with the same solutions and volumes as noted above (i.e., 20 mL normal saline plus 5 mL heparin (100 units/mL)). The policy also recommends turbulent flushing (see Appendix A). The turbulent flushing technique is accomplished by a push-pause rhythm every one mL for the entire flush volume. Turbulent flushing helps remove built-up residue, medication, and fibrin from the walls of the catheter. There is no policy stating frequency of maintenance port flushes at UCMC Barret Infusion Center. Additionally, TriHealth and UCMC have adopted the use of a neutral displacement needle-free connector with a clear housing (the MicroCLAVE® Clear, ICU Medical, Inc., San Clemente, CA, USA) that features a split septum with a straight internal fluid path design and minimal dead space to help minimize blood reflux into the tip of the catheter upon connection and disconnection of the luerloc, thus reducing the risk of occlusions due to blood reflux. This connector meets recommendations of the Infusion Nursing Society, Center for Disease Control, Federal Drug Administration and Society for Healthcare Epidemiology in America regarding the prevention of intravascular catheter-related bloodstream infections and enables clinicians to view the fluid pathway to verify effective flushing and clamp the IV line without requiring a specific clamping sequence.

State of the Evidence: Heparin plus Saline versus Saline Only for Flushing Central Venous Access Devices.

The most common reason for placing a long term central venous access device (CVAD) in the cancer patient is to deliver chemotherapy. For the cancer patient receiving vesicant drugs, a CVAD is very common for treatment.

The benefits of the CVAD are many and include the ability to deliver large doses of medications and fluids, blood products, total parenteral nutrition (TPN), and to obtain blood specimens. Long term CVADS include peripherally inserted central catheters (PICCs), implantable ports, and tunneled catheters. Commonalities among these devices are termination of the distal tips in the upper 1/3 of the superior vena cava, in the atrium, or in the upper portion of the inferior vena cava and the ability to be maintained for months to years (Gallieni, Pittiruti, & Biffi, 2008).

Maintaining patency of the CVAD in patients with cancer is of primary concern yet a review of the literature did not reveal consistent evidence-based recommendations regarding the type of flushing solution. At this time most procedures for maintenance and care of CVADs are based on manufacturers' recommendations and lack the evidence supported by randomized trials. Currently these devices are maintained with either normal saline or saline plus heparin flushes; there is no consensus as to which method is most effective in preventing catheter occlusions (Camp-Sorrell, 2010).

Complicating the issue of which solution to use is the fact that economics and safety are also prime considerations. Heparin flush solutions are not only more expensive but have the added risk of heparin induced thrombocytopenia (HIT) even in very small concentrations such as those used for routine heparin flushes (Golembliewski, 2008). Safety of heparin use with regards to labeling, administration, and medication errors has been documented in the literature (Otoya, 2009) and in the media in recent years adding to the need for studies to substantiate the value of its use over saline alone.

Studies favoring the use of heparin for flushing CVADs include a prospective, randomized trial by Cesaro et al. (2009) which compared flushing with saline plus heparin versus saline alone among 203 pediatric cancer patients with tunneled central venous catheters. A positive-pressure-valve connector was in place on the catheters of all study participants. Conclusions indicated an increased complication rate with saline only flushing but they could not exclude the fact that the frequency of flushing and the use of the positive-pressure-valve connector were influential in this outcome. Bowers et al. (2008) conducted a similar prospective, randomized study using 102 subjects with PICCs and positive-pressure-valve connectors. In this study, the normal saline only group experienced a non-significant 6% higher complication rate. The study did evaluate the monetary cost of this complication rate by considering the cost of the drug, the nursing time to restore patency, and replacement of the PICC line. They concluded that, even though the use of saline only flushes was a cost savings, the cost of replacing a PICC due to occlusion was economically relevant. Jonker et al. (2010) investigated the use of saline alone versus heparin for flushing CVAD in a period of heparin shortage. This retrospective, cohort study queried a pharmacy database for alteplase usage from April 23, 2007 to December 31, 2008 and concluded that significant increases ($P=.04$) in alteplase usage were reported during the heparin shortage and significant increases in PICC line replacements were also noted ($P<.05$) for this timeframe.

The authors therefore concluded that the absence of the heparin flush was the factor that led to these increases in occlusion rates and PICC replacements.

Studies that favored the use of saline alone for flushing CVAD included a study by Rotello et al. (2007). Data on 500 triple lumen central venous catheter line days and 1500 port days flushed with 10 mL of normal saline every eight (8) hours while patients were in the ICU resulted in occlusions rates of 4.8% and 2.9% respectively. Thus, it was concluded that the use of normal saline flushes are effective in preventing line occlusions and prevent unnecessary exposure to heparin. In a prospective study of pediatric patients by Shilling et al. (2006) it was discovered that using a positive pressure valve and saline proved just as effective as using heparin in preventing occlusion of central venous catheters.

Most compelling were the results of two systematic reviews regarding the management of CVADs. Kannan (2008) concluded that there is no evidence to support the use of heparinized saline over normal saline and the use of heparin may cause exposure risks such as HIT or other adverse reactions. In another systematic review by Lee and Johnson (2005) it was concluded that there was a lack of randomized controlled trial evidence on the benefit of heparin flushes as well as other management aspects of central venous catheters and sites. As previously mentioned, Camp-Sorrell (2010) outlines a concise literature review or state of the science with regards to oncology vascular access devices including recommendations of professional organizations with CVAD guidelines. The recommendations outlined by most organizations such as Centers for Disease Control (CDC), Oncology Nursing Society (ONS), Vascular Access Society (VAS), Infusion Nurses Society (INS), and Association for Professionals in Infection Control and Epidemiology (APIC) have either no guidelines for flushing or cite manufacturers recommendations which are based on trials used by US Food and Drug Administration (FDA) for device or product approval and not with randomized controlled studies (Camp-Sorrell, 2010).

In conclusion, Level 1 evidence for the use heparin flushes versus saline flushes for the maintenance of CVAD is lacking in the current literature. The small numbers of randomized clinical studies that do exist are not in agreement and include other variables such as positive pressure valves, inconsistent flush intervals, and varied patient populations. Many of the previous studies did not include patients with implanted port catheters; no study has been conducted exclusively among patients with implanted port catheters. For nursing to establish an evidence-based practice guideline for flushing of implanted port catheters, more research is needed to generate the knowledge necessary to make recommendations that will change and standardize practice.

Research Plan

Study Design: Non-inferiority trial in which participants will be randomly assigned to one of two groups: the control group or the intervention group.

S**etting for the Study: TCI Infusion Centers,** specifically: the TCI Good Samaritan (GS) Infusion Center at GSH; the TCI GS Infusion Center Butler County; the the TCI GS Infusion Center at the Thomas Center; the TCI GS Infusion Center, Cheviot; the TCI GS Infusion Center, Medicenter; the TCI GS Infusion Center, Anderson; and the McCullough Hyde

Memorial Hospital infusion center. In January 2018, University of Cincinnati Medical Center Barrett Infusion Center was added as a data collection site.

Participants: Patients receiving care in the identified settings who have an implanted port catheter will be recruited to participate in this study.

Inclusion Criteria:

- over the age of 18 years
- able to read and understand English
- has an implanted port in place less than one (1) year
- evidence of a patent port catheter prior to enrollment in the study
- is receiving active treatment i.e., receiving a therapeutic drug through the implanted port
- current treatment protocol projected to continue for a minimum of three (3) months
- anticipates receiving care at the identified centers for 6 months following enrollment in the study
- receives routine care of the implanted port catheter at any of the identified data collection sites

Exclusion Criteria:

- has documented Heparin platelet antibody (could not be randomized to either group) or other allergy to Heparin
- receiving therapeutic dose of an anticoagulant, i.e., warfarin, heparin, enoxaparin, etc.
- has a heparin-coated port (for example BioFlo port)
- does not meet one or more of the inclusion criteria

Recruitment

Prospective study participants will be identified the day prior to their appointment in the treatment center by a member of the research team. Their chart will be reviewed for inclusion criteria and flagged as a potential study participant.

When the potential study participant arrives in the treatment center, a member of the research team will escort the patient into a treatment room and explain the study by reading a prepared script (see Appendix B). If the patient expresses interest, the Informed Consent Statement and HIPAA Authorization form will be reviewed and signed. After obtaining informed consent, a participant will be randomly assigned to the heparinized saline flush (control group) or saline only flush study group (intervention group). A color-coded sticker will be placed on the patient's treatment folder indicating participation in the study and group assignment. The random assignment process will be achieved using sequentially-numbered opaque sealed envelopes (SNOSE) containing the group assignment. A yellow colored data collection face sheet (see Appendix C) will indicate control group; a blue colored data collection face sheet will indicate the intervention group.

During FY 2012, 391 patients with implanted port catheters were treated in the OPCC. Seventy of these patients experienced an occlusion of their port that required the administration of alteplase (CathFlo) (Kelly Dornheggen, personal communication, October 12, 2012). Thus, 70 of 391 experienced an occlusion resulting in an occlusion rate of 18%. Some of these 70 patients experienced an occlusion more than once during that time. Additionally, during that time, a few patients had their implanted port catheters removed due to infection or malfunction. The exact number of patients who experienced multiple occlusions or had their implanted ports removed/replaced during FY2012 is unknown.

We engaged the consultation of a biostatistician through the Center for Clinical and Translational Science and Training (CCTST) to conduct a power analysis to establish the number of participants needed in each group to determine the non-inferiority of the alternative therapy (saline only flush). Consultation was provided by Mekibib Altaye, PhD, Associate Professor Cincinnati Children's Hospital Medical Center, University of Cincinnati.

Based on the literature and our own experience we estimated an approximate occlusion rate of 20% with the standard treatment (saline + heparinized saline flush as described above). The power analysis conducted by Dr. Altaye determined that, using a two-group normal approximation test of proportions with a one-sided .05 significance level, a sample size of 198 participants per group will have 80% power to reject the null hypothesis that the proposed method is not inferior (i.e. the difference in proportions between the proposed method and the standard method is greater than 0.10). Thus, we will continue data collection until 198 have been completed in each group for a total of 396 study participants who completed 6 months of data collection. To date (July 3, 2019), 69.7% of patients enrolled in the study are able to complete 6 months of data collection without withdrawing for an exclusion criterion (ex: transferring to hospice, being started on an anticoagulant, etc). Therefore, we plan to consent 575 patients to result in 396 who complete the study. Once 396 patients have completed 6 months of data collection, data collection will stop and any remaining active participants will be withdrawn from the study.

Data Collection:

Independent Variables: Method for flushing implanted port catheters:

- 20 mL of saline followed by 5 mL of Heparinized saline in a concentration of 100 units/mL

OR

- 20 mL of saline only

Dependent Variables:

Primary Outcomes

- Occurrence of first complete (can neither withdraw blood nor flush the catheter) occlusion
- Occurrence of first partial (able to flush but unable to withdraw blood) occlusion
- Frequency with which alteplase (CathFlo) has to be utilized to resolve an occlusion

Secondary Outcomes

- Number of subsequent occurrences of complete or partial occlusions after the first occurrence.
- Amount of time in days that a port remains patent (flushes easily and able to obtain a blood return).
    - Amount of time between entrance in study and first incidence of partial or complete occlusion
    - Amount of time between incidences of partial or complete occlusion.
- Occurrence of other complications:
    - Central Line-Associated Blood Stream Infection (CLABSI) – a laboratory-confirmed (recognized pathogen cultured from one or more blood cultures; organism cultured from blood is not related to an infection at another site) blood stream infection that is considered central line associated (CDC, 2012).
    - Develops complication related to Heparin
        - HIT (Heparin induced thrombocytopenia as measured by a positive HIT antibody test)
        - Other heparin allergy

Moderating variables: other things that could also affect patency of the port

- Number of times port flushed per month or frequency of flushing.
- Use of prophylactic doses of anticoagulant drugs (e.g., enoxaparin, heparin, warfarin)
- Development of a hypercoaguable state, as diagnosed by primary hematologist/oncologist
- Mechanical difficulties related to port placement e.g. “Pinch-off syndrome”
- Length of time port has been in place prior to entrance in study

Extraneous variables:

- Type of cancer
- Age of participant

Data collection tool

The data collection tool (see Implanted Port Catheter Flushing Data Collection Form – Face Sheet: Appendix C and Record of Flushes: Appendix D) were developed by the principal and sub-investigators specifically for the purpose of this study. The tool was reviewed by the OPCC nurses for completeness and clarity. In addition to basic demographic information (age, gender), the nurse will record the patient’s type of cancer, and the diagnosis or history of any hypercoaguable state or use of anticoagulant medication as documented in the patient chart. The nurse will also document the type of implanted port catheter (single/double), the port location (right/left, subclavian vein (described in the operative note or chest x-ray), and the date the port was inserted so

that length of time the port has been in place can be calculated. Data will be recorded on the Face Sheet when the patient is enrolled in the study and as pertinent information/events become known, i.e., as complications occur.

With each visit to the identified treatment center, the nurse will document the date and characteristics related to the patency of the port catheter on the Record of Flushes data collection tool. In the event the blood withdrawal is sluggish or absent, the patient will receive a dose of alteplase (CathFlo) according to the data collection site's policy as ordered by the physician. Dosage and results of that intervention will also be recorded on the Record of Flushes data collection tool. In the event that any study participant (regardless of group assignment) requires alteplase (CathFlo) on three (3) consecutive visits to the treatment center, the patient's participation in the study will be terminated and they will be excluded from further data collection. The patient will be returned to a standard maintenance protocol for flushing of the port as prescribed by the afore-mentioned site policy or as prescribed by attending physician.

Participants in the control group will have yellow colored data collection Face Sheets while participants in the intervention group will have blue colored data collection Face Sheets. The Record of Flushes sheet will be white for patients in both groups. A blue or yellow sticker will be placed on the cover of the patient folder housed in treatment center noting the patient's involvement in the study. The data collection Face Sheet and the current Record of Flushes sheet will be kept in the individual patient folder as long as they remain a participant in the study. As the Record of Flushes data sheet becomes full, they will be collected by study staff and placed in locked drawer in a TriHealth or UCMC Barrett Infusion center office.

In January 2018, UCMC Barrett Infusion Center was added as a new site. The study nurses at UCMC Barrett Infusion Center will use the same data collection forms and will store them along with completed informed consent forms at a locked office at UCMC Barrett Infusion Center. Periodically, the lead research coordinator will bring de-identified data collection forms back to TriHealth. Signed informed consent forms will remain locked on UCMC Barrett Infusion Center property.

Experimental Aspect of the Study:

Patients who agree to participate in this study will be randomized to either the control group or intervention group as explained above.

Participants in the control group will have their implanted port catheters flushed according to the established site's policy. Following the use of the port catheter with no continuous fluids running, or before de-accessing a port catheter (removing the port needle), the port will be flushed with 20 ml of normal saline and 5 ml of heparinized saline in the concentration of 100 units of heparin per ml.

Participants in the intervention group will have their ports flushed with normal saline only. That is, following the use of the port catheter with no continuous fluids running, or before de-accessing a port catheter (removing the port needle), the port will be flushed with 20 ml of normal saline. Turbulent flushing technique (the solution is injected using a push/pause technique every 1 mL) will be used in both groups and all accessed port catheters will have a neutral displacement connector. The MicroCLAVE® Clear displacement connector (ICU Medical, Inc., San Clemente, CA, USA) is the current product in use. Participants in both groups will be seen in a TriHealth Cancer Institute Infusion Center or the UCMC Barrett Infusion Center at a frequency consistent with their individual treatment plan and as outlined in the site's policy. Participants will remain in the study for 6 months or until they experience one of the potential risks noted below. Participants will be considered as having completed the study if they participate for 6 months.

Potential risks for study participants in either arm of the study include partial occlusion (can instill flush solution but not withdraw blood) and complete occlusion (can neither instill flush solution nor withdraw blood). Study participants could require removal of the port if an occlusion cannot be resolved, and possibly require re-insertion of a new implanted port. In the event of any occlusion, alteplase (CathFlo) in the policy established dose and frequency (see Appendix A) will be instilled to resolve the occlusion. Study participants whose implanted ports are found occluded on three (3) consecutive visits to the treatment center will be excluded from further data collection, i.e., their participation in the study will be terminated. The standard flushing as prescribed by the site's policy or as prescribed by the attending physician will be used. Study participants whose occlusion cannot be resolved with alteplase and require removal of the port will also be terminated and excluded from further data collection. Patients who develop port infections necessitating port removal will be terminated and excluded from further data collection. Study participants who develop HIT (heparin induced thrombocytopenia) or other heparin allergy will be terminated and excluded from further data collection. Likewise, patients who have thrombotic or embolic phenomenon requiring therapeutic anticoagulation will be terminated and excluded from further data collection. If a participant in the intervention group receives clinical care and their port is flushed with heparin (following standard hospital policy), the participant will be withdrawn from the study.

The study will be closed if there is evidence that study participants in the intervention arm experience implanted port occlusion at a disproportionate rate. The amount of alteplase (CathFlo) used in each group will be assessed each

month for monitoring purposes. Additionally interim data analysis will occur (1) once 1/3 of the participants have been enrolled in each group; (2) once 2/3 of the participants have been enrolled in each group (3) at the conclusion of the study. These intervals are based on the recommendation of our CCTST consultant Dr. Altaye. The variable of interest in the interim data analysis at time (1) and (2) will be the occurrence of first partial occlusion plus the occurrence of the first complete occlusion in each group. At final analysis the occurrence of first partial occlusion and first complete occlusion will be considered together as well as separately in each group. Dr. Altaye also advised that to control for the Type I error rate not to exceed the nominal .05 level, the p-value should be adjusted at each data interim analysis. Dr. Altaye used the O'Brien Fleming alpha spending method to calculate the alpha levels for each interim analysis (O'Brien & Fleming, 1979). Thus, in order to reject the null hypothesis that the proposed procedure will produce a failure rate greater than 10% over the occlusion rate experienced using the standard procedure, the p-value at the 1st, 2nd and final analysis should be compared with an alpha value of 0.0006, 0.0151 and 0.0471 respectively. Thus if, using the p-values noted, interim calculations at time (1) or time (2) note a significant increase in the occlusion rate among participants in the intervention group, the study will be prematurely closed.

The undertaking of this research does require the participation of other personnel, facilities or departments other than those used in data collection. In the event the study participant is admitted to the hospital or requires some intervention using their implanted port catheter (e.g., CT scan with contrast), the study participant will have an information card describing his/her participation in the study and the group to which he/she has been randomized, so that the assigned flush solution is used, and integrity of the study can be maintained. The study participant will receive the card with instructions at the time of his/her enrollment in the study (see Appendix E Wallet Study Card).

Statistical Analysis: Descriptive statistics will be used to describe the participants. Differences between groups on the dependent variables will be calculated using t-test, Chi-Square or Fisher's exact test as appropriate for the level of data under analysis (also see discussion regarding interim analysis). Regression analysis will be used to determine the effect of the moderating variables on the occurrence of occlusion in the implanted ports. Participants in the control group and intervention group will be further stratified based on frequency of port flushing. Differences in the rate of occlusion between stratified groups will also be calculated.

Ethical Considerations: The purpose of this study is to determine the safest and most effective flushing solution(s) for maintaining patency in implanted port catheters. In so doing, study participants could be placed at potential risk for catheter occlusion. All catheter occlusion will be treated according to the site's policy, i.e., the instillation of alteplase (CathFlo) (see Appendix A). Potential study participants will be made aware of

the risk when enrolled in the study (See Appendix B (V.2, 2-20-2015) script for recruiting patients into the study and Appendix F, the Informed Consent Statement).

- **Informed Consent:** Patients who meet inclusion criteria will be approached by a member of the research team who will explain the study, implications of their participation and review the Informed Consent Statement and HIPAA Authorization Form(s) (see Appendix F and G). Participants will receive a copy of the signed Informed Consent Statement and HIPAA Authorization. The original signed Informed Consent Statement and HIPAA will be stored in a locked cabinet at a TriHealth office or locked location at UCMC, or an off-site locked storage area, for six years after the study is closed at which time the documents will be destroyed via mechanical shredder.

- **Privacy Information:** Once enrolled in the study, each participant will be assigned a study code and referred to by that code on all study related documentation. A study enrollment log will be created to record each participant's initials and medical record number, which will be correlated with the study code so that information may be retrieved to check or verify missing data. To maintain confidentiality, the study enrollment log will be kept in a password protected file in the Nursing Research Folder on the Udrive of the secure TriHealth server. All completed data collection forms will stored in a locked location in a TriHealth or UCMC office. Upon completion of the study, the data collection sheets will be entered into a statistical database. Once all data have been entered and cleaned, the study enrollment log will be destroyed via mechanical shredder. After all data have been entered, the data collection tools and spreadsheets will be returned to lead research coordinator and stored in a locked drawer in a TriHealth office for six years. The data file will be stored in the Nursing Research Implanted Port Catheters research subfolder on the U drive on the TriHealth server for six years. Only the study PI and Sub-investigators will have access to the Nursing Research Implanted Port Catheters folder on the U drive.

  Once IRB approval for the study is granted, all nurses in the treatment center who deliver care to patients with implanted ports will receive training from Sarah Pelgen, BSN, RN, OCN, Rachel Baker, PhD, RN, Robbin Blau, RN, Marsha Swango, RN, Dawn Grabill, RN, Sharon Sanker, RN, OCN (previous Principal Investigator, removed from study 9/2019), Sue Partusch RN, MSN, AOCNS, (previous Principal Investigator, removed from study 6/2017), Ruth Schwarz RN (previous co-Investigator, removed from study 10/18/2017), and Joy Dienger PhD (previous co-Investigator, removed from study 6/2017), RN regarding study procedures. The nurses designated on the personnel roster who will be obtaining Informed Consent will also receive training specific to that process.

Cost/Budget:

There is no increase in cost related to the maintenance of implanted port anticipated among study participants. Patient will be billed for care received based on the current TriHealth or UCMC Barrett Infusion Center standards of care.

Estimated Period of Time to Complete the Study:
The study will begin as soon as IRB approval is granted. Estimated duration of data collection is two years. There is no pre-data collection needed. The research team will meet bi-weekly to assess enrollment status and status of enrolled participants, particularly the incidence of occlusions and other complications during the previous week. Actual usage rate of alteplase (CathFlo) in each study group will be calculated monthly. Data analysis will be conducted at the conclusion of the study. Study results will be disseminated by TriHealth publication and UCMC PPO Newsletter, changes to the TriHealth and the UCMC Nursing VAD policy as appropriate as well as through presentation at profession nursing conferences (e.g, Oncology Nursing Society Infusion Nursing Society) and publication in peer reviewed nursing publications.

Administrative Approval:
A letter seeking permission to approach patients was sent to physicians who currently treat most of the patients at the data collection sites. All the physicians approached responded positively. The physicians approached at the beginning of the study were: Ranga Brahmamdam, MD, James Pavelka, MD, Jack Basil, MD, and Robert Albright, MD. Permission from other physicians whose patients are treated at any of the identified treatment centers and meet eligibility, will be acquired prior to presenting the patient with any information about the study.

Copies of permission/support of the study from nursing administration are detailed below and noted on Appendix I. See attachment to this document for permission to include additional TCI Infusion Center sites.

Facility/Department	**Name, Title and Signature of Appropriate Administrator**	**Date**
OPCC	**Julie Van Curen, RN, BSN**	**10/10/2012**
ATC Bethesda North Hospital	**Sue Weber, RN, MEd**	**7/2/2013**
Good Samaritan Infusion Center, Butler County	**Julie Van Curren RN, BSN**	**10/21/2013**
Good Samaritan Hospital, Nursing	**Paula Niederbaumer**	**9/24/2012**
Exec Director Cancer Institute	**Mark Witte**	**9/10/2012**
Sr. Nurse Manager, TriHealth Cancer Institute	**Julie Van Curen,** BSN, RN, OCN, CNN	**11/6/2014**

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