HIPPO SAT PILOT STUDY DESIGN

**A Design Thesis: Hemodialysis Infection Prevention using Polysporin Ointment with Shower Technique in Satellite hemodialysis Centres**

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A Thesis Submitted to the School of Health Sciences in Partial Fulfillment of the Requirements for

the Degree Master of Science

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McMaster University MASTER OF SCIENCE (2014) Hamilton, Ontario (Health Research Methodology)

TITLE: A Design Thesis: Hemodialysis Infection Prevention using Polysporin Ointment with Shower Technique in Satellite Hemodialysis Centres AUTHOR: Sarah Daisy Kosa, B.HSc. (McMaster University) SUPERVISOR: Doctor C.E. Lok NUMBER OF PAGES: vii, 98

**Abstract**

**Background:** As part of this thesis work, we developed a Shower Technique protocol (‘STP’) for hemodialysis patients with healed central venous catheter (catheter) exit sites, designed to permit showering but not increase infection risk.

**Research question:** Is it feasible to conduct a randomized control trial called the Hemodialysis Infection Prevention using Polysporin Ointment with Shower Technique in Satellite Centres (HIPPO SAT) study comparing the rate of CRB in adult satellite hemodialysis patients using STP versus standard catheter care alone with 6 month follow up?

**Study Design:** The HIPPO SAT pilot study is a multi-centre randomized control trial. Eligible participants will be randomized to STP versus standard care after meeting predefined criteria to confirm healed tunneled catheter exit site.

**Primary Outcome:** Feasibility will be determined based on 5 outcome measures: accuracy of the CRB rate documentation in the satellite setting, and percentage of patients screened, recruited, educated successfully in the STP (intervention arm), and using aspects of STP (% of contaminated patients in the control arm).

**Study Setting:** In satellite units affiliated with 2 academic and 3 community centres in south central Ontario, Canada.

**Patient Population:**  Adult satellite Hemodialysis patients dialyzing via catheter with healed catheter exit sites.

**Intervention:** STP and standard catheter care; or **Control:** standard catheter care;

**Analysis:** Each measure of feasibility has its statistical threshold for success. If the threshold is reached in 4 of the 5 measures, the full HIPPO SAT study will be deemed feasible.

**Discussion**: A pilot feasibility study of the larger study is critical due to the potential challenges associated with recruitment, compliance and contamination.

**Word Count Abstract: 262**

**Acknowledgements**

Foremost, I would like to express my sincere gratitude to my advisor Dr. Charmaine E Lok for the continuous support of my masters study and research. I have worked closely with Dr. Charmaine Lok since April 2011, first as an undergraduate research student and more recently, she has been my primary supervisor for my Master’s Degree (Clinical Epidemiology) in the Health Research Methodology Program at McMaster University. I have been consistently impressed by both Dr. Lok's enthusiasm for her work and her extremely high levels of productivity. Her interpersonal and communication skills have allowed her to lead a highly successful research team with strong working relationships and a collaborative approach. Her ability to remain calm during stressful periods like the grant submissions to national granting agencies provides a strong example to her team to work well under pressure.

I believe that I have been extremely fortunate to have found a supervisor and mentor as dedicated, accessible and generous as Dr. Lok. She has set time aside to meet with me weekly and has taught me a range of skills – how to perform reviews as a journal manuscript reviewer; how to write, apply for, and successfully obtain a research grant; how to submit to and reply to various research ethics review boards; how to navigate through the research implementation process from developing a data collection form to providing in-services to medical staff and finally to consenting and enrolling patients into a study. She has taught me the basics of using a statistical program and has guided me to experts in the field to further develop my skills. Dr. Lok has been integral in developing my writing skills, which have enabled me to compose quality correspondence and manuscripts. Dr. Lok has been extremely helpful in providing me guidance on how to maintain my focus while juggling a number of activities to ensure my personal and professional goals are met. I could not have asked for a better advisor and mentor for my master’s studies.

Besides my supervisor, I would like to thank the rest of my thesis committee: Dr. Lehana Thabane, Dr. Amiram Gafni, and Dr. Louise Moist, for their encouragement, insightful comments, and challenging questions. I also would like to express my sincere thanks to my colleagues in the Lok Nephrology Research Group: Cathy Forrester, Alexandra Cotoi, Svetlana Tzvetkova, Gillian Monize, Sara Rachel Katz, Sara West, Maryam, and Tanya Dahonick. Also I thank my student volunteers that were essential to the completion of this thesis work: Mehnaz Tanveer, Lara Pazek, Maryum Yousefi, Andre Violante, Gabrielle Eme, Vivian Feng, David Tang, Cindy Ma, Elgene Peter Yranon, Hannah Ferguson, Saidul Al Jaishi, Enoch Lam, and Sung Wohn.

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**List of Abbreviations used in the Manuscript**

Antibiotic Locking Solution (ALS)

Catheter Related Bacteremia (CRB)

Central Venous Catheter (Catheter)

Hemodialysis Infection Control Subcommittee (HICS)

Polysporin Triple Ointment (PTO)

Randomized Control Trial (RCT)

Shower Technique Protocol (STP) – As developed for the HIPPO SAT pilot study, distinct from previous “shower techniques”

Tissue Plasminogen Activator (TPA)

**Declaration of Academic Achievement**

Below I will declare my research contribution and, as appropriate, those of colleagues or other contributors to the contents of this thesis work:

In Chapter 1, the results are reported for a knowledge translation survey conducted across Canada on Infection Prophylaxis for Central Venous Catheters: Trained students in design of the survey and data collection forms, data entry, analysis of the data, and writing of abstracts for submission to conferences. The results of the survey informed the cost analysis and narrative review on Infection Prophylaxis. (January 2012- September 2012). Also in Chapter 1, the results of the central venous catheter (CVC) care survey, a short 15 min survey, measured the adherence to the prescribed CVC dressing protocol, and the impact of current dressing protocols on patient’s quality of life. I administered approximately 100 surveys, set up the databases, and trained additional students to administer the surveys. Over 274 patients were surveyed in the short survey (July 2011 to January 2012). Also cited in Chapter 1 of this thesis work is a cost analysis of the Hemodialysis Infection Prevention with Polysporin Ointment (HIPPO) Study, involving analysis of the Ontario Case Costing Initiative data with the supervision of Dr. Gafni (January 2012-December 2013).

In Chapter 2, the design of the HIPPO SAT Pilot Study is detailed. This HIPPO SAT Pilot study is an ongoing study in which my role included writing and submit ethics board applications and grant applications, setting up the database and data collection forms, recruiting patients, randomizing patients, applying the educational intervention, collecting data, entering data, and ultimately to complete the analysis and manuscript write up with the support of my supervisors, Dr. Lok, Dr. Thabane, and Dr. Gafni. Kidney Foundation of Canada funding has been obtained for this project. Recruitment began in November 2012 is complete as of December 16, 2013. The publication of the HIPPO SAT pilot study results is planned as part of doctoral studies and my thesis dissertation. (July 2011 – present)

In Chapter 3, the work on the Vascular Access Survey is detailed. The long form Vascular Access Survey encompassed multiple parameters of the patient’s experience and perceptions of hemodialysis vascular access. I administered approximately 25 surveys, set up the databases, and spent considerable time training additional students to this survey. Over 150 patients were administered the long survey. Based on the results of a factor analysis the survey was refined to produce the 10 min vascular access questionnaire which was tested for reliability in 68 patients twice over a period of two months. The validation of the vascular access questionnaire is part of the HIPPO SAT protocol (May 2011 to present).

There were many student volunteers from Toronto General Hospital that assisted in the conduct of the surveys in this project. Their assistance is greatly appreciated.

## CHAPTER 1: BACKGROUND

The purpose of this thesis research is to design a clinical research study to determine the feasibility of conducting a multi centre randomized trial comparing two approaches to infection prophylaxis in central venous catheter (catheter) dependent hemodialysis patients. In the first chapter, the background research establishes a) the burden of central venous catheter related infection in hemodialysis patients in Canada and worldwide, b) which catheter related infection prophylaxis strategies have been shown to be clinically effective and economical, c) the uptake of these catheter related infection prophylaxis strategies across Canada, and d) the patient perspective on these catheter related infection prophylaxis strategies. The second chapter of this thesis describes the design of the Hemodialysis Infection Prevention using Polypsorin Ointment with Shower Technique in Satellite Centres (HIPPO SAT) pilot study. The third chapter details the challenges associated with the design of the HIPPO SAT pilot study and the potential impact and implications of the study results.

#### 1.1 The Burden of End Stage Kidney Disease

1.1.1. Prevalence and Incidence of End Stage Kidney Disease

In Canada, an estimated 2.6 million people have chronic kidney disease, which is defined as abnormal kidney structure or function that persists for at least three months.[1](#_ENREF_1) Chronic kidney disease is classified classified based on the Glomerular Filtration Rate category and albuminuria category. When the glomerular filtration rate falls below 15 ml/min/ 1.73 m2 , a chronic kidney disease patient’s kidney function is so poor that they require renal replacement therapy.[1](#_ENREF_1) In 2011 5,489 incident cases of chronic kidney disease required renal replacement therapy in Canada, double the number in 1992.[2](#_ENREF_2) Renal replacement therapy can take the form of dialysis, in which the filtration function of the kidney is replaced by an external filter in a dialysis machine, or kidney transplantation, in which a kidney from a donor is transplanted into the patient. Kidney transplant in less expensive and offers tremendous quality of life benefit over dialysis.[3](#_ENREF_3) However, as there are limited kidneys available for transplant in Canada: there were 3,406 patients waiting for a transplant at the end of 2011, an increase of 23% since 2005. [2](#_ENREF_2) In 2011, 23,424 patients in Canada received dialysis to treat their endstage kidney disease.[2](#_ENREF_2)

The magnitude of the problem of providing renal replacement therapy is not a uniquely Canadian problem; the reported global prevalent dialysis population was 2.2 million in 2011, which increased by 6.4% from 2010.[4](#_ENREF_4) The prevalent dialysis population is concentrated in Europe, the Americas and other developed regions: in 2010, 403,070 [5](#_ENREF_5),[6](#_ENREF_6) in North America and 288, 475 in Japan[7](#_ENREF_7), and in 2011, 10,039 patients in Australia and New Zealand.[8](#_ENREF_8) The dialysis population in China, India, Brazil and other developing countries are on the rapid rise.[4](#_ENREF_4)

1.1.2 The Cost of Hemodialysis for Renal Replacement Therapy

Worldwide, approximately 68% of individuals on renal replacement therapy are on hemodialysis.[9](#_ENREF_9) Hemodialysis is very costly; in 2011 hemodialysis cost approximately $60,000 per person in Canada[10](#_ENREF_10) and approximately $87,500 per person per year in the United States (Medicare).[5](#_ENREF_5) The steady growth of this costly treatment modality worldwide puts significant financial strain on healthcare systems everywhere. For example, total Medicare costs for End Stage Kidney Disease in the United States increased 8.0 percent in 2010 to $33 billion, accounting for 6.3% of the total Medicare budget for only 0.4% of the population.[5](#_ENREF_5)

Hemodialysis may be delivered in-centre at a hospital or nursing home, in a satellite unit, or at home. Home hemodialysis requires patients to be able to perform considerable amount of self-care, and to have a fixed home address with appropriate plumbing. Home hemodialysis is increasingly gaining popularity but is currently not widely available. Furthermore, many patients are not home hemodialysis candidates. Since in-centre hemodialysis patients have the most immediate access to nephrologists and other care as required, the best option for the less medically stable or those requiring significant support, is in-centre hemodialysis. However for many patients, hospitals are not conveniently located. Some patients are also medically stable enough that they do not generally require frequent monitoring by nephrologists and other practitioners. The satellite hemodialysis unit is an attractive “in between” option for those patients stable enough to dialyze out of the main hospital, but do not wish do completely take charge of their care at home. In a 2002 cost study in Canada, dialysis delivered at home was the least expensive ($29,961 per patient per year), with satellite ($42,057 per patient per year) still statistically significantly less costly than in-centre dialysis ($51,252 per patient per year). [10](#_ENREF_10)

1.1.3 Vascular Access- Catheters- the Last and Only Option?

In order for the dialysis machine to filter the patient’s blood a stable connection, called a vascular access, between the patient’s vascular system and the machine is required. The vascular access must be able to sustain a consistent blood flow pump rate. A hemodialysis vascular access may take one of three forms: a central venous catheter (“catheter”), a native arteriovenous fistula (“fistula”) or a synthetic arteriovenous graft (“graft”). Both fistulas and grafts are a surgically created anastomosis between an artery and a vein. For a fistula, the anastomosis is a direct connection between the artery and the vein; the high flow from the artery slowly enlarges and thickens the vein walls (called maturation) allowing the vein to be punctured (cannulated) with large needles three to five times a week for dialysis. Fistula maturation requires 2-6 months, whereas grafts require 2 -4 weeks to mature because Polytetrafluoroethylene (PTFE) or other synthetic materials are used to connect the artery and the vein and this synthetic material is directly cannulated, not requiring the same type of access maturation.

The third type of vascular access, the catheter, is a flexible synthetic tube inserted into a large vein and rests in the right atrium. The distal portion of the catheter that protrudes from the skin allows the lines to the dialysis machine to be connected. The non-tunnelled and/or non-cuffed catheter is intended for short-term hemodialysis use. Tunnelling catheters and adding a distal cuff reduces catheter related infection risk and permits longer, more “permanent” use of catheters. The distal cuff becomes endothelialized creating a seal and together with the long subcutaneous tunnel act as a barrier against extraluminal organisms entry. Observational studies have consistently demonstrated that non-tunnelled catheters have a higher risk of infection (2-9 fold)[11-15](#_ENREF_11) than tunnelled catheters, emphasizing the need to limit the duration of their use.[16](#_ENREF_16)

Fistulas are associated with the lowest morbidity and mortality of all types of vascular access if they mature enough to be used to deliver adequate dialysis. Many patients require immediate vascular access to provide hemodialysis due to urgent dialysis needs, with catheters as the predominant choice until either a graft or a fistula can be placed. This is a heavy drain on health care resources, as it is well established that patients with a catheters have the highest financial costs of all vascular access types and also have the highest associated morbidity and mortality.[17-24](#_ENREF_17)

Despite efforts in North America to promote increased fistula creation and use,[25](#_ENREF_25) the problem of catheter use and their associated infections has not dissipated, with many patients continuing to require catheters for hemodialysis.[23](#_ENREF_23),[25](#_ENREF_25) Because placement of fistulas and grafts can be very challenging in some patients,[26](#_ENREF_26) especially given the increasing number of elderly hemodialysis patients with significant comorbidity and complex life circumstances the catheter may be left as the primary option for hemodialysis vascular access.[27](#_ENREF_27) This is reflected in current practice patterns with up to 80% of incident patients initiating hemodialysis with a catheter and up to 50% of prevalent hemodialysis patients dialyzing via a catheter in North America.[28](#_ENREF_28),[29](#_ENREF_29) According to a prospective cohort study of dialysis outcomes and practice patterns, called the DOPPS study, which draws data from 22 countries worldwide, the prevalent catheter use in 2010 was 52.06% in a random sample of units in Canada. This represents a dramatic rise from 34.2% in 2002, the highest of any countries participating in the DOPPS study.[30](#_ENREF_30),[31](#_ENREF_31)

1.1.4 The Impact of Catheter Related Infection

Catheter-related infection drives much of the cost associated with catheter use. [10](#_ENREF_10) Estimates of the total direct and indirect costs associated with hospitalizations due to catheter-related infection range from $17,000 USD to $32,000 USD.[18](#_ENREF_18),[32-34](#_ENREF_32) The magnitude of the cost associated with catheter-related infection varies depending on the type, severity, and frequency of that infection. Catheter-related infections encompass exit site infections, tunnel infections and bacteremia. Hemodialysis catheter related bacteremia (CRB) are the most clinically important due to their high occurrence and potential to progress to sepsis [17](#_ENREF_17). For example, as part of my graduate studies, I performed a recent analysis that calculated the total and itemized Canadian healthcare costs for hemodialysis patients hospitalized for CRB with a mean cost of $23,451 (CAN) per hospitalization[35](#_ENREF_35). This information was presented at an international conference (American Society of Nephrology Kidney Week, San Diego, CA, 2012).[35](#_ENREF_35) It is critically important, therefore, to have effective strategies to limit catheter-related infection.

1.2. Literature Review: Catheter Care Strategies to Prevent Infection

The ultimate goal of all dialysis units who care for patients using a catheter as their vascular access is to minimize the CRB rate. The rates of CRB in non-clinical trial settings range between 2.5-5.5/1000 catheter days.[17](#_ENREF_17),[36](#_ENREF_36) The optimal catheter infection prophylactic strategy should work to limit infection risk with minimal risk, inconvenience and discomfort to the patient, and at minimal cost. Many prophylactic strategies have been evaluated in randomized control trials and shown to be effective in lowering CRB rates. These strategies are categorized according to the pathophysiology of CRB and the two main routes of organism entry into the bloodstream: the extraluminal pathway along the external surface of the catheter and the intraluminal pathway through contamination of the internal surfaces of the catheter.[37](#_ENREF_37) Standard catheter care has three main components performed by hemodialysis personnel a minimum once weekly: 1) cleansing of the catheter entry site with an antiseptic cleansing solution, 2) changing of a dressing either occlusive or transparent dressing at the catheter entry site to prevent extraluminal route of bacterial entry) and 3) locking the catheter lumens with a locking solution that minimizes the risk of clot formation and the risk of infection from intraluminal sources. Additionally, some centres have hemodialysis personnel apply an antimicrobial ointment at each dressing change to prevent extraluminal bacterial entry. As part of my graduate studies, I have reviewed and published some commonly described catheter infection prophylactic strategies and their North American applications, their clinical efficacy, and relative costs;[38](#_ENREF_38) findings of this review are highlighted below.

1.2.1 Antiseptic Agents

International Guidelines [11](#_ENREF_11),[15](#_ENREF_15),[39-41](#_ENREF_39) recommend cleansing the hemodialysis catheter exit site and surrounding area with chlorhexidine (>0.5% with alcohol) when the catheter dressing is changed; povidone-iodine is an alternative. A meta-analysis of 8 randomized trials in the intensive care population demonstrated that the application of chlorhexidine at the catheter exit site significantly reduced the incidence of CRB (summary risk ratio 0.49 [CI, 0.28 to 0.88]), when compared to povidone-iodine solution.[42](#_ENREF_42) While chlorhexidine is approximately twice as expensive as povidone-iodine, the absolute difference in cost is relatively small (approximately $0.92 vs. $0.41 per catheter exit site application). The authors suggested that chlorhexidine is likely to be cost-effective or even cost saving.[42](#_ENREF_42) In a recent international study (DOPPS) that included 12,122 hemodialysis patients from DOPPS I, II, and III that evaluated dressing protocols, the use of chlorhexidine was associated with the fewest episodes of CRB or septicaemia.[43](#_ENREF_43) If chlorhexidine is demonstrated to be superior to povidone-iodine in hemodialysis patients, even by a relatively small margin, the potential for cost savings exists, even if the absolute cost of chlorhexidine is higher as the costs related to CRB are very high (see 1.1.4). Aside from cost and efficacy, individual patient reactions to the cleansing agents (i.e. mild allergic reactions and skin irritation) make it important to have both chlorhexidine and povidone-iodine available for hemodialysis catheter care.

1.2.2 Antimicrobial Locking Solutions

Hemodialysis catheters are “locked” with an anticoagulant, called a locking solution, during the intradialytic period to prevent intraluminal thrombosis. Catheter locking solutions comprising antibiotics or antimicrobials in addition to anticoagulants (“antibiotic/antimicrobial locking solution (ALS)”) have been investigated to target the intraluminal source of infection. [44-46](#_ENREF_44) Certain ALS have demonstrated in-vitro ability to reduce microorganisms and biofilm. [47-49](#_ENREF_47) Components of ALS include antibiotics such as vancomycin, gentamicin, ciprofloxacin, minocycline, amikacin, cefazolin, cefotaxime, and ceftazidime, or non-antibiotic locks such as alcohol, taurolidine, and methylene blue-parabens, often used in combination with an anticoagulant, such as heparin, trisodium citrate (TSC) or ethylenediaminetetraacetic acid (EDTA).

Four meta-analyses published in 2008 and a systematic review published in 2010 all concluded that ALS reduce the risk of CRB in hemodialysis patients (see Table 1)[50-53](#_ENREF_50). Six RCTs have been conducted since the publication of the last systematic review (Table 2).

Moran et al. conducted a multicenter single blinded randomized control trial (RCT) in 303 hemodialysis patients with catheters, comparing an ALS containing gentamicin 320 mg/mL in 4% TSC to 1,000 U/mL heparin. The rate of CRB was 0.28 episodes/1,000 catheter days in the gentamicin-TSC group and 0.91 episodes/1,000 catheter days in the heparin group (P = 0.003).[54](#_ENREF_54) Heparin 1,000 U/mL-gentamicin lock costs approximately $280 per month compared to $140 for the gentamicin-citrate, both of which are less expensive than locking with heparin 1,000 U/mL only[55](#_ENREF_55). However, recent emergence of gentamicin-resistant gram positive organisms has been reported with long-term prophylactic use of gentamicin ALS in hemodialysis catheters [56-58](#_ENREF_56). Furthermore, caution is required as gentamicin-based ALS may overspill into the circulation and put patients at risk of additional toxicity and allergic reaction[59](#_ENREF_59).

The recent Pre-CLOT (Prevention of Catheter Lumen Occlusion with r-TPA versus heparin) study by Hemmelgarn et al. compared a standard locking regimen of heparin (5000 U per milliliter) (HL) administered three times per week to recombinant tissue plasminogen activator (TPA) (1 mg in each lumen) substituted for heparin at the midweek session (with HL used in the other two sessions).. The rate of CRB was 1.37/1000 patient-days and 0.40/ 1000 patient-days in the HL and TPA groups, respectively (P = 0.02). [60](#_ENREF_60) TPA locking solution does not have the problems of antibiotic resistance and antibiotic related toxicity as the gentamicin based ALS (discussed above). However, the high cost of weekly TPA catheter locking ($130 CAN/catheter per week) may be prohibitive for widespread implementation as CRB prophylaxis in all hemodialysis patients.

Trisodium citrate lock has been studied as a locking agent. At high concentrations, there is some RCT evidence to suggest this trisodium citrate lock may reduce CRB rates, [61](#_ENREF_61),[62](#_ENREF_62) however a serious concern with these higher concentrations of trisodium citrate is that if trisodium citrate is injected into the systemic circulation it can cause serious hypocalcaemia, cardiac dysrhythmias, and death. In the USA the FDA has limited trisodium citrate use to concentrations of <4% due to a fatality as a result of an accidental over-spillage of high concentration trisodium citrate.[63](#_ENREF_63),[64](#_ENREF_64) Based on two observational studies, the trisodium citrate lock at much lower concentrations (4%) appears to have comparable CRB rates at significantly lower costs than heparin 1000 U/mL.[65-67](#_ENREF_65) Low concentrations of trisodium citrate locking solution offers cost savings over heparin locking solution but does not lower the CRB rate. Overall, the ideal ALS for infection prophylaxis has yet to be found, with concerns surrounding cost, problems of antibiotic resistance, and toxicity plaguing the ALS solutions currently available for use in hemodialysis patients.

1.2.3 Antimicrobial Ointments

Antimicrobial ointments applied topically at the catheter exit site act to prevent organism entry through small spaces between the catheter exit site and the subcutaneous tunnel. Antimicrobial ointments are typically applied 1x/week or every time the catheter dressing is changed.[68](#_ENREF_68) There are few associated side effects with direct delivery of the antimicrobial agent at the application site. Four types of topical ointments have been evaluated in randomized control trials in hemodialysis patients: Povidone-iodine [69](#_ENREF_69), Mupirocin,[70](#_ENREF_70),[71](#_ENREF_71) Medihoney,[72](#_ENREF_72) and Polysporin Triple ointment (PTO).[68](#_ENREF_68) A recent meta-analysis of catheter infection prophylaxis found that the application of antimicrobial ointment at the catheter entry reduced the risk of exit site infection and CRB when compared to no ointment or placebo (RR 0.33, 95% CI 0.18 - 0.61).[73](#_ENREF_73) Further, topical antimicrobial ointments compared to no ointment or placebo significantly reduced catheter removal due to infection caused by all types of organisms (RR 0.35, 95% CI 0.25 to 0.50). Importantly, prophylactic topical antimicrobial ointment at the catheter exit site was also significantly associated with reduced mortality related to infection (RR 0.15, 95% CI 0.03 to 0.81).

Levin et al. compared prophylactic application of povidone-iodine at the exit site of subclavian catheters to no application in a randomized controlled trial (n=129) and found that the risk of catheter related bacteremia in the povidone-iodine group was 40% lower than those who did not have povidone-iodine applied [69](#_ENREF_69). However, while povidone-iodine has demonstrated residual antibacterial effect at the site of application, it can cause allergic reactions and other local side effects [69](#_ENREF_69).

Sesso et al. exclusively studied the effect of topical Mupirocin prophylaxis on *S. aureus* catheter-related infections.[70](#_ENREF_70) Mupirocin ointment significantly reduced the risk of *S. aureus* related exit site infection, CRB (HR=7.2; 95% CI 1.6 to 31.6) and catheter removal compared with no Mupirocin. While prophylactic Mupirocin at the catheter exit site has been shown to be effective against *S. aureus* CRB, there are concerns regarding Mupirocin resistance[74-76](#_ENREF_74) and incompatibility of Mupirocin with catheter materials causing catheter degradation.[77](#_ENREF_77)

Two studies compared topical medicinal honey barrier with topical antibiotic agents. Johnson et al. compared Medihoney and Mupirocin ointment (101 hemodialysis patients) and Quadri et.al. compared the Manuka honey with povidone-iodine (49 hemodialysis patients) [72](#_ENREF_72) applied at the catheter exit site. Medihoney and Manuka honey, when compared to Mupirocin or povidone-iodine, did not significantly reduce the risk of exit site infection or CRB. Currently, most international guidelines do not recommend the routine use of medicinal honey in the prevention of catheter infection in hemodialysis patients.

The Hemodialysis Infection Prevention With Polysporin Ointment (HIPPO) study was a multi-centre randomized control trial that demonstrated that prophylactic PTO at the catheter exit site significantly decreased CRB (2.48 versus 0.63/1000 catheter days; p = 0.0004), infection related hospitalizations and improved patient survival (relative risk reduction 78%) compared with matching placebo.[68](#_ENREF_68) The number of patients needed to treat with PTO to prevent one CRB was 7 and the number patients needed to prevent one death was 8.[68](#_ENREF_68) Mild side effects, a 10% risk of redness and skin irritation around the catheter, were reported. A 6-year prospective follow-up of the original HIPPO study demonstrated sustained reductions in catheter -related infections and excellent CRB rates (<1.0/1000 catheter-days).[78](#_ENREF_78) When compared to the total monthly cost of Mupirocin ointment at catheter exit site of $5.00/month CAN (list price $8.71/15g X 1g/admin), PTO is less expensive, $3.50/month (list price $6.24/15g X 1g/admin). The implementation of PTO application for prophylaxis against catheter related infections offers significant benefit at relatively low cost, because estimates of costs associated with CRB are so high, with the potential for significant cost savings.[35](#_ENREF_35),[79](#_ENREF_79)

1.2.4 Types of Catheter Dressings

The main purposes of a catheter dressing are to protect the catheter exit site from external contamination and to anchor the catheter to prevent trauma or accidental dislodgement. [80](#_ENREF_80) Two primary types of dressings are typically used: transparent occlusive semipermeable polyurethane dressing and a dry gauze type dressing (with or without attached adhesive). Transparent dressings are sufficiently permeable to enable moisture from the skin to evaporate through. If, however, blood or serous fluid leakage occurs at the catheter exit site, its accumulation under a transparent dressing may create an environment that is conducive to micro-organism growth. A recent Cochrane review[81](#_ENREF_81) on the use of gauze plus tape vs. transparent polyurethane dressings for catheter in a variety of clinical settings, found that CRB infection was higher in the transparent polyurethane group when compared with gauze and tape; odds ratio (OR) 4.19 (95%CI 1.02 to 17.23). However, the authors caution that the evidence was low quality and the confidence intervals very wide. The authors concluded that choice of catheter dressing can be based on patient preference and cost, and that more research is required. While dressing prices depend on brand and size, generally, transparent dressings ($4.00-$9.00) are more expensive per unit, than dry gauze dressing with attached adhesive ($2.50-3.50)[55](#_ENREF_55); however, some centres change transparent dressings less frequently (see below), which might impact cost and/or infection rate.

Recent catheter dressing advances in critical care medicine include a dressing impregnated with chlorhexidine. The Dressing Study was conducted in 1879 acute care patients with catheters inserted for an expected duration of 48 hours or more in a 2:1:1 assessor-blinded large 2 x 2 factorial randomized trial in patients in 12 French intensive care units.[82-84](#_ENREF_82) This study evaluated a strategy of changing unsoiled adherent dressings every 7 days vs. every 3 days (standard practice) and concurrently compared semipermeable transparent dressing with chlorhexidine sponge dressing underneath versus semipermeable transparent dressing alone (standard care). Chlorhexidine-impregnated sponge dressing placed at the catheter exit site was found to be associated with a lower incidence of major catheter-related bloodstream infections by 67% (0.7/1000 vs. 2.1/1000 catheter-days) and the CRB rate by 60% (0.5/1000 vs. 1.3/1000 catheter-days) when compared to non-chlorhexidine dressings.[82](#_ENREF_82),[84](#_ENREF_84) In total there were 4163 nontunnelled catheters included over the study period (34,339 catheter-days). In the Dressing Study a cost analysis was performed where the costs were calculated prospectively using micro-costing methods. The median direct cost of major catheter-related infection was $792 while the overall cost of major catheter-related infection was $24,090/episode. Each non-chlorhexidine catheter dressing cost was $9.08 and each chlorhexidine-impregnated sponge (i.e. Biopatch®) cost was $9.73. However, while appearing to be cost-saving with improved CRB rates, caution is required in interpreting and generalizing these results to the hemodialysis population with tunneled catheters. Hemodialysis patients require long-term therapy, often with very prolonged dependence on their catheter beyond typical timeframes seen in ICU patients. In studies of chlorhexidine-impregnated sponge dressings in hemodialysis patients with tunneled catheters, such as the one by Camins et al,[85](#_ENREF_85) no benefit in CRB rate was seen. Such dressings are currently not used as standard of care in hemodialysis units across North America.

1.2.5 Catheter Dressings- Frequency of Change

International guidelines vary on their recommendations for frequency of dressing changes. One option is thrice weekly dressing changes, where the catheter exit site is manipulated more often (with a theoretical risk for increased infection), but is also visually inspected by a hemodialysis personnel for signs of infection. Interestingly, the Centre for Disease Control guidelines state that no recommendation can be made regarding the necessity for any dressing on well-healed exit sites of long-term cuffed and tunneled catheters. However, if a dressing is used, it is recommended to replace it if it becomes ‘damp, loosened, or visibly soiled’.[15](#_ENREF_15),[86](#_ENREF_86) This recommendation is for both transparent and gauze type dressings. The question of dressing change frequency has been recently addressed in a study of 1,879 acute care patients with non-tunnelled catheters via the “Dressing Study” mentioned above.[82-84](#_ENREF_82) This study evaluated a strategy of changing unsoiled adherent dressings every 7 days vs. every 3 days (standard practice). Dressing changes every 7 days were not found to be inferior to changes every 3 days. However, 67% of dressing changes performed in the study were performed before the planned date, even more frequently in patients receiving renal replacement therapies. Once weekly dressing changes are probably cost saving, due to the reduced nursing time and supplies required, [87](#_ENREF_87),[88](#_ENREF_88) with no reduction in safety.

1.2.6 Conclusion of Literature Review of Prophylactic Strategies

Several infection prophylaxis approaches have been shown to be clinically and cost effective. However what was less clear at the beginning of this thesis work (April of 2011) was what the uptake of these infection prophylaxis strategies was across Canada. A crucial initial step to understanding the state of infection prophylaxis strategies across Canada was to understand what the standard catheter care was nationally, and what was the state of knowledge translation from guideline recommendations to clinical practice, which will be described in Part 3 of Chapter 1.

#### 1.3 Catheter Care Practice Patterns Across Canada

1.3.1 Rationale and Methods for the Cross Canada Survey: “Canadian Dressing Survey”

With multiple options for catheter infection prophylaxis available, it can be challenging to decide on the most cost effective first step at a health care system level, or at a given hemodialysis centre. A Canadian survey was undertaken of all dialysis centres registered with the Canadian Organ Replacement Register (CORR) to determine the practice patterns surrounding catheter care and infection prophylaxis in in-centre hemodialysis patients dialyzing via tunnelled catheters in Canada.[89](#_ENREF_89),[90](#_ENREF_90). One hundred and fifty one dialysis centres across Canada were surveyed (Appendix 2) using a standardized questionnaire via email and telephone to identify the patterns of catheter care that included: dressing usage, use of antimicrobial ointments, cleansing agents, and catheter locking solutions from March 1, 2012 to August 31, 2012. Dialysis centres were contacted twice in follow-up at two week intervals if there was no response to the original survey sent Centres were given a month to respond to the original survery.

1.3.2 Survey Results

Sixty eight centres completed the first portion of the Canadian Dressing Survey, where 58% of centres reported once weekly dressing changes (for both transparent and non-transparent dressings), 37% change transparent dressings once weekly and non- transparent dressings three times a week, and 5% perform thrice weekly dressing changes (for both transparent and non-transparent dressings). Cleansing with Chlorhexidine (>0.05% with alcohol) appears first line in many units; for example, in Canada over 95% of dialysis centres use chlorhexidine or have it available as an antiseptic for catheter care. Povidone is also used or available in >70% of hemodialysis units with fewer hemodialysis units using isopropyl alcohol. [89](#_ENREF_89) Seventy five percent of centres indicated that they recommend patients to clean themselves by bathing (non submerged) or sponge bath, ***38% recommended showering,*** and 5% of centres made no recommendation to patients with regard to personal hygiene.

*Antibiotic Ointments*

Thirty seven percent of centres used Polysporin Triple Ointment at the exit site. In a recent Canadian survey, 35% of centres used Mupirocin at the catheter exit site, though it is unclear how many of those centres used Mupirocin for prophylaxis, or just for treatment.[89](#_ENREF_89) Fifty seven percent of centres indicated that they were aware of the Canadian Clinical Practice Guidelines recommending the application of Polysporin Triple Ointment at the catheter exit site to prevent infection, and only 45% of centres were aware of the HIPPO Follow-Up study that demonstrated that Polysporin Triple is safe for long term use (no catheter breakdown, no microbial resistance, and no increase in fungal infection) and has long term prophylactic efficacy.

*Dressings*

A variety of dressings (non-mutually exclusive) were noted to be used in the 68 dialysis centres that responded: 92% were using transparent dressing, 55% Medipore® and 17% were using Hypafix® (both are dry gauze dressings with an adhesive), and 3% were using no dressing at all.

*Locking Solutions*

Fifty-four dialysis centres completed the follow up survey on catheter locking solutions. The recent observational study [65](#_ENREF_65) findings about the cost savings associated with TSC have had rapid dissemination in Canada; of the 54 centres who responded to a survey of hemodialysis catheter locking solution use, 92% were using tri sodium citrate lock while 37% of the surveyed centers used heparin. [89](#_ENREF_89)

1.3.3 Implications of Survey Results

Consistent with the uptake of other guidelines,[91](#_ENREF_91) the uptake of RCT-proven infection prophylaxis strategies is low, slow, and varied[89](#_ENREF_89), particularly surrounding the recommendations made to patients for personal hygiene. There was contradiction in the recommendations made to patients with regards to their personal hygiene, some centres indicting they suggested both showering and sponge bath, others only encouraging sponge baths, and a small percentage making no recommendation. Therefore, hemodialysis patients across Canada are going home with confusing recommendations, in some cases no recommendations at all, with regards to what methods or personal hygiene techniques should be used to preserve the dryness of their dressings and prevent catheter related infection. The critical next step, described in Chapter 1, Part 4, in optimizing catheter care is to understand the patient perspective on their catheter care program in detail, as their preferences and level of satisfaction with their care is paramount.

#### 1.4 The Patient’s Viewpoint on Catheter Care

1.4.1 Rationale for the “Catheter Care Survey”

A variety of catheter care protocols exist as noted above; it is unclear precisely how adherent patients are to dialysis unit prescribed catheter care protocols. Guideline recommendations for catheter infection prophylaxis include the use of an occlusive dressing over the patient’s catheter while they have a catheter in situ in order to minimize the risk of infection that may occur in non-sterile, dirty, and/or damp environments. [11](#_ENREF_11),[14](#_ENREF_14),[15](#_ENREF_15),[86](#_ENREF_86),[92](#_ENREF_92) Guidelines also state that patients should be educated to preserve the integrity and dryness of their catheter dressings.[11](#_ENREF_11),[14](#_ENREF_14),[15](#_ENREF_15),[92](#_ENREF_92) Submersion of the catheter or catheter exit site in water is generally not advised. Showering might also increase catheter-related infection risk. Therefore, swimming, submerged baths, and showering are discouraged,[93](#_ENREF_93) as it is not possible to ensure full protective coverage of their catheter exit site during a shower with dressings, ointments or other protective coverings. Moist or damp dressings may create an environment that facilitates catheter exit site microrganism colonization, especially if the catheter exit site is not fully healed. In some cases, patient compliance may be less than desired by the nephrologist and health care team. Hemodialysis nurses report that patients often arrive to dialysis with wet and non-intact dressings from showering.[94](#_ENREF_94) A quality assurance project was undertaken to determine the degree of patient compliance and satisfaction with different catheter care protocols.

1.4.2 Methods

The Catheter Care Survey is a brief 15 minute questionnaire (Appendix 3) aimed to measure patient adherence to the prescribed catheter dressing protocol, and the impact of current catheter dressing protocols on patient’s quality of life. Data was prospectively collected by trained research assistants at three dialysis units (2 university and 1 community based) in Ontario. All three dialysis units used different catheter care protocols, with one unit using the PTO protocol.

The questionnaire asked about six components of the patient’s catheter care routine: 1) who performs catheter care (patient, nurse, family member etc.); 2) the type of cleansing agent; 3) the type of dressing; 4) frequency of dressing change; 5) the antimicrobial ointment used (if any), and 6) the patient’s personal hygiene practices (bathing, showering, sponge bath). For example, for personal hygiene, patients were specifically asked if they shower with their catheter, if they protect their catheter in the shower, and if they had been advised by a health care professional not to shower. Descriptive statistics of percentages of patients responding ‘yes’ or ‘no’ to each question were performed.

The questionnaire has two questions that utilize a 5 point likert scale to determine the level of inconvenience associated with the current catheter dressing protocol. The quality of life infringement was inferred from the 5 point likert scale i.e. increased inconvenience is detrimental to patient’s quality of life. Non-compliance with catheter care was assessed by the proportion of patients who took a shower when advised not to. A chi-squared analysis was performed comparing the effect of various independent factors (i.e. whether or not the dialysis centre used PTO, if a healthcare professional told them not to shower, and if they had previously had an infection related to their catheter) on whether or not the patient showered with their catheter, and whether or not they find the guideline not to shower with their catheter inconvenient. All statistical analyses were conducted using SPSS 17.0.

1.4.3 Survey results

Two hundred and seventy four consecutive patients were interviewed. Seventy four percent of patients reported their catheter dressing to be a little or not at all inconvenient while 25% of patients reported their catheter dressing to be a moderate to extreme inconvenience. The majority (69%) of patients prefer to have their dressing, even if they were given the option to go without. Less than 1% of patients surveyed changed their own dressings at home, which means that 99% of those patients surveyed adhered to their CVC care protocol and did not remove or change the dressings in between weekly dressing changes.

Just under half of those surveyed indicated that they had not been told by a medical professional not to shower with their CVC. Those patients that recalled being instructed not to shower by a medical professional were asked a follow up question: How much do you find the recommendation not to shower bothers/or inconveniences you? Twenty nine precent of patients that reported that not being able to shower bothered or inconvenienced them a little or not at all (1-2 on Likert scale). 71% of patients that reported that not being able to shower bothered or inconvenienced them moderately to extremely (3-5 on Likert scale).

The results of the survey with regards to compliance with health care professional’s recommendation not to shower are reported in Table 4: 77% of patients shower with their catheter against guideline recommendations not to shower. Only 21% of patients recall their healthcare provider recommended them not to shower. The results of the chi-square analysis showed that patients were 3.8 times more likely not to shower if they remembered a healthcare provider telling them not to, then if they had no such recollection (95% CI = 1.217, 4.502).

1.4.4 The Impact of the Catheter Care Survey for Catheter Care Programs

A limitation of this survey is that it was only conducted in three dialysis units. It is likely that many factors contribute to patient compliance with the catheter care protocol that were not adequately captured or controlled for in this survey. However, the finding that 77% of patients shower with their catheter against guideline recommendations not to shower, suggests a need to better understand patient considerations and practical implementation of guideline recommendations. There are limited and costly catheter covers available for purchase in the US (e.g. $6-8.00 USD/shower use, or $45.00 for a Korshield™ shower cape)[95](#_ENREF_95) but they are not widely available, do not fully prevent water entry, and are cost prohibitive to the majority of the hemodialysis population[29](#_ENREF_29)

The finding that patients are more likely to adhere to the recommendation not to shower when aware of it, suggests the need for ***improved patient education and consistent reinforcement of proper catheter dressing care and infection prevention***. Overall, there is a need to better understand patient preferences when implementing a catheter care program. To address the patient’s desire to shower for hygiene and quality of life issues and to simultaneously adhere to infection prophylactic measures, several dialysis facilities have developed a “shower technique”, as an alternative method of catheter care[94](#_ENREF_94),[96](#_ENREF_96),[97](#_ENREF_97); however, “shower techniques” have not yet been formally evaluated to ensure that they do not increase catheter-related infection risk.

#### 1.5 The Objectives and Scope of the Thesis

The objective of this thesis is to design testing the feasibility of conducting a randomized control trial that addresses the hemodialysis patient’s need to shower and the health care provider’s need to limit catheter related infection risk. The design for this study, entitled the Hemodialysis Infection Prevention using Polysporin Ointment with Shower Technique in Satellite Centres (HIPPO SAT) pilot study, will be detailed in Chapter 2. This study design manuscript in its form in Chapter 2 has been submitted for publication to a peer reviewed journal. Funding has been obtained for this study from the Kidney Foundation of Canada, and the study has been approved by 5 research ethics boards at the participating sites, London Health Sciences, Mackenzie Health Hospital, The Scarborough Hospital Trillium Health Hospitals, and University Health Network, in south central Ontario. All authors on the HIPPO SAT pilot study have had an opportunity to review the design manuscript. Chapter 3 will detail some of the challenges and limitations with this study design and its implementation as well as discuss it’s implications.

Chapter 1. Table 1. Systematic Reviews and Meta Analyses of Antimicrobial Lock Solution (ALS) for CRB Prophylaxis in Hemodialysis patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Meta-analysis or review, year** | **No. of studies** | **CRB Summary**  **(Risk Ratio [RR] or Incidence Density Difference [IDD] where available)** | **Comments** |
| Jaffer et al.,[52](#_ENREF_52) 2008 | 7 | RR 7.72 (95% CI, 5.1 to 10.3), RR > 1 Favours ALS | No significant side effects with ALS.  Short follow up periods limit examination of antibiotic resistance. |
| James et al.,[53](#_ENREF_53) 2008 | 11 | ALS reduced CRB rate from 3.2 to 1.2 cases per 1,000 CDs. | ALS also decreases need for catheter removal. Short follow up periods limit examination of antibiotic resistance. |
| Labriola et al., 2008 | 8 | RR = 0.32 (95% CI 0.10–0.42), RR < 1 Favours ALS | Short follow up periods limit examination of antibiotic resistance.  Presence of heterogeneity suggests studies should not be pooled. |
| Yahav et al.,[51](#_ENREF_51)2008 | 11 | RR = 0.37 (95% CI, 0.30–0.47), RR < 1 Favours ALS | Presence of heterogeneity suggests studies should not be pooled. |
| Rabindranath et al.,[98](#_ENREF_98) 2010 | 19 | RR = 0.28 (95% CI 0.18–0.43), RR < 1 Favours ALS |  |
| Snaterse et al.,[50](#_ENREF_50)2010 | 9 | IDD: -1.96 (95% CI: -2.63 to -1.30); IDD<0 Favours ALS | CRB more common in the control group than with ALS (3/1000 catheter days);  Only one trial performed an intention to treat analysis  3 catheters need to be prophylactically locked with ALS with a mean insertion time of 146 days to avoid one case of CRB |

Chapter 1 Table 2 Randomized Control Trials of ALS versus Heparin Lock published since Jan 1, 2010

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Trial, year** | **No. of patients** | **CRB rate, cases/1000 catheter days** | | | **ALS constituents** |
| **Control group** | **ALS group** | ***P*** |
| Solomon et al.,[99](#_ENREF_99)2010 | 110 | 2.4 | 1.4 | .1 | Taurolidine-citrate |
| Campos et al.,[100](#_ENREF_100) 2011 | 150 | 4.3 | 1.1 | .005 | Minocycline-ethylenediaminetetraacetic acid |
| Hemmelgarn et al.,[60](#_ENREF_60) 2011 | 225 | 1.37 | 0.4 | .02 | Recombinant tissue plasminogen activator –heparin |
| Maki et al.,[101](#_ENREF_101) 2011 | 407 | 0.82 | 0.24 | .005 | Citrate–methylene blue–methylparaben–propylparaben |
| Moran et al., 2012 | 303 | 0.91 | 0.28 | .003 | Gentamicin-citrate |

Chapter 1 Table 3- Percentage of Patients Non Compliant with Guideline Recommendations not to Shower

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | | Healthcare professional told them not to shower | | Total |
| No | Yes |
| Currently Showers | No | Count | 28 | 15 | 43 |
| % of Total | 15.0% | 8.0% | 23.0% |
| Yes | Count | 119 | 25 | 144 |
| % of Total | 63.6% | 13.4% | 77.0% |
| Total | | Count | 147 | 40 | 187 |
| % of Total | 78.6% | 21.4% | 100.0% |

## CHAPTER TWO: Hemodialysis Infection Prevention using Polysporin Ointment with Shower Technique in Satellite Units (HIPPO SAT) Pilot Study Design

#### 2.1 Administrative Information

**Clinical Trial Registration:** ClinicalTrials.gov

**Protocol Version Date:** October 7, 2013

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**Trial Sponsor:** The study sponsor is the Kidney Foundation of Canada. The Kidney Foundation of Canada had no role in the study design, collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

**Coordinating Centre:** Toronto General Hospital is responsible for collection, management, analysis and interpretation of data.

**Trial Steering Committee:** Lok C.E., Gafni A., Moist L., Thabane L.

**Endpoint adjudication committee:** Batistella M., Bhola C.

#### 2.2 Introduction

2.2.1 Background and Rationale

Worldwide, increasing numbers of people are reaching end stage kidney disease (End Stage Kidney Disease) and require renal replacement therapy. The majority (1.80 million) is on hemodialysis (Hemodialysis).[29](#_ENREF_29),[102](#_ENREF_102),[103](#_ENREF_103) In order to receive Hemodialysis, a safe and secure vascular access between the patient’s blood circulation and the dialysis machine is required. For approximately 80% of incident and 50% of prevalent Hemodialysis patients in North America, this vascular access is a catheter.[28](#_ENREF_28),[29](#_ENREF_29) Catheter use is associated with the highest morbidity and mortality of all vascular access types, primarily related to infection.

Catheter related infections are associated with increased morbidity and hospitalization rates, high treatment costs, and poor survival compared to use of an arteriovenous access.[17-24](#_ENREF_17),[104](#_ENREF_104) Of the catheter related infections: bacteremias (CRB), exit site, and tunnel , CRB are the most clinically important due to their common occurrence and potential to progress to sepsis.[105](#_ENREF_105) The rate of CRB in usual clinical practice (i.e. non-clinical trial setting) range between 2.5-5.5 to 1000 catheter days.[36](#_ENREF_36) A CRB rate of <1.0/1000 catheter days is considered excellent.[106](#_ENREF_106)

To prevent infection, patients should preserve the integrity and dryness of their catheter dressings[11](#_ENREF_11),[14](#_ENREF_14),[15](#_ENREF_15),[92](#_ENREF_92). Showering should be avoided, as it is difficult to attain full protective coverage of the exit site using dressings and barriers. Wet dressings place patients at increased infection risk, especially if their catheter exit site is not fully healed. However, in a survey of 274 catheter dependent Hemodialysis patients, 64% indicated that the recommended prohibition to shower was moderately to extremely inconvenient and reduced their quality of life. Additionally 77% of patients admitted to showering at least once while they had a catheter.[107](#_ENREF_107) This is consistent with reports by Hemodialysis nurses that patients often arrive to Hemodialysis with wet and non-intact dressings due to showering.[94](#_ENREF_94) In the USA, there are limited catheter shower covers available for patient purchase (e.g. $6-8.00/shower use) and are cost prohibitive to the majority of the Hemodialysis population.[29](#_ENREF_29)

While submersion of the catheter in water is discouraged by clinical practice guidelines, they also state that if precautions can be taken to reduce the likelihood of bacterial catheter entry then showering may be acceptable. However, this guidance is opinion based with no evidence to support specific precautions. Thus, to address the patients’ desire to shower safely, at least 2 separate dialysis facilities in Ontario, Canada have developed a showering procedure as an alternative method of catheter care.[94](#_ENREF_94),[96](#_ENREF_96) Preliminary data from a small proof-of-concept study of 65 patients suggests acceptable CRB rates (0.46/1000 catheter days) using such showering procedures.[96](#_ENREF_96) The study was conducted in satellite Hemodialysis units on a select population of patients who were infection-free for 6 months using the same catheter. Satellite units offer dialysis in an outpatient setting for those patients who are stable and require less intensive care than in-centre patients.[108](#_ENREF_108) The satellite Hemodialysis population is typically younger and healthier,[109](#_ENREF_109),[110](#_ENREF_110) and likely more able to perform showering procedures than in-centre patients. With increasing patients in satellite Hemodialysis, it is crucial that a pragmatic, yet effective, prophylactic catheter infection strategy be formally tested and established for this setting.

Following the proof-of-concept study, nephrologists, vascular access coordinators, and Hemodialysis centres from five dialysis centres across Ontario, collaborated to create a formal Shower Technique Protocol (STP) which includes chlorhexidine applicators after showering to minimize the risk of bacterial entry at the catheter exit site. STP is designed specifically for patients with a fully endothelialized catheter tunnel and healed exit site. Participants allocated to STP are able to shower and change their dressing up to 3 times per week.

Prior to more widespread implementation of the STP, it is critical to determine whether it is safe for use in patients with healed catheter exit sites. In other words, to confirm that CRB rates in patients using STP are not greater than the CRB rates in patients using the gold standard of catheter care. It is unknown whether using the STP improves patient satisfaction with their catheter care. In any non-randomized study designed to answer these two important clinical questions there is real potential for confounding as those selected to use the STP are likely to be the patients with minimal co morbidity, lowest infection risk, and highest level of compliance. Therefore it is critical that the new STP be formally evaluated in a rigorously designed and implemented clinical trial prior to its widespread application.

2.1.2 Objectives

*Primary Feasibility Objective*: To determine if it is feasible to conduct a large multi-centre randomized control trial in satellite Hemodialysis patients dialyzing via catheter to test whether the CRB rate is non inferior to the STP compared to standard catheter care over 6 months. Feasibility is defined by 5 outcomes (see table 1 for details) including the accuracy of CRB event rate capture, successful recruiting and consenting of patients in satellite centres, retention of using the STP at 3 and 6 months, and measuring the degree of contamination in the control arm.

*Exploratory Secondary Feasibility Objectives:* To validate both the Vascular Access Questionnaire (VAQ) and the catheter exit site healing tests (below).

The results of the HIPPO SAT pilot study will allow for estimation of sample size requirements for the following clinical objectives for the full study:

*Primary Clinical Objective:*  To determine the CRB rate using the STP in addition to standard catheter care in Hemodialysis satellite patients with healed catheter exit sites over 6 months.

*Secondary Clinical Objectives*: 1) To compare the change in patient satisfaction with their vascular access over six months (measured by VAQ), using the STP and standard care versus standard catheter care alone, and 2) To capture the cost associated with STP in addition to standard care.

*Tertiary Clinical Objectives*: To compare the proportion of CRB, catheter-related infections, and tunnel infections; the time to first catheter-related infection after study randomization, the rate of removal of the catheter to prevent or halt progression of catheter related infection morbidity, hospitalization rate due to catheter- related infection, and mortality rate due to catheter-related infection in patients using the STP and standard care versus patients using standard catheter care alone at 6 months.

2.2.3 Trial Design

This will be a multi-centre, single-blinded randomized feasibility study for a larger trial of the same design. The HIPPO-SAT pilot study will primarily test thehypothesis that it is feasible to implement a randomized non inferiority trial comparing the rate of CRB in satellite Hemodialysis patients who dialyze with a tunneled catheter using the STP in addition to standard catheter care versus standard catheter care. The proposed pilot study will secondarily test the hypothesis that the STP will improve patient satisfaction with their vascular access at low additional cost. There are several challenges in conducting a randomized trial to test the STP, including capturing the CRB event rate and recruiting in satellite centres, teaching of the STP, testing healing at the catheter exit site, as well as measuring the degree of contamination and non compliance with STP.

#### 2.3 Methods: Participants, interventions, and outcomes

2.3.1 Study Setting

This pragmatic study will take place in the satellite units affiliated with 2 academic centres, Toronto General Hospital and London Health Sciences; and 3 community centres, the Scarborough Hospital, Trillium Health Centre- The Credit Valley Hospital, and Mackenzie Health Hospital in South Central Ontario, Canada.

2.3.2 Eligibility Criteria

The study population will consist of individuals requiring chronic Hemodialysis who have tunneled catheter in situ for longer than six weeks who meet the study inclusion criteria.

*Inclusion Criteria:* 1. Informed written consent obtained (English speaking); 2. Age >18 years; 3. Requires a catheter as the vascular access: a) End Stage Kidney Disease without a functioning surgically created access; b) End Stage Kidney Disease whose peritoneal dialysis problems require transfer to Hemodialysis for an anticipated prolonged period; 4. Passed 2/3 tests of catheter exit site healing (see below); 5. Must be willing and able to take a shower as the standard form of body cleansing if randomized to STP; 6. Trisodium citrate (4%) as standard catheter locking solution; 7. catheter has been in situ for > 6 weeks

###### Exclusion criteria: 1. Acute kidney failure, likely to be reversible with recovery of renal function; 2. Non-Tunneled catheter; 3. Antibiotic use by any route in the week prior to enrolling in the study, including intranasal mupirocin; 4. On immunosuppressant therapy; 5. Use of the catheter for purposes other than access for hemodialysis e.g. TPN; 6. Involvement in another interventional study related to their vascular access; 7. Catheter or patient life expectancy <6 months (e.g. active malignancy; serious comorbidity such as hepatic failure); 8. Routine use of TPA or antibiotic as a locking solution;9. Catheter insertion in location other than the neck/chest region (IJ or subclavian acceptable)

2.3.3 Interventions

The planned trial intervention in participants with healed catheter exit sites will be either: 1) training and use of the STP when the participant wishes to shower plus standard catheter care provided by Hemodialysis nurses at the satellite centre; or 2) standard catheter care provided by Hemodialysis nurses at the satellite centre. The duration of the intervention will be 6 months from the time of randomization. In order to ensure as much standardization as possible, if a participating site uses a prophylactic barrier at the catheter exit site as part of their catheter care protocol, they may only apply Polysporin Triple Ointment (PTO) as a topical prophylactic agent. Showering is not anticipated to impact the efficacy of PTO prophylaxis, as patients can be taught to re-apply the PTO according to standardized catheter care technique.

i) ***Standard Catheter Care*** consists of cleansing with chlorhexidine 2% or povidone (if allergic to chlorhexidine) at the catheter exit site by trained Hemodialysis nurses followed by placement of a dry gauze dressing by the Hemodialysis nurse 1x/week (Tues, on a Tuesday-Thursday-Saturday (TTS) or Monday on a Monday-Wednesday-Friday (MWF) dialysis schedule) or when clinically indicated. Nuanced differences may be present at participating units; however, the key components of the intervention are 1) Hemodialysis nurse delivery of catheter care 2) chlorhexidine or povidone cleansing 3) dry gauze dressing 4) standardized frequency. For both STP and control arms, participants whose Hemodialysis centre uses PTO as part of standard catheter care will continue to have it applied as per program policy. In order to participate in the standard catheter care arm, participating sites must have in their policy that it is trained Hemodialysis nurses who will apply the PTO after standard cleansing with chlorhexidine 2% or povidone during Hemodialysis, according to guideline recommendations or as per hospital patient care standards and nursing regulations. Study coordinators will check dialysis run sheets on a monthly basis so confirm that the nurse administered dressing changes are compliant with standard of catheter care (in terms of frequency and application of PTO), and will report non-compliance to the Principal Investigator as well as the appropriate vascular access coordinator/local investigator.

ii) ***Shower Technique Protocol (‘STP’)*** Participants will be given a minimum 30 minute personalized educational session by the study coordinator. They will be taught safe and clean techniques for showering with their catheter. Video and educational pamphlets of the STP will be used to assist in training participants randomized to this intervention. Details of the STP will be published with the results of the HIPPO-SAT pilot trial to prevent problems with contamination. The participant must successfully demonstrate the STP on a training mannequin and be deemed by the study coordinator as ready to independently and correctly perform it before proceeding (objectively measured by a STP Demonstration Test check list -see Table 1). If the participant passes the STP Test, they will be provided a pamphlet on the STP, not to be shared with other participants, to be kept as a reference and placed in their bathroom/household. They will also be given the necessary supplies for the STP, itemized in individual sequentially numbered storage bags (kits), to take home. Twelve kits are given to each patient at a time, which is equivalent to three showers a week worth of supplies. The patient will call the study coordinator if they run out of supplies early; otherwise, patients will be given new kits once monthly. The study coordinator will track all these supplies for use in the cost analysis. Participants will be reassessed using the training mannequin 3 and 6 months following randomization.

Study personnel will be available to answer any questions during Hemodialysis or by telephone for both study arms any time throughout the study.

2.3.4 Outcomes

Feasibility objectives and their corresponding outcome measures are listed in table 1.

The primary clinical objective will be detected and measured as follows: Participants are clinically evaluated 3x/week on Hemodialysis by their Hemodialysis nurses, who are experienced at recognizing and managing patients with a suspected catheter related infection, especially a CRB. The Hemodialysis nurse will carefully inspect the participant’s catheter exit site and surrounding area 1x/week or more if infection is suspected. At the first sign of infection the nurse will notify a Provider (Nurse Practitioner or Physician) and the study coordinator immediately, take the appropriate swabs, and blood cultures to obtain organism growth and sensitivities. Signs of infection will include temperature greater than 37.7C, rigors on Hemodialysis, and pain, redness, swelling, warmth or discharge at the catheter exit site or along the subcutaneous tunnel.[68](#_ENREF_68) If the participant’s Nurse Practitioner or Physician determines that it is clinically indicated, the catheter will be removed and the catheter tip will be cultured. The study coordinator will follow up with the nurse and complete a data collection form for each suspected infection.

The data collection form and laboratory results of blood culture and swabs will be submitted to the Hemodialysis Infection Control Subcommittee (HICS)[78](#_ENREF_78) at Toronto General Hospital (TGH) (blinded to patient allocation) for confirmation and classification of the diagnosis according to the Health Canada definitions.[111](#_ENREF_111) This previously established independent panel of nephrologists, vascular access coordinator, hemodialysis pharmacist, and infection control practitioner will act as the blinded outcome adjudication committee for this study. As the HICS only routinely monitors in-centre patients at TGH, they will be independent and blinded to satellite patients from all centres. All secondary and tertiary clinical objectives will measure outcomes defined in table 1.

2.3.5 Participant Timeline

The planned recruitment period is 12 months and the total duration of follow-up will be 6 months (see Table 2). Study visits will take place at baseline, 3 months, and 6 months post randomization. Baseline clinical (e.g. etiology of ESRD, comorbidities), demographic (e.g. age, sex), and vascular access (e.g. previous and current catheter) information will be obtained from the chart and/or a short interview with the participant. The catheter care survey, a measure of participant’s compliance and contamination with their catheter care protocol, and the VAQ, a measure of vascular access specific satisfaction and quality of life, will be administered to all participants at each study visit.

Participants randomized to the STP will be educated within a week of randomization. They will then undergo the “STP demonstration test”. During the study, participants will be tested at 3 and 6 months. Supplies for the STP will be distributed to patients once monthly.

Since this is a feasibility pilot study, feasibility outcomes will be evaluated at each phase of the study e.g. screening, recruitment, education, event determination and documentation, with successes defined in Table 1 and timeline outlined in Table 2.

2.3.5 Sample Size

This is a pilot study that will help determine sample size and analysis plan for the larger HIPPO-SAT study. The current sample size considers 50% eligibility, 25% refusal, 10% non-compliance and <1% loss to follow-up and is based on the following infection rates. The rate of CRB achieved with PTO is 0.26-0.63/1000 catheter and the CRB rate using STP, based on preliminary data is 0.39-0.46/1000 catheter days. However the STP was only used in select patients (no prior infection, used the same catheter for 6 months), so the CRB rate may be higher using the study inclusion criteria. Planned recruitment is 90 patients for the pilot study (see Table 3). There will be one analysis at the completion of this feasibility study of satellites.

2.3.6 Recruitment

Each site will have 6 months in total to recruit patients from which a recruitment rate will be determined. Since ethics approval and regulatory /administrative timelines vary by site, the pilot study will have a 12 month recruitment period from the time the study initiates until closing recruitment. Recruitment will be performed by research coordinators. In order to protect against selection bias, all satellite Hemodialysis patients with a catheter *in situ* for at least 6 weeks will be approached. A screening log will be maintained and evaluated weekly during the recruitment period, to document reasons for exclusion and reasons why eligible participants are not participating i.e. refusal to consent, lack of available translator. Recruitment progress and goals will be assessed at weekly research meetings of the central trial research coordinator and the principal investigator. If targets are not met, reasons will be examined and rectified; for example, if the rate of non-participating but eligible participants is high, study coordinators may require re-examination of the consenting process.

In a previous study in a similar population, the overall rate of recruitment (prevalent and incident catheter together) was >14 patients/month (2 sites).[68](#_ENREF_68) However the inclusion criteria are quite distinct in the HIPPO SAT from the original HIPPO trial population. The HIPPO SAT population must be willing and able to learn the STP.

#### 2.4 Methods: Assignment of Interventions (for controlled trials)

2.4.1 Allocation

Once written consent is obtained, the participant will undergo formal testing for catheter exit site healing. The tests of catheter exit site healing are as follows: **1)** **Deep Breath Stability Test** measures the migration of the catheter as marked by a 2 cm indicator on the catheter from the skin at catheter exit. There should be < 3 mm movement between complete exhalation and inhalation; **2) catheter Seal Test** is a visual inspection against an objective checklist to determine healing; and **3) Blinded Photo Test** where two photos are taken of the catheter exit site to be evaluated for healing by independent blinded trained assessors. Both assessors must agree that the exit site is healed to pass the test. These catheter exit Site Healing Tests will be repeated at the first Hemodialysis session until 2/3 tests are passed, i.e. will be reevaluated at each dialysis session until 2/3 criteria are met or recruitment ends. These tests are only used on catheters that are at least 6 weeks old to ensure that all catheter exit sites are fully healed prior to patients being randomized to the study intervention arms. If any of the tests are failed, standard catheter care will continue; the patient can be reassessed weekly until recruitment ends. Randomization will occur immediately after the eligible participant from whom consent has been obtained meets the entry criteria of “healed catheter exit site”.

*Allocation concealment mechanism*

The participants’ necessary details will be forwarded to a 24-hour, telephone accessed independent central randomization facility (McMaster University) where they will receive a unique study number. The study coordinator will notify the patient of their allocation, and if randomized to the intervention arm, will immediately administer the STP education session. Patients and the study coordinator cannot be blinded to allocation status due to the nature of the intervention; however, the outcome adjudication committee will be blinded to allocation status.

*Sequence generation and implementation*

Randomization will take place within strata formed by study site. The randomization schedule will be produced by a computer generated random number list, and will use a random permutated block design, with blocks sizes randomly selected. The central randomization facility (McMaster University) will know the randomization code. None of the study personnel or investigators will have direct access to the code.

2.4.2 Blinding

Allocation of patients to the intervention will be concealed to the randomization desk (responsible for allocation) and will occur according tor randomization sequence. The study coordinator who will inform the patient of the intervention allocation and health care professionals will not be blinded due to the nature of the intervention; however, outcome assessors will be blinded.

#### 2.5 Methods: Data collection, management, and analysis

2.5.1 Data collection methods

All baseline and outcome data will be collected on paper data collection forms by the study coordinator, Hemodialysis nurse, or HICS committee member. They will then be entered into the computerized HIPPO-SAT database. There are no patient administered forms as the VAQ and catheter care survey are both administered by the study coordinator to the patient.

*Participant retention*

In order to enhance patient retention and reduce loss to follow up study coordinators are all trained in Good Clinical Practice guidelines i.e. to ensure proper patient selection and consent. Participants may rescind consent from the study at any time e.g. if they find the STP too challenging. Loss to follow up should be minimal as hemodialysis patients represent a “captive” study population due to their dialysis needs.

2.5.2 Data management

All study data will be entered by the study coordinator into the HIPPO-SAT database. The HIPPO-SAT database will be developed by the study coordinator and the study statistician so that the coding is suitable for analysis in the SAS (c) statistical program. A data dictionary is maintained for ease of data exit and analysis.

2.5.3 Statistical methods

The CONSORT criteria will be followed in the statistical analysis and reporting of this RCT. Feasibility is defined by 5 outcomes, each with it’s own statistical test and measure of success: all 5 must be achieved for the full study to be feasible (see table 1). Secondary feasibility objectives and the corresponding measure of success and statistical test are also listed in table 1. The primary clinical objective is to compare the rate of patients with healed catheter exit sites who develop a CRB using a protocolized STP in addition to standard care versus standard catheter care alone. The rate of CRB development is hypothesized to be non inferior in the STP arm as compared to control. The number of events per 1,000 access days will be analyzed using Poisson distribution methods. Comparisons between intervention and control arm will use the incidence rate ratio from a Poisson regression. Secondary and tertiary clinical objectives and the corresponding hypothesis and statistical test are also listed in table 1. P-values < 0.05 will be considered statistically significant. All P-values will be two-sided and are unadjusted for multiple comparisons. All analysis will use SAS v 9.4 and be carried out by a statistician blind to the intervention groups. There will be one analysis at the completion of this pilot study.

*Definition of analysis population*

Analyses will be based on an intention-to-treat approach, a sensitivity analysis will be conducted using the as-treated approach. In sensitivity analyses, missing data will be imputed using multiple imputation methods

#### 2.6 Methods: Monitoring

2.6.1 Data Safety Monitoring Board

A Data Safety and Monitoring Board (DSMB) will not be required for this pilot study. However the study data will be continuously monitored for safety of the novel procedure. A DSMB will be assembled for the larger study, if this study is found to be feasible. For the full study the DMSB will be a group of independent experienced clinical trialists. At least one DSMB member should be a statistician. Additionally, nephrologists knowledgeable about the infection prophylaxis in vascular access and previous experience running clinical trials should be represented. Other possible members include an ethicist or a representative from a patient advocacy group. It is important that members have previous experience on DSMBs as they will be of great import in the conduct of the full HIPPO SAT study. The DMSB will meet at predetermined intervals every six months and review unblinded results. No member should have any conflicts of interest with the results of the trial, the study investigators, or the study sponsor.

There will be no interim analysis conducted in the pilot study. If deemed feasible, for the full HIPPO SAT study an interim analysis will be conducted.

**2.7 Ethics and dissemination**

2.7.1 Research ethics

Ethics board approval for this study has obtained at the Scarborough Hospital, University Health Network- Toronto General Hospital, London Health Sciences, and Mackenzie Health Hospital. The study protocol and appendices have been submitted to the Ethics Board at Trillium Health – The Credit Valley Hospital.

2.7.2 Protocol Amendments

Protocol ammendments such as changes to eligibility criteria, outcomes, analyses will be communicated to relevant parties in writing by the study coordinator with the approval of the principal investigator to the investigators, Research Ethics Boards, trial participants, and trial registries. There are no relevant financial and other competing interests for principal investigators for the overall trial to disclose.

2.7.3 Confidentiality

In order to protect confidentiality before, during, and after the trial, personal information about potential and enrolled participants will be collected and maintained by the study coordinator at the study coordinating centre**.** In order to protect confidentiality before, during, and after the trial, personal information about potential and enrolled participants will be collected and maintained by the study coordinator at the study coordinating centre**.**

2.7.4 Access to Data

The principal investigator, study coordinator, study statistician and monitors from the research ethics boards will be the only parties with access to the final dataset.

2.7.5 Dissemination Policy

The results of this study will disseminated at local, national, and international conferences and be the final manuscript submitted to an indexed journal for publication. The local and principal investigators, as well as the trial steering committee will be included as authors in the final manuscript. No professional writers will be used to write the manuscript.

#### 2.8 Discussion

It is critically important to pilot the HIPPO SAT study design due to the potential challenges associated with recruitment, consenting, CRB rate measurement, compliance, and contamination in satellite centres. Each measure of feasibility in this pilot study tests whether these methodologic challenges are serious threats to the implementation of the full study. The most pressing concern that necessitates a pilot study is the issue of contamination and compliance. Patient compliance with standard catheter care protocols were measured in a recently conducted survey at TGH and Scarborough General Hospital: >98% of patients were compliant with their nurse applied dressing protocol[107](#_ENREF_107), i.e. they did not remove or change their dressing at home. Therefore non-compliance with the nurse applied dressing aspect of the standard catheter care is not likely to be a major source of bias. However, in this same survey, 77% of patients on the standard catheter care protocol were showering against the Hemodialysis unit recommendation not to shower. These patients were protecting their catheter with a plastic bag or saran wrap and tape, or just avoiding getting the area wet in the shower. They frequently came into the Hemodialysis unit with wet dressings as a result. In the context of the HIPPO-SAT study, patients allocated to standard catheter care who do not comply with the recommendation not to shower are non compliant. In the control arm of the HIPPO SAT study patients will be educated on the importance of not showering with their catheter. The survey above found that patients were 3.8 times more likely to comply with the recommendation not to shower if they remember being told not to do so by a healthcare professional. Crossover will not be permitted in this study; in other words, patients randomized to the standard catheter care group will not be taught how to use the STP protocol. It is expected that a significant portion of patients in the control arm will shower against guideline recommendation, as per baseline; however, these patients are not considered crossovers as they are not using other aspects of the STP, such as use of chlorhexidine swabs. As this is a pragmatic trial design, *both compliant and non compliant patients will be included in this study in order to* reflect the clinical reality of Hemodialysis patients in satellite units.

There is potential for contamination in this study design. While participants in the intervention arm may communicate about the STP, the control arm will not have access to the training or necessary supplies required to properly perform the STP. However, where contamination exists, the extent of the problem will be measured in the pilot study. This is important for generalizability of the HIPPO SAT study results because in regular clinical practice only patients with a catheter with a healed exit site would be eligible for the STP. This means that there will be patients intermittently using the STP within the same satellite unit. It is therefore necessary to understand the risks of contamination for those patients not using the STP.

For the full HIPPO SAT study alternate study designs may be considered in the context of the rates of contamination and non compliance, based on the results from the pilot study. For example, if there is a high level of contamination in the pilot study, the use of a cluster randomized design may be justifiable for the full trial. By randomizing at the cluster level, for example, the satellite Hemodialysis unit, the advantage is of reduced risk of experimental contamination and potential accompanying increase in compliance. However, cluster randomized trials must be designed with great caution as they are very statistically inefficient and present many challenges in their analysis. In patient level randomization stratified by centre, the variation between centres is distributed equally between the control and treatment arms, so are not considered in sample size calculation and analysis. In cluster randomization, by contrast, the variance between centres must be considered both in sample size calculation and in the analysis, otherwise the variances and standard errors will be too low and statistical tests too liberal. Hemodialysis facilities have many natural levels of natural clusters, as there are multiple units per centre and 6 shifts at each unit: morning, afternoon, evening shifts and days (Mon-Wed-Fri shift and Tues-Thurs-Sat shift). If each shift within a unit was to act as a cluster, the variance between shifts would need to be estimated and the sample size would need be inflated by a factor reflective of that variance between shifts. In the pilot study, estimates of the between centre variance (the intracluster correlation coefficient) and level of contamination will be important factors when considering the design of the full study. Overall, the implication of this current pragmatic pilot design is the maintenance of study integrity while ensuring proper external validity and ultimately, greater practical generalizability to the real world setting.

#### 2.9 Conclusion

The proposed pilot study will determine the feasibility of conducting a multi centre randomized trial in satellite dialysis patients with healed catheter exit sites, testing whether the CRB rate over six months using the STP plus standard catheter care is not inferior to standard catheter care alone. This pilot study is critical to understand whether a pragmatic study design testing an educational intervention can be implemented in the satellite Hemodialysis population, which is not often studied in randomized trial design. Practical, patient centered programs for infection prophylaxis that cater to the needs of the satellite Hemodialysis population are in short supply.

Chapter 2 Table 1- Feasibility and Clinical Objectives for the HIPPO SAT Pilot Study

|  |  |  |  |
| --- | --- | --- | --- |
| **Nature of Objective** | **Outcome Measure** | **Criteria for Success (Feasibility) / Hypothesis (Clinical)** | **Method of Analysis** |
| Primary Feasibility: To determine if it is feasible to conduct a large multi-centre randomized control trial in satellite Hemodialysis patients dialyzing via catheter to test whether the CRB rate is non inferior over 6 months using ST plus standard catheter care compared to standard catheter care. Feasibility is defined by 5 outcomes below, for the trial to be feasibility 4 of the 5 criteria for feasibility much be met | | | |
| To assess the accuracy of the CRB rate in the satellite Hemodialysis setting | The level of agreement between the date the nurse contacts the coordinator to inform them of a suspected infectiona and the date the culture was sent to the lab from the Hemodialysis unit | Kappa level >0.80 | Kappa statistic |
| Determine the percentage of eligible Hemodialysis patients who consent | The percentage of eligible patients who consent to participate in each participating satellite unit | For each unit > 80% | Descriptive statistics: percentages and confidence intervals |
| Determine the percentage of satellite Hemodialysis patients with catheters who are screenedb | The percentage of satellite Hemodialysis patients with catheters who are screened for eligibility | For each unit > 95% | Descriptive statistics: percentages and confidence intervals |
| Measure the success of ST teaching | The percentage of patients in the STP arm passing the STP test at 3 and 6 monthsc | >=80% of patients randomized to ST | Descriptive statistics: percentages and confidence intervals |
| Determine the percentage of participants in the control arm who are contaminated by the ST | The percentage of patients in the control arm who are contaminated i.e. using aspects of the ST such as chlorhexidine swabs and PTO at the exit site which they were not using at baseline | <5% participants in the control arm | Descriptive statistics: percentages and confidence intervals |
| Secondary Feasibility | | | |
| Construct Validation of the Vascular Access Questionnaire (VAQ)d | The change in VAQ score over time using the ST compared to standard care. The VAQ is a measure of patient satisfaction with their vascular access that is previously un validated in this population | The ST group sees a greater improvement in VAQ scores than the control group over 6 months | Longitudinal regression model |
| Validation of the catheter exit site healing testsd | The level agreement between the Deep Breath and catheter Seal tests agree with the blinded photo test | Kappa level >0.80 | Kappa statistic |
| Primary Clinical | | | |
| Compare the rate of patients with healed catheter exit sites who develop a CRB using ST versus standard catheter care | The number of confirmed CRB per 1,000 access days, each CRB will be confirmed by the HICS committeed | Rate of CRB is hypothesized to be non inferior in the ST as compared to standard care | Poisson regression |
| Secondary Clinical | | | |
| Compare patient satisfaction using ST versus standard catheter care as measured by the change in VAQ scores over time | Patient satisfaction will be measured by the VAQ score at baseline, 3 and 6 months | An greater improvement in VAQ score of time in the ST group as compared to standard care | Longitudinal regression model |
| Determine the cost associated using ST versus standard catheter care | The mean cost per patient of using the ST versus standard care. The frequency and type of dressings, as well as the frequency of dressing changes by nurse and patient will be prospectively recorded for all patients in the study | The ST is hypothesized to cost more per patient than standard care | Student’s t-test |
| Tertiary Clinical | | | |
| Compare the proportion of CRB, catheter-related infections, and tunnel infections using ST versus standard catheter care | Proportions of patients with CRB, catheter related infection and tunnel infection as determined by HICS committeed | Proportions of patients with CRB, catheter related infection and tunnel infection are non inferior in the ST arm as compared to standard care | Chi-square test |
| Compare the time to first catheter-related infection after study randomization using ST versus standard catheter care | The number of days to this first catheter related infection from the date of randomization | Time to first catheter related infection in the ST is not inferior to that of standard care | Kaplan-Meier method (time to event distributions) and Cox proportional hazards model (to compare groups) |
| Compare rate of removal of the catheter to prevent or halt progression of catheter related infection morbidity using ST versus standard catheter care | The rate of catheter removal due catheter related infection as recorded in the vascular access record, the cause of catheter removal will be confirmed by the HICS committeed | Rate of catheter removal is not inferior in the ST arm as compared to control | Poisson regression |
| Compare hospitalization due to catheter related infection using ST versus standard catheter care | The number of days in hospital due to catheter related infection, the HICS committee will confirm the number of days in hospital that were related to catheter infectiond | Mean number of days in hospital is hypothesized to be not inferior in the STP arm as compared to standard care | Wilcoxon rank-sum test or t-test depending on distribution |
| Compare death due to catheter-related infection using ST versus standard catheter care | The proportion of patients who die from catheter related infection, the cause of death will be confirmed by the HICS committeed | Proportion of patients who die due to catheter related infection is hypothesized to be not inferior in the ST arm as compared to standard care | Chi-square test |

a. The Hemodialysis nurses must phone/inform the coordinator within 72 hours so that the “Suspected catheter related infection outcome reporting form” is completed promptly.

b. Screening can be challenging as satellite units are remotely located as compared to incentre patients and shifts are on evenings and weekends.

c. The standardized teaching materials for the STP are administered immediately after randomization. A STP test on a training mannequin is administered immediately after the education session, and then again at 3 and 6 months.

d. As defined by the Health Canada, determined by the independent event adjudication committee (Hemodialysis Infection Control Subcommittee (HICS) using the “Suspected catheter related infection outcome reporting form” completed by the nurse at the time infection is suspected, the lab reports, and a detailed chart review following a suspected infection for any related catheter removal, hospilitization, and death.

e. This is exploratory as the pilot study may not be powered for this objective.

Chapter 2 Table 2- Schedule of enrolment, interventions, and assessments

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **STUDY PERIOD** | | | | |
|  | **Enrolment** | **Allocation** | **Post-allocation** | | |
| **TIMEPOINT\*\*** | ***- (1-2) wk*** | **0** | ***1 wk*** | ***3 m*** | ***6 m*** |
| **ENROLMENT:** |  |  |  |  |  |
| **Eligibility screen** | X |  |  |  |  |
| **Informed consent** | X |  |  |  |  |
| **Catheter Exit Site Healing Test** | X |  |  |  |  |
| **Allocation** |  | X |  |  |  |
| **INTERVENTIONS:** |  | X | X | X | X |
| **STP**  *Education session at randomization on showering with Catheter, changing dressing and applying PTO at home (in addition to gold standard care)* |
| **Control**  *Gold standard care PTO applied at Catheter exit site once per week* |  |  |  |  |  |
| **ASSESSMENTS:** | X |  |  |  |  |
| ***Baseline Characteristics, catheter exit site healing*** |
| ***Continuous monitoring for signs of catheter related infection at least once per week at hemodialysis*** |  |  |  |  |  |
| ***Catheter Care Survey monitoring compliance and contamination, Vascular Access Questionnaire*** | X |  |  | X | X |

Chapter 2 Table 3- Expected Recruitment based on Current Data known from each of the participating sites

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Current** | **Expected Recruitment and Rates** | | | | | | | | | |
| **Approx. number of catheters over 8 months based on current data** | Assumed Eligibility | 50% | | | 50% | | | 50% | | |
| Assumed Refusal Rate | 20% | | | 25% | | | 30% | | |
|  | # of pts | # CRB\*\* (rate 0.26\*\*\*) | # CRB (rate 0.63) | # of pts | # CRB (rate 0.26) | # CRB (rate 0.63) | # of pts | # CRB (rate 0.26) | # CRB (rate 0.63) |
| **80** | Toronto General Hospital satellite (2) | 12 | 1 | 3 | 10 | 1 | 3 | 8 | 1 | 2 |
| **40** | London Health Sciences satellite (9)\* | 12 | 1 | 3 | 10 | 1 | 2 | 8 | 1 | 2 |
| **100** | The Scarborough Hospital satellite (3) | 30 | 3 | 7 | 25 | 2 | 6 | 20 | 2 | 5 |
| **70** | Mackenzie Health Hospital satellites (2) | 21 | 2 | 5 | 18 | 2 | 4 | 14 | 1 | 3 |
| **70** | Credit Valley Hospital satellite (2) | 21 | 2 | 5 | 18 | 2 | 4 | 14 | 1 | 3 |
| **360** | Total | 96 | 9 | 23 | **81** | **8** | **19** | 64 | 6 | 15 |

\* However only select satellites due to prior ST use in some satellites

\*\* Number of CRB in 6 months = Number of patients \* CRB Rate/pt/yr \* 6 months

\*\*\* From HIPPO study CRB rate in control ranges from 0.26-0.63/1000 catheter days

Total of 81 patients in intention to treat analysis (accounting for 25 % refusal, and 50% eligibility) and 78 patients in as treated analysis (10 % non compliance)

## CHAPTER 3 CHALLENGES AND IMPLICATION OF STUDY DESIGN

This thesis work is composed of three chapters. In chapter 1, the context of the research question for the Hemodilaysis Infection Prevention using Polyporin Ointment with Shower Technique in Satellite Centres (HIPPO SAT) pilot study was detailed. Chapter 1 includes a comprehensive literature review of hemodialysis central venous catheter (catheter) related infection prophylaxis and the results of two surveys that were conducted prior to HIPPO SAT pilot study to inform it’s design. After careful review of the literature, a survey of dialysis unit leaders of hemodialysis units across Canada, and a survey of satellite and incentre hemodialysis patients from three separate centres. The research target was refined as follows*: to determine the feasibility of capturing the costs, patient satisfaction, and the risk of catheter related infection associated with the use of a shower technique protocol (STP) in satellite hemodialysis patients with healed catheter entry sites.* Chapter 2 is the design of the HIPPO SAT pilot study in the form in which it was submitted for publication, in accordance with SPIRIT guidelines. This third chapter will outline three methodological challenges we faced in the design and implementation of the HIPPO SAT pilot study: 1) development of the STP protocol, 2) testing healing of the catheter exit site, and 3) measuring patient satisfaction with their vascular access. All three of these challenges required development and testing of novel educational and measurement tools in the design and implementation phases of the HIPPO SAT pilot study so that they may ultimately be used in the full HIPPO SAT trial. To conclude this thesis, the potential impact and limitations of this pilot study for patients, methodologists, and clinicians, and the future directions for this program of research will be discussed.

#### 3.1 The Shower Technique Protocol (STP) in the HIPPO SAT Pilot Study

Prior to the conduct of this HIPPO SAT pilot study no formal published “shower technique” existed in the literature for hemodialysis patients. However, input from our network of international leaders in hemodialysis from south central Ontario, and our cross Canada survey, we found that several facilities had developed their own methods of facilitating patients to shower. Indeed, they had borrowed ideas from the peritoneal dialysis literature. Both Credit Valley Hospital and London Health Sciences had independently developed their own versions of the “shower technique” however they had not formally tested in a clinical trial setting.

3.1.1 HIPPO SAT Pilot Study Shower Technique Protocol

The STP used in the HIPPO SAT pilot study is a marriage between the shower techniques used at Credit Valley Hospital, London Health Sciences Centre “No Dressing- Shower Technique”, and Toronto General Hospital Polysporin triple ointment dialysis catheter care protocol based on the original HIPPO Study (see section 3.1.3 for development of the STP).[68](#_ENREF_68) Participants randomized to the STP in the HIPPO SAT pilot study receive a 30 minute personalized STP training session with the study coordinator in which they are taught how to: 1) prepare the all the supplies required to change their catheter exit site dressing prior to showering; 2) carefully shower to clean their body and avoid the catheter exit site, no coverage of the catheter dressing is required; 3) after showering, dry their body, again avoiding the catheter exit site; 4) wash their hands with soap thoroughly, 5) carefully and gently remove and discard existing catheter exit site dressing; 5) remove the chlorhexidine soaked Q-tip applicator (supplied by the study) from its packaging and then cleanse the skin around the catheter exit site and catheter tube; 7) if on Polypsoring Triple Ointment (PTO), they will be taught to reapply the PTO; this PTO will have their study number affixed and participants will be strictly taught that this PTO is not to be used for other reasons or to be shared by other household members; 8) apply new dry dressing at the catheter exit site. During the STP training session, each participant randomized to STP is shown an STP training video on a computer laptop or tablet, given an STP educational pamphlet, and practices the dressing change on a demonstration that watch during their hemodialysis session.

The video, educational pamphlets, and a demonstration mannequin for STP training were developed were carefully developed prior to the HIPPO SAT pilot study to assist in training participants randomized to this intervention (Appendix 7):

I) Video: Two patient volunteers, one from the incentre hemodialysis unit and the other from the home dialysis programme at Toronto General Hospital, assisted in the filming of the video. The two patients were separately filmed by a research student from Dr. Lok’s clinical research team while I instructed the patient from behind the camera on each step of the STP to be demonstrated. The filming session was supervised by the vascular access coordinator and the hemodialysis nurse in charge of patient education from Toronto General Hospital. The patient from home dialysis was approached by myself to participate after being recommended by the home dialysis program at Toronto General Hospital. The patient was already comfortable changing his catheter dressing as he had been previously educated as part of the home dialysis program. The patient demonstrated how to carefully shower with his CVC, then change his dressing afterward. After this video was edited, I found that it was difficult to properly see the cleansing technique. Therefore, the same team was assembled for a second filming session. I approached a patient suggested by Dr. Lok from the hemodialysis unit incentre to participate. This patient was taught to perform the cleansing technique prior to filming. He was filmed from a closer angle and only demonstrated the cleansing technique with the chlorhexidine swabstick that were not clear from the first filming. The video was edited and produced by a third party. It is exclusively for use in the HIPPO SAT pilot study.

The STP training video shows the two patient volunteers (male) discussed above were shown from the waist up. The video is edited so that it appears that only one patient is in the video. Each step of the STP is simultaneously displayed in subtitles on the bottom of the screen while the ‘patient’ performs the STP. Copies of the video have only been made available to the principal investigator and the study coordinator, and are only shown to patients during their STP training session.

II) Educational Pamphlets: The educational pamphlet was developed by a panel of vascular access experts and patient educators at Toronto General Hospital and London Health Sciences centre including: two nephrologists (Dr. Charmaine Lok and Dr. Louise Moist), a Level III Clinical Research Coordinator (Cathy Forrester RN), a vascular access coordinator (Cynthia Bhola RN), a hemodialysis nurse educator (Vanessa Godfrey RN), a home hemodialysis and peritoneal dialysis educator (Debra Appleton RN) and a master’s student in clinical epidemiology (Sarah Daisy Kosa). Each step of the STP is listed on the pamphlet in lay terms, as well as signs of infection for the patient to watch for. The pamphlet also contains a diagram of a male chest with a catheter inserted, with the catheter exit site and catheter tube clearly labeled. Contact information is clearly listed on the back of the pamphlet. After being approved by all of the above panel, the pamphlet was given two the two patients who volunteered to act in the STP training video mentioned above. Both patients recommended increasing the font size and replacing the abbreviation ‘CVC’ for central venous catheter, with just ‘catheter’. The pamphlet was then finalized by the principal investigator before submission to the research ethics boards at all participating sites for the HIPPO SAT pilot study.

In the HIPPO SAT pilot study, the educational pamphlet is given to the patient to follow along while they are watching the STP video. Additionally, if a participant randomized to STP passes the STP Test, they will be told to keep the educational pamphlet in their bathroom/household and NOT share it with other patients, to prevent contamination of patients in the control arm. The study coordinator instructs the patient following the STP training session to tape the pamphlet to the patient’s mirror in their bathroom, so that the instructions are available for very dressing change.

III) Demonstration Mannequin: In order to educate patients on the STP, a tool for patients was required to practice cleansing the catheter exit site with chlorhexidine and applying a new catheter dressing. London Health Sciences previously used a flat board with a diagram of a chest with a catheter protruding from it. This type of educational tool would not work for the HIPPO SAT pilot study however, because the STP in the HIPPO has a full dressing change. The dressing adheres very strongly to the flat board. Instead, for HIPPO SAT pilot, a catheter was inserted into a repurposed Cardio Pulmonary Resuscitation mannequin. Using this mannequin the patient can practice removing the dressing, cleansing the catheter exit site, and replacing the dressing on a surface to which the dressing adheres normally and that is contoured like the patient’s own chest.

3.1.2 Shower Technique Protocol Test

After watching the educational video, reviewing the pamphlet, and practicing with the study coordinators assistance on the demonstration mannequin, the participant must successfully demonstrate the STP on the demonstration mannequin. The study coordinator must deem that the participant is able to correctly perform the STP independently before proceeding (STP Test). The participant’s ability to perform the STP on the Mannequin will be evaluated against a test check-list (Appendix 7) by the study coordinator. Participants will only proceed to independent showering after passing the STP Test and will be reassessed using the training mannequin 3 and 6 months following randomization. The patients will be allowed to use their pamphlet during these demonstration tests, as they are able to use the pamphlets at home when changing the catheter exit site dressing. Study personnel will be available to answer any questions during hemodialysis or by the telephone number provided (on the STP pamphlet) any time throughout the study.

3.1.3 Development of the Shower Technique Protocol

In order to develop the STP used in the HIPPO SAT pilot study, the HIPPO SAT pilot study team at Toronto General organized a meeting of all the principal investigators involved in the HIPPO SAT pilot study as well as the vascular access coordinators from each site (London Health Sciences, the Credit Valley Hospital, Toronto General Hospital, The Scarborough Hospital, and Mackenzie Health Hospital). This meeting was conducted in September of 2012. The Credit Valley Hospital “shower technique”, London Health Sciences “No Dressing- Shower Technique” and the Toronto General Polysporin triple ointment dialysis catheter care protocol were displayed step by step on a powerpoint for all the investigators and coordinators, in order to develop by consensus one protocol for all five centres, which collectively had nine satellite units committed to participate in this study. Three major steps in the final STP that were debated at length were I) the technique for cleansing the catheter exit site, II) the use of antimicrobial ointments at the catheter exit site, and III) the necessity of a dressing at the catheter exit site.

I) Chlorhexidine Application- Circles or Friction:An important component of catheter exit site prophylaxis is the cleansing of the catheter exit site with chlorhexidine (or povodine-iodine where chlorhexidine is not well tolerated -see section 1.2.2). One technique for cleansing involves the use of friction of the chlorhexidine swabstick against the skin at the catheter exit site. The chlorhexidine swab stick is swabbed up and down on the external surface of the catheter and on the skin around the exit site. London Health Sciences used the friction cleansing technique in their “No Dressing - shower technique” prior to the HIPPO SAT pilot study. This friction method of CVC exit site cleansing has the advantage that it can scour the loose skin and adhesive from the dressing around the catheter exit site. While this technique may be of value to trained and experienced hemodialysis nurses when removing such debris from around the exit site, the group of nephrologists and vascular access coordinators who convened to develop the STP for the HIPPO SAT pilot study agreed by consensus that patients using the friction cleansing technique may inadvertently transfer organisms back towards the exit site using the friction method, or scrub too hard and irritate the skin. As such, the circular motion method used in the Credit Valley Hospital “shower technique” was used in STP for the HIPPO SAT pilot study. The Credit Valley Hospital “shower technique” is based on the catheter care protocol used by peritoneal dialysis patients when showering and cleansing their catheter exit site at home.[112](#_ENREF_112) The circular method of cleansing involves more teaching time than the friction method, and necessitates the use of a mannequin during the education session on which the patients can practice. Patients are taught to spiral out from the catheter exit site in a clockwise motion, and then turn the swab stick over and spiral outward from the catheter exit site in a counter clockwise motion. This prevents organisms from being tracked back down towards the exit site.

II) Antimicrobial Ointments: The Centre for Disease Control Guidelines , as well as the Canadian Society of Nephrology guidelines, for the prevention of intravascular catheter related infections recommends that for antibiotic/antiseptic Ointments, either povidone iodine antiseptic ointment or bacitracin/gramicidin/ polymyxin B ointment (PTO) at the hemodialysis catheter exit site at each dressing change only if this ointment does not interact with the material of the hemodialysis catheter per manufacturer’s recommendation.[113](#_ENREF_113) As such if the center’s standard of care included Polysporin triple ointment, it was also included in the STP pamphlet and the education sessions for all patients enrolled at that centre.

III) Necessity of Dressing at the Catheter Exit Site: An important difference between the STP developed for the HIPPO SAT pilot study and the London Health Sciences and Credit Valley Hospital “shower techniques” is that patients are encouraged have no dressing at the catheter exit site in the latter two protocols. The CDC Guidelines for the prevention of intravascular catheter related infections makes no recommendation regarding the necessity for any dressing on well-healed exit sites of long-term cuffed and tunneled catheters. Both London Health Sciences Centre and Credit Valley Hospital Vascular Access coordinators cited patient complaints of itchiness and skin irritation at the catheter exit site associated with dressing, especially it’s adhesive, as reasons for using no dressing at the catheter exit site. The majority of the patients on the “shower techniques” at London Health Sciences and Credit Valley Hospital prior to the HIPPO SAT pilot study had no dressing at the catheter exit site as part of their dressing care protocol. However, “No dressing” was not emphasized in the STP for the HIPPO SAT pilot study as it does not address the main purpose of the STP which is to allow patients to have the quality of life benefit associated with showering with no additional risk associated with infection. Having no dressing at the catheter exit site is optional in the HIPPO SAT pilot study, and all patients are taught how to reapply their dressing following the shower. This increases the generalizability of the STP, as the catheter care survey (see section 1.2) performed at Scarborough General Hospital, London Health Sciences, and Toronto General Hospital in 277 hemodialysis patients found that less than 5% of patients wanted to go without a dressing, if given the option, while almost all surveyed patients wanted to shower. Additionally, the Centre for Disease Control Guidelines for the prevention of intravascular catheter related infections recommends health care providers encourage patients to report any changes in their catheter exit site or any new discomfort to their provider and was incorporated in the HIPPO SAT pilot study STP. The STP used in the HIPPO SAT pilot study is designed to meet the needs and preferences of hemodialysis patients in all of our participating centres.

#### 3.2 Measuring Catheter Exit site Healing

3.2.1 Rationale for Measuring Catheter Exit site Healing

An important safety concern with the use of STP in the HIPPO SAT pilot study is that the catheter exit site seal must be well healed prior to randomization. If the catheter exit site is not well healed, there will not be a seal between the catheter tube and the skin to prevent organism entry, which may put patients at risk for infection. Additionally, the STP involves exposing the catheter exit site more frequently due to increasing the number of dressing changes. On the STP, the dressing changes are also conducted by patients who will be less experienced with dressing changes than the hemodialysis nurses. The patients in the intervention arm will be eligible to use the STP after the catheter being in situ 6 weeks, which is consistent with prior practice. After 6 weeks the catheter is no longer considered ‘incident’ by definition even though exit site healing is not formally tested. However, it is not clear if after 6 weeks the catheter exit site is well healed. It is critical to be able to confirm the healing of the CVC exit site before patients can be randomized to STP. Prior to the initiation of this study there existed no tests of catheter exit site healing for hemodialysis patients in the literature.

The prior shower technique practices at Credit Valley Hospital and London Health Sciences Centre required either the nephrologist or vascular access coordinator to sign off on the use of the STP: No formal assessment of catheter healing was used. In some satellite units, where the access to nephrologists and vascular access coordinators is limited this policy may limit the generalizability of the STP. Additionally, in prior practice at all five centres involved in the HIPPO SAT pilot study, with the exception of the STP decisions regarding types of dressing and dressing changes were left to the discretion of the patient and hemodialysis nurse, unless all the standard dressings and cleansing solutions available in the hemodialysis unit are not tolerated by the patient, in which case the nephrologist or vascular access coordinator is consulted. Therefore, in order to increase generalizability of the HIPPO SAT pilot study and formalize the criteria for catheter exit site healing in the context of using the STP, three tests to assess catheter exit site healing were developed for use by the attending hemodialysis nurse.

3.2.2 Development of Three Tests of Catheter Exit site Healing

In order to brainstorm concepts for possible tests, a panel of experts was assembled including a vascular access coordinator, nephrology fellow, nephrologist, and clinical epidemiologist. The panel found that determination of catheter exit site healing has three components that assesses: 1) stability of the catheter, 2) appearance of the catheter exit site, and 3) integrity of the seal.

***Test 1 Stability of the Catheter:*** Migration of the catheter can occur when the weight and natural movement (e.g. as the chest wall moves) of the catheter gradually pulls it forward out of the body if it is not endothlialized insitu as would occur when the exit site is healed, sometimes even leading to the catheter falling out of the chest. When the catheter is first inserted, sutures are placed to stabilize the catheter. As the skin at the exit site heals around the catheter and the catheter is endothelialized along the subcutaneous tunnel the sutures are removed, usually within 2 weeks post catheter insertion. The catheter dressing also provides stability to the catheter. The panel posited catheter stability could be quantified by measuring the distance from the hub of the catheter to the exit site with a small disposable paper ruler before and after the patient takes a deep breath. The catheter is generally inserted into the internal jugular vein, and protrudes from the chest just below the collar bone. If the catheter is not endothlialized in situ the catheter may move as the patient takes a deep breath due to the muscles in the chest wall contracting. For the HIPPO SAT pilot study, in the first test of CVC exit site healing, the difference between full exhalation and full inspiration is recorded in centimetres with a small paper ruler. The measurement is taken during the catheter dressing change conducted once weekly routinely by the nurses. A difference between full exhalation and full inspiration > 0.2cm indicates a failed test (see Chapter 3, figure 1). The paper ruler is discarded after each test to reduce risk of transfer of contaminants from the paper ruler to the catheter exit site of each patient.

***Test 2 Appearance of the Catheter exit site:*** A second component of assessing healing is a visual assessment of the skin around the point of catheter entry into the chest for signs of irritation and infection. In the HIPPO SAT pilot study a hemodialysis nurse with the assistance of the study coordinator will visually inspect the appearance of the catheter exit site. The appearance of redness, discharge, or swelling at the catheter exit site may be indicative of poor healing, infection, or irritation at the exit site. Poor healing and/or signs of infection will make the patient ineligible for randomization to the study. The presence any two of redness, discharge, or swelling constitute a failure of this test. Some chronic redness may be indicative of skin irritation from the dressing adhesive, antimicrobial ointment, or cleansing solution. This type of skin irritation will not constitute a failure of this test, though alternate cleansing solutions or dressing types may be considered at the patient’s and providers’ discretion so as to reduce the irritation at the exit site.

***Test 3 Integrity of the Skin Seal:*** For the HIPPO SAT pilot study, a hemodialysis nurse will visually inspect the integrity of the seal with the assistance of the study coordinator. The integrity of the skin seal is how tightly the skin is sealed around the catheter tube. The integrity of the skin seal around the catheter is rated in the test as Good, Fair, or Poor. Examples are pictured in Chapter 3, figure 2.

If >2/3 of the above CVC exit site healing tests are failed, standard care will be applied and dressings changed 1x/week on dialysis as per protocol. Catheter Exit site Healing Tests will be repeated at the first dialysis session (i.e. Monday for Monday-Wednesday-Friday, and Tuesday for Tuesday-Thursday-Saturday shifts) until 2/3 tests are passed, and the patient can proceed to randomization, or the study ends.

3.2.3 Validation of Catheter Exit site Healing Tests

The catheter exit site healing tests were developed prior to the HIPPO SAT pilot study and piloted by the vascular access coordinator at Toronto General Hospital and the study coordinator for the HIPPO SAT pilot study in ten patients to refine the protocol for the three tests for ease of use. The catheter exit healing tests have not yet been validated. Convergent validation of the catheter exit site healing tests would involve measuring the correlation of the catheter exit site healing tests with a “gold standard” measure of catheter exit site healing, or at least another measure of the same construct. In this case, there is no practical gold standard of measurement of catheter exit site healing. Ideally, convergent validation of the catheter healing tests would involve each study participant’s catheter exit site being assessed by a vascular access coordinator and vascular access expert nephrologist on the same day as the hemodialysis nurse and study coordinator. If the level of agreement between the vascular access coordinator/nephrologist’s assessment and the hemodialysis nurse’s assessment assisted by the study coordinator was high, the catheter healing tests as completed by hemodialysis nurse would be validated. However, this was not feasible in the context of the HIPPO SAT pilot study, as nephrologists only visit the satellite units once monthly, and most units to not have a vascular access coordinator on site. For a vascular access coordinator and/or expert nephrologist to travel from site to site would not be feasible either, as some of the satellite units included in the study are a two-hour drive from the main study site, one way.

To address this problem a photo test was added to the protocol, as our next best alternative to having the experts travel to the satellites to allow convergent validation of the hemodialysis nurses assessment of CVC exit site healing. In the HIPPO SAT pilot study, two photos of the catheter exit site will be taken during the catheter exit site-healing test using the study camera, in which only the catheter exit site is clearly visible. These photos labeled only with a study ID number are sent to an expert panel on vascular access from University Health Network composed of nephrologist Dr. Charmaine Lok who is recognized worldwide for her research in hemodialysis catheters,[43](#_ENREF_43),[64](#_ENREF_64),[65](#_ENREF_65),[74](#_ENREF_74),[114](#_ENREF_114),[115](#_ENREF_115) and vascular access coordinator Cynthia Bhola, who is a nurse leader across North America in vascular access [65](#_ENREF_65),[78](#_ENREF_78),[116-122](#_ENREF_116). The expert panel will be independent from the study population as neither sees patients outside of in-centre hemodialysis at University Health Network, and only satellite hemodialysis patients are eligible for the study. The expert panel will assess the integrity of the skin seal and the appearance of the catheter exit site from the photograph. If the level of agreement between the independent expert panel and the two catheter exit site tests above is high, the test will be validated.

#### 3.2 The Development of a Tool to Measure Patient Satisfaction with their Vascular Access

3.2.1 The Rationale for Measuring Patient Satisfaction

If we are to understand the potential benefit of the STP in the HIPPO SAT pilot study we need to understand how happy patients are with the STP. Do they feel their care is better; are they satisfied? If one solely considers the bacteremia rate, which is hypothesized to be non-inferior, the full potential benefit of the STP is not captured. Therefore, a carefully selected patient reported outcome (a soft outcome) is important to the study design. Patient reports were not made the primary outcome in this study as patients may not be able to realize the long-term effects of the treatment and account for the full disease modifying effects of the treatment. Additionally, validity questions are important to raise when it comes to a patient reported outcome. An equilibrium between hard and soft outcome measures in this study design is crucial to fully understanding the impact of the STP. Therefore the HIPPO SAT pilot study has a hard primary outcome that is important quantifying both the morbidity and mortality associated with the intervention being studied, and has a soft secondary patient reported outcome in order to measure patient’s satisfaction with their vascular access.

The HIPPO-SAT pilot study will compare the STP versus standard catheter care in hemodialysis patients measuring the proportion of catheter related bactermias (CRBs) (hard outcome) as its primary clinical outcome, but will also measure the change in patient satisfaction with their vascular access as it’s secondary clinical outcome (soft outcome).[123](#_ENREF_123) There is a specific measure of hemodialysis patient satisfaction with their vascular access called the Vascular Access Questionnaire (VAQ) developed by Quinn et al (appendix 9). The VAQ is a direct estimation rating scale of the level of hemodialysis patient’s satisfaction with their vascular access.[124](#_ENREF_124) The concept of measuring patient satisfaction, rather than `quality of life`, makes sense in the context of the HIPPO SAT pilot study, especially because of the temporality problem associated with trying to accurately capture quality of life changes associated with infection over time. Additionally, improving patient satisfaction is an important goal in and of itself: the catheter care survey (section 1.2) conducted in 2011 in 277 patients at Scarborough General Hospital, London Health Sciences, and Toronto General Hospital provided evidence that if patients were inconvenienced and unsatisfied with their catheter care protocol they were non-compliant with it. Changes in patient satisfaction with their vascular access are important to measure in the HIPPO SAT pilot study as we hypothesize that with improved patient satisfaction, there will likely be more compliant patients with fewer infections.

3.2.2 Development and Testing of the Vascular Access Questionnaire

The VAQ as developed by Quinn et al.[124](#_ENREF_124) was not previously formally developed, tested for its reliability, or validated for use in measuring patient satisfaction with their vascular access over time. The further development and testing of the VAQ for use in the HIPPO SAT pilot study was conducted in a separate quality assurance project at the Toronto General Hospital and is described briefly below. The VAQ as developed by Quinn et al[124](#_ENREF_124) was taken as a starting point for the process of 1) new item generation, 2) item selection, 3) item rescaling and 4) reliability testing of the VAQ, detailed below:

1) Item Generation: A comprehensive list of items related to patient’s views and satisfaction with their vascular access was generated by a multidisciplinary team in vascular access. Over 150 items were proposed for the long form VAQ. The long form VAQ was then administered to all in-centre hemodialysis patients at TGH who could speak English and were willing to partake in the first phase of the quality assurance project from May 1 –August 31, 2011.

2) Item Selection: In order to select the items that may be useful in the final VAQ, a factor analysis was performed of the long form VAQ data. Factors were selected based on high eigenvalues (above 1.0) and clinical plausibility. Items were then reworded based on patient feedback. Items were also rescaled (see scaling below) with the goal of normalizing the distribution of responses to each item. Ultimately 4 domains were selected: overall satisfaction, physical symptoms, social functioning, and complications. Each domain represents a parameter of the patient’s experience with their vascular access that will be captured by the short form VAQ.

3) Item rescaling: In the long form VAQ a five point Likert scale that measured the degree of ``bother`` associated with each complication was employed. This scaling method suffered from polarization, as patients had trouble distinguishing between the ``not at all`` end of the scale when they actually felt ``neutral``. A bipolar scale with a neutral middle value was employed for the short form VAQ, to resolve the dichotomization of outcomes seen in the long form VAQ. The new short form VAQ was designed which utilized a 7 point Likert scale. The Likert Scale, while ordinal, has sufficient symmetry and equidistance to approximate an interval-level measurement. [125](#_ENREF_125)

4) Reliability testing: The resulting short form VAQ with 12 items and 4 domains was administered to 31 patients on two occasions two weeks apart. It took approximately 10 min to complete. The patient population included all in-centre hemodialysis patients who volunteered to take part in the second phase of this quality assurance project and had not previously taken the long form VAQ. A repeated measures analysis of variance was conducted to obtain an estimate of the internal consistency and test re test reliability. Overall the results of the reliability testing of the short form VAQ are that the internal consistency (0.84, and above 0.9 within domains) may be too high, therefore further item reduction may be necessary, and the test re test reliability is acceptable (for two occasions 0.92). The obtained standard error of measurement associated with any individual score is 28% of the standard deviation indicating that the VAQ is a fairly precise measure.[126](#_ENREF_126) Overall, the results of the reliability testing indicate that the short form VAQ has high internal consistency, test re test reliability and is fairly precise.

3.2.3 Validating the Vascular Access Questionnaire in the HIPPO SAT Pilot Study

The short form VAQ remains to be validated. A “valid” scale makes accurate inferences about a person.[125](#_ENREF_125),[127](#_ENREF_127) The HIPPO-SAT pilot study provides an ideal opportunity to validate this measure. Construct validation works well for hypothetical constructs like quality of life and patient satisfaction. In construct validation both theory and measure are tested concurrently. It is predicted that high patient satisfaction on the VAQ will be associated with use of the STP (as patients who can shower freely will be more satisfied with their vascular access). If this hypothesis is confirmed, both the theory is supported (the hypothesized association between patient satisfaction and STP use) and our measure (the VAQ). However if the prediction if not confirmed there are several possibilities: 1) the questionnaire is a good measure but the theory is wrong, 2) the theory is good and the instrument is poor, or 3) the theory and the instrument are both poor. The validation of the VAQ in the HIPPO-SAT pilot study is the critical next step in the development of this measurement tool of patient satisfaction with their vascular access. The validity of the VAQ informs how accurately conclusions may be drawn about the relative satisfaction of participants on STP arm versus standard catheter care with their vascular access on the basis of their VAQ score The estimate of validity will be specific to the sample used in the HIPPO SAT pilot study, as it is strongly influenced by the circumstances under which the test is conducted. This implies this implies that following the HIPPO SAT pilot study, if the hypothesized association between patient satisfaction and STP use is confirmed, the VAQ will be validated for use in the full HIPPO SAT trial.

3.2.4 Why not Measure Quality of Life in the HIPPO SAT pilot study?

The HIPPO SAT pilot study does not use a quality of life measure as it’s soft patient reported outcome. There are several reasons for this decision. Firstly, while there are over 20 generic quality of life instruments[128](#_ENREF_128),[129](#_ENREF_129) and 5 preference based generic quality of life measures[130-132](#_ENREF_130) that have been used in the hemodialysis population, there are sensitivity problems with generic quality of life measures[133](#_ENREF_133) that have been used in the hemodialysis population. The STP is suspected to have an impact on patient quality of life as 64% of patients indicated on the catheter care survey (see section 1.2) that they found the recommendation not to shower moderately to extremely inconvenient. However the improvement in quality of life hypothesized with STP is not likely to have an impact on a generic utility score or quality of life measure because most quality of life measures do not contain very many items that are relevant in vascular access to detect changes within patients, or differences between them. For example, the often-used Health Utilities Index has eight domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition, pain. Each domain requires the patient to indicate their level of functioning on a scale of one to five. The occurrence of a CRB would undoubtedly have a negative impact a patient’s quality of life at the time of the infection.[15](#_ENREF_15) However, the full HIPPO SAT trial is ultimately designed as a non inferiority trial (see Chapter 2), that is to say there is no difference between the CRB rate using the STP versus standard catheter care. Therefore there is no anticipated benefit in quality life associated as there is no anticipated reduction in CRB using the STP. Any quality of life benefit would be associated with patient’s freedom to shower with their catheter. The ability to shower freely the STP would logically be unlikely to have an impact on any of the HUI3 domains.[16](#_ENREF_16) The potential benefit associated with patient’s ability to shower freely on the STP will be better quantified by measuring patient’s satisfaction with their vascular access with the short form VAQ.

#### 3.4 Impact of this Research

3.4.1 Importance of this study to Endstage Kidney Disease patients

It is critical to understand the infection rates and patient satisfaction associated with the shower technique in hemodialysis patients with healed catheter entry sites. Centres for Disease Control guidelines state that the optimal method of catheter infection prophylaxis in patient with healed entry sites is an unresolved issue.[134](#_ENREF_134) This means that recommendations surrounding catheter care for hemodialysis with healed catheter entry site can not be made based on the best available evidence which is one small observational study.[94](#_ENREF_94) This leaves patients, hemodialysis personnel, and nephrologists adrift, unable make an informed choice about their catheter care. Given the burden of catheter related infection (section 1.1), and the reduced quality of life of patients by restricting their ability to shower (section 1.3), the study question remains a pressing issue that the full HIPPO SAT trial will ultimately address.

3.4.2 Methodological Implications- Alternate Designs

The results of the HIPPO SAT pilot study will allow us to refine the design for the full HIPPO SAT trial. The RCT design is highly ranked in terms of the hierarchy of evidence, but can be expensive and challenging especially with an education- based intervention such as the shower technique. An observational design has been considered for this question. An observational study can provide insight into whether this shower technique approach is safe by measuring whether there is a spike in infections following the implementation of the STP. However an observational study design cannot make it clear whether the CRB rate for patients on STP is truly non-inferior as compared to standard care. This is because patients are selected for shower technique in an observational design. The most compliant, healthiest and most able patients are likely to be selected for the intervention arm for a cohort study. It would be very challenging to adjust for all known confounders, let alone those that are unknown. The research architecture is paramount: randomization can ultimately best address confounding and bias. The RCT design is however, not inherently bias free. It is critical for an RCT to be carefully designed and implemented. In this research question there is significant potential for contamination, which may systematically bias the results. Patients in hemodialysis units are free to communicate with each other, which creates challenges with any education-based intervention in the hemodialysis setting. This pilot study will determine the patient non-compliance rate (an expected reality in the hemodialysis unit) and contamination and considered in the context of the larger study design. For example, if there is a high level of contamination in the pilot study, the use of a cluster randomized design may be justifiable for the full trial.

By randomizing at the cluster level, for example the hemodialysis centre, there is the advantage of reduced risk of experimental contamination and often an accompanying increase in compliance. However, cluster randomized trials must be designed with great caution as they are very statistically inefficient and present many challenges in their analysis. In patient level randomization stratified by centre, the variation between centres is distributed equally between the control and treatment arms, so they are generally ignored in sample size calculation and analysis. However in cluster randomization, the between centre variance must be considered both in sample size calculation and in the analysis, otherwise the variances and standard errors will be too low and statistical tests too liberal. Hemodialysis facilities have many levels of natural clusters, as there are multiple units and 6 shifts comprised of 3 time shifts (morning, afternoon, evening shifts) and 2 day shifts (Mon-Wed-Fri shift and Tues-Thurs-Sat shift). The between shift and unit variance, for example, would need to be estimated if each shift within a unit was to act as a cluster. By way of example, the sample size would be inflated by a factor of 40% (Appendix 10 and 11 for sample size estimates for cluster design). In the pilot study, estimates of the between centre variance (the intracluster correlation coefficient) for the CRB rate and level of contamination will be important outcomes in determining the design of the full study.

Additionally, recruitment is challenging when conducting any clinical research study, but particularly plagues the RCT. Patients are generally reluctant to be randomized, especially to an educational intervention. In the HIPPO SAT pilot study we will identify a nurse leader at each centre and in-service with this nurse and all unit nurses, as nurses are essential to championing this study. Another source of assistance with recruitment is study participants themselves. Though also a potential source of contamination, but study participants may champion the study as happy participants will encourage others to participate. In advance of a large simple trial, it is critically important that the groundwork be laid with this pilot study to address issues of contamination, recruitment, and measurement tools to ensure we have the right design to answer this unresolved clinical question.

3.4.3 Conclusion

When designing the full HIPPO SAT trial it is important to note we are not aiming to show a large difference in one outcome; rather there are a myriad of equally important outcomes and we are looking to incrementally improve care. This is reflective of recent randomized trials worldwide: as a community we are conducting larger and larger trials to measure smaller and smaller differences. The impact of patient experience and their physical and emotional well-being is becoming increasingly important when considering and designing trials. Overall, the implication of this current pragmatic design is the maintenance of internal study integrity while ensuring proper external validity and ultimately, greater practical generalizability to the real world setting.

Chapter 3 Table 1 The Development of the Shower Technique Protocol (STP)

For the table below text in blue is from the London Health Sciences Centre “No Dressing – Shower Technique Protocol” and text in green is from the Credit Valley Hospital “Shower Technique. Text in italics in the London Health Sciences and Credit Valley Hospital Columns were used in the HIPPO SAT Pilot Study STP. Text underlined in red is from the UHN Polysporin Triple Ointment Protocol.

|  |  |  |
| --- | --- | --- |
| **HIPPO SAT Pilot Study STP** | London Health Sciences “No Dressing - Shower Technique” | Credit Valley Hospital “Shower Technique” |
| Make sure catheter caps are secure before showeringGather all equipment before entering shower.In the shower, wash and rinse hair, face and the rest of body. Do not wash the catheter exit site.Once out of the shower, dry the rest of the body with clean bath towel avoiding the catheter exit site.With clean gauze, gently pat the skin around the catheter so that it is dry.Remove the Chlorhexidine swab stick from its package.Using one side of the Chlorhexidine swab stick, work in a clockwise circular motion from the skin around the catheter entry outward until the swab tip is 2 cm away from the catheter exit site.Using the other side of the Chlorhexidine swab stick, work in a counter clockwise circular motion from the skin around the catheter entry outward until the swab tip is 2 cm away from the catheter exit site.Throw away the gauze and chlorhexidine swab stick. Apply clean gauze dressing around both catheter lumens and tape ONLY IF DESIRED. Some patients desire catheter ends to be taped to reduce friction against skin. | *Make sure catheter caps are secure before showering**Gather all equipment before entering shower**In shower, wash and rinse face, hair and the rest of body* leaving catheter care for last.Wash hands with soap and water. With clean hands gently wash the skin around the catheter with mild soapRinse well and do not wash area again. This reduces re-introduction of contaminants to catheter exit site.*Once out of the shower: gently pat the skin around the catheter first with a clean gauze, dry the rest of the body with clean bath towel**Remove the Chlohexidine swab stick from its package*Using one side of the Chlorhexidine swab stick, cleanse skin around the catheter, using friction, side to sideTurn Chlorhexidine swab stick over and using friction cleanse up and down*Apply clean gauze dressing around both catheter lumens and tape ONLY IF DESIRED. Some patients desire catheter ends to be taped to reduce friction against skin.* | When Showering allow water to run over the exit site but *Do Not Use Soap to clean the area.*Allow the area to air dry.*Open an antiseptic swab provided by the Renal Unit and wipe around catheter in a circular motion starting from the exit site and working outward approx. 2 inches. Discard swab.* Open a new swab and repeat step 3.Allow the area to completely dry before covering with clothing. |
| Signs of infection to watch out for:*Fever (temp > 37.7°c)**Exit site becomes reddened or appears inflamed.**Exit site has discharge.**Exit site and/or surrounding area are painful.* | Infection PreventionIf you have any of these symptoms of infection contact the dialysis unit immediately for advice:*Fever develops (temp > 37.7°c)**Exit site becomes reddened/inflamed**Exit site has discharge**Exit site is painful* | Be sure to *inform your nurse if you notice any pain, redness, or discharge around the catheter site*. This may be a sign of infection and needs prompt attention.Sutures need to be secure and may need to be replaced if they fall out. This is at the doctor’s discretion |
|  |  |  |

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Chapter 3 Figure 1 Catheter Migration Test



Skin at Catheter exit site

Hub of the Catheter

Paper ruler

Chapter 3 Figure 2 Catheter Exit site Seal

|  |  |
| --- | --- |
| **GOOD SEAL** | **POOR SEAL** |
| Scott  Catheter exit site seal | Frutuoso  Catheter exit site seal |

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#### Appendices

Appendix 1 - Cross Canada Survey

Appendix 2 - Catheter care questionnaire

Appendix 3 - Suspected Catheter Related Infection Form - To be completed by each member of the outcome adjucation committee

Appendix 4 - Spirit Guidelines Checklist

Appendix 5 - STP Training Tools

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**Appendix 1 Cross Canada Survey**

**Appendix 2 Catheter care questionnaire**

Study ID number: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date of form completion: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Catheter Care

Who does catheter care (circle): RN / MD / Patient / Family member/ None

*Do you do your own dressing changes*? Yes No

*Would you be willing to take responsibility for your own catheter care?* Yes No

1. Cleansing Agent – Which of the following is/are used to clean the catheter and exit site?

Chlorhexidene with/without alcohol Yes No

Proviodine Yes No

Isopropyl alcohol Yes No

Saline Yes No

Other \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Yes No

None Yes No

1. Dressing

How often is the dressing changed per week? \_\_\_\_\_\_\_\_\_\_\_\_\_

Which of the follow dressing type(s) is/are used?

Tape and dry gauze Yes No

Transparent dressing Yes No

Medipore Yes No

Hypafix Yes No

Other: \_\_\_\_\_\_\_\_\_\_\_\_

*How much do you agree that your catheter dressing bothers and/or inconveniences you*?

Likert Scale: \_\_\_\_\_\_

*Would you prefer not to have the dressing for your catheter?* Yes No

1. Antimicrobial Barrier

Any topical ointment/ barrier applied at exit site?

Polysporin Triple Yes No

Mupirocin Yes No

Gentamicin Yes No

Other \_\_\_\_\_\_\_\_\_\_\_\_\_\_ Yes No

None Yes No

1. Personal Hygiene

*What method do you use to clean yourself?*  Shower Bath Other:\_\_\_\_\_\_\_\_\_

*Do you protect your catheter during the shower?* Yes No

If yes, how:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

*Do you want to shower?*  Yes No

*Did any healthcare professional tell you not to shower?*  Yes No

*How much do you agree that not being able to shower with your catheter bothers and/or inconveniences you?* Likert Scale: \_\_\_\_\_\_

1. Catheter Infection

*Have you ever had an infection related to your catheter?* Yes No

*If yes, were you hospitalized?* Yes No

*Were you in the intensive care unit for your infection?* Yes No

**Appendix 3 - Suspected Catheter Related Infection Form - To be completed by each member of the outcome adjucation committee**

|  |  |  |  |
| --- | --- | --- | --- |
| Criteria | Location | | |
| Catheter Exit site | Tunnel | Pocket site not contiguous with Catheter exit site |
| Erythema | o Yes  o No | o Yes  o No | o Yes  o No |
| Tenderness | o Yes  o No | o Yes  o No | o Yes  o No |
| Induration | o Yes  o No | o Yes  o No | o Yes  o No |
| Purulent Discharge | o Yes  o No | o Yes  o No | o Yes  o No |
| Positive Culture of serous discharge or aspirate | o Yes  o No  If yes how many positive cultures:\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  If yes which organisms:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | o Yes  o No  If yes how many positive cultures:\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  If yes which organisms:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ | o Yes  o No  If yes how many positive cultures:\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  If yes which organisms:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |

- Was the blood culture positive for septic thrombophlebitis? o Yes o No

* Is there a greater than 10 fold colony count difference in blood cultures drawn from device and peripheral blood? o Yes o No
* Patient ceceiving immunosuppressive medication? o Yes o No
* Patient neutropenic? o Yes o No
* Patient receiving total parenteral nutrition? o Yes o No

**Appendix 4- Spirit Guidelines Checklist**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

|  |  |  |  |
| --- | --- | --- | --- |
| Section/item | Item No | Description | Addressed on page number |
| **Administrative information** | | |  |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 1 |
| 2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | 3 | Date and version identifier | 1 |
| Funding | 4 | Sources and types of financial, material, and other support | 1 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 |
| 5b | Name and contact information for the trial sponsor | 1 |
|  | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 1 |
|  | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 1 |
| Introduction |  |  |  |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-6 |
|  | 6b | Explanation for choice of comparators | 6 |
| Objectives | 7 | Specific objectives or hypotheses | 6-7, 24-25 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 7 |
| Methods: Participants, interventions, and outcomes | | |  |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8-9 |
| 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 9-10 |
| 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10 |
| 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 9 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 10-11, 24-25 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 11-12, 27 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 12 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 12-13 |
| **Methods: Assignment of interventions (for controlled trials)** | | |  |
| Allocation: |  |  |  |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 13-14 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 14 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 14-15 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 14-15 |
|  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial | 14-15 |
| **Methods: Data collection, management, and analysis** | | |  |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 16 |
|  | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 16 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 16 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 16-17, 24-25 |
|  | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 16-17, 24-25 |
|  | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 16, 24-25 |
| **Methods: Monitoring** | | |  |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 29 |
|  | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 29 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 29 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 29 |
| Ethics and dissemination | | |  |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 29-30 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 30 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 30 |
|  | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 30 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 30 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 30 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 30 |
|  | 31b | Authorship eligibility guidelines and any intended use of professional writers | 30 |
|  | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 30 |
| Appendices |  |  |  |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Not included |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “[Attribution-NonCommercial-NoDerivs 3.0 Unported](http://www.creativecommons.org/licenses/by-nc-nd/3.0/)” license.

**Appendix 5 Shower Technique Protocol (STP) Training Tool**

Study ID number: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Date of STP training completion: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

|  |
| --- |
| **STP Training Checklist** |
| **Shower Preparation** |
| Can the patient secure the catheter caps? Yes No |
| Does the patient know what equipment is required for the STP: |
| Chlorhexidine (unit provided) Yes No |
| Soap (patient provided) Yes No |
| Clean Towel (patient provided) Yes No |
| Can the patient remove their catheter dressing? (if applicable) Yes No |
| **Test Passed?**  Yes No |
|  |
| **In Shower** |
| Does the patient know to wash and rinse face, hair and the rest of body first? Yes No |
| Can patient demonstrate thorough washing of their hands with soap and water? Yes No |
| Can the patient wash the skin around their catheter with mild soap and rinse area? Yes No |
| **Test Passed?**  Yes No |
|  |
| **After Shower** |
| Gently pat the skin around the catheter first with a clean gauze |
| Dry the rest of the body with clean bath towel |
| Can patient use of the Chlorhexidine swab stick to cleanse skin around the catheter:  First using clockwise circular motion Yes No  Second using counter clockwise circular motion Yes No |
| Does the patient want to put a new dressing on after they shower? (if applicable) Yes No |
| Can the patient apply clean gauze dressing around both catheter lumens and tape? Yes No |
| **Test Passed?**  Yes No |

Patient has demonstrated knowledge and safety using the training mannequin:

* Yes
* No

**Appendix 6 Documentation of Tests of Healing of Catheter exit site**

Form to be completed by nurse.

Important:

Proceed to randomization when the patient has successfully passed **two of three** of these tests.

Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Study ID:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

|  |
| --- |
| **Catheter Exit site Healing Tests** |
| **Catheter Skin Seal Test** |
| Is the catheter more than six weeks old? Yes No |
| At the Catheter exit site: |
| Is there redness? Yes No |
| Is there discharge? Yes No |
| Is there swelling? Yes No |
| How well is skin sealed around the exit site? Good Fair Poor |
| **Test Passed?**  Yes No |
|  |
| **Catheter Deep Breath Stability Test** |
| Distance from the hub of the catheter to the skin? \_\_\_\_\_\_\_\_ cm |
| Distance from the hub of the catheter to the skin when the patient takes a deep breath? \_\_\_\_\_\_\_\_ cm |
| **Test Passed?**  Yes No |
|  |
| **Photograph Assessment** |
| Reviewer 1: Catheter exit site healed? Yes No |
| Reviewer 2: Catheter exit site healed? Yes No |
| **Test Passed?**  Yes No |

**Appendix 7- Vascular Access Questionnaire**

Instructions: We are interested in finding out more about your views on your vascular access- what you like or don’t like about your access and what problems you are bothered by. Your vascular access can be either a catheter, fistula, or graft. We would be grateful if you could help us out by filling out this questionnaire. All of the information you give is COMPLETELY CONFIDENTIAL. Although we appreciate answers to all questions, you may pass any questions you do not wish to answer.

**First, are some general questions about yourself and your access:**

1. What type(s) of vascular access do you have? (Check all that apply):

Catheter \_\_\_\_\_ Fistula \_\_\_\_\_ Graft \_\_\_\_\_

1. During the past 4 weeks, which access did you use for most of your dialysis treatments? (Check all that apply): Catheter \_\_\_\_\_ Fistula \_\_\_\_\_ Graft \_\_\_\_\_
2. Circle a number on the scale that indicates your level of agreement with this statement: *I am satisfied with my vascular access.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

**Physical Symptoms**

1. Circle a number on the scale that indicates your level of agreement with each statement: *During the past 4 weeks I was bothered by pain associated with my vascular access*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks I was bothered by bleeding associated with my vascular access*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks I was bothered by swelling associated with my vascular access*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks I was bothered by bruising associated with my vascular access*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

**Social Functioning**

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks my access interfered with my daily activities (e.g. work, social, leisure activities or other regular daily activities)*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks I was bothered by the appearance of my vascular access*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks my access interfered with my sleep*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks my access caused me problems when bathing or showering*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

**Complications**

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks my vascular access had problems (i.e. didn’t work properly)*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks my vascular access was difficult to care for (i.e. dressings, trying to keep access clean and protected)*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks I was worried about being hospitalized because of problems with my access.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

1. Circle a number on the scale that indicates your level of agreement with the following statement: *During the past 4 weeks I was worried about how long my vascular access will last.*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Strongly disagree | Somewhat disagree | Disagree a little | No opinion | Agree a little | Somewhat Agree | Strongly agree |

**Appendix 8 Sample Size Calculations for the full HIPPO-SAT STUDY**

Null hypothesis: bacteremia rateSTP≠ bacteremia rate standard Catheter care

Alternative hypothesis: bacteremia rateSTP= bacteremia rate standard Catheter care

bacteremia rate standard Catheter care = 0.41/1000 Catheter days (based on current CRB rates at multiple sites)

Alpha = .05

**Power Calculation for**

**rateSTP = .34**

Lower = 217, upper = 277

Effect size = .048029

n power

500 .69431

510 .7082

520 .72154

530 .73434

540 .7466

550 .75836

560 .7474

570 .75896

580 .77005

590 .78067

**600 .79084**

610 .80058

620 .79101

630 .80062

640 .80983

650 .81864

660 .82707

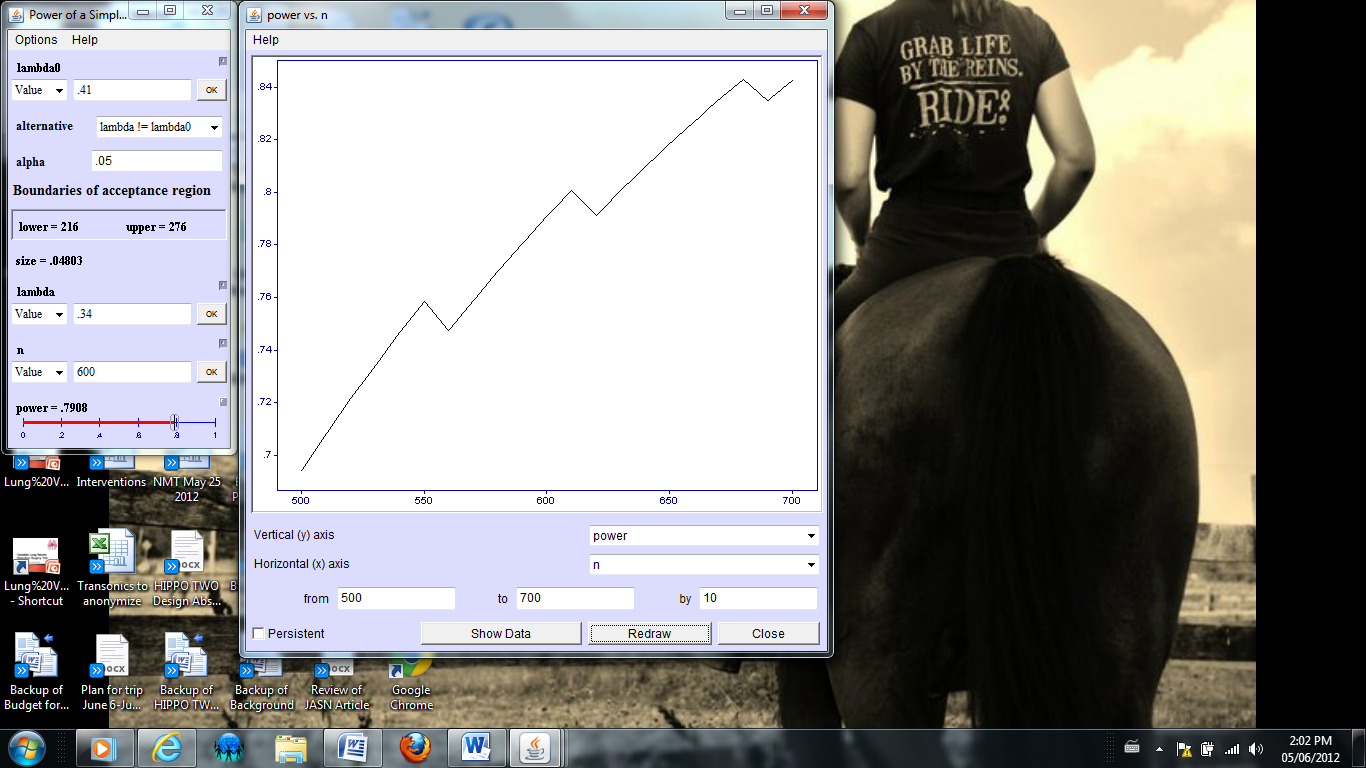
67 .83514

680 .84286

690 .83486

700 .8425

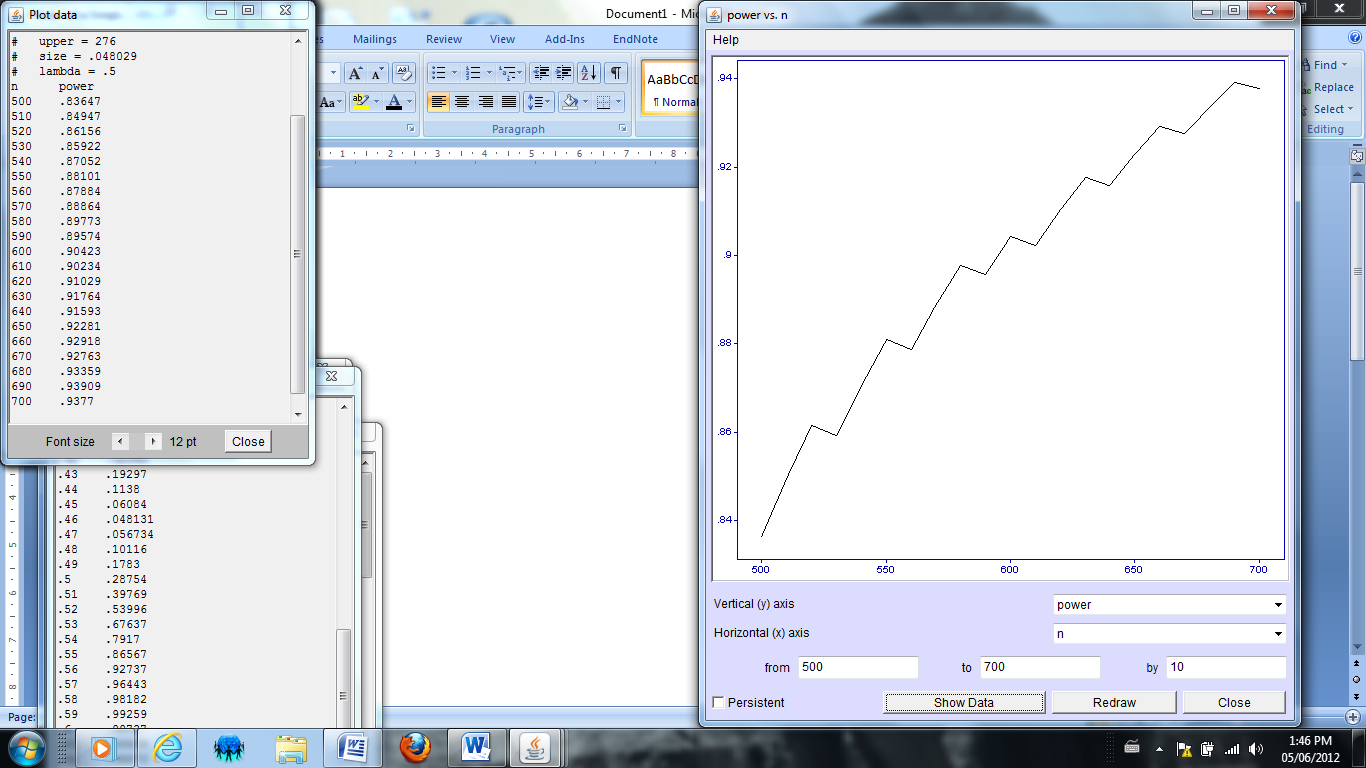
**Graph of n vs power for rate of 0.34**



x-axis: number of participants

y-axis: power

**Graph of n vs power for rate of 0.50**



x-axis: number of participants

y-axis: power

**Power Calculation for**

**rateSTP = .50**

Lower = 216, upper = 276

Effect size = .048029

n power

500 .83647

510 .84947

520 .86156

530 .85922

540 .87052

550 .88101

560 .87884

570 .88864

580 .89773

590 .89574

**600 .90423**

610 .90234

620 .91029

630 .91764

640 .91593

650 .92281

660 .92918

670 .92763

680 .93359

690 .93909

700 .9377

**Appendix 9 Sample Size Calculations Continued- Cluster Randomized Trials**

n = number of subjects in the study

m = size of clusters

k = number of clusters = m / n

n = (Zα/2 + Zβ)2 (2σ2) VIF

(μ1 - μ2) 2

n = (1.96 + 0.84) 2 (2σ2) VIF

(μPTO - μST) 2

VIF = (1+(m-1)(σ2B/ σ2)

* σ2 = total variance = σ2B+ σ2W
* σ2B = between cluster component of variance, with dialysis centres this is likely to be large, as bacteremia rates vary by as much as **40%** between centres included in this study
* σ2W = within cluster component of variance

The bigger σ2B is the larger the sample size needs to be and there is little statistical advantage to cluster sizes over 30 (Donner et al. 2010).

Potential Clusters

* Cluster by centre
  + Problem: massive intracluster correlation coefficient value as there is lots of between cluster variance
  + Needs a very large study with many more centres, with about 30-50 patients per centre, centres would need to be matched
* Small clusters created within centres i.e. hemodialysis wing, days (TTS/MWF), shifts (am/pm/eve)
  + Potentially many small clusters could have a sample size, as the intracluster correlation coefficient would be lower
    - Clusters within centre will be more similar to each then between centre lowering the intracluster correlation coefficient
  + Major Problem: This approach does not really resolve contamination issues because of patients switching shifts